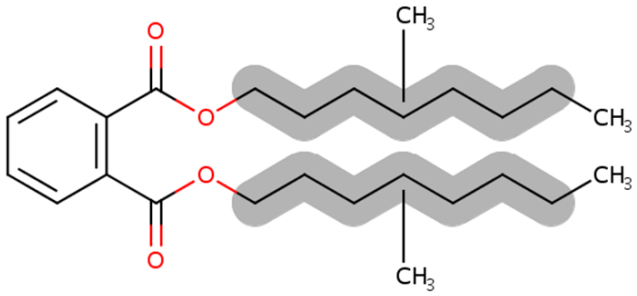
United States
Environmental Protection Agency

January 2025
Office of Chemical Safety and
Pollution Prevention

Data Quality Evaluation and Data Extraction Information for Dermal Absorption for Diisononyl Phthalate (DINP)

Systematic Review Support Document for the Risk Evaluation

CASRNs: 28553-12-0 and 68515-48-0



January 2025

This supplemental file contains information regarding the data extraction and evaluation results for data sources that met the PECO screening criteria for the *Risk Evaluation for Diisononyl Phthalate* 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 the Risk Evaluation for Diisononyl Phthalate*.

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 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). Within the contents of this document, diisononyl phthalate may be referred to as the acronym DINP.

Table of Contents

Study Citation: Pan, T. L., Wang, P. W., Aljuffali, I. A., Hung, Y. Y., Lin, C. F., Fang, J. Y. (2014). Dermal toxicity elicited by phthalates: Evaluation of skin absorption, immunohistology, and functional proteomics. Food and Chemical Toxicology 65:105-114.

HERO ID: 2219803

EXTRACTION

Parameter	Data
Extraction ID; Chemical:	Pig-DINP; Diisononyl Phthalate (DINP)-Parent compound
Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type:	ex vivo pig; Full thickness; Not Reported; Static; Notes: Ex vivo mouse
Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent):	Not Reported; 40% ethanol solution; Not Reported
Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin:	Not Reported; Other; 12 hours
Duration of Absorbance Measured; Frequency of Samples:	Other; every 3 hours in receptor fluid; Notes: 12 hours
Time Skin was Washed and Method used; Radiolabel Presence:	Skin was washed at 12 hours. No further details were provided.; No
Total Recovery (percent); Dose Type:	Not Reported; Not Reported
Percent Found in Skin Depot After Washing and Tape Stripping; Comments:	Not Reported; Notes: Skin absorption was not reported as a percent. The accumulation in skin was 0.36 $\pm$ 0.16 nmol/mg (CV= 44%). Tape stripping was mentioned in another part of the study, but this measurement is presumed to be for total skin after washing.
Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments:	Not Reported; Notes: Skin absorption was not reported as a percent. The accumulation in skin was 0.36 $\pm$ 0.16 nmol/mg (CV= 44%). Tape stripping was mentioned in another part of the study, but this measurement is presumed to be for total skin after washing.
Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments:	Not Reported; Notes: This information was not reported.
Total Percent Absorbed:	0
Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maxium Permeability Coefficient (Kp) (cm/hr); Maxium Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments):	Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; 0; Notes: Flux could not be calculated. "No permeant was found in receptor after treatment..."

EVALUATION

Domain	Metric	Rating	Comments
Domain 1: Test Substance			
Metric 1:	Test substance identity	High	The test substance was identified as DINP. A CASRN was not provided. The test substance was not radiolabeled.
Metric 2:	Test substance source	High	The test substance was obtained from Sigma-Aldrich (St. Louis, MO). The batch/lot number was not provided. Test substance identity was not certifid by the in the publication but could be verified on manufacturer's website.
Metric 3:	Test substance purity	High	The reported purity was >99%
Domain 2: Test Design			

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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 4:	Reference compounds	Low	No reference compound was used and no history of test performance in the laboratory was reported.
	Metric 5:	Assay procedures	Medium	Tests were conducted in a Franz diffusion cell, presumably under static conditions. Freshly excised skin samples were mounted onto the cells (n = 4) leaving a diffusion area of 0.785 cm2. The exposure solution in the donor chamber contained a 5.4mM concentration of the test substance in 40% ethanol, and the receptor fluid was 40% ethanol. It is unclear if this was intended to be an infinite or finite exposure. A magnetic stir bar was used and the receptor was maintained at 37 degrees C. The pH was 7.4. Humidity was not reported, and it was not stated whether the chambers were left open or closed. The exposure duration was 12 hours. During exposure, receptor fluid aliquots were taken every 3 hours, and the volume was replaced with fresh fluid. HPLC was used to analyze the test substance in the receptor fluid and also in homogenized skin at the end of the exposure period. The limits of detection were reported.
	Metric 6:	Standards for tests	Uninformative	This study did not conduct the typical standard tests to determine the validity, reliability, or quality of the experiments. Skin integrity was not tested prior to use, and percent recovery was not determined. The variation across replicates for the reported endpoints could be determined by the data provided, see Metric 19 for more details. There is no text indicating the test met pre-established criteria. Inadequate data were provided in the results to demonstrate that the test conformed to current standards or guidelines.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Limited details on the test substance preparation were provided. No details on stability, homogeneity, mixing, or storage conditions were reported. The test substance was delivered in 40% ethanol, which is often used, and is appropriate as a receptor fluid for lipophilic test substances, but it is unclear if it is also appropriate in the donor chamber. Solubility was not confirmed. Generally, the use of radiolabeled test substances is preferred for penetration studies. This study only used unlabeled test substances. The lack of details could substantially impact the study results.
	Metric 8:	Consistency of exposure administration	Low	The diffusion area was reported (0.785 cm2) and consistent across replicates. Each replicate was exposed to a 5.4 mM concentration of the test substance; however, the volume added to each donor chamber and the skin thicknesses were not reported. These missing details could have a substantial impact on the study results.
	Metric 9:	Reporting of concentrations	Low	Insufficient information on dosing was provided. The reported concentration was 5.4 mM, which is presumed to be nominal. There is no indication that the exposure concentration was analytically verified. The mass per skin area (mg/cm2) or volume per area (mL/cm2) were not reported. It is unclear if conditions were met for an infinite exposure.
	Metric 10:	Exposure frequency	Low	The exposure duration of 12 hours was not justified by the study authors. It may reflect an appropriate 'in-use' practice; however, no test substance was measured in the receptor fluid indicating that the exposure duration may have been too short, especially when full-thickness skin is used. Longer times (sometimes >24 hrs) are often required for highly lipophilic substances.
	Metric 11:	Number of exposure groups and concentration spacing	Low	Fewer than three concentrations were tested. This study only tested one concentration and it was not justified by the study authors.

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EVALUATION

Domain	Metric		Rating	Comments
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	Full-thickness skin was excised from the dorsal regions of 8-week-old mice and 1-week-old pigs. It was not specified how many animals were used to obtain the samples. Mice are not a typical species for dermal absorption studies, and it is unclear whether this species is appropriate for this study type. However, the authors justified the use of nude mouse skin by indicating that it has a similar number of layers (3-4 cell layers) as the epidermis of infants. They also noted that nude mouse skin has greater permeability than human skin, but it may be a good model for human facial skin, which has a 4-fold higher permeability than other sites. Pigs are an acceptable model for dermal absorption studies. The source of the animals was reported. Full-thickness skin can be used when properly justified and if the thickness is not excessive. However, OECD TG 156 specifies that fill-thickness skin should not be used for calculating fluxes, which was the main outcome of this study. Viable skin was used, but no details of its preparation prior to being placed in the diffusion cells were provided. Skin integrity was not tested. The skin thickness was not reported. There was no information on storage, but it appears that the skin was used immediately. The missing details are likely to have a substantial impact on the study results.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates was not explicitly reported in the study methods and there is some lack of clarity. The data results indicate an n = 4, suggesting that there were at least four samples/ replicates of the single concentration tested. This is the minimum number of replicates required as per OECD TG 428. However, there were 4 replicates in which the entire skin sample was homogenized for analysis, yet there are also data measuring concentrations in hair follicles following tape stripping (also noted as 4 replicates). It is presumed that these are two separate experiments, but the reporting details were not clear.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	The outcome assessment methodology deviated significantly from OECD TG 428 recommendations. This study did not determine a mean mass balance recovery. This study analyzed concentrations of the test substance in the receptor fluid and in the skin at the end of the study using HPLC. Based on the figures provided, receptor fluid was sampled every 2 hours for the duration of the study. Flux was specified as an outcome, but Kp was not reported. The study did not report total absorption or percentage applied. Insufficient information on dosing was provided to determine whether an appropriate (infinite) exposure condition was used. The missing details make it difficult to determine the appropriateness of the outcome assessments and have a substantial impact on results.
	Metric 15:	Consistency of outcome assessment	High	Based on the available information, the same duration of exposure, and receptor fluid collection times were applied to all of the replicates. All replicates had the same donor vehicle and receptor fluid. Based on the information provided, there is no indication that there were significant differences between replicates.
	Metric 16:	Sampling adequacy and sensitivity	Medium	All data were derived from an n = 4. Details of HLPC, including the LOD were reported. It is unclear whether the sampling intervals for the receptor fluid were sufficient to allow at least 4 data points at steady state for calculation of flux.
Domain 6: Confounding/Variable Control				

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HERO ID: 2219803

			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 17:	Confounding variables in test design and procedures	Low	Insufficient information was provided to determine confounding. The number of donors, skin integrity, and skin thicknesses were not reported. % Recovery was not assessed.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	There were no reported differences among the study replicates that were unrelated to exposure. It was not specified whether the test substance was soluble in the receptor fluid; however, a 50% ethanol solution (this study used 40%) is common and acceptable, particularly for lipophilic compounds.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Limited details on data analysis were provided. Flux was calculated from the slope of the permeated amount vs. time. It was not specified that it was a linear portion of the curve. No data were reported as percentage estimates. The coefficient of variation for the skin accumulation endpoint were >25% and ≤50% for both mice and pigs. standard deviations were provided which will allow for EPA to calculate an alternate upper end value to account for variability in the results. Fluxes were not determined due to the lack of permeation through the skin.
	Metric 20:	Data interpretation	Medium	The lack of exposure details, and deviations from guideline in outcome assessments make this study difficult to interpret. The authors do not make any unreasonable claims, but also do not report standard outcomes (e.g., % recovery, % absorption, Kp). It is also unclear if dosing was infinite or finite.
	Metric 21:	Reporting of data	Low	Data for some specified outcomes were adequately reported as means ± SD. Permeation The study did not report concentrations in receptor fluid by time. A figure showing the plotted data with a corresponding linear slope was not provided.

Overall Quality Determination Uninformative

Study Citation: Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.
HERO ID: 1325430

EXTRACTION

Parameter	Data
Extraction ID; Chemical:	Group 1; 1.2 ml/kg; 1 day; Diisononyl Phthalate (DINP)-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):	Not Reported; Not Reported
Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))):	16.3; 1113
Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments):	24 hrs; Not Reported; Notes: Not Reported
Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments):	24 hrs; Not Reported; Notes: Not Reported
Time Skin was Washed and Method used; Radiolabel Presence:	Skin was not washed; Yes
Total Recovery (percent); Dose Type:	96.56; Finite
Percent Found in Skin Depot after Washing and Tape Stripping:	Not Reported; Notes: Not Reported
Percent Found in Urine ; Comments:	0.09; Notes: Not Reported
Percent Found in Feces ; Comments:	0.03; Notes: Not Reported
Percent Found in Blood/Serum ; Comments:	0.001; Notes: Not Reported
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: Not Reported
Total Percent Absorbed:	0
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: 0.19% measured in tissues and GI tract; Total absorbed 0.343% with CV of 18%

EVALUATION

Domain	Metric	Rating	Comments
Domain 1: Test Substance			
Metric 1:	Test substance identity	High	The test substance was identified as 14C-di-isononylphthalate (DINP); CASRN 68515-48. Location of radiolabel was indicated.

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Study Citation: Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.
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EVALUATION

Domain	Metric		Rating	Comments
	Metric 2:	Test substance source	High	The labeled and unlabeled test substance was supplied by Exxon Corporation. The radiolabeled test substance was prepared by Amersham Corporation (Arlington Heights, Illinois). The chemical identity of the radiolabeled test material was confirmed by the performing laboratory using HPLC. It is assumed that the test substance was a liquid since it was applied to the skin using a micropipette.
	Metric 3:	Test substance purity	High	The purity was reported to be 97-98%, determined by TLC.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Medium	The study states animals were selected at random for each test group; however, the method of randomization was not specified.
	Metric 5:	Standards for Tests	Low	This in vivo study was not conducted according to any specified guidelines. The percent recovery was acceptable (100+/-10%) and consistent with current guidelines. The backs of the rats were shaved shortly before treatment specific timing not specified). This is not consistent with OECD guidelines which state the area of skin should be clipped approximately 24 hours prior to dosing. It was not specified whether care was taken to minimize abrasion, and it was not reported whether the area was wiped with acetone as specified in OECD TG 427.The test substance was applied neat to a 3x4 cm area of skin, which is appropriate. The text indicated that a stock solution was prepared containing the labeled compound in ether. It is unclear whether this stock was used only for analysis of the test compound or if this stock was applied to the skin of animals. Elsewhere in the report, it indicates that the test material was applied neat. The study specified that the skin was kept occluded, however, an atypical method was used. Specifically, the application site was covered with a Styrofoam cup lined with aluminum, which was secured onto the animal's back with adhesive tape. This setup suggests more protection of the application site, rather than occlusion. This is not expected to have a significant impact on the study results because the test material is not volatile. The skin was not washed, and tape stripping was not conducted.
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	Medium	A stock solution of labeled compound was prepared and stored at -20oC. The solution was prepared in ether however details of the preparation are not provided (e.g. concentration in ether). It is unclear whether this stock was used only for analysis of the test compound or if this stock was applied to the skin of animals. Elsewhere, it was indicated that the test substance was applied neat suggesting no preparation was needed. The study protocol also specified that "the test compound will be stored in a cool, dark place or under specified conditions which minimize decomposition."
	Metric 7:	Consistency of exposure administration	Medium	The study applied 0.2 ml of test substance on the back of the animal without adjusting for the body weight. Slight differences in body weights between the animals resulted in slight differences in the dose (ml/kg). Dosing differed by (0.9 %) between the two animals at this time point. This difference is not likely to have a significant impact on the study results. Additionally, OECD guidelines specify an optimal application of up to 10ul/cm2 for an animal that is 200-250 g bw); this study applied 16.7uL/cm2 in animals that were 174 and 175g bw. No justification was provided by the study authors. Amounts larger than recommended may run off the application site leading to inconsistencies across groups.

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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 8:	Reporting of concentrations	Medium	The study reported doses in ml/kg, the amount applied in ul/cm2 was not specified; however, individual animal body weights and the skin surface area were provided, and this could be calculated. The dose in mg/kg was not provided but can be determined using the density of the test substance.
	Metric 9:	Exposure duration	Low	Typical exposure durations are 6 or 24 hours or are relevant to "in use" exposures.This study used durations of 1, 3, or 7 days and the authors provided no indication whether these durations were relevant to conditions of use. No skin washes were conducted and this study also did not continue measurements post-exposure to account for any further absorption from test material retained in the skin.
	Metric 10:	Number of exposure groups and concentration spacing	Low	There were less than 3 dose groups tested; It was stated that the doses were based on preliminary findings; however, for neat exposure, the preliminary study only tested a single dose of 0.5 mL/kg vs. the 1.14-1.15 mL/kg used at this timepoint. Other preliminary data were generated using a corn oil vehicle whereas this study used no vehicle. No further justifications were provided for the dose tested, and it is unknown whether it was appropriate for common formulations.
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	Medium	Adult male Fischer 344 rats (63-66 days old) were obtained from Charles River Breeding Laboratories (Kingston Facility, Stoneridge, NY). Starting body weights were reported. The weight range of animals at initiation was 140 to 182 g. These weights are lower than the protocol specified by the sponsor (~200g) and lower than the guideline recommendation of 200-150g for male rats.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	High	Husbandry conditions were reported and in agreement with OECD 427 guidelines.
	Metric 13:	Number of animals per group	Low	The number of animals were less than the recommended 4 per termination time (n= 2/timepoint).
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	This study measured concentrations in the tissue (blood, liver, kidneys, testes, muscle, fat, non-treated skin, and GI tract) and excretum (urine, feces). The study did not conduct skin washes or do tape stripping and reported recovery for the" application area" which included the skin at the application site and the cover. The authors indicated this as non-absorbed radioactivity. They did not consider any additional systemic absorption over time from the skin. These are significant deviations from current guidelines. No Kp or flux determinations were made for a finite study; percent absorption was calculated. However, the text did mention that the average rate of absorption for the studies was 0.3% of the applied dose per day, and this appears to be based on a ~0.3% recovery from tissues and excreta at 24 hrs.
	Metric 15:	Consistency of outcome assessment	High	Outcomes were assessed consistently between animals from each group and across study groups.
	Metric 16:	Sampling adequacy and sensitivity	High	The study adequately analyzed samples in duplicate when possible. Samples were reassayed when radioactivity counts were less than two times background (30.6 cpm).
Domain 6: Confounding/Variable Control				

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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 17:	Confounding variables in test design and procedures	Medium	Although the study did not report all information to determine whether confounding bias may exist, reported information did not identify differences that would confound results.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	The authors mentioned that no irritation was observed at the application site. Skin integrity was not discussed. It was not mentioned whether measures were taken during shaving to limit abrasion.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	This study only used 2 replicates. The percent total absorbed was calculated based on test material detected in tissues and excreta at a single time point and did not include material in the skin of the application site. The authors did not report CV values, but these could be calculated using individual animal data. The CV for total absorption was $<$25%, which is appropriate. In the discussion, the authors did state that "the rates of daily absorption of the applied doses were similar (average 0.3% of the applied dose per day). No information on rate calculations was provided in the study methods, and it is unclear how this value was derived, and would only be appropriate under an infinite exposure scenario.
	Metric 20:	Data interpretation	Low	Recovery was 100% $\pm$ 10%. The majority of the test material was found in the skin of the application site plus the cover; denoted as the "application area" by the study authors and represented the non-absorbed radioactivity. The authors did not include the skin at the application site in the 24-hr absorption estimate. This excludes potentially absorbable material in the stratum corneum and likely underestimates the total absorption. This is supported by data from animals exposed to the same dose for longer durations (3 and 7 days) where higher total absorptions were observed. Because the study did not conduct skin washing or provide recovery from the application site alone, separate from the cover material, there is considerable uncertainty in the % absorbed value. Percent absorbed was reported in a finite exposure study.
	Metric 21:	Reporting of Data	High	Data were fully reported for all of the outcomes specified based on the study design. The authors noted that no irritation was identified.

Overall Quality Determination Medium

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EXTRACTION

Parameter	Data
Extraction ID; Chemical:	Group 1; 1.2 ml/kg; 3 days; Diisononyl Phthalate (DINP)-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):	Not Reported; Not Reported
Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))):	16.3; 1152
Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments):	Other; Not Reported; Notes: 3 days
Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments):	Other; Not Reported; Notes: 3 day
Time Skin was Washed and Method used; Radiolabel Presence:	Skin was not washed; Yes
Total Recovery (percent); Dose Type:	101.54; Finite
Percent Found in Skin Depot after Washing and Tape Stripping:	Not Reported; Notes: Not Reported
Percent Found in Urine ; Comments:	1.46; Notes: Not Reported
Percent Found in Feces ; Comments:	0.83; Notes: Not Reported
Percent Found in Blood/Serum ; Comments:	0.01; Notes: Not Reported
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: Not Reported
Total Percent Absorbed:	2
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: 0.93% measured in tissues and GI tract; Total absorbed 3.20% with CV= 70%

EVALUATION

Domain	Metric	Rating	Comments
Domain 1: Test Substance			
Metric 1:	Test substance identity	High	The test substance was identified as 14C-di-isononylphthalate (DINP); CASRN 68515-48. Location of radiolabel was indicated.
Metric 2:	Test substance source	High	The labeled and unlabeled test substance was supplied by Exxon Corporation. The radiolabeled test substance was prepared by Amersham Corporation (Arlington Heights, Illinois). The chemical identity of the radiolabeled test material was confirmed by the performing laboratory using HPLC. It is assumed that the test substance was a liquid since it was applied to the skin using a micropipette.

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HERO ID: 1325430

			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 3:	Test substance purity	High	The purity was reported to be 97-98%, determined by TLC.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Medium	The study states animals were selected at random for each test group; however, the method of randomization was not specified.
	Metric 5:	Standards for Tests	Low	This in vivo study was not conducted according to any specified guidelines. The percent recovery was acceptable (100+/-10%) and consistent with current guidelines. The backs of the rats were shaved shortly before treatment specific timing not specified). This is not consistent with OECD guidelines which states the area of skin should be clipped approximately 24 hours prior to dosing. It was not specified whether care was taken to minimize abrasion, and it was not reported whether the area was wiped with acetone as specified in OECD TG 427.The test substance was applied neat to a 3x4 cm area of skin, which is appropriate. The text indicated that a stock solution was prepared containing the labeled compound in ether. It is unclear whether this stock was used only for analysis of the test compound or if this stock was applied to the skin of animals. Elsewhere in the report it indicates that the test material was applied neat. The study specified that the skin was kept occluded, however, an atypical method was used. Specifically, the application site was covered with a Styrofoam cup lined with aluminum, which was secured onto the animals back with adhesive tape. This setup suggests more protection of the application site, rather than occlusion. This is not expected to have significant impact on the study results because the test material is not volatile. The skin was not washed, and tape stripping was not conducted.
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	Medium	A stock solution of labeled compound was prepared and stored at -20oC. The solution was prepared in ether however details of the preparation are not provided (e.g. concentration in ether). It is unclear whether this stock was used only for analysis of the test compound or if this stock was applied to the skin of animals. Elsewhere, it was indicated that the test substance was applied neat suggesting no preparation was needed. The study protocol also specified that “the test compound will be stored in a cool, dark place or under specified conditions which minimize decomposition.”
	Metric 7:	Consistency of exposure administration	Uninformative	The study applied 0.2 ml of test substance on the back of the animal without adjusting for the body weight. Slight differences in body weights between the animals resulted in differences in the dose (ml/kg). Dosing differed by (12 %) between the two animals/timepoint. This is a large difference that makes the results for this time point unusable. Additionally, OECD guidelines specify an optimal application of up to 10ul/cm2 for an animal that is 200-250 g bw); this study applied 16.7uL/cm2 in animals that were 159 and 180 g bw. No justification was provided by the study authors. Amounts larger than recommended may run off the application site leading to further inconsistencies across groups.
	Metric 8:	Reporting of concentrations	Medium	The study reported doses in ml/kg, the amount applied in ul/cm2 was not specified; however, individual animal body weights and the skin surface area were provided, and this could be calculated. The dose in mg/kg was not provided but can be determined using the density of the test substance.

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Study Citation: Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.
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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 9:	Exposure duration	Low	Typical exposure durations are 6 or 24 hours or are relevant to "in use" exposures.This study used durations of 1, 3, or 7 days and the authors provided no indication whether these durations were relevant to conditions of use. No skin washes were conducted and this study also did not continue measurements post-exposure to account for any further absorption from test material retained in the skin.
	Metric 10:	Number of exposure groups and concentration spacing	Low	There were less than 3 dose groups tested; It was stated that the doses were based on preliminary findings; however, for neat exposure, the preliminary study only tested a single dose of 0.5 mL/kg vs. the 1.0-1.43 mL/kg used in this study. Other preliminary data were generated using a corn oil vehicle whereas this study used no vehicle. No further justifications were provided for the dose tested, and it is unknown whether it was appropriate for common formulations.
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	Medium	Adult male Fischer 344 rats (63-66 days old) were obtained from Charles River Breeding Laboratories (Kingston Facility, Stoneridge, NY). Starting body weights were reported. The weight range of animals at initiation was 140 to 182 g. These weights are lower than the protocol specified by the sponsor (~200g) and lower than the guideline recommendation of 200-150g for male rats.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	High	Husbandry conditions were reported and in agreement with OECD 427 guidelines.
	Metric 13:	Number of animals per group	Uninformative	The number of animals was less than the recommended 4 per termination time (n= 2/timepoint). Due to the insufficient number of animals studied and the high variance, this metric was deemed critically deficient.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	This study measured concentrations in the tissue (blood, liver, kidneys, testes, muscle, fat, non-treated skin, and GI tract) and excretum (urine, feces). The study did not conduct skin washes or tape stripping and reported recovery for the" application area" which included the skin at the application site and the cover. The authors indicated this as non-absorbed radioactivity. They did not consider any additional systemic absorption over time from the skin. These are significant deviations from current guidelines. No Kp or flux determinations were made for a finite study; percent absorption was calculated. However, the text did mention that the average rate of absorption for the studies was 0.3% of the applied dose per day, and this appears to be based on a ~0.3% recovery from tissues and excreta at 24 hrs.
	Metric 15:	Consistency of outcome assessment	High	Outcomes were assessed consistently between animals from each group and across study groups.
	Metric 16:	Sampling adequacy and sensitivity	High	The study adequately analyzed samples in duplicate when possible. Samples were reassayed when radioactivity counts were less than two times background (30.6 cpm).
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Although the study did not report all information to determine whether confounding bias may exist, reported information did not identify differences that would confound results.

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Study Citation: Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.
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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	The authors mentioned that no irritation was observed at the application site. Skin integrity was not discussed. It was not mentioned whether measures were taken during shaving to limit abrasion.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	This study only used 2 replicates. The percent total absorbed was calculated based on test material detected in tissues and excreta at a single time point and did not include material in the skin of the application site. The authors did not report CV values, but these could be calculated using individual animal data. The variation in the percent total absorbed was high across replicates (CV =70.2%); however, sufficient data were provided to allow for alternate calculations. In the discussion, the authors did state that "the rates of daily absorption of the applied doses were similar (average 0.3% of the applied dose per day). No information on rate calculations were provided in the study methods, and it is unclear how this value was derived, and would only be appropriate under an infinite exposure scenario.
	Metric 20:	Data interpretation	Low	Total Recovery was 100% $\pm$ 10%. The majority of the test material was found in the skin of the application site plus the cover; denoted as the "application area" by the study authors and represented the non-absorbed radioactivity. The authors did not include the skin at the application site in the 3-day absorption estimate. This excludes potentially absorbable material in the stratum corneum and may underestimate the total absorption. However, the percent total absorbed was lower in a separate experiment exposing animals to the same dose for 7 days, suggesting any amount in the skin may be unabsorbable. Because the study did not conduct skin washing or provide recovery information from the skin application site alone, there is uncertainty in the accuracy of the study results. Additionally, the authors noted that 1 out of the 2 rats in this group had abnormally high recovery of material in tissues+excreta compared to the other rat, which likely contributed to the high CV. Percent absorbed was reported in a finite exposure study.
	Metric 21:	Reporting of Data	High	Data were fully reported for all of the outcomes specified based on the study design. The authors noted that no irritation was identified.

Overall Quality Determination — Uninformative

Study Citation: Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.
HERO ID: 1325430

EXTRACTION

Parameter	Data
Extraction ID; Chemical:	Group 1; 1.2 ml/kg; 7 days; Diisononyl Phthalate (DINP)-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):	Not Reported; Not Reported
Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))):	16.3; 1079
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; Not Reported; Notes: 7 days
Time Skin was Washed and Method used; Radiolabel Presence:	Skin was not washed.; Yes
Total Recovery (percent); Dose Type:	102.99; Finite
Percent Found in Skin Depot after Washing and Tape Stripping:	Not Reported; Notes: Not Reported
Percent Found in Urine ; Comments:	1.06; Notes: Not Reported
Percent Found in Feces ; Comments:	0.54; Notes: Not Reported
Percent Found in Blood/Serum ; Comments:	0.005; Notes: Not Reported
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: Not Reported
Total Percent Absorbed:	2
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: 0.45% measured in tissues and GI tract; Total absorbed 2.05% with CV= 9%

EVALUATION

Domain	Metric	Rating	Comments
Domain 1: Test Substance			
Metric 1:	Test substance identity	High	The test substance was identified as 14C-di-isononylphthalate (DINP); CASRN 68515-48. Location of radiolabel was indicated.
Metric 2:	Test substance source	High	The labeled and unlabeled test substance was supplied by Exxon Corporation. The radiolabeled test substance was prepared by Amersham Corporation (Arlington Heights, Illinois). The chemical identity of the radiolabeled test material was confirmed by the performing laboratory using HPLC. It is assumed that the test substance was a liquid since it was applied to the skin using a micropipette.

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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 3:	Test substance purity	High	The purity was reported to be 97-98%, determined by TLC.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Medium	The study states animals were selected at random for each test group; however, the method of randomization was not specified.
	Metric 5:	Standards for Tests	Low	This in vivo study was not conducted according to any specified guidelines. The percent recovery was acceptable (100+/-10%) and consistent with current guidelines. The backs of the rats were shaved shortly before treatment specific timing not specified). This is not consistent with OECD guidelines which state the area of skin should be clipped approximately 24 hours prior to dosing. It was not specified whether care was taken to minimize abrasion, and it was not reported whether the area was wiped with acetone as specified in OECD TG 427.The test substance was applied neat to a 3x4 cm area of skin, which is appropriate. The text indicated that a stock solution was prepared containing the labeled compound in ether. It is unclear whether this stock was used only for analysis of the test compound or if this stock was applied to the skin of animals. Elsewhere in the report, it indicates that the test material was applied neat. The study specified that the skin was kept occluded, however, an atypical method was used. Specifically, the application site was covered with a Styrofoam cup lined with aluminum, which was secured onto the animal's back with adhesive tape. This setup suggests more protection of the application site, rather than occlusion. This is not expected to have a significant impact on the study results because the test material is not volatile. The skin was not washed, and tape stripping was not conducted.
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	Medium	A stock solution of labeled compound was prepared and stored at -20oC. The solution was prepared in ether however details of the preparation are not provided (e.g. concentration in ether). It is unclear whether this stock was used only for analysis of the test compound or if this stock was applied to the skin of animals. Elsewhere, it was indicated that the test substance was applied neat suggesting no preparation was needed. The study protocol also specified that "the test compound will be stored in a cool, dark place or under specified conditions which minimize decomposition."
	Metric 7:	Consistency of exposure administration	Low	The study applied 0.2 ml of test substance on the back of the animal without adjusting for the body weight. Slight differences in body weights between the animals resulted in slight differences in the dose (ml/kg). Dosing differed by (1.8 %) between the two animals for this timepoint. It is unclear if this difference had an impact on the study results. Additionally, OECD guidelines specify an optimal application of up to 10ul/cm2 for an animal that is 200-250 g bw); this study applied 16.7 uL/cm2 in animals that were 1.12 and 1.10g bw. No justification was provided by the study authors. Amounts larger than recommended may run-off the application site leading to inconsistencies across groups.
	Metric 8:	Reporting of concentrations	Medium	The study reported doses in ml/kg, the amount applied in ul/cm2 was not specified; however, individual animal body weights and the skin surface area were provided, and this could be calculated. The dose in mg/kg was not provided but can be determined using the density of the test substance.

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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 9:	Exposure duration	Low	Typical exposure durations are 6 or 24 hours or are relevant to "in use" exposures.This study used durations of 1, 3, or 7 days and the authors provided no indication whether these durations were relevant to conditions of use. No skin washes were conducted and this study also did not continue measurements post-exposure to account for any further absorption from test material retained in the skin.
	Metric 10:	Number of exposure groups and concentration spacing	Low	There were less than 3 dose groups tested; It was stated that the doses were based on preliminary findings; however, for neat exposure, the preliminary study only tested a single dose of 0.5 mL/kg vs. the 1.0-1.43 mL/kg used in this study. Other preliminary data were generated using a corn oil vehicle whereas this study used no vehicle. No further justifications were provided for the dose tested, and it is unknown whether it was appropriate for common formulations.
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	Medium	Adult male Fischer 344 rats (63-66 days old) were obtained from Charles River Breeding Laboratories (Kingston Facility, Stoneridge, NY). Starting body weights were reported. The weight range of animals at initiation was 140 to 182 g. These weights are lower than the protocol specified by the sponsor (~200g) and lower than the guideline recommendation of 200-150g for male rats.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	High	Husbandry conditions were reported and in agreement with OECD 427 guidelines.
	Metric 13:	Number of animals per group	Low	The number of animals were less than the recommended 4 per termination time (n= 2/timepoint).
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	This study measured concentrations in the tissue (blood, liver, kidneys, testes, muscle, fat, non-treated skin, and GI tract) and excretum (urine, feces). The study did not conduct skin washes or do tape stripping and reported recovery for the" application area" which included the skin at the application site and the cover. The authors indicated this as non-absorbed radioactivity. They did not consider any additional systemic absorption over time from the skin. These are significant deviations from current guidelines. No Kp or flux determinations were made for a finite study; percent absorption was calculated. However, the text did mention that the average rate of absorption for the studies was 0.3% of the applied dose per day, and this appears to be based on a ~0.3% recovery from tissues and excreta at 24 hrs.
	Metric 15:	Consistency of outcome assessment	High	Outcomes were assessed consistently between animals from each group and across study groups.
	Metric 16:	Sampling adequacy and sensitivity	High	The study adequately analyzed samples in duplicate when possible. Samples were reassayed when radioactivity counts were less than two times background (30.6 cpm).
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Although the study did not report all information to determine whether confounding bias may exist, reported information did not identify differences that would confound results.

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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	The authors mentioned that no irritation was observed at the application site. Skin integrity was not discussed. It was not mentioned whether measures were taken during shaving to limit abrasion.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	This study only used 2 replicates. The percent total absorbed was calculated based on test material detected in tissues and excreta at a single time point and did not include material in the skin of the application site. The authors did not report CV values but these could be calculated using individual animal data. The CV for total absorption was 9.3%, which is appropriate. In the discussion, the authors did state that "the rates of daily absorption of the applied doses were similar (average 0.3% of the applied dose per day). No information on rate calculations was provided in the study methods, and it is unclear how this value was derived, and would only be appropriate under an infinite exposure scenario.
	Metric 20:	Data interpretation	Low	Recovery was 100% $\pm$ 10%. The majority of the test material was found in the skin of the application site plus the cover; denoted as the "application area" by the study authors and represented the non-absorbed radioactivity. Because the study did not conduct skin washing or provide recovery information from the skin application site alone, any potentially absorbable material in the stratum corneum was excluded. However, this exclusion may be appropriate for a 7-day duration test as it is likely that any amount left on the skin may have been unabsorbable.
	Metric 21:	Reporting of Data	High	Data were fully reported for all of the outcomes specified based on the study design. The authors noted that no irritation was identified.

Overall Quality Determination — Medium

Study Citation: Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.
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EXTRACTION

Parameter	Data
Extraction ID; Chemical:	Group 2- conditioned; 1.2 ml/kg; 1 day; Diisononyl Phthalate (DINP)-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):	Not Reported; Not Reported
Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))):	16.3; 1288
Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments):	24 hrs; Not Reported; Notes: Not Reported
Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments):	24 hrs; Not Reported; Notes: Not Reported
Time Skin was Washed and Method used; Radiolabel Presence:	Skin was not washed.; Yes
Total Recovery (percent); Dose Type:	99.45; Finite
Percent Found in Skin Depot after Washing and Tape Stripping:	Not Reported; Notes: Not Reported
Percent Found in Urine ; Comments:	0.07; Notes: Not Reported
Percent Found in Feces ; Comments:	0.02; Notes: Not Reported
Percent Found in Blood/Serum ; Comments:	0.001; Notes: Not Reported
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: Not Reported
Total Percent Absorbed:	0
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: 0.17% measured in tissues; Total absorbed 0.33% with CV= 10%.

EVALUATION

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified as 14C-di-isononylphthalate (DINP); CASRN 68515-48. Location of radiolabel was indicated.
	Metric 2:	Test substance source	High	The labeled and unlabeled test substance was supplied by Exxon Corporation. The radiolabeled test substance was prepared by Amersham Corporation (Arlington Heights, Illinois). The chemical identity of the radiolabeled test material was confirmed by the performing laboratory using HPLC. It is assumed that the test substance was a liquid since it was applied to the skin using a micropipette.

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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 3:	Test substance purity	High	The purity was reported to be 97-98%, determined by TLC.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Medium	The study states animals were selected at random for each test group; however, the method of randomization was not specified.
	Metric 5:	Standards for Tests	Low	This in vivo study was not conducted according to any specified guidelines and included an initial conditioning exposure that is atypical. Rats were conditioned with unlabeled test material for 3 days. The excess material was wiped away and radiolabeled material was applied to the same site.The percent recovery was acceptable (100+/-10%) and consistent with current guidelines. The backs of the rats were shaved shortly before treatment specific timing not specified). This is not consistent with OECD guidelines which state the area of skin should be clipped approximately 24 hours prior to dosing. It was not specified whether care was taken to minimize abrasion, and it was not reported whether the area was wiped with acetone as specified in OECD TG 427.The test substance was applied neat to a 3x4 cm area of skin, which is appropriate. The text indicated that a stock solution was prepared containing the labeled compound in ether. It is unclear whether this stock was used only for analysis of the test compound or if this stock was applied to the skin of animals. Elsewhere in the report, it indicates that the test material was applied neat. The study specified that the skin was kept occluded, however, an atypical method was used. Specifically, the application site was covered with a Styrofoam cup lined with aluminum, which was secured onto the animal's back with adhesive tape. This setup suggests more protection of the application site, rather than occlusion. This is not expected to have a significant impact on the study results because the test material is not volatile. The skin was not washed, and tape stripping was not conducted.
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	Medium	A stock solution of labeled compound was prepared and stored at -20oC. The solution was prepared in ether however details of the preparation are not provided (e.g. concentration in ether). It is unclear whether this stock was used only for analysis of the test compound or if this stock was applied to the skin of animals. Elsewhere, it was indicated that the test substance was applied neat suggesting no preparation was needed. The study protocol also specified that "the test compound will be stored in a cool, dark place or under specified conditions which minimize decomposition."
	Metric 7:	Consistency of exposure administration	Low	The study applied 0.2 ml of test substance on the back of the animal without adjusting for the body weight. Differences in body weights between the two animals resulted in a 15% difference in the dose (ml/kg) applied. This is a large difference that could significantly impact the study results, although the variance for most of the measured endpoints for these animals was acceptab. Additionally, OECD guidelines specify an optimal application of up to 10ul/cm2 for an animal that is 200-250 g bw); this study applied 16.7ul/cm2 in animals that were 140 and 160 g bw. No justification was provided by the study authors. Amounts larger than recommended may run-off the application site leading to inconsistencies across groups.
	Metric 8:	Reporting of concentrations	Medium	The study reported doses in ml/kg, the amount applied in ul/cm2 was not specified; however, individual animal body weights and the skin surface area were provided, and this could be calculated. The dose in mg/kg was not provided but can be determined using the density of the test substance.

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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 9:	Exposure duration	Low	Typical exposure durations are 6 or 24 hours or are relevant to "in use" exposures.This study used durations of 1, 3, or 7 days and the authors provided no indication whether these durations were relevant to conditions of use. No skin washes were conducted and this study also did not continue measurements post-exposure to account for any further absorption from test material retained in the skin.
	Metric 10:	Number of exposure groups and concentration spacing	Low	There were less than 3 dose groups tested; It was stated that the doses were based on preliminary findings; however, for neat exposure, the preliminary study only tested a single dose of 0.5 mL/kg vs. the 1.0-1.43 mL/kg used in this study. Other preliminary data were generated using a corn oil vehicle whereas this study used no vehicle. No further justifications were provided for the dose tested, and it is unknown whether it was appropriate for common formulations.
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	Medium	Adult male Fischer 344 rats (63-66 days old) were obtained from Charles River Breeding Laboratories (Kingston Facility, Stoneridge, NY). Starting body weights were reported. The weight range of animals at initiation was 140 to 182 g. These weights are lower than the protocol specified by the sponsor (~200g) and lower than the guideline recommendation of 200-150g for male rats.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	High	Husbandry conditions were reported and in agreement with OECD 427 guidelines.
	Metric 13:	Number of animals per group	Low	The number of animals were less than the recommended 4 per termination time (n= 2/timepoint).
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	This study measured concentrations in the tissue (blood, liver, kidneys, testes, muscle, fat, non-treated skin, and GI tract) and excretum (urine, feces). The study did not conduct skin washes or do tape stripping and reported recovery for the" application area" which included the skin at the application site and the cover. The authors indicated this as non-absorbed radioactivity. They did not consider any additional systemic absorption over time from the skin. These are significant deviations from current guidelines. No Kp or flux determinations were made for a finite study; percent absorption was calculated. However, the text did mention that the average rate of absorption for the studies was 0.3% of the applied dose per day, and this appears to be based on a ~0.3% recovery from tissues and excreta at 24 hrs.
	Metric 15:	Consistency of outcome assessment	High	Outcomes were assessed consistently between animals from each group and across study groups.
	Metric 16:	Sampling adequacy and sensitivity	High	The study adequately analyzed samples in duplicate when possible. Samples were reassayed when radioactivity counts were less than two times background (30.6 cpm).
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Although the study did not report all information to determine whether confounding bias may exist, reported information did not identify differences that would confound results.

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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	The authors mentioned that no irritation was observed at the application site. Skin integrity was not discussed. It was not mentioned whether measures were taken during shaving to limit abrasion.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	This study only used 2 replicates. The percent total absorbed was calculated based on test material detected in tissues and excreta at a single time point and did not include material in the skin of the application site. The authors did not report CV values but these could be calculated using individual animal data. The CV for total absorption was 9.6%, which is appropriate. In the discussion, the authors did state that "the rates of daily absorption of the applied doses were similar (average 0.3% of the applied dose per day). No information on rate calculations was provided in the study methods, and it is unclear how this value was derived, and would only be appropriate under an infinite exposure scenario.
	Metric 20:	Data interpretation	Low	Recovery was 100% $\pm$ 10%. The majority of the test material was found in the skin of the application site plus the cover; denoted as the "application area" by the study authors and represented the non-absorbed radioactivity. The authors did not include the skin at the application site in the 24-hr absorption estimate. This excludes potentially absorbable material in the stratum corneum, and likely underestimates the total absorption. This is supported by data from animals exposed to the same dose for longer durations (3 and 7 days) where higher total absorptions were observed. Because the study did not conduct skin washing or provide recovery from the application site alone, separate from the cover material, there is considerable uncertainty in the % absorbed value. Percent absorbed was reported in a finite exposure study.
	Metric 21:	Reporting of Data	High	Data were fully reported for all of the outcomes specified based on the study design. The authors noted that no irritation was identified.

Overall Quality Determination — Medium

Study Citation: Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.
HERO ID: 1325430

EXTRACTION

Parameter	Data
Extraction ID; Chemical:	Group 2-conditioned; 1.2 ml/kg; 3 days; Diisononyl Phthalate (DINP)-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):	Not Reported; Not Reported
Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))):	16.3; 1283
Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments):	Other; Not Reported; Notes: 3 days
Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments):	Other; Not Reported; Notes: 3 days
Time Skin was Washed and Method used; Radiolabel Presence:	Skin was not washed.; Yes
Total Recovery (percent); Dose Type:	101.27; Finite
Percent Found in Skin Depot after Washing and Tape Stripping:	Not Reported; Notes: Not Reported
Percent Found in Urine ; Comments:	0.58; Notes: Not Reported
Percent Found in Feces ; Comments:	0.25; Notes: Not Reported
Percent Found in Blood/Serum ; Comments:	0.004; Notes: Not Reported
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: Not Reported
Total Percent Absorbed:	1
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: 0.77% measured in tissues and GI tract; Total absorbed 1.6% with CV= 51%.

EVALUATION

Domain	Metric	Rating	Comments
Domain 1: Test Substance			
Metric 1:	Test substance identity	High	The test substance was identified as 14C-di-isononylphthalate (DINP); CASRN 68515-48. Location of radiolabel was indicated.
Metric 2:	Test substance source	High	The labeled and unlabeled test substance was supplied by Exxon Corporation. The radiolabeled test substance was prepared by Amersham Corporation (Arlington Heights, Illinois). The chemical identity of the radiolabeled test material was confirmed by the performing laboratory using HPLC. It is assumed that the test substance was a liquid since it was applied to the skin using a micropipette.

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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 3:	Test substance purity	High	The purity was reported to be 97-98%, determined by TLC.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Medium	The study states animals were selected at random for each test group; however, the method of randomization was not specified.
	Metric 5:	Standards for Tests	Low	This in vivo study was not conducted according to any specified guidelines. The percent recovery was acceptable (100+/-10%) and consistent with current guidelines. The backs of the rats were shaved shortly before treatment specific timing not specified). This is not consistent with OECD guidelines which state the area of skin should be clipped approximately 24 hours prior to dosing. It was not specified whether care was taken to minimize abrasion, and it was not reported whether the area was wiped with acetone as specified in OECD TG 427.The test substance was applied neat to a 3x4 cm area of skin, which is appropriate. The text indicated that a stock solution was prepared containing the labeled compound in ether. It is unclear whether this stock was used only for analysis of the test compound or if this stock was applied to the skin of animals. Elsewhere in the report, it indicates that the test material was applied neat. The study specified that the skin was kept occluded, however, an atypical method was used. Specifically, the application site was covered with a Styrofoam cup lined with aluminum, which was secured onto the animal's back with adhesive tape. This setup suggests more protection of the application site, rather than occlusion. This is not expected to have a significant impact on the study results because the test material is not volatile. The skin was not washed, and tape stripping was not conducted. Rats were conditioned with unlabeled test material for 3 days. The excess material was wiped away and radiolabeled material was applied to the same site.
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	Medium	A stock solution of labeled compound was prepared and stored at -20oC. The solution was prepared in ether however details of the preparation are not provided (e.g. concentration in ether). It is unclear whether this stock was used only for analysis of the test compound or if this stock was applied to the skin of animals. Elsewhere, it was indicated that the test substance was applied neat suggesting no preparation was needed. The study protocol also specified that "the test compound will be stored in a cool, dark place or under specified conditions which minimize decomposition."
	Metric 7:	Consistency of exposure administration	Low	The study applied 0.2 ml of test substance on the back of the animal without adjusting for the body weight. Slight differences in body weights between the animals resulted in differences in the dose (ml/kg). Dosing differed by (1.5 %) between the two animals/timepoint. It is unclear if this difference had an impact on the study results. Additionally, OECD guidelines specify an optimal application of up to 10ul/cm2 for an animal that is 200-250 g bw); this study applied 16.7uL/cm2 in animals that were 150 and 153 g bw. No justification was provided by the study authors. Amounts larger than recommended may run-off the application site leading to inconsistencies across groups.
	Metric 8:	Reporting of concentrations	Medium	The study reported doses in ml/kg, the amount applied in ul/cm2 was not specified; however, individual animal body weights and the skin surface area were provided, and this could be calculated. The dose in mg/kg was not provided but can be determined using the density of the test substance.

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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 9:	Exposure duration	Low	Typical exposure durations are 6 or 24 hours or are relevant to "in use" exposures.This study used durations of 1, 3, or 7 days and the authors provided no indication whether these durations were relevant to conditions of use. No skin washes were conducted and this study also did not continue measurements post-exposure to account for any further absorption from test material retained in the skin.
	Metric 10:	Number of exposure groups and concentration spacing	Low	There were less than 3 dose groups tested; It was stated that the doses were based on preliminary findings; however, for neat exposure, the preliminary study only tested a single dose of 0.5 mL/kg vs. the 1.0-1.43 mL/kg used in this study. Other preliminary data were generated using a corn oil vehicle whereas this study used no vehicle. No further justifications were provided for the dose tested, and it is unknown whether it was appropriate for common formulations.
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	Medium	Adult male Fischer 344 rats (63-66 days old) were obtained from Charles River Breeding Laboratories (Kingston Facility, Stoneridge, NY). Starting body weights were reported. The weight range of animals at initiation was 140 to 182 g. These weights are lower than the protocol specified by the sponsor (~200g) and lower than the guideline recommendation of 200-150g for male rats.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	High	Husbandry conditions were reported and in agreement with OECD 427 guidelines.
	Metric 13:	Number of animals per group	Uninformative	The number of animals were less than the recommended 4 per termination time (n= 2/timepoint). Due to the insufficient number of animals studied and the high variance, in several of the measured outcomes, this metric was deemed critically deficient.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	This study measured concentrations in the tissue (blood, liver, kidneys, testes, muscle, fat, non-treated skin, and GI tract) and excretum (urine, feces). The study did not conduct skin washes or do tape stripping and reported recovery for the" application area" which included the skin at the application site and the cover. The authors indicated this as non-absorbed radioactivity. They did not consider any additional systemic absorption over time from the skin. These are significant deviations from current guidelines. No Kp or flux determinations were made for a finite study; percent absorption was calculated. However, the text did mention that the average rate of absorption for the studies was 0.3% of the applied dose per day, and this appears to be based on a ~0.3% recovery from tissues and excreta at 24 hrs.
	Metric 15:	Consistency of outcome assessment	High	Outcomes were assessed consistently between animals from each group and across study groups.
	Metric 16:	Sampling adequacy and sensitivity	High	The study adequately analyzed samples in duplicate when possible. Samples were reassayed when radioactivity counts were less than two times background (30.6 cpm).
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Although the study did not report all information to determine whether confounding bias may exist, reported information did not identify differences that would confound results.

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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	The authors mentioned that no irritation was observed at the application site. Skin integrity was not discussed. It was not mentioned whether measures were taken during shaving to limit abrasion.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	This study only used 2 replicates. The percent total absorbed was calculated based on test material detected in tissues and excreta at a single time point and did not include material in the skin of the application site. The authors did not report CV values but these could be calculated using individual animal data. The coefficient of variation in the percent total absorbed was 50.6% . The CV for measures in blood, urine, and adjacent skin were also >25%.; however, sufficient data were provided for alternate calculations. In the discussion, the authors did state that "the rates of daily absorption of the applied doses were similar (average 0.3% of the applied dose per day). No information on rate calculations was provided in the study methods, and it is unclear how this value was derived, and would only be appropriate under an infinite exposure scenario.
	Metric 20:	Data interpretation	Low	Recovery was 100% ± 10%. The majority of the test material was found in the skin of the application site plus the cover; denoted as the "application area" by the study authors and represented the non-absorbed radioactivity. The authors did not include the skin at the application site in the 3-day-hr absorption estimate. This excludes potentially absorbable material in the stratum corneum, and likely underestimates the total absorption. This is supported by a separate experiment showing a higher percent absorbed in animals exposed for 7 days. Because the study did not conduct skin washing or provide recovery information from the skin application site alone, there is uncertainty in the accuracy of the study results. Percent absorbed was reported in a finite exposure study.
	Metric 21:	Reporting of Data	High	Data were fully reported for all of the outcomes specified based on the study design. The authors noted that no irritation was identified.

Overall Quality Determination — Uninformative

Study Citation: Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.
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EXTRACTION

Parameter	Data
Extraction ID; Chemical:	Group 2-conditioned; 1.2 ml/kg; 7 days; Diisononyl Phthalate (DINP)-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):	Not Reported; Not Reported
Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))):	16.3; 1113
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; Not Reported; Notes: 7 days
Time Skin was Washed and Method used; Radiolabel Presence:	Skin was not washed.; Yes
Total Recovery (percent); Dose Type:	97.75; Finite
Percent Found in Skin Depot after Washing and Tape Stripping:	Not Reported; Notes: Not Reported
Percent Found in Urine ; Comments:	1.94; Notes: Not Reported
Percent Found in Feces ; Comments:	1.1; Notes: Not Reported
Percent Found in Blood/Serum ; Comments:	0.005; Notes: Not Reported
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: Not Reported
Total Percent Absorbed:	3
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: 0.67% measured in tissues and GI tract; Total absorbed 3.71% with CV=25%

EVALUATION

Domain	Metric	Rating	Comments
Domain 1: Test Substance			
Metric 1:	Test substance identity	High	The test substance was identified as 14C-di-isononylphthalate (DINP); CASRN 68515-48. Location of radiolabel was indicated.
Metric 2:	Test substance source	High	The labeled and unlabeled test substance was supplied by Exxon Corporation. The radiolabeled test substance was prepared by Amersham Corporation (Arlington Heights, Illinois). The chemical identity of the radiolabeled test material was confirmed by the performing laboratory using HPLC. It is assumed that the test substance was a liquid since it was applied to the skin using a micropipette.

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EVALUATION

Domain		Metric	Rating	Comments
	Metric 3:	Test substance purity	High	The purity was reported to be 97-98%, determined by TLC.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Medium	The study states animals were selected at random for each test group; however, the method of randomization was not specified.
	Metric 5:	Standards for Tests	Low	This in vivo study was not conducted according to any specified guidelines. Rats were conditioned with unlabeled test material for 3 days. The excess material was wiped away and radiolabeled material was applied to the same site. The percent recovery was acceptable (100+/-10%) and consistent with current guidelines. The backs of the rats were shaved shortly before treatment specific timing not specified). This is not consistent with OECD guidelines which state the area of skin should be clipped approximately 24 hours prior to dosing. It was not specified whether care was taken to minimize abrasion, and it was not reported whether the area was wiped with acetone as specified in OECD TG 427.The test substance was applied neat to a 3x4 cm area of skin, which is appropriate. The text indicated that a stock solution was prepared containing the labeled compound in ether. It is unclear whether this stock was used only for analysis of the test compound or if this stock was applied to the skin of animals. Elsewhere in the report, it indicates that the test material was applied neat. The study specified that the skin was kept occluded, however, an atypical method was used. Specifically, the application site was covered with a Styrofoam cup lined with aluminum, which was secured onto the animal's back with adhesive tape. This setup suggests more protection of the application site, rather than occlusion. This is not expected to have a significant impact on the study results because the test material is not volatile. The skin was not washed, and tape stripping was not conducted.
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	Medium	A stock solution of labeled compound was prepared and stored at -20oC. The solution was prepared in ether however details of the preparation are not provided (e.g. concentration in ether). It is unclear whether this stock was used only for analysis of the test compound or if this stock was applied to the skin of animals. Elsewhere, it was indicated that the test substance was applied neat suggesting no preparation was needed. The study protocol also specified that "the test compound will be stored in a cool, dark place or under specified conditions which minimize decomposition."
	Metric 7:	Consistency of exposure administration	Low	The study applied 0.2 ml of test substance on the back of the animal without adjusting for the body weight. Slight differences in body weights between the animals resulted in differences in the dose (ml/kg). Dosing differed by (6 %) between the two animals at this time point. This likely had an impact on the study results as the variation in measurements between the two animals was high. Additionally, OECD guidelines specify an optimal application of up to 10ul/cm2 for an animal that is 200-250 g bw); this study applied (put in range appropriate for each form) in animals that were 170 and 180g bw. No justification was provided by the study authors. Amounts larger than recommended may run-off the application site leading to inconsistencies across groups.
	Metric 8:	Reporting of concentrations	Medium	The study reported doses in ml/kg, the amount applied in ul/cm2 was not specified; however, individual animal body weights and the skin surface area were provided, and this could be calculated. The dose in mg/kg was not provided but can be determined using the density of the test substance.

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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 9:	Exposure duration	Low	Typical exposure durations are 6 or 24 hours or are relevant to "in use" exposures.This study used durations of 1, 3, or 7 days and the authors provided no indication whether these durations were relevant to conditions of use. No skin washes were conducted and this study also did not continue measurements post-exposure to account for any further absorption from test material retained in the skin.
	Metric 10:	Number of exposure groups and concentration spacing	Low	There were less than 3 dose groups tested; It was stated that the doses were based on preliminary findings; however, for neat exposure, the preliminary study only tested a single dose of 0.5 mL/kg vs. the 1.0-1.43 mL/kg used in this study. Other preliminary data were generated using a corn oil vehicle whereas this study used no vehicle. No further justifications were provided for the dose tested, and it is unknown whether it was appropriate for common formulations.
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	Medium	Adult male Fischer 344 rats (63-66 days old) were obtained from Charles River Breeding Laboratories (Kingston Facility, Stoneridge, NY). Starting body weights were reported. The weight range of animals at initiation was 140 to 182 g. These weights are lower than the protocol specified by the sponsor (~200g) and lower than the guideline recommendation of 200-150g for male rats.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	High	Husbandry conditions were reported and in agreement with OECD 427 guidelines.
	Metric 13:	Number of animals per group	Uninformative	The number of animals were less than the recommended 4 per termination time (n= 2/timepoint). Due to the insufficient number of animals studied and the high variance, this metric was deemed critically deficient.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	This study measured concentrations in the tissue (blood, liver, kidneys, testes, muscle, fat, non-treated skin, and GI tract) and excretum (urine, feces). The study did not conduct skin washes or do tape stripping and reported recovery for the" application area" which included the skin at the application site and the cover. The authors indicated this as non-absorbed radioactivity. They did not consider any additional systemic absorption over time from the skin. These are significant deviations from current guidelines. No Kp or flux determinations were made for a finite study; percent absorption was calculated. However, the text did mention that the average rate of absorption for the studies was 0.3% of the applied dose per day, and this appears to be based on a ~0.3% recovery from tissues and excreta at 24 hrs.
	Metric 15:	Consistency of outcome assessment	High	Outcomes were assessed consistently between animals from each group and across study groups.
	Metric 16:	Sampling adequacy and sensitivity	High	The study adequately analyzed samples in duplicate when possible. Samples were reassayed when radioactivity counts were less than two times background (30.6 cpm).
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Although the study did not report all information to determine whether confounding bias may exist, reported information did not identify differences that would confound results.

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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	The authors mentioned that no irritation was observed at the application site. Skin integrity was not discussed. It was not mentioned whether measures were taken during shaving to limit abrasion.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	This study only used 2 replicates. Percent total absorbed was calculated based on test material detected in tissues and excreta at a single time point and did not include material in the skin of the application site. The authors did not report CV values but these could be calculated using individual animal data. The coefficient of variation of the percent total absorbed was 25.3%. The CVs for recovery in feces, urine, and adjacent skin were also >25%; however, sufficient data were provided to conduct alternate calcuations. In the discussion, the authors did state that "the rates of daily absorption of the applied doses were similar (average 0.3% of the applied dose per day). No information on rate calculations was provided in the study methods, and it is unclear how this value was derived, and would only be appropriate under an infinite exposure scenario.
	Metric 20:	Data interpretation	Low	Recovery was 100% ± 10%. The majority of the test material was found in the skin of the application site plus the cover; denoted as the "application area" by the study authors and represented the non-absorbed radioactivity. Because the study did not conduct skin washing or provide recovery information from the skin application site alone, any potentially absorbable material in the stratum corneum was excluded. However, this exclusion may appropriate for a 7-day duration test as it is likely that any amount left on the skin may have been unabsorbable.
	Metric 21:	Reporting of Data	High	Data were fully reported for all of the outcomes specified based on the study design. The authors noted that no irritation was identified.

Overall Quality Determination — Uninformative

Study Citation: Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.
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EXTRACTION

Parameter	Data
Extraction ID; Chemical:	Group 3; 0.6 ml/kg; 1 day; Diisononyl Phthalate (DINP)-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):	Not Reported; Not Reported
Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))):	8.2; 583
Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments):	24 hrs; Not Reported; Notes: Not Reported
Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments):	24 hrs; Not Reported; Notes: Not Reported
Time Skin was Washed and Method used; Radiolabel Presence:	Skin was not washed; Yes
Total Recovery (percent); Dose Type:	96.33; Finite
Percent Found in Skin Depot after Washing and Tape Stripping:	Not Reported; Notes: Not Reported
Percent Found in Urine ; Comments:	0.09; Notes: Not Reported
Percent Found in Feces ; Comments:	0.01; Notes: Not Reported
Percent Found in Blood/Serum ; Comments:	0.001; Notes: Not Reported
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: Not Reported
Total Percent Absorbed:	0
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: 0.24% measured in tissues and GI tract; Total absorbed 0.35%

EVALUATION

Domain	Metric	Rating	Comments
Domain 1: Test Substance			
Metric 1:	Test substance identity	High	The test substance was identified as 14C-di-isononylphthalate (DINP); CASRN 68515-48. Location of radiolabel was indicated.
Metric 2:	Test substance source	High	The labeled and unlabeled test substance was supplied by Exxon Corporation. The radiolabeled test substance was prepared by Amersham Corporation (Arlington Heights, Illinois). The chemical identity of the radiolabeled test material was confirmed by the performing laboratory using HPLC. It is assumed that the test substance was a liquid since it was applied to the skin using a micropipette.

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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 3:	Test substance purity	High	The purity was reported to be 97-98%, determined by TLC.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Medium	The study states animals were selected at random for each test group; however, the method of randomization was not specified.
	Metric 5:	Standards for Tests	Low	This in vivo study was not conducted according to any specified guidelines. The percent recovery was acceptable (100+/-10%) and consistent with current guidelines. The backs of the rats were shaved shortly before treatment (specific timing not specified). This is not consistent with OECD guidelines which state the area of skin should be clipped approximately 24 hours prior to dosing. It was not specified whether care was taken to minimize abrasion, and it was not reported whether the area was wiped with acetone as specified in OECD TG 427.The test substance was applied neat to a 3x4 cm area of skin, which is appropriate. The text indicated that a stock solution was prepared containing the labeled compound in ether. It is unclear whether this stock was used only for analysis of the test compound or if this stock was applied to the skin of animals. Elsewhere in the report, it indicates that the test material was applied neat. The study specified that the skin was kept occluded, however, an atypical method was used. Specifically, the application site was covered with a Styrofoam cup lined with aluminum, which was secured onto the animal's back with adhesive tape. This setup suggests more protection of the application site, rather than occlusion. This is not expected to have a significant impact on the study results because the test material is not volatile.The skin was not washed, and tape stripping was not conducted. Coefficients of variation were not reported but could be determined using individual animal data. The adequacy of the CV values is addressed in Metric 19.
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	Medium	A stock solution of labeled compound was prepared and stored at -20oC. The solution was prepared in ether however details of the preparation are not provided (e.g. concentration in ether). It is unclear whether this stock was used only for analysis of the test compound or if this stock was applied to the skin of animals. Elsewhere, it was indicated that the test substance was applied neat suggesting no preparation was needed. The study protocol also specified that "the test compound will be stored in a cool, dark place or under specified conditions which minimize decomposition."
	Metric 7:	Consistency of exposure administration	Medium	Only a single animal was used. The study applied 0.1 ml of the test substance on the back of the animal. OECD guidelines specify an optimal application of up to 10ul/cm2 for an animal that is 200-250 g bw; this study applied 8.3uL/cm2 in an animal weighing 158g which was likely appropriate.
	Metric 8:	Reporting of concentrations	Medium	The study reported doses in ml/kg, the amount applied in ul/cm2 was not specified; however, individual animal body weights and the skin surface area were provided, and this could be calculated. The dose in mg/kg was not provided but can be determined using the density of the test substance.
	Metric 9:	Exposure duration	Low	Typical exposure durations are 6 or 24 hours or are relevant to "in use" exposures.This study used durations of 1, 3, or 7 days and the authors did not indicate whether these durations were relevant to conditions of use. No skin washes were conducted and this study also did not continue measurements post-exposure to account for any further absorption from test material retained in the skin.

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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 10:	Number of exposure groups and concentration spacing	Low	There were less than 3 dose groups tested; It was stated that the doses were based on preliminary findings; however, for neat exposure, the preliminary study only tested a single dose of 0.5 mL/kg . Other preliminary data were generated using a corn oil vehicle whereas this study used no vehicle. No further justifications were provided for the dose tested, and it is unknown whether it was appropriate for common formulations.
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	Medium	Adult male Fischer 344 rats (63-66 days old) were obtained from Charles River Breeding Laboratories (Kingston Facility, Stoneridge, NY). Starting body weights were reported. The weight range of animals at initiation was 140 to 182 g. These weights are lower than the protocol specified by the sponsor (~200g) and lower than the guideline recommendation of 200-150g for male rats.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	High	Husbandry conditions were reported and in agreement with OECD 427 guidelines.
	Metric 13:	Number of animals per group	Uninformative	The number of animals was less than the recommended 4 per termination time (n= 1/timepoint). A single animal per time point is insufficient for characterizing dermal absorption.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	This study measured concentrations in the tissue (blood, liver, kidneys, testes, muscle, fat, non-treated skin, and GI tract) and excretum (urine, feces). The study did not conduct skin washes or tape stripping and reported recovery for the" application area" which included the skin at the application site and the cover. The authors indicated this as non-absorbed radioactivity. They did not consider any additional systemic absorption over time from the skin. These are significant deviations from current guidelines. No Kp or flux determinations were made for a finite study; percent absorption was calculated. However, the text did mention that the average rate of absorption for the studies was 0.3% of the applied dose per day, and this appears to be based on a ~0.3% recovery from tissues and excreta at 24 hrs.
	Metric 15:	Consistency of outcome assessment	High	Outcomes were assessed consistently between animals from each timepoint.
	Metric 16:	Sampling adequacy and sensitivity	High	The study adequately analyzed samples in duplicate when possible. Samples were reassayed when radioactivity counts were less than two times background (30.6 cpm).
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Although the study did not report all information to determine whether confounding bias may exist, reported information did not identify differences that would confound results.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	The authors mentioned that no irritation was observed at the application site. Skin integrity was not discussed. It was not mentioned whether measures were taken during shaving to limit abrasion.
Domain 7: Data Presentation and Analysis				

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EVALUATION

Domain	Metric		Rating	Comments
	Metric 19:	Data analysis	N/A	This study only used a single animal and statistical analysis was not possible. Percent total absorbed was calculated based on test material detected in tissues and excreta at a single time point and did not include material in the skin of the application site. In the discussion, the authors did state that "the rates of daily absorption of the applied doses were similar (average 0.3% of the applied dose per day). No information on rate calculations were provided in the study methods, and it is unclear how this value was derived, and would only be appropriate under an infinite exposure scenario.
	Metric 20:	Data interpretation	Low	Recovery was 100% $\pm$ 10% at each time point. The majority of the test material was found in the skin of the application site plus the cover; denoted as the "application area" by the study authors and represented the non-absorbed radioactivity. The authors did not include the skin at the application sites in the absorption estimates. This excludes potentially absorbable material in the stratum corneum, and likely underestimates the total absorption, particularly at the 24-hour timepoint. This is supported by data from animals exposed to the same dose for longer durations (3 and 7 days) where higher total absorptions were observed. Exclusion of the skin may be appropriate for a 7-day duration test as it is likely that any amount left on the skin may have been unabsorbable. Because the study did not conduct skin washing or provide recovery from the application site alone, separate from the cover material, there is considerable uncertainty in the % absorbed value. Percent absorbed was reported in a finite exposure study.
	Metric 21:	Reporting of Data	High	Data were fully reported for all of the outcomes specified based on the study design. The authors noted that no irritation was identified.

Overall Quality Determination — Uninformative

Study Citation: Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.
HERO ID: 1325430

EXTRACTION

Parameter	Data
Extraction ID; Chemical:	Group 3; 0.6 ml/kg; 3 days; Diisononyl Phthalate (DINP)-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):	Not Reported; Not Reported
Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))):	8.2; 583
Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments):	Other; Not Reported; Notes: 3 days
Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments):	Other; Not Reported; Notes: 3 days
Time Skin was Washed and Method used; Radiolabel Presence:	Skin was not washed.; Yes
Total Recovery (percent); Dose Type:	93.78; Finite
Percent Found in Skin Depot after Washing and Tape Stripping:	Not Reported; Notes: Not Reported
Percent Found in Urine ; Comments:	0.5; Notes: Not Reported
Percent Found in Feces ; Comments:	0.16; Notes: Not Reported
Percent Found in Blood/Serum ; Comments:	0.003; Notes: Not Reported
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: Not Reported
Total Percent Absorbed:	1
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: 0.38% measured in tissues and GI tract; Total absorbed 1.04%

EVALUATION

Domain	Metric	Rating	Comments
Domain 1: Test Substance			
Metric 1:	Test substance identity	High	The test substance was identified as 14C-di-isononylphthalate (DINP); CASRN 68515-48. Location of radiolabel was indicated.
Metric 2:	Test substance source	High	The labeled and unlabeled test substance was supplied by Exxon Corporation. The radiolabeled test substance was prepared by Amersham Corporation (Arlington Heights, Illinois). The chemical identity of the radiolabeled test material was confirmed by the performing laboratory using HPLC. It is assumed that the test substance was a liquid since it was applied to the skin using a micropipette.

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Study Citation: Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.
HERO ID: 1325430

			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 3:	Test substance purity	High	The purity was reported to be 97-98%, determined by TLC.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Medium	The study states animals were selected at random for each test group; however, the method of randomization was not specified.
	Metric 5:	Standards for Tests	Low	This in vivo study was not conducted according to any specified guidelines. The percent recovery was acceptable (100+/-10%) and consistent with current guidelines. The backs of the rats were shaved shortly before treatment (specific timing not specified). This is not consistent with OECD guidelines which state the area of skin should be clipped approximately 24 hours prior to dosing. It was not specified whether care was taken to minimize abrasion, and it was not reported whether the area was wiped with acetone as specified in OECD TG 427.The test substance was applied neat to a 3x4 cm area of skin, which is appropriate. The text indicated that a stock solution was prepared containing the labeled compound in ether. It is unclear whether this stock was used only for analysis of the test compound or if this stock was applied to the skin of animals. Elsewhere in the report, it indicates that the test material was applied neat. The study specified that the skin was kept occluded, however, an atypical method was used. Specifically, the application site was covered with a Styrofoam cup lined with aluminum, which was secured onto the animal's back with adhesive tape. This setup suggests more protection of the application site, rather than occlusion. This is not expected to have a significant impact on the study results because the test material is not volatile.The skin was not washed, and tape stripping was not conducted. Coefficients of variation were not reported but could be determined using individual animal data. The adequacy of the CV values is addressed in Metric 19.
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	Medium	A stock solution of labeled compound was prepared and stored at -20oC. The solution was prepared in ether however details of the preparation are not provided (e.g. concentration in ether). It is unclear whether this stock was used only for analysis of the test compound or if this stock was applied to the skin of animals. Elsewhere, it was indicated that the test substance was applied neat suggesting no preparation was needed. The study protocol also specified that "the test compound will be stored in a cool, dark place or under specified conditions which minimize decomposition."
	Metric 7:	Consistency of exposure administration	Medium	Only a single animal was used. The study applied 0.1 ml of the test substance on the back of the animal. OECD guidelines specify an optimal application of up to 10ul/cm2 for an animal that is 200-250 g bw; this study applied 8.3uL/cm2 in an animal weighing 158g which was likely appropriate.
	Metric 8:	Reporting of concentrations	Medium	The study reported doses in ml/kg, the amount applied in ul/cm2 was not specified; however, individual animal body weights and the skin surface area were provided, and this could be calculated. The dose in mg/kg was not provided but can be determined using the density of the test substance.
	Metric 9:	Exposure duration	Low	Typical exposure durations are 6 or 24 hours or are relevant to "in use" exposures.This study used durations of 1, 3, or 7 days and the authors did not indicate whether these durations were relevant to conditions of use. No skin washes were conducted and this study also did not continue measurements post-exposure to account for any further absorption from test material retained in the skin.

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Study Citation: Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.
HERO ID: 1325430

Domain		Metric	EVALUATION Rating	Comments
	Metric 10:	Number of exposure groups and concentration spacing	Low	There were less than 3 dose groups tested; It was stated that the doses were based on preliminary findings; however, for neat exposure, the preliminary study only tested a single dose of 0.5 mL/kg . Other preliminary data were generated using a corn oil vehicle whereas this study used no vehicle. No further justifications were provided for the dose tested, and it is unknown whether it was appropriate for common formulations.
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	Medium	Adult male Fischer 344 rats (63-66 days old) were obtained from Charles River Breeding Laboratories (Kingston Facility, Stoneridge, NY). Starting body weights were reported. The weight range of animals at initiation was 140 to 182 g. These weights are lower than the protocol specified by the sponsor (~200g) and lower than the guideline recommendation of 200-150g for male rats.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	High	Husbandry conditions were reported and in agreement with OECD 427 guidelines.
	Metric 13:	Number of animals per group	Uninformative	The number of animals was less than the recommended 4 per termination time (n= 1/timepoint). A single animal per time point is insufficient for characterizing dermal absorption.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	This study measured concentrations in the tissue (blood, liver, kidneys, testes, muscle, fat, non-treated skin, and GI tract) and excretum (urine, feces). The study did not conduct skin washes or tape stripping and reported recovery for the" application area" which included the skin at the application site and the cover. The authors indicated this as non-absorbed radioactivity. They did not consider any additional systemic absorption over time from the skin. These are significant deviations from current guidelines. No Kp or flux determinations were made for a finite study; percent absorption was calculated. However, the text did mention that the average rate of absorption for the studies was 0.3% of the applied dose per day, and this appears to be based on a ~0.3% recovery from tissues and excreta at 24 hrs.
	Metric 15:	Consistency of outcome assessment	High	Outcomes were assessed consistently between animals from each timepoint.
	Metric 16:	Sampling adequacy and sensitivity	High	The study adequately analyzed samples in duplicate when possible. Samples were reassayed when radioactivity counts were less than two times background (30.6 cpm).
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Although the study did not report all information to determine whether confounding bias may exist, reported information did not identify differences that would confound results.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	The authors mentioned that no irritation was observed at the application site. Skin integrity was not discussed. It was not mentioned whether measures were taken during shaving to limit abrasion.
Domain 7: Data Presentation and Analysis				

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EVALUATION

Domain	Metric		Rating	Comments
	Metric 19:	Data analysis	N/A	This study only used a single animal and statistical analysis was not possible. Percent total absorbed was calculated based on test material detected in tissues and excreta at a single time point and did not include material in the skin of the application site. In the discussion, the authors did state that "the rates of daily absorption of the applied doses were similar (average 0.3% of the applied dose per day). No information on rate calculations were provided in the study methods, and it is unclear how this value was derived, and would only be appropriate under an infinite exposure scenario.
	Metric 20:	Data interpretation	Low	Recovery was 100% $\pm$ 10% at each time point. The majority of the test material was found in the skin of the application site plus the cover; denoted as the "application area" by the study authors and represented the non-absorbed radioactivity. The authors did not include the skin at the application sites in the absorption estimates. This excludes potentially absorbable material in the stratum corneum, and likely underestimates the total absorption, particularly at the 24-hour timepoint. This is supported by data from animals exposed to the same dose for longer durations (3 and 7 days) where higher total absorptions were observed. Exclusion of the skin may be appropriate for a 7-day duration test as it is likely that any amount left on the skin may have been unabsorbable. Because the study did not conduct skin washing or provide recovery from the application site alone, separate from the cover material, there is considerable uncertainty in the % absorbed value. Percent absorbed was reported in a finite exposure study.
	Metric 21:	Reporting of Data	High	Data were fully reported for all of the outcomes specified based on the study design. The authors noted that no irritation was identified.

Overall Quality Determination — Uninformative

Study Citation: Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.
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EXTRACTION

Parameter	Data
Extraction ID; Chemical:	Group 3; 0.6 ml/kg; 7 days; Diisononyl Phthalate (DINP)-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):	Not Reported; Not Reported
Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))):	8.2; 573
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; Not Reported; Notes: 7 days
Time Skin was Washed and Method used; Radiolabel Presence:	Skin was not washed.; Yes
Total Recovery (percent); Dose Type:	96.55; Finite
Percent Found in Skin Depot after Washing and Tape Stripping:	Not Reported; Notes: Not Reported
Percent Found in Urine ; Comments:	1.11; Notes: Not Reported
Percent Found in Feces ; Comments:	0.91; Notes: Not Reported
Percent Found in Blood/Serum ; Comments:	0.003; Notes: Not Reported
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: Not Reported
Total Percent Absorbed:	2
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: 1.02% measured in tissues and GI tract; Total absorbed 3.06%

EVALUATION

Domain	Metric	Rating	Comments
Domain 1: Test Substance			
Metric 1:	Test substance identity	High	The test substance was identified as 14C-di-isononylphthalate (DINP); CASRN 68515-48. Location of radiolabel was indicated.
Metric 2:	Test substance source	High	The labeled and unlabeled test substance was supplied by Exxon Corporation. The radiolabeled test substance was prepared by Amersham Corporation (Arlington Heights, Illinois). The chemical identity of the radiolabeled test material was confirmed by the performing laboratory using HPLC. It is assumed that the test substance was a liquid since it was applied to the skin using a micropipette.

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			EVALUATION	
Domain		Metric	Rating	Comments
	Metric 3:	Test substance purity	High	The purity was reported to be 97-98%, determined by TLC.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Medium	The study states animals were selected at random for each test group; however, the method of randomization was not specified.
	Metric 5:	Standards for Tests	Low	This in vivo study was not conducted according to any specified guidelines. The percent recovery was acceptable (100+/-10%) and consistent with current guidelines. The backs of the rats were shaved shortly before treatment (specific timing not specified). This is not consistent with OECD guidelines which state the area of skin should be clipped approximately 24 hours prior to dosing. It was not specified whether care was taken to minimize abrasion, and it was not reported whether the area was wiped with acetone as specified in OECD TG 427.The test substance was applied neat to a 3x4 cm area of skin, which is appropriate. The text indicated that a stock solution was prepared containing the labeled compound in ether. It is unclear whether this stock was used only for analysis of the test compound or if this stock was applied to the skin of animals. Elsewhere in the report, it indicates that the test material was applied neat. The study specified that the skin was kept occluded, however, an atypical method was used. Specifically, the application site was covered with a Styrofoam cup lined with aluminum, which was secured onto the animal's back with adhesive tape. This setup suggests more protection of the application site, rather than occlusion. This is not expected to have a significant impact on the study results because the test material is not volatile.The skin was not washed, and tape stripping was not conducted. Coefficients of variation were not reported but could be determined using individual animal data. The adequacy of the CV values is addressed in Metric 19.
Domain 3: Exposure Characterization				
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	Metric 7:	Consistency of exposure administration	Medium	Only a single animal was used. The study applied 0.1 ml of the test substance on the back of the animal. OECD guidelines specify an optimal application of up to 10ul/cm2 for an animal that is 200-250 g bw; this study applied 8.3uL/cm2 in an animal weighing 158g which was likely appropriate.
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	Metric 9:	Exposure duration	Low	Typical exposure durations are 6 or 24 hours or are relevant to "in use" exposures.This study used durations of 1, 3, or 7 days and the authors did not indicate whether these durations were relevant to conditions of use. No skin washes were conducted and this study also did not continue measurements post-exposure to account for any further absorption from test material retained in the skin.

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EVALUATION

Domain		Metric	Rating	Comments
	Metric 10:	Number of exposure groups and concentration spacing	Low	There were less than 3 dose groups tested; It was stated that the doses were based on preliminary findings; however, for neat exposure, the preliminary study only tested a single dose of 0.5 mL/kg . Other preliminary data were generated using a corn oil vehicle whereas this study used no vehicle. No further justifications were provided for the dose tested, and it is unknown whether it was appropriate for common formulations.
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	Medium	Adult male Fischer 344 rats (63-66 days old) were obtained from Charles River Breeding Laboratories (Kingston Facility, Stoneridge, NY). Starting body weights were reported. The weight range of animals at initiation was 140 to 182 g. These weights are lower than the protocol specified by the sponsor (~200g) and lower than the guideline recommendation of 200-150g for male rats.
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	Metric 13:	Number of animals per group	Uninformative	The number of animals was less than the recommended 4 per termination time (n= 1/timepoint). A single animal per time point is insufficient for characterizing dermal absorption.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	This study measured concentrations in the tissue (blood, liver, kidneys, testes, muscle, fat, non-treated skin, and GI tract) and excretum (urine, feces). The study did not conduct skin washes or tape stripping and reported recovery for the" application area" which included the skin at the application site and the cover. The authors indicated this as non-absorbed radioactivity. They did not consider any additional systemic absorption over time from the skin. These are significant deviations from current guidelines. No Kp or flux determinations were made for a finite study; percent absorption was calculated. However, the text did mention that the average rate of absorption for the studies was 0.3% of the applied dose per day, and this appears to be based on a ~0.3% recovery from tissues and excreta at 24 hrs.
	Metric 15:	Consistency of outcome assessment	High	Outcomes were assessed consistently between animals from each timepoint.
	Metric 16:	Sampling adequacy and sensitivity	High	The study adequately analyzed samples in duplicate when possible. Samples were reassayed when radioactivity counts were less than two times background (30.6 cpm).
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Although the study did not report all information to determine whether confounding bias may exist, reported information did not identify differences that would confound results.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	The authors mentioned that no irritation was observed at the application site. Skin integrity was not discussed. It was not mentioned whether measures were taken during shaving to limit abrasion.
Domain 7: Data Presentation and Analysis				

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EVALUATION

Domain	Metric		Rating	Comments
	Metric 19:	Data analysis	N/A	This study only used a single animal and statistical analysis was not possible. Percent total absorbed was calculated based on test material detected in tissues and excreta at a single time point and did not include material in the skin of the application site. In the discussion, the authors did state that "the rates of daily absorption of the applied doses were similar (average 0.3% of the applied dose per day). No information on rate calculations were provided in the study methods, and it is unclear how this value was derived, and would only be appropriate under an infinite exposure scenario.
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	Metric 21:	Reporting of Data	High	Data were fully reported for all of the outcomes specified based on the study design. The authors noted that no irritation was identified.

Overall Quality Determination — Uninformative