

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

HERO ID	Reference	Page
In vitro		
2219803	Pan, T. L., Wang, P. W., Aljuffali, I. A., Hung, Y. Y., Lin, C. F., Fang, J. Y. (2014). Dermal toxicity elicited by phthalates: Evaluation of skin absorption, immunohistology, and functional proteomics. Food and Chemical Toxicology 65:105-114.	4
In vivo - Animal		
1325430	Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.	8

The test substance was identified as DINP. A CASRN was not provided. The test sub-

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 publica-

stance was not radiolabeled.

The reported purity was >99%

tion but could be verified on manufacturer's website.

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 a	absorption.
	,
Immunohistology, and functional proteomics. Food and Chemical Toxicology 65:105-114.	
EXTRACTION	
Parameter Data	
Extraction ID: Chemical: Pig-DINP: Diisononyl Phthalate (DINP)-Parent compound	
Skin Material/Species: Skin Prenaration: Skin exvivo nice Full thickness: Not Reported: Static Notes: Exvivo mouse	
Thickness (um) Diffusion Cell Exposure Setun	
Type:	
Occlusion Type: Donor Chamber Vehicle: Con- Not Reported: 40% ethanol solution: Not Reported	
centration of Test Substance in Vehicle (enter as	
percent):	
Mass per Surface Area on Skin (mg/cm2); Dura- Not Reported; Other; 12 hours	
tion of Test Substance on Skin:	
Duration of Absorbance Measured; Frequency of Other; every 3 hours in receptor fluid; Notes: 12 hours	
Samples: Time We had and Mathed and Dedi — Shin meneral had at 12 hours. No far hand daile meneranaid de Na	
label Browned	
Total Recovery (percent): Dose Type: Not Reported: Not Reported	
Percent Found in Skin Depot After Washing and Not Reported: Notes: Skin absorption was not reported as a percent. The accumulation in skin was 0.36 + 0.16 nmol/mg (CV= 44%).). Tape
Tape Stripping: Comments:	, Tupe
Percent Found in All Tape Strips, Excluding the Not Reported; Notes: Skin absorption was not reported as a percent. The accumulation in skin was 0.36 ± 0.16 nmol/mg (CV= 44%)). Tape
Upper Two Strips; Comments: stripping was mentioned in another part of the study, but this measurement is presumed to be for total skin after washing.	, I
Percent Found in Receptor Fluid and Receptor Not Reported; Notes: This information was not reported.	
Fluid Rinse; Comments:	
Total Percent Absorbed: 0	
Steady State Permeability Coefficient (Kp) Not Reported; O; Notes: Flux could	not be
(cm/hr); Steady State Permeability Coefficient calculated. "No permeant was found in receptor after treatment"	
(Comments); Steady State Flux (ug/cm2/hr);	
Steady State Flux (Comments); Maxium Perme-	
ability Coefficient (Kp) (cm/hr); Maxium Perme-	
ability Coefficient (Comments); Maximum Flux	
(ug/cm2/m); maximum riux (Comments):	
EVALUATION	
Domain Matric Pating Comments	
Domain 1: Test Substance	

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Test substance identity

Test substance source

Test substance purity

Metric 1:

Metric 2:

Metric 3:

Domain 2: Test Design

High

High

High

		conti	nued from previous pa	ge
Study Citation: HERO ID:	Pan, T. L., War immunohistolo 2219803	ng, P. W., Aljuffali, I. A., Hung, Y. Y., Lin, C. F., gy, and functional proteomics. Food and Chemic	, Fang, J. Y. (2014). De al Toxicology 65:105-1	rmal toxicity elicited by phthalates: Evaluation of skin absorption, 14.
			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 con- centration 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 2: Exposure	Characterization			
Domain 3. Exposure	Metric 7:	Preparation and storage of test sub- stance (chemical)	Low	Limited details on the test substance preparation were provided. No details on stabil- ity, 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 pre- ferred 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 recep- tor 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 con- centration 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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Study Citation:	Pan, T. L., Wai immunohistolo 2219803	ng, P. W., Aljuffali, I. A., Hung, Y. Y., Lin, C. Jogy, and functional proteomics. Food and Chem	F., Fang, J. Y. (2014). D nical Toxicology 65:105-	Dermal toxicity elicited by phthalates: Evaluation of skin absorption, -114.
HERO ID.	2219803		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 speci- fies 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 repli- cates). It is presumed that these are two separate experiments, but the reporting details were not clear.
Domain 5. Outcome As	a a a a m a m t			
Jonani J. Oucome As	Metric 14:	Outcome assessment methodology	Low	The outcome assessment methodology deviated significantly from OECD TG 428 rec- ommendations. 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 sam- pled 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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Study Citation: HERO ID:	Pan, T. L., War immunohistolo 2219803	ng, P. W., Aljuffali, I. A., Hung, Y. Y., Lin, C. F., gy, and functional proteomics. Food and Chemica	Fang, J. Y. (2014). Derr l Toxicology 65:105-114	nal toxicity elicited by phthalates: Evaluation of skin absorption, 4.
		I	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 un- related 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 Pres	entation and Analys	is		
	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 $\le50\%$ 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 \pm SD. Permeation The study did not report concentrations in receptor fluid by time. A figure showing the plotted data with a corresponding linear slope was not provided.
Overall Qua	lity Determi	ination (J ninformative	

Study Citation: Midwest Rese	arch 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; 1	Diisononyl Phthalate (DINP)-Parent compound			
Species; Comments:	Rat; Not Reported; Notes: N	Not Reported			
Sex; Covering used in Test System:	Male; Occluded				
Vehicle; Concentration of Test Substance in hicle (percent):	Ve- Not Reported; Not Reported	d			
Mass per Surface Area on Skin (mg/cm2); D (include units (e.g., mg/kg bw))):	ose 16.3; 1113				
Test Substance on Skin; Exposure Repeat (Days): Test Substance on Skin (Comments):	ted 24 hrs; Not Reported; Notes	s: Not Reported			
Time of Absorption Measured (Comments):	me 24 hrs; Not Reported; Notes	s: Not Reported			
Time Skin was Washed and Method used; R	adi- Skin was not washed; Yes				
Total Recovery (percent); Dose Type:	96.56; Finite	96.56; Finite			
Percent Found in Skin Depot after Washing	and Not Reported; Notes: Not R	Reported			
Tape Stripping:					
Percent Found in Urine ; Comments:	0.09; Notes: Not Reported	0.09; Notes: Not Reported			
Percent Found in Feces ; Comments:	0.03; Notes: Not Reported	0.03; Notes: Not Reported			
Percent Found in Blood/Serum ; Comments:	0.001; Notes: Not Reported	1			
Percent Found in Air ; Comments:	Not Reported; Notes: Not R	Not Reported; Notes: Not Reported			
Percent Found in Cage Wash ; Comments:	Not Reported; Notes: Not R	Not Reported; Notes: Not Reported			
Percent Found in All Tape Strips, Excluding Upper Two Strips:	the Not Reported; Notes: Not R	Reported			
Total Percent Absorbed:	0				
Steady State Permeability Coefficient ((cm/hr); Steady State Permeability Coeffic (Comments); Steady State Flux (ug/cm2/ Steady State Flux (Comments); Maximum I meability Coefficient (Kp) (cm/hr); Maxim Permeability Coefficient (Comments); M mum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments:	 Kp) Not Reported; Notes: Not R Notes: 0.19% measured in t hr); Per- um axi- om- 	Reported; Not Reported; Notes: Not Reported; Not Re tissues and GI tract; Total absorbed 0.343% with CV	eported; Notes: Not Reported; Not Reported; Notes: Not Reported; of 18%		
		EVALUATION			
Domain	Metric	Rating	Comments		

Domani		Wieure	Rating	Comments
Domain 1: Test Substa	ance			
	Metric 1:	Test substance identity	High	The test substance was identified as 14C-di-isononylphthalate (DINP); CASRN 68515- 48. Location of radiolabel was indicated.
			Continued on next page .	

Study Citation:	Midwest Resea	rch Institute, (1983). Dermal disposition of 14C	C-diisononyl ph	thalate in rats, final report with cover letter.
HERO ID:	1325430			
Domain		EVA Matria	ALUATION	Commente
Domain	Metric 2.	Test substance source	High	The lobeled and unlabeled test substance was supplied by Exxon Corporation. The ra
	Metric 2.	Test substance source	rigii	diolabeled 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 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 Ch	aracterization Metric 6:	Preparation and storage of test sub- stance (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.

Study Citation: HERO ID:	Midwest Resear 1325430	ch Institute, (1983). Dermal disposition of 14C	C-diisononyl ph	thalate in rats, final report with cover letter.
		EVA	ALUATION	
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 con- centration 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 Breed- ing Laboratories (Kingston Facility, Stoneridge, NY). Starting body weights were re- ported. 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 As	sessment			
	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 reas- sayed when radioactivity counts were less than two times background (30.6 cpm).

Domain 6: Confounding/Variable Control

Study Citation: HERO ID:	Midwest Research 1325430	Institute, (1983). Dermal disposition of 140	C-diisononyl phtł	halate in rats, final report with cover letter.
		EV	ALUATION	
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 un- related to exposure	Medium	The authors mentioned that no irritation was observed at the application site. Skin in- tegrity was not discussed. It was not mentioned whether measures were taken during shaving to limit abrasion.
Domain 7: Data Present	ation 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 au- thors 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 ab- sorbable 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 Qualit	ty Determina	ation	Medium	

Study Citation: HERO ID:	Midwest Research	Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.				
IIERO ID.	1525450	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 S	ystem:	Male; Occluded				
Vehicle; Concentration of Te hicle (percent):	est Substance in Ve-	Not Reported; Not Reported				
Mass per Surface Area on S	kin (mg/cm2); Dose	16.3; 1152				
(include units (e.g., mg/kg by Test Substance on Skin; (Days): Test Substance on Sk	w))): Exposure Repeated (comments):	Other; Not Reported; Notes: 3 days				
Time of Absorption Measure of Absorption Measured (Co	ed; Frequency; Time mments):	Other; Not Reported; Notes: 3 day				
Time Skin was Washed and	Method used; Radi-	Skin was not washed; Yes				
Total Recovery (percent); Do	ose Type:	101.54; Finite				
Percent Found in Skin Depo	t after Washing and	Not Reported; Notes: Not Reported				
Tape Stripping: Percent Found in Urine : Cor	nmente	1 16: Notes: Not Peparted				
Percent Found in Feces : Cor	nments:	0.83: Notes: Not Reported				
Percent Found in Blood/Seru	im · Comments·	0.01: Notes: Not Reported				
Percent Found in Air : Com	nents:	Not Reported: Notes: Not Reported				
Percent Found in Cage Wash	: Comments:	Not Reported: Notes: Not Reported				
Percent Found in All Tape S	trips. Excluding the	Not Reported: Notes: Not Reported				
Upper Two Strips:						
Total Percent Absorbed:		2				
Steady State Permeability (cm/hr); Steady State Perm (Comments); Steady State	Coefficient (Kp) neability Coefficient Flux (ug/cm2/hr);	Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: 0.93% measured in tissues and GI tract; Total absorbed 3.20% with CV= 70%				
Steady State Flux (Commen meability Coefficient (Kp)	nts); Maximum Per- (cm/hr); Maximum					
Permeability Coefficient (C mum Flux (ug/cm2/hr); Ma ments); Additional Commen	Comments); Maxi- ximum Flux (Com- ts:					
		EVALUATION				

		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 ra- diolabeled 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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		contin	nued from previous pa	nge
Study Citation: HERO ID:	Midwest Resea 1325430	rch Institute, (1983). Dermal disposition of 14C-	-diisononyl phthalate in	rats, final report with cover letter.
			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				
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 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.
Damain 2. European Ch				
Domain 5: Exposure Cr	Metric 6:	Preparation and storage of test sub- stance (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.
		Conti	nued on next page	

Study Citation:	Midwest Research	h Institute, (1983). Dermal disposition of 14	C-diisononyl phthalate in	rats, final report with cover letter.
HERO ID:	1325430		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 con- centration 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 Breed- ing Laboratories (Kingston Facility, Stoneridge, NY). Starting body weights were re- ported. 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 As	sessment			
	Metric 14:	Outcome assessment methodology	Low	This study measured concentrations in the tissue (blood, liver, kidneys, testes, mus- cle, 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 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 reas- sayed when radioactivity counts were less than two times background (30.6 cpm).
Domain 6. Confour dia	Wariahla Cantral			
	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.
		Con	tinued on next page	

		contin	nued from previous pa	ge
Study Citation: HERO ID:	Midwest Resear 1325430	ch Institute, (1983). Dermal disposition of 14C-	-diisononyl phthalate in	rats, final report with cover letter.
Domain		Metric	Rating	Comments
	Metric 18:	Confounding variables in outcomes un- related to exposure	Medium	The authors mentioned that no irritation was observed at the application site. Skin in- tegrity was not discussed. It was not mentioned whether measures were taken during shaving to limit abrasion.
Domain 7: Data Pres	entation and Analysis	3		
	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 Qua	lity Determi	nation	Uninformative	e

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Domain

Domain 1: Test Substance

Metric 1:

Metric 2:

Study Citation:	Midwest Research	search Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.				
HERO ID:	1525450	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 S	System:	Male; Occluded				
Vehicle; Concentration of T hicle (percent):	est Substance in Ve-	Not Reported; Not Reported				
Mass per Surface Area on S (include units (e.g. mg/kg b	Skin (mg/cm2); Dose	16.3; 1079				
Test Substance on Skin; (Days): Test Substance on S	Exposure Repeated kin (Comments):	Other; Not Reported; Notes: 7 days				
Time of Absorption Measured (Co	ed; Frequency; Time	Other; Not Reported; Notes: 7 days				
Time Skin was Washed and olabel Presence:	Method used; Radi-	Skin was not washed.; Yes				
Total Recovery (percent); De	ose Type:	102.99; Finite				
Percent Found in Skin Depo	ot after Washing and	Not Reported; Notes: Not Reported				
Tape Stripping:						
Percent Found in Urine ; Co	omments:	1.06; Notes: Not Reported				
Percent Found in Feces ; Co	omments:	0.54; Notes: Not Reported				
Percent Found in Blood/Ser	um ; Comments:	0.005; Notes: Not Reported				
Percent Found in Air ; Com	ments:	Not Reported; Notes: Not Reported				
Percent Found in Cage Wash	h ; Comments:	Not Reported; Notes: Not Reported				
Upper Two Strips:	Strips, Excluding the	Not Reported; Notes: Not Reported				
Total Percent Absorbed:		2				
Steady State Permeability (cm/hr); Steady State Perm (Comments); Steady State Steady State Flux (Commen meability Coefficient (Kp) Permeability Coefficient (mum Flux (ug/cm2/hr); Ma ments); Additional Commen	y Coefficient (Kp) neability Coefficient e Flux (ug/cm2/hr); nts); Maximum Per- (cm/hr); Maximum Comments); Maxi- aximum Flux (Com- nts:	Not Reported; Notes: Not Reported; Not Reported; Notes: 0.45% measured in tissues and GI tract; Total absorbed 2.05% with CV= 9%				

Continued on next page ...

EVALUATION

Rating

High

High

Comments

The test substance was identified as 14C-di-isononylphthalate (DINP); CASRN 68515-

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

48. Location of radiolabel was indicated.

since it was applied to the skin using a micropipette.

Metric

Test substance identity

Test substance source

		continued	from previou	s page
Study Citation: HERO ID:	Midwest Resear 1325430	rch Institute, (1983). Dermal disposition of 14C	diisononyl ph	thalate in rats, final report with cover letter.
		EVA	LUATION	
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				
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 acctone 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 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 Ch	aracterization			
Domain 5. Exposure en	Metric 6:	Preparation and storage of test sub- stance (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.
		Continued	l on next page	•••

Study Citation: HERO ID:	Midwest Research 1325430	h Institute, (1983). Dermal disposition of 14C	-diisononyl ph	thalate in rats, final report with cover letter.
		EVA	LUATION	
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 con- centration 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 Breed- ing Laboratories (Kingston Facility, Stoneridge, NY). Starting body weights were re- ported. 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 As	sessment			
Domain 5. Outcome As	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 reas- sayed when radioactivity counts were less than two times background (30.6 cpm).
Domain 6: Confounding	y/Variable Control Metric 17:	Confounding variables in test design and procedures Continued	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: HERO ID:	Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter. 1325430					
		EV	ALUATION			
Domain		Metric	Rating	Comments		
	Metric 18:	Confounding variables in outcomes un- related to exposure	Medium	The authors mentioned that no irritation was observed at the application site. Skin in- tegrity was not discussed. It was not mentioned whether measures were taken during shaving to limit abrasion.		
Domain 7: Data Pres	sentation and Analys	is				
	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 Qua	lity Determi	ination	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; 1 day; Diisononyl Phthalate (DINP)-Parent compound			
Species; Comments:		Rat; Not Reported; Notes: Not Reported			
Sex; Covering used in Test S	System:	Male; Occluded			
Vehicle; Concentration of Tehicle (percent):	est Substance in Ve-	Not Reported; Not Reported			
Mass per Surface Area on S (include units (e.g., mg/kg b)	kin (mg/cm2); Dose w))):	16.3; 1288			
Test Substance on Skin; (Days): Test Substance on Sl	Exposure Repeated kin (Comments):	24 hrs; Not Reported; Notes: Not Reported			
Time of Absorption Measured	ed; Frequency; Time	24 hrs; Not Reported; Notes: Not Reported			
Time Skin was Washed and olabel Presence:	Method used; Radi-	Skin was not washed.; Yes			
Total Recovery (percent); Do	ose Type:	99.45; Finite			
Percent Found in Skin Depo	ot after Washing and	Not Reported; Notes: Not Reported			
Tape Stripping:					
Percent Found in Urine ; Co	mments:	0.07; Notes: Not Reported			
Percent Found in Feces ; Cor	mments:	0.02; Notes: Not Reported			
Percent Found in Blood/Seru	um ; Comments:	0.001; Notes: Not Reported			
Percent Found in Air ; Comr	ments:	Not Reported; Notes: Not Reported			
Percent Found in Cage Wash	i; Comments:	Not Reported; Notes: Not Reported			
Percent Found in All Tape S Upper Two Strips:	Strips, Excluding the	Not Reported; Notes: Not Reported			
Total Percent Absorbed:		0			
Steady State Permeability (cm/hr); Steady State Perm (Comments); Steady State Steady State Flux (Commer meability Coefficient (Kp) Permeability Coefficient (mum Flux (ug/cm2/hr); Ma ments); Additional Commen	v Coefficient (Kp) neability Coefficient Flux (ug/cm2/hr); nts); Maximum Per- (cm/hr); Maximum Comments); Maxi- uximum Flux (Com- ts:	Not Reported; Notes: Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: 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 Subst	tance			
	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 ra- diolabeled 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: HERO ID:	Midwest Resea 1325430	rch Institute, (1983). Dermal disposition of 140	C-diisononyl ph	thalate in rats, final report with cover letter.
Ъ.		EV	ALUATION	
Domain	Metric 3:	Metric Test substance purity	High	The purity was reported to be 07.08% determined by TLC
	Wiettie 5.		IIIgii	The parity was reported to be 97-96%, 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 mate- rial 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 re- ported 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 in- dicated 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 Styro- foam 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 Ch	aracterization			
Domain 3. Exposure Ch	Metric 6:	Preparation and storage of test sub- stance (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 adjust- ing 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 ap- plied 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.

Study Citation: HERO ID:	Midwest Research 1325430	n Institute, (1983). Dermal disposition of 14C	diisononyl ph	thalate in rats, final report with cover letter.
		EVA	LUATION	
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 con- centration 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				
Domain 4. Test Woder	Metric 11:	Test animal characteristics	Medium	Adult male Fischer 344 rats (63-66 days old) were obtained from Charles River Breed- ing Laboratories (Kingston Facility, Stoneridge, NY). Starting body weights were re- ported. 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 As	accoment			
Domain 5. Outcome As	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 reas- sayed 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 Continued	Medium I on next page	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.

		····Continued	i iioiii pieviou	is page
Study Citation: HERO ID:	itation:Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.D:1325430			
		EV	ALUATION	
Domain		Metric	Rating	Comments
	Metric 18:	Confounding variables in outcomes un- related to exposure	Medium	The authors mentioned that no irritation was observed at the application site. Skin in- tegrity was not discussed. It was not mentioned whether measures were taken during shaving to limit abrasion.
Domain 7: Data Pres	sentation and Analysi	s		
	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 Qua	lity Determi	nation	Medium	l

Study Citation: HERO ID:	Midwest Research	Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.
IILKO ID.	1525 150	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 hicle (percent):	Test Substance in Ve-	Not Reported; Not Reported
Mass per Surface Area on	Skin (mg/cm2); Dose	16.3; 1283
Test Substance on Skin; (Days); Test Substance on	Exposure Repeated Skin (Comments):	Other; Not Reported; Notes: 3 days
Time of Absorption Measu of Absorption Measured (C	red; Frequency; Time Comments):	Other; Not Reported; Notes: 3 days
Time Skin was Washed an	d Method used; Radi-	Skin was not washed.; Yes
Total Recovery (percent); I	Dose Type:	101.27; Finite
Percent Found in Skin Dep	pot after Washing and	Not Reported; Notes: Not Reported
Percent Found in Urine : C	comments:	0.58: Notes: Not Reported
Percent Found in Feces ; C	comments:	0.25; Notes: Not Reported
Percent Found in Blood/Se	erum ; Comments:	0.004; Notes: Not Reported
Percent Found in Air ; Con	nments:	Not Reported; Notes: Not Reported
Percent Found in Cage Wa	sh ; Comments:	Not Reported; Notes: Not Reported
Percent Found in All Tape	Strips, Excluding the	Not Reported; Notes: Not Reported
Upper Two Strips:		
Total Percent Absorbed:		1
Steady State Permeabili (cm/hr); Steady State Per (Comments); Steady Sta Steady State Flux (Comm meability Coefficient (Kp Permeability Coefficient mum Flux (ug/cm2/hr); M mento): Additional Comme	ity Coefficient (Kp) rmeability Coefficient te Flux (ug/cm2/hr); ents); Maximum Per-) (cm/hr); Maximum (Comments); Maxi- Maximum Flux (Com-	Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Not Reported; Notes: Not Reported; Notes: 0.77% measured in tissues and GI tract; Total absorbed 1.6% with CV= 51%.
ments), Additional Colline	ents.	
		EVALUATION

			EVALUATION	
Domain		Metric	Rating	Comments
Domain 1: Test Substance				
Metr	ric 1:	Test substance identity	High	The test substance was identified as 14C-di-isononylphthalate (DINP); CASRN 68515- 48. Location of radiolabel was indicated.
Meti	ric 2:	Test substance source	High	The labeled and unlabeled test substance was supplied by Exxon Corporation. The ra- diolabeled 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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		contin	ued from previous p	Dage
Study Citation: HERO ID:	Midwest Resea 1325430	rch Institute, (1983). Dermal disposition of 14C-	diisononyl phthalate i	in rats, final report with cover letter.
Damain		N. L. L.	EVALUATION	Commente
Domain	Metric 3:	Melfic Test substance purity	High	Comments The purity was reported to be 97-98% determined by TLC
	Mettre 5.	Test substance purity	Ingn	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 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 Ch	naracterization Metric 6:	Preparation and storage of test sub- stance (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.
		Conti	nued on next page	

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Study Citation:	Midwest Research	h Institute, (1983). Dermal disposition of 14	C-diisononyl phthalate in	rats, final report with cover letter.
HERO ID:	1325430		EVALUATION	
Domain		Metric	EVALUATION 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 con- centration 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 Breed- ing Laboratories (Kingston Facility, Stoneridge, NY). Starting body weights were re- ported. 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 As	sessment			
	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 mas 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 excret 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 reas- sayed when radioactivity counts were less than two times background (30.6 cpm).
Domain & Conformation	Wariahla Control			
Domain of Confounding	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.
		Con	tinued on next page	

	continued from previous page						
Study Citation: HERO ID:	Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter. 1325430						
			EVALUATION				
Domain		Metric	Rating	Comments			
	Metric 18:	Confounding variables in outcomes un- related to exposure	Medium	The authors mentioned that no irritation was observed at the application site. Skin in- tegrity was not discussed. It was not mentioned whether measures were taken during shaving to limit abrasion.			
Domain 7: Data Pres	sentation and Analys	is					
	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 $100\% \pm 10\%$. 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-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 Qua	lity Determ	ination	Uninformative				

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Study Citation:Midwest RHERO ID:1325430	esearch Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.			
	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 hicle (percent):	in Ve- Not Reported; Not Reported			
Mass per Surface Area on Skin (mg/cm2) (include units (e.g., mg/kg.bw)));); Dose 16.3; 1113			
Test Substance on Skin; Exposure Re (Days): Test Substance on Skin (Commen	epeated Other; Not Reported; Notes: 7 days			
Time of Absorption Measured (Comments):	; Time Other; Not Reported; Notes: 7 days			
Time Skin was Washed and Method used	; Radi- Skin was not washed.; Yes			
Total Recovery (percent); Dose Type:	97.75; Finite			
Percent Found in Skin Depot after Washi	ing and Not Reported; Notes: Not Reported			
Tape Stripping:	1.04. Natas Not Departed			
Percent Found in Urine ; Comments:	1.94; Notes: Not Reported			
Percent Found in Pload/Samm : Common	1.1, 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 Exclude	ing the Not Reported: Notes: Not Reported			
Upper Two Strips:	ing the Not Reported, Notes. Not Reported			
Total Percent Absorbed:	3			
Steady State Permeability Coefficient (cm/hr); Steady State Permeability Coe (Comments); Steady State Flux (ug/c: Steady State Flux (Comments); Maximu meability Coefficient (Kp) (cm/hr); Ma Permeability Coefficient (Comments); mum Flux (ug/cm2/hr); Maximum Flux ments); Additional Comments:	 k (Kp) Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not			
	EVALUATION			

			EVALUATION	
Domain		Metric	Rating	Comments
Domain 1: Test Substan	ce			
	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 ra- diolabeled 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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		continu	ed from previous p	bage		
Study Citation: HERO ID:	Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter. 1325430					
D		H	EVALUATION			
Domain	Matria 2:	Metric Test substance purity	Rating	Comments		
	Metric 5:	Test substance purity	підп	The purity was reported to be 97-98%, determined by TLC.		
Domain 2: Test Design						
C	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 or if this stock 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 Ch	aracterization					
	Metric 6:	Preparation and storage of test sub- stance (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.		

Study Citation:	Midwest Research	h Institute, (1983). Dermal disposition of 14	C-diisononyl phthalate in	rats, final report with cover letter.
HERO ID:	1325430		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 con- centration 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 Breed- ing Laboratories (Kingston Facility, Stoneridge, NY). Starting body weights were re- ported. 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 As	sessment			
	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 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 reas- sayed when radioactivity counts were less than two times background (30.6 cpm).
Domain 6. Confour din	Wariahla Cantral			
Domain o: Contounding	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: HERO ID:	Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter. 1325430						
			EVALUATION				
Domain		Metric	Rating	Comments			
	Metric 18:	Confounding variables in outcomes un- related to exposure	Medium	The authors mentioned that no irritation was observed at the application site. Skin in- tegrity was not discussed. It was not mentioned whether measures were taken during shaving to limit abrasion.			
Domain 7: Data Pres	sentation and Analys	is					
	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% \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 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 Qua	lity Determi	ination	Uninformative				

Study Citation:	Midwest Research	Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.				
HEKU ID:	1525450	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 T hicle (percent):	Fest Substance in Ve-	Not Reported; Not Reported				
Mass per Surface Area on S (include units (e.g., mg/kg l	Skin (mg/cm2); Dose	8.2; 583				
Test Substance on Skin; (Days); Test Substance on S	Exposure Repeated Skin (Comments):	24 hrs; Not Reported; Notes: Not Reported				
Time of Absorption Measur of Absorption Measured (C	red; Frequency; Time omments):	24 hrs; Not Reported; Notes: Not Reported				
Time Skin was Washed and olabel Presence:	Method used; Radi-	Skin was not washed; Yes				
Total Recovery (percent); D	Oose Type:	96.33; Finite				
Percent Found in Skin Dep	ot after Washing and	Not Reported; Notes: Not Reported				
Tape Stripping:	mananta	0.00. Notes: Not Reported				
Percent Found in Unite ; Co	omments:	0.03, Notes: Not Reported				
Percent Found in Blood/Set	Jum : Comments:	0.001: Notes: Not Reported				
Percent Found in Air : Com	um, comments.	Not Reported Notes: Not Reported				
Percent Found in Cage Was	h : Commente:	Not Reported: Notes: Not Reported				
Percent Found in All Tape	String Excluding the	Not Reported, Notes: Not Reported				
Upper Two Strips:	Surps, Excluding the	Not Reported, Notes. Not Reported				
Total Percent Absorbed:		0				
Steady State Permeabilit (cm/hr); Steady State Pern (Comments); Steady Stat Steady State Flux (Comme meability Coefficient (Kp) Permeability Coefficient (mum Flux (ug/cm2/hr); M ments); Additional Comme	y Coefficient (Kp) meability Coefficient e Flux (ug/cm2/hr); nts); Maximum Per- (cm/hr); Maximum (Comments); Maxi- aximum Flux (Com- nts:	Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Not Reported; Notes: Not Reported; Notes: 0.24% measured in tissues and GI tract; Total absorbed 0.35%				
		EVALUATION				

			EVALUATION		
Domain		Metric	Rating	Comments	
Domain 1: Test Subst	ance				
	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 ra- diolabeled 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: HERO ID:	Midwest Resea 1325430	arch Institute, (1983). Dermal disposition of 14C	-diisononyl phthalate i	in rats, final report with cover letter.
D .			EVALUATION	
Domain	Metric 3:	Metric Test substance purity	High	Comments The purity was reported to be 07.08% determined by TLC
	Wiettie 5.	Test substance purity	Ingn	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 2: Exposure Ch	arastarization			
Domani 5: Exposure Ch	Metric 6:	Preparation and storage of test sub- stance (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.
		Cont	inued on next page	•

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continued from previous page					
Study Citation: HERO ID:	Midwest Research 1325430	h Institute, (1983). Dermal disposition of 14C	-diisononyl phthalate in	rats, final report with cover letter.	
			EVALUATION		
Domain		Metric	Rating	Comments	
	Metric 10:	Number of exposure groups and con- centration 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					
Domani 4. Test Moder	Metric 11:	Test animal characteristics	Medium	Adult male Fischer 344 rats (63-66 days old) were obtained from Charles River Breed- ing Laboratories (Kingston Facility, Stoneridge, NY). Starting body weights were re- ported. 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	High	Husbandry conditions were reported and in agreement with OECD 427 guidelines.	
	Metric 13:	husbandry conditions 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 As	sessment 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: Metric 16:	Consistency of outcome assessment Sampling adequacy and sensitivity	High High	Outcomes were assessed consistently between animals from each timepoint. The study adequately analyzed samples in duplicate when possible. Samples were reas- sayed when radioactivity counts were less than two times background (30.6 cpm).	
Domain 6: Confounding	g/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 un- related to exposure	Medium	The authors mentioned that no irritation was observed at the application site. Skin in- tegrity was not discussed. It was not mentioned whether measures were taken during shaving to limit abrasion.	
Domain 7: Data Presentation and Analysis					
Continued on next page					

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Study Citation: HERO ID:	Midwest Resea	rch Institute, (1983). Dermal dispo	sition of 14C-diisononyl phthalate in ra	ats, final report with cover letter.
			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 po- tentially 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 absorp- tions 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 Qua	lity Determi	nation	Uninformative	

Study Citation:	Midwest Research	Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.			
HERO ID.	1525450	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 S	System:	Male; Occluded			
Vehicle; Concentration of T hicle (percent):	est Substance in Ve-	Not Reported; Not Reported			
Mass per Surface Area on S	Skin (mg/cm2); Dose	8.2; 583			
Test Substance on Skin; (Days); Test Substance on S	Exposure Repeated kin (Comments):	Other; Not Reported; Notes: 3 days			
Time of Absorption Measured	ed; Frequency; Time	Other; Not Reported; Notes: 3 days			
Time Skin was Washed and	Method used; Radi-	Skin was not washed.; Yes			
Total Recovery (percent); De	ose Type:	93.78; Finite			
Percent Found in Skin Depo	ot after Washing and	Not Reported; Notes: Not Reported			
Percent Found in Urine : Co	mments:	0.5: Notes: Not Reported			
Percent Found in Feces : Co	mments:	0.16: Notes: Not Reported			
Percent Found in Blood/Serr	um ; Comments:	0.003; Notes: Not Reported			
Percent Found in Air ; Com	ments:	Not Reported; Notes: Not Reported			
Percent Found in Cage Wash	h; Comments:	Not Reported; Notes: Not Reported			
Percent Found in All Tape S	Strips, Excluding the	Not Reported; Notes: Not Reported			
Upper Two Strips: Total Percent Absorbed:		1			
Steady State Permeability (cm/hr); Steady State Perm (Comments); Steady State Steady State Flux (Commen meability Coefficient (Kp) Permeability Coefficient (mum Flux (ug/cm2/hr); Ma ments); Additional Commen	y Coefficient (Kp) neability Coefficient E Flux (ug/cm2/hr); nts); Maximum Per- (cm/hr); Maximum Comments); Maxi- aximum Flux (Com- tts:	Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: 0.38% measured in tissues and GI tract; Total absorbed 1.04%			
		EVALUATION			

		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 ra- diolabeled 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.
		Continued on next page	

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Study Citation: HERO ID:	Midwest Resear 1325430	ch Institute, (1983). Dermal disposition of 140	C-diisononyl phthalate in	rats, final report with cover letter.		
D .			EVALUATION			
Domain	Matric 3:	Metric Test substance purity	Rating	Comments		
	Metric 5.	Test substance purity	nıgıı	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 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 Ch	aracterization					
Domain 5. Exposure Ch	Metric 6:	Preparation and storage of test sub- stance (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: HERO ID:	Midwest Research 1325430	h Institute, (1983). Dermal disposition of 14C	-diisononyl phthalate in	rats, final report with cover letter.	
			EVALUATION		
Domain		Metric	Rating	Comments	
	Metric 10:	Number of exposure groups and con- centration 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					
Domani 4. Test Moder	Metric 11:	Test animal characteristics	Medium	Adult male Fischer 344 rats (63-66 days old) were obtained from Charles River Breed- ing Laboratories (Kingston Facility, Stoneridge, NY). Starting body weights were re- ported. 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	High	Husbandry conditions were reported and in agreement with OECD 427 guidelines.	
	Metric 13:	husbandry conditions 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 As	sessment 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: Metric 16:	Consistency of outcome assessment Sampling adequacy and sensitivity	High High	Outcomes were assessed consistently between animals from each timepoint. The study adequately analyzed samples in duplicate when possible. Samples were reas- sayed when radioactivity counts were less than two times background (30.6 cpm).	
Domain 6: Confounding	g/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 un- related to exposure	Medium	The authors mentioned that no irritation was observed at the application site. Skin in- tegrity was not discussed. It was not mentioned whether measures were taken during shaving to limit abrasion.	
Domain 7: Data Presentation and Analysis					
Continued on next page					

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Study Citation: HERO ID:	Midwest Resea	rch Institute, (1983). Dermal dispo	sition of 14C-diisononyl phthalate in ra	ts, final report with cover letter.
	1020100		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 po- tentially 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 absorp- tions 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 Qua	lity Determi	nation	Uninformative	

Study Citation:	Midwest Research	Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter.			
HERO ID.	1525450	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 S	System:	Male; Occluded			
Vehicle; Concentration of T hicle (percent):	Test Substance in Ve-	Not Reported; Not Reported			
Mass per Surface Area on S	Skin (mg/cm2); Dose	8.2; 573			
(include units (e.g., mg/kg b Test Substance on Skin;	bw))): Exposure Repeated	Other; Not Reported; Notes: 7 days			
(Days); Test Substance on S Time of Absorption Measur of Absorption Measured (Co	red; Frequency; Time omments):	Other; Not Reported; Notes: 7 days			
Time Skin was Washed and	Method used; Radi-	Skin was not washed.; Yes			
olabel Presence: Total Recovery (percent); D	ose Type:	96.55; Finite			
Percent Found in Skin Dep	ot after Washing and	Not Reported; Notes: Not Reported			
Tape Stripping:					
Percent Found in Urine ; Co	omments:	1.11; Notes: Not Reported			
Percent Found in Feces ; Co	omments:	0.91; Notes: Not Reported			
Percent Found in Blood/Ser	um ; Comments:	0.003; Notes: Not Reported			
Percent Found in Air ; Com	ments:	Not Reported; Notes: Not Reported			
Percent Found in Cage Wasl	h; Comments:	Not Reported; Notes: Not Reported			
Percent Found in All Tape S	Strips, Excluding the	Not Reported; Notes: Not Reported			
Upper Two Strips: Total Percent Absorbed:		2			
Steady State Permeability	v Coefficient (Kn)	2 Nat Reported: Nates: Nat Reported: Nat Reported: Nates: Nat Reported: Nat Reported: Nat Reported: Nat Reported:			
(cm/hr): Steady State Pern	neability Coefficient	Not Reported, Notes: Not Reported, Not Repor			
(Comments); Steady State Flux (ug/cm2/hr);					
Steady State Flux (Comme	nts); Maximum Per-				
meability Coefficient (Kp) (cm/hr); Maximum					
Permeability Coefficient (Comments); Maxi-				
ments); Additional Commer	nts:				
		EVALUATION			

		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 ra- diolabeled 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 Cluston: HERO D: Midwest Research Institute, (1983). Dernal disposition of 14C diisononyl phthablar in rats, final report with cover letter. BERO D: Kikwest Research Institute, (1983). Dernal disposition of 14C diisononyl phthablar in rats, final report with cover letter. Bornain Ketric 4: 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 uase animals were selected at random for each test group; however, the random for use test group; however, the random for each test gr	continued from previous page					
IFVALUATION Domain 1 Metric 2 Rating to the start of the	Study Citation: HERO ID:	Midwest Resea 1325430	rch Institute, (1983). Dermal disposition of 14C	-diisononyl phthalate ir	n rats, final report with cover letter.	
Domain 1: Netric 3: Test subsame purity High The purity was reported to be 77-88, determined by TLC. Domain 2: Test subsame purity High The purity was reported to be 77-88, determined by TLC. Domain 2: Test subsame purity High The purity was reported to be 77-88, determined by TLC. Domain 2: Test subsame purity High The purity was reported to be 77-88, determined by TLC. Domain 2: Test subsame purity High The purity was reported to be 77-88, determined by TLC. Domain 2: Test subsame purity High The purity was reported to be 77-88, determined by TLC. Domain 3: Exposure Characterization Metric 5: Standards for Tests Low The study states animals were selected at motion for each test group; however, the metrid was not reported whether the state the area of skin, parrovinned 2: Most state the area of skin, parrovinned 2: Most state the area of skin, parrovinned 2: Most state the state of skin state the state state of skin state the state of skin state the state state area of skin, parrovinned 2: Most state the state state of skin state state of skin state state state of skin state state state of skin state state state state of skin state state state of skin state state skin skin state the state state state state state stat	Demein		M	EVALUATION	Commente	
Domain 2: Test Design Near Section of animals Medium Metric 4: Randonized allocation of animals Medium Metric 5: Standards for Tests Low The study states animals were selected an conducted according to any specified publichnes. The percent revery was accordinated according to any specified publichnes. The heads of the new vers shared shortly before treatment ispecifie (inting no specified). This is not enable of animals with DLGD publichnes with study the area of skin should be cipped approximately 24 hours prior to doing. It was not specified whether area was staken to minimize abrassism, and it was not repetide whether hear awas wipped with wess second with a skin should was used. Specifically, the area of skin should be state and skin should be state of animals. These there is the component of the any test abstrates was applied to hear the state and skin should be second to be skin o minimals. These there is the component of the skin or summary state of think is specifically, the ageingtical on the skin of animals. The should be state of animals. The should be state of animals. The should be state of animals were not accounted to the state of animals. The should be state of animals were not accounted to the state of animals. The should be state of animals were not accounted to the state of animals. The should be state of animals were not accounted to the should be state of animals. The should be state of animals were not accounted to the should be and the should be state of animals. The should be state of animals were not accounted to the should be and the should be should be an and the should be shoul	Domain	Metric 3:	Metric Test substance purity	High	Comments The purity was reported to be 97-98% determined by TLC	
Domain 2: Test Design Metric 4: Randomized allocation of animals Medium The truty states animals were selected at random for each test group, however, the method of randomization was not specified. Metric 5: Standards for Tests Law This in vivo rady was accorable (100-/108) and consistent with correct guidelines. The heack of the rans were selected at random for each test group, however, the and the ear of skin should be elipped approximately 24 hours prior to bosing. It was not specified with the area of skin should be elipped approximately 24 hours prior to bosing. It was not specified with the area of skin should be elipped approximately 24 hours prior to the sit substance was wiped with accord only for many the label compound in effect. It is subcleave shear and only for many prior the sit subcleave sheares should be elipped approximately and the sit subcleave sheares of the prior test substance was wiped in the sit should be elipped approximately		Methe 5.	Test substance purity	Ingn	The purity was reported to be 77-96%, determined by The.	
Metric 5:Standards for TestsLowThe reverting you wand you w	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	
Domain 3: Exposure Characterization Metric 6: Preparation and storage of test substance (chemical) Metric 6: Preparation and storage of test substance (chemical) 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. Elsewhere, it was indicate of the animal. Compound of the study applied 0.1 ml of the test substance on the back of the animal. Elsewhere, it was indicated that the test substance was applied to 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 gov; this study applied 3.3uL/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; and this could be acleulated. 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 of u.s. No skin washes were conducted and this study used durations of u.s. No skin washes were conducted and this study used durations of u.s. No skin washes were conducted and this study used durations of u.s. No skin washes were conducted and this study used durations of u.s. No skin washes were conducted and this soupports of uses or support of the skin were supports on the support of the skin were animal weighing 158g which was likely appropriate.		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 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.	
Metric 6: Preparation and storage of test sub- stance (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. concen- tration 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 indi- cated that the test substance was applied to the skin of animals. Elsewhere, it was indi- cated that the test substance was applied to the skin of animals. Elsewhere, it was indi- cated that the test substance was applied to the skin of animals. Elsewhere, it was indi- cated that the test substance was applied to the skin of animals. Elsewhere, it was indi- cated that the test substance was applied to the skin of animals. Elsewhere, it was indi- cated that the test substance was applied to the skin of animals. Elsewhere, it was indi- cated that the test substance on the back of the animal. OECD guidelines specify an optimal application of up to 10u/cm2 for an animal that is 200-250 g bw; this study applied 3.3u1/cm2 in an animal weighing 158g which was likely appropriate. Metric 8: Reporting of concentrations Medium The study reported doses in mJ/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 were relevant to conditions of use. No skin washes were conducted and this study also did not continue measurements post-exposure	Domain 3: Exposure Ch	aracterization				
Metric 7:Consistency of exposure administrationMediumOnly 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 concentrationsMediumThe 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 durationLowTypical 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 ab- sorption from test material retained in the skin.	Domain 5. Exposure Ch	Metric 6:	Preparation and storage of test sub- stance (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 8:Reporting of concentrationsMediumThe 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 durationLowTypical 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 ab- sorption from test material retained in the skin.		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 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.		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: HERO ID:	Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter. 1325430						
EVALUATION							
Domain		Metric	Rating	Comments			
	Metric 10:	Number of exposure groups and con- centration 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: Tast Madal							
Domain 4. Test Moder	Metric 11:	Test animal characteristics	Medium	Adult male Fischer 344 rats (63-66 days old) were obtained from Charles River Breed- ing Laboratories (Kingston Facility, Stoneridge, NY). Starting body weights were re- ported. 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	High	Husbandry conditions were reported and in agreement with OECD 427 guidelines.			
	Metric 13:	husbandry conditions 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 As	sessment 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 mas 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: Metric 16:	Consistency of outcome assessment Sampling adequacy and sensitivity	High High	Outcomes were assessed consistently between animals from each timepoint. The study adequately analyzed samples in duplicate when possible. Samples were reas- sayed when radioactivity counts were less than two times background (30.6 cpm).			
Domain 6: Confounding	g/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 un- related to exposure	Medium	The authors mentioned that no irritation was observed at the application site. Skin in- tegrity 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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Study Citation: HERO ID:	Midwest Research Institute, (1983). Dermal disposition of 14C-diisononyl phthalate in rats, final report with cover letter. 1325430					
	1020100		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 po- tentially 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 absorp- tions 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 Uni			Uninformative			