United States
Environmental Protection Agency

April 2026
Office of Chemical Safety and
Pollution Prevention

Data Quality Evaluation Information for Dermal Absorption for 1,2-Dichloroethane

Systematic Review Support Document for the Risk Evaluation

CASRN: 107-06-2

April 2026

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 1,2-Dichloroethane* 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 1,2-Dichloroethane*.

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 specific experimental designs) is evaluated independently within a given reference. Therefore, each reference may have more than one overall quality determination (OQD) to more appropriately reflect the quality of each condition. No OQD is determined for each reference as a whole if it contains data from more than one condition. A single reference may evaluate only a limited number of conditions (*e.g.*, use of only the neat compound). If all other methods and results are adequate, the study may be considered acceptable for certain conditions of use. However, the study may still be limited for use in the risk evaluation because it may not address other uses (*e.g.*, lower concentrations, certain solvents/diluents). Within the contents of this document, 1,2-dichloroethane may be referred to as the acronyms 1,2-DCA and 1,2-DCE. The acronyms 1,2-DCA, 1,2-DCE, and DCE refer to the chemical 1,2-dichloroethane. The acronyms 1,1,2-TCE, 1,1,2-TCA, and TCE refer to the chemical 1,1,2-trichloroethane. The acronym trans-1,2-DCE refers to the chemical trans-1,2-dichloroethylene. The acronym 1,2-DCP refers to the chemical 1,2-dichloropropane.

Table of Contents

Study Citation: DuPont Haskell Lab, (2005). Ethylene dichloride: In vitro dermal absorption rate testing.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 7490381
Unique ID: Infinite dosing

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled 1,2-dichloroethane and radiolabeled 1,2-14C EDC, CAS number: 107-06-2; the structure was reported for the radiolabeled substance noting the location of the radiolabel within the substance.
	Metric 2:	Test substance source	High	The non-radiolabeled, high-grade technical EDC was sourced from Occidental Chemical Corporation; the radiolabeled EDC was sourced from Perkin-Elmer Life Sciences. The study included certificates of analyses that included lot/batch numbers and verification by GC.
	Metric 3:	Test substance purity	High	The radiochemical purity of the radiolabeled test substance was 98.1% by HPLC; when mixed with technical EDC, radiochemical purity was $>$ 98%;. The purity of the non-radiolabeled substance was 99.94%. Impurity analysis was done via GC.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No reference compound was used and no history of test performance in the laboratory was reported.
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428 and OECD 28. The assay procedures specified in the report were described in detail, although some information was missing. After a 15 min equilibration period, an infinite dose of EDC (1,235 mg/cm2) (based on a dose volume of 1200 uL/cm2 and a density of 1.2351g/mL) was applied to human skin (6 replicates; surface area of 0.64 cm2, epidermal layer only, thickness ranged from 50 to 98 um) in a static diffusion cell model under occluded conditions (rubber stopper) for 8 hours. The specific activity of the applied substance was 0.02686uCi/mg. Receptor fluid (0.9% saline fortified with 6% polyethoxyoleate; 5 mL volume) was maintained at 32 degrees C; humidity was not reported. It was not specified whether the fluid was continuously stirred as per OECD 428 guidelines. Receptor fluid samples (50ul aliquots) were collected at 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hours post-application and analyzed for radioactivity. A steady state was reached. Tape stripping was not conducted, but this can be difficult with epidermal membranes. Radioactivity was measured in receptor fluid aliquots, in the excess dose removed at the end of exposure, in the stopper extract, the skin wash/rinse, the skin post-washing, and in the donor chamber rinse. The time and number of scintillation counts were reported. The scintillation time was 10 minutes for one sample and 5 minutes for all other samples, which the study authors deemed adequate. "The limit of detection (LOD) for the analysis of each sample was taken as twice the background disintegration rate obtained from the analysis of appropriate blank samples. "

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Chemical: 1,2-Dichloroethane
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Domain	Metric		Rating	Comments
	Metric 6:	Standards for tests	Medium	The appropriate tests for quality control were conducted, and results were reported. The skin was allowed to equilibrate for 30 minutes before use. The integrity of the epidermal membranes was then tested prior to the start of the study via electrical impedance, and only membranes with an EI of $\geq$ 17 k´Ω were used in the study. Skin integrity was also assessed via electrical impedance at the end of the experiment. A decrease in integrity from the values measured prior to the start of the study was noted. The percent recovery of 85.9% was reported and is acceptable for volatile substances as per OECD TG 28 (100 $\pm$ 20%). However, recovery determination is not generally relevant for studies only determining a Kp. Coefficients of variation (CV) values were not reported but could be determined based on the SD relative to the mean. Except for data reporting total recovery, the CVs were all $>$ 25%. Further discussion of the CVs is provided in Metric 19.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Information on preparation and storage was not thoroughly reported. The non-radiolabeled test substance was spiked with the radiolabeled test substance. The homogeneity and amount of radiolabeled EDC in the formulation was determined by radioanalysis via liquid scintillation counting. The concentration of EDC in the prepared solution was taken at its density, 1.2351 g/mL, and the homogeneity analysis was used to calculate the specific activity of the formulation. No further dilutions or use of a vehicle were described. No information on storage was provided, but it was indicated at the beginning of the report that the test substance was stable under the conditions of the study. The solubility of the test substance in the receptor fluid was tested, (9,690 ug/mL) and was appropriate. The authors also took measures during exposure to account for the volatility of the test substance (use of occluded conditions and a carbon trap (for short-term exposures reported in a separate form).
	Metric 8:	Consistency of exposure administration	Low	The study used the same volume (1,200 uL/cm2) across all samples and the skin surface area of 0.64 cm2 was consistent. However, the skin thickness was reported as a range (50 to 98 uM). It is unclear of the variation in thicknesses was consistent across groups, and this may have contributed to some of the endpoint variations (and subsequently high CVs) observed.
	Metric 9:	Reporting of concentrations	High	The target rate was 1,200 uL/cm2. For infinite dose experiments concentrations of 100 uL/cm2 or greater are appropriate as per OECD 28. “The actual dose applied to each replicate was determined by subjecting aliquots of the prepared solution to liquid scintillation counting. The total amount of EDC applied to the skin was determined by the total radioactivity applied and the verified specific activity.” The verified specific activity for the prepared solution was 0.02686 uCi/mg, and the concentration in the applied formulation was taken at its density (1,235,1000 ug/cm3).” With the information provided, the actual applied concentration in mg/cm2 can be calculated.
	Metric 10:	Exposure frequency	High	Exposure duration was reported and appropriate for Kp determination, an 8-hour exposure was used and a steady state was reached. The shorter duration was appropriate for a volatile test substance.

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 7490381
Unique ID: Infinite dosing

Domain	Metric		Rating	Comments
	Metric 11:	Number of exposure groups and concentration spacing	Low	Fewer than three concentrations were tested. This study only tested one concentration.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	The test model and descriptive information were reported. Samples of full thickness human cadaver skin were sourced from the National Disease Research Interchange. Abdominal skin samples from 3 Caucasian females were used. The samples were stored frozen at -20 degrees C. It was noted that the samples were removed from the donors within 24 hours of death, and were used within three months. Prior to use, the skin samples were thawed, soaked in water, and the epidermal layer was isolated then stored refrigerated (max duration not specified) until use. The thickness ranged from 50 to 98 uM. The OECD TG 156 specifies that use of epidermal membrane may, in some cases, overestimate human in vivo skin absorption due to the lack of a sufficient barrier function and split thickness (dermatomed) skin is preferred.
	Metric 13:	Number/Replicates per group	Medium	The study used 6 replicates (from 3 donors). The number of replicates was appropriate as per OECD 428.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28; FR volume 69, number 80; and European Commission Guidance Document on Dermal Absorption. Measurement techniques and timing were reported and appropriate. An infinite dose of the test substance was used to determine the Kp. A dose volume of 1200 uL/cm2 was used.
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assess consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period was consistent across replicates.
	Metric 16:	Sampling adequacy and sensitivity	High	The study reported adequate sampling for the outcomes of interest; measurement sensitivity was sufficient. The sampling intervals were adequate to allow at least 4 data points at a steady state. The time and number of scintillation counts were reported for one of the receptor fluid samples, 10 minutes (160,000 disintegration counts). The other samples were counted for 5 minutes, which the authors deemed adequate. Analysis of a mock dose showed an appropriate signal-to-noise ratio.
Domain 6: Confounding/Variable Control				

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 7490381
Unique ID: Infinite dosing

Domain	Metric		Rating	Comments
	Metric 17:	Confounding variables in test design and procedures	Medium	There were no differences reported among study groups (test substance lot, number of skin samples, or quality of tissues) that could influence the outcome assessment. Skin integrity was confirmed by EI and only membranes with an EI of $\geq$ 17 kΩ were retained for use in the study. The study did indicate that, relative to pre-exposure EI results, there was a decrease in EI after exposure (the ratio of post-EI values to pre-EI values was 0.59). The study authors indicated that the decrease did not affect the results of the experiment. Scintillation counts were done for 5 minutes for most samples. The authors indicated that this deviated from the protocol, but that it had no impact on the interpretation of the study results.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	The Kp was determined by first plotting the cumulative amount of ug equivalents in the receptor compartment at each serial collection time-point, adjusted for total receptor fluid volume, against time (hrs) to produce an absorption profile. The Kp was then calculated by dividing the penetration rate or slope of the line at steady-state, by the concentration of the applied chemical. The total recovery was determined and was the sum of the amount extracted from the rubber stopper, and what was detected in the receptor fluid, in skin washes, in the donor chamber, and in the skin. The permeability coefficient (Kp) was 9.69 x 10-4 $\pm$ 2.84 x 10-4 (Mean $\pm$ SD). The CV is >25%. The CVs were also >25% for the cumulative amount penetrated (at each collection time point) and the steady-state penetration rate. CVs are >25% for individual scenarios, however data are available for EPA to calculate an alternate (upper end) value to account for variability in the results. When the CV is > 25%, one recommendation within OECD 156 is to use a value higher than the mean absorption value, such as the 95th percent upper confidence limit.
	Metric 20:	Data interpretation	High	The Kp was derived from an appropriate exposure condition (infinite dose). Recovery determination is not relevant for infinite dose applications; however, the authors still reported total recovery, which fell within guideline specifications for a volatile test material (100% $\pm$ 20%)
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means $\pm$ SE.

Overall Quality Determination Medium

Study Citation:	DuPont Haskell Lab, (2005). Ethylene dichloride: In vitro dermal absorption rate testing.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	7490381
Unique ID:	Finite dosing - 10 min

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled 1,2-dichloroethane and radiolabeled 1,2-14C EDC, CAS number: 107-06-2; the structure was reported for the radiolabeled substance noting the location of the radiolabel within the substance.
	Metric 2:	Test substance source	High	The non-radiolabeled, high-grade technical EDC was sourced from Occidental Chemical Corporation; the radiolabeled EDC was sourced from Perkin-Elmer Life Sciences. The study included certificates of analyses that included lot/batch numbers and verification by GC.
	Metric 3:	Test substance purity	High	The radiochemical purity of the radiolabeled test substance was 98.1% by HPLC; when mixed with technical EDC, radiochemical purity was $>$ 98%;. The purity of the non-radiolabeled substance was 99.94%. Impurity analysis was done via GC.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No reference compound was used and no history of test performance in the laboratory was reported.
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428 and OECD 28. The assay procedures specified in the report were described in detail, although some information was missing. After a 15 min equilibration period, a finite dose of EDC (12.35 mg/cm2) (based on a dose volume of 10 uL/cm2 and a density of 1.2351g/mL) was applied to human skin (12 replicates; surface area of 0.64 cm2, epidermal layer only, thickness ranged from 50 to 98 um) in a static diffusion cell model under occluded conditions (charcoal trap). Absorption rates and recovery data were collected 10 minutes (6 replicates) and 60 minutes (6 replicates) post-dosing. During exposure, the receptor fluid (0.9% saline fortified with 6% polyethoxyoleate; 5 mL volume) was maintained at 32 degrees C; humidity was not reported. It was not specified whether the fluid was continuously stirred as per OECD 428 guidelines. Tape stripping was not conducted, but this can be difficult with epidermal membranes. Radioactivity was measured in receptor fluid aliquots, the skin wash/rinse, the skin post-washing, the donor chamber, and in the charcoal trap extraction. The time and number of scintillation counts were reported. The scintillation times (5 or 10 minutes) and counts were reported. "The limit of detection (LOD) for the analysis of each sample was taken as twice the background disintegration rate obtained from the analysis of appropriate blank samples."
	Metric 6:	Standards for tests	Medium	The appropriate tests for quality control were conducted, and results were reported. The skin was allowed to equilibrate for 30 minutes before use. The integrity of the epidermal membranes was then tested prior to the start of the study via electrical impedance, and only membranes with an EI of $\geq$ 17 k´Ω were used in the study. Skin integrity was also assessed via electrical impedance at the end of the experiment and the ratios of the post-EI values to pre-EI values were 0.73 and 0.92 for the 10 min and 60 min exposures, respectively. The percent recoveries were 80.3% and 86.4%, for the 10 min and 60 min groups, respectively, and were acceptable for volatile substances as per OECD TG 28 (100 $\pm$ 20%). Coefficients of variation (CV) values were not reported but could be determined based on the SD relative to the mean. For all endpoints (except total recovery), the CVs were $>$ 25%. Further discussion of the CVs is provided in Metric 19.

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Study Citation: DuPont Haskell Lab, (2005). Ethylene dichloride: In vitro dermal absorption rate testing.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 7490381
Unique ID: Finite dosing - 10 min

Domain	Metric		Rating	Comments
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Information on preparation and storage was not thoroughly reported. The non-radiolabeled test substance was spiked with the radiolabeled test substance. The homogeneity and amount of radiolabeled EDC in the formulation were determined by radioanalysis via liquid scintillation counting. The concentration of EDC in the prepared solution was taken at its density, 1.2351 g/mL, and the homogeneity analysis was used to calculate the specific activity of the formulation. No further dilutions or use of other vehicles were described. No information on storage was provided, but it was indicated at the beginning of the report that the test substance was stable under the conditions of the study. The solubility of the test substance in the receptor fluid was tested, (9,690 ug/mL) and was appropriate. The authors also took measures during exposure to account for the volatility of the test substance (use of occluded conditions and a carbon trap for short-term exposures).
	Metric 8:	Consistency of exposure administration	Low	The study used the same volume (10 uL/cm2) across all samples and the skin surface area of 0.64 cm2 was consistent. However, the skin thickness was reported as a range (50 to 98 uM). It is unclear if the variation in thicknesses was consistent across groups, and this may have contributed to some of the endpoint variations (and subsequently high CVs) observed.
	Metric 9:	Reporting of concentrations	High	The target rate was 10 uL/cm2, which for a finite dose experiment is consistent with OECD TG 28 recommendations. “The actual dose applied to each replicate was determined by subjecting aliquots of the prepared solution to liquid scintillation counting. The total amount of EDC applied to the skin was determined by the total radioactivity applied and the verified specific activity.” The verified specific activity for the prepared solution was 0.02686 uCi/mg, and the concentration in the applied formulation was taken at its density (1,235,1000 ug/cm3).” With the information provided, the actual applied concentration in mg/cm2 can be calculated.
	Metric 10:	Exposure frequency	High	The study authors specifically wanted to determine short-term absorption rates, therefore the durations (10 and 60 min) were appropriate based on the purposes of the study.
	Metric 11:	Number of exposure groups and concentration spacing	Low	Fewer than three concentrations were tested. This study only tested one concentration.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	The test model and descriptive information were reported. Samples of full thickness human cadaver skin were sourced from the National Disease Research Interchange. Abdominal skin samples from 3 Caucasian females were used. The samples were stored frozen at -20 degrees C. It was noted that the samples were removed from the donors within 24 hours of death, and were used within three months. Prior to use, the skin samples were thawed, soaked in water, and the epidermal layer was isolated then stored refrigerated (max duration not specified) until use. The thickness ranged from 50 to 98 uM. The OECD TG 156 specifies that use of epidermal membrane may, in some cases, overestimate human in vivo skin absorption due to the lack of a sufficient barrier function and split thickness (dermatomed) skin is preferred.

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 7490381
Unique ID: Finite dosing - 10 min

Domain	Metric		Rating	Comments
	Metric 13:	Number/Replicates per group	Medium	The study used 12 replicates in total (4 samples x 3 donors). At each time point, 6 replicates (2 replicates per donor) were examined. The number of replicates was appropriate (>4 as per OECD 428)
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28; FR volume 69, number 80; and European Commission Guidance Document on Dermal Absorption. Measurement techniques and timing were reported and appropriate for the purposes of the study. A finite dose of the test substance was used to determine short-term maximum absorption rates. A dose volume of 10 uL/cm2 was used.
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assess consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period was consistent across replicates.
	Metric 16:	Sampling adequacy and sensitivity	High	The study reported adequate sampling for the outcomes of interest; measurement sensitivity was sufficient. The time and number of scintillation counts were reported. Analysis of a mock dose showed an appropriate signal-to-noise ratio.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	There were no differences reported among study groups (test substance lot, number of skin samples, or quality of tissues) that could influence the outcome assessment. Skin integrity was confirmed by EI and only membranes with an EI of $\geq$ 17 kΩ were retained for use in the study. Scintillation counts were done for 5 minutes for most samples. The authors indicated that this deviated from the protocol, but that it had no impact on the interpretation of the study results.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	The short-term absorption rates were calculated by dividing the sum of the ug equivalents in the receptor fluid by the skin area and exposure time. The total recovery was determined and was the sum of the amount extracted from the charcoal trap, and what was detected in the receptor fluid, in skin washes, in the donor chamber, and in the skin. The coefficients of variation were all >25%, however data are available for EPA to calculate an alternate (upper end) value to account for variability in the results. When the CV is $>$ 25%, one recommendation within OECD 156 is to use a value higher than the mean absorption value, such as the 95th percent upper confidence limit.
	Metric 20:	Data interpretation	High	Short-term maximum absorption rates were derived from appropriate exposure conditions (finite dose). Recovery of the applied test substance was adequate and fell within guideline specifications for a volatile test material (100% $\pm$ 20%)
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means $\pm$ SE.

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Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	7490381
Unique ID:	Finite dosing - 10 min

Domain	Metric	Rating	Comments
Overall Quality Determination		**Medium**	

Study Citation:	DuPont Haskell Lab, (2005). Ethylene dichloride: In vitro dermal absorption rate testing.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	7490381
Unique ID:	Finite dosing - 60 min

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled 1,2-dichloroethane and radiolabeled 1,2-14C EDC, CAS number: 107-06-2; the structure was reported for the radiolabeled substance noting the location of the radiolabel within the substance.
	Metric 2:	Test substance source	High	The non-radiolabeled, high-grade technical EDC was sourced from Occidental Chemical Corporation; the radiolabeled EDC was sourced from Perkin-Elmer Life Sciences. The study included certificates of analyses that included lot/batch numbers and verification by GC.
	Metric 3:	Test substance purity	High	The radiochemical purity of the radiolabeled test substance was 98.1% by HPLC; when mixed with technical EDC, radiochemical purity was $>$ 98%;. The purity of the non-radiolabeled substance was 99.94%. Impurity analysis was done via GC.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No reference compound was used and no history of test performance in the laboratory was reported.
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428 and OECD 28. The assay procedures specified in the report were described in detail, although some information was missing. After a 15 min equilibration period, a finite dose of EDC (12.35 mg/cm2) (based on a dose volume of 10 uL/cm2 and a density of 1.2351g/mL) was applied to human skin (12 replicates; surface area of 0.64 cm2, epidermal layer only, thickness ranged from 50 to 98 um) in a static diffusion cell model under occluded conditions (charcoal trap). Absorption rates and recovery data were collected 10 minutes (6 replicates) and 60 minutes (6 replicates) post-dosing. During exposure, the receptor fluid (0.9% saline fortified with 6% polyethoxyoleate; 5 mL volume) was maintained at 32 degrees C; humidity was not reported. It was not specified whether the fluid was continuously stirred as per OECD 428 guidelines. Tape stripping was not conducted, but this can be difficult with epidermal membranes. Radioactivity was measured in receptor fluid aliquots, the skin wash/rinse, the skin post-washing, the donor chamber, and in the charcoal trap extraction. The time and number of scintillation counts were reported. The scintillation times (5 or 10 minutes) and counts were reported. "The limit of detection (LOD) for the analysis of each sample was taken as twice the background disintegration rate obtained from the analysis of appropriate blank samples."
	Metric 6:	Standards for tests	Medium	The appropriate tests for quality control were conducted, and results were reported. The skin was allowed to equilibrate for 30 minutes before use. The integrity of the epidermal membranes was then tested prior to the start of the study via electrical impedance, and only membranes with an EI of $\geq$ 17 k´Ω were used in the study. Skin integrity was also assessed via electrical impedance at the end of the experiment and the ratios of the post-EI values to pre-EI values were 0.73 and 0.92 for the 10 min and 60 min exposures, respectively. The percent recoveries were 80.3% and 86.4%, for the 10 min and 60 min groups, respectively, and were acceptable for volatile substances as per OECD TG 28 (100 $\pm$ 20%). Coefficients of variation (CV) values were not reported but could be determined based on the SD relative to the mean. For all endpoints (except total recovery), the CVs were $>$ 25%. Further discussion of the CVs is provided in Metric 19.

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 7490381
Unique ID: Finite dosing - 60 min

Domain	Metric		Rating	Comments
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Information on preparation and storage was not thoroughly reported. The non-radiolabeled test substance was spiked with the radiolabeled test substance. The homogeneity and amount of radiolabeled EDC in the formulation were determined by radioanalysis via liquid scintillation counting. The concentration of EDC in the prepared solution was taken at its density, 1.2351 g/mL, and the homogeneity analysis was used to calculate the specific activity of the formulation. No further dilutions or use of other vehicles were described. No information on storage was provided, but it was indicated at the beginning of the report that the test substance was stable under the conditions of the study. The solubility of the test substance in the receptor fluid was tested, (9,690 ug/mL) and was appropriate. The authors also took measures during exposure to account for the volatility of the test substance (use of occluded conditions and a carbon trap for short-term exposures).
	Metric 8:	Consistency of exposure administration	Low	The study used the same volume (10 uL/cm2) across all samples and the skin surface area of 0.64 cm2 was consistent. However, the skin thickness was reported as a range (50 to 98 uM). It is unclear if the variation in thicknesses was consistent across groups, and this may have contributed to some of the endpoint variations (and subsequently high CVs) observed.
	Metric 9:	Reporting of concentrations	High	The target rate was 10 uL/cm2, which for a finite dose experiment is consistent with OECD TG 28 recommendations. “The actual dose applied to each replicate was determined by subjecting aliquots of the prepared solution to liquid scintillation counting. The total amount of EDC applied to the skin was determined by the total radioactivity applied and the verified specific activity.” The verified specific activity for the prepared solution was 0.02686 uCi/mg, and the concentration in the applied formulation was taken at its density (1,235,1000 ug/cm3).” With the information provided, the actual applied concentration in mg/cm2 can be calculated.
	Metric 10:	Exposure frequency	High	The study authors specifically wanted to determine short-term absorption rates, therefore the durations (10 and 60 min) were appropriate based on the purposes of the study.
	Metric 11:	Number of exposure groups and concentration spacing	Low	Fewer than three concentrations were tested. This study only tested one concentration.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	The test model and descriptive information were reported. Samples of full thickness human cadaver skin were sourced from the National Disease Research Interchange. Abdominal skin samples from 3 Caucasian females were used. The samples were stored frozen at -20 degrees C. It was noted that the samples were removed from the donors within 24 hours of death, and were used within three months. Prior to use, the skin samples were thawed, soaked in water, and the epidermal layer was isolated then stored refrigerated (max duration not specified) until use. The thickness ranged from 50 to 98 uM. The OECD TG 156 specifies that use of epidermal membrane may, in some cases, overestimate human in vivo skin absorption due to the lack of a sufficient barrier function and split thickness (dermatomed) skin is preferred.

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 7490381
Unique ID: Finite dosing - 60 min

Domain	Metric		Rating	Comments
	Metric 13:	Number/Replicates per group	Medium	The study used 12 replicates in total (4 samples x 3 donors). At each time point, 6 replicates (2 replicates per donor) were examined. The number of replicates was appropriate (>4 as per OECD 428)
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28; FR volume 69, number 80; and European Commission Guidance Document on Dermal Absorption. Measurement techniques and timing were reported and appropriate for the purposes of the study. A finite dose of the test substance was used to determine short-term maximum absorption rates. A dose volume of 10 uL/cm2 was used.
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assess consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period was consistent across replicates.
	Metric 16:	Sampling adequacy and sensitivity	High	The study reported adequate sampling for the outcomes of interest; measurement sensitivity was sufficient. The time and number of scintillation counts were reported. Analysis of a mock dose showed an appropriate signal-to-noise ratio.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	There were no differences reported among study groups (test substance lot, number of skin samples, or quality of tissues) that could influence the outcome assessment. Skin integrity was confirmed by EI and only membranes with an EI of $\geq$ 17 kΩ were retained for use in the study. Scintillation counts were done for 5 minutes for most samples. The authors indicated that this deviated from the protocol, but that it had no impact on the interpretation of the study results.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	The short-term absorption rates were calculated by dividing the sum of the ug equivalents in the receptor fluid by the skin area and exposure time. The total recovery was determined and was the sum of the amount extracted from the charcoal trap, and what was detected in the receptor fluid, in skin washes, in the donor chamber, and in the skin. The coefficients of variation were all >25%, however data are available for EPA to calculate an alternate (upper end) value to account for variability in the results. When the CV is $>$ 25%, one recommendation within OECD 156 is to use a value higher than the mean absorption value, such as the 95th percent upper confidence limit.
	Metric 20:	Data interpretation	High	Short-term maximum absorption rates were derived from appropriate exposure conditions (finite dose). Recovery of the applied test substance was adequate and fell within guideline specifications for a volatile test material (100% $\pm$ 20%)
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means $\pm$ SE.

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Study Citation:	DuPont Haskell Lab, (2005). Ethylene dichloride: In vitro dermal absorption rate testing.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	7490381
Unique ID:	Finite dosing - 60 min

Domain	Metric	Rating	Comments
Overall Quality Determination		**Medium**	

Study Citation: Frasch, H. F., Barbero, A. M. (2009). A paired comparison between human skin and hairless guinea pig skin in vitro permeability and lag time measurements for 6 industrial chemicals. Cutaneous and Ocular Toxicology 28(3):107-113.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 734137
Unique ID: Permeability coefficient (kp) in human skin

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified as 1,2-dichloroethane with CAS No. 107-06-2.
	Metric 2:	Test substance source	High	The source of the test substance was Sigma-Aldrich (St. Louis, MO, USA). Lot or batch number were not provided, but not required for a rating of high.
	Metric 3:	Test substance purity	High	The purity of the test substance was reported to be ≥99.8%.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	A concurrent reference compound was not tested along with the test substance. The study also tested and report data for 5 other chemical (aniline, benzene, diethyl phthalate, naphthalene, and tetrachloroethylene); however, these are not considered reference compounds.
	Metric 5:	Assay procedures	Low	The assay procedure was partially described. The study used a vertical static diffusion set up. The temperature of the skin surface was maintained at 32oC; humidity was not reported. The donor compartment was filled with 0.5 ml of saturated donor solution, the receptor compartment was filled with 5 ml of warmed HEPES-buffered Hanks' balanced salt solution. The study did not report if the receptor compartment fluid was stirred constantly (OECD guidelines recommends constant stirring of receptor fluid). The exposed skin surface area was 9mm. The donor compartment was covered with parafilm, donor solutions were replaced periodically to maintain "infinite" dose conditions. The integrity of the skin was verified under a dissecting microscope before testing for obvious holes, but not by any other means (i.e. electrical resistance, penetration with tritiated water, or checking g for trans-epidermal water loss).
	Metric 6:	Standards for tests	Low	Human skin was obtained from breast reduction or panniculectomies and stored at -85oC the day of surgery. The skin was used for these tests within 191 days. According to OECD Guidance No 28, skin should not be stored at -80oC because it can enhance permeability. The skin should be tested for integrity by either 1) checking electrical resistance; 2) checking trans-epidermal water loss is in normal range; or 3) measure penetration characteristics of a reference material (e.g. tritiated water). None of the three suggestions were done in this study. The study used a dissecting microscope to visually inspect the skin for obvious defects (holes). The coefficient of variance for permeability (kp) was 27%.
Domain 3: Exposure Characterization				

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Study Citation: Frasch, H. F., Barbero, A. M. (2009). A paired comparison between human skin and hairless guinea pig skin in vitro permeability and lag time measurements for 6 industrial chemicals. Cutaneous and Ocular Toxicology 28(3):107-113.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 734137
Unique ID: Permeability coefficient (kp) in human skin

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of test substance is adequately reported. Saturated solutions were made by adding excess test chemical to buffer and vortexing overnight at room temperature, and then warming solution to 32oC. When added to donor cell, a small excess of chemical remained to maintain saturation. The storage conditions were not reported. It is not clear if test solutions were prepared immediately before each exposure test or if solutions were stored. Given that the test solution was a saturated solution, with small excess in donor cells, lack of storage information is unlikely to substantially impact results.
	Metric 8:	Consistency of exposure administration	Low	The diameter of skin studied was consistent (9mm) and volume of donor and receptor compartments were consistent. The study did not report the thickness of the skin. It states the epidermis was teased from the dermis using cotton swabs but does not report the thickness. Therefore, it is not known how identical each of the samples were. Permeability and lag time are reported with variance. Coefficient of variation was 27% for permeability and 42% for lag time suggesting substantial variation between donors. It is difficult to know if this is due to human donor variability or lack of consistency in preparation of skin samples.
	Metric 9:	Reporting of concentrations	High	The concentration in the donor solution was sampled in triplicate from each experiment and analyzed using gas chromatography. Concentration is presented with standard deviation.
	Metric 10:	Exposure frequency	High	The exposure duration of 2 hours was appropriate for outcome of interest (Kp/flux and lag time).
	Metric 11:	Number of exposure groups and concentration spacing	High	The number of exposure groups was appropriate for study design. An infinite dose was studied to determine Kp, in agreement with OECD guidelines.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Uninformative	Human skin was obtained from breast reduction or panniculectomies and stored at -85oC the day of surgery. The skin was used for these tests within 191 days. According to OECD 28, skin should not be stored at very low temperatures (with an example of -80oC) because it can enhance permeability. The skin should be tested for integrity by either 1) checking electrical resistance; 2) checking trans-epidermal water loss is in normal range; or 3) measure penetration characteristics of a reference material (e.g. tritiated water). None of the three approaches were taken in this study. The study used a dissecting microscope to visually inspect the skin for obvious defects (holes). Also, the thickness of the skin was not reported. The lack of information and verification of the skin integrity makes this study uninformative for this metric.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates/group (n=4) and replicates per donor (3) were appropriate according to OECD guidelines.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	Outcome assessment methodology was appropriate. 0.5 ml of an infinite dose was added to the donor compartment. The diameter of the exposed skin was 9mm. The area of the skin was calculated by the reviewer to be 0.63 cm2, therefore a 793 uL/cm2 of saturated solution was studied and in line with guidance.

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Study Citation: Frasch, H. F., Barbero, A. M. (2009). A paired comparison between human skin and hairless guinea pig skin in vitro permeability and lag time measurements for 6 industrial chemicals. Cutaneous and Ocular Toxicology 28(3):107-113.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 734137
Unique ID: Permeability coefficient (kp) in human skin

Domain	Metric		Rating	Comments
	Metric 15:	Consistency of outcome assessment	High	The outcome assessment was carried out consistently across study groups. 0.2 ml samples were taken from the receptor compartment at specified and consistent timepoints. Receptor volume was replaced with the same volume of buffer. Assessment of concentration in receptor fluid was analyzed consistently with gas chromatography.
	Metric 16:	Sampling adequacy and sensitivity	High	The sampling intervals were adequate (0.25, 0.5, 0.75, 1.0, 1.5, and 2.0 hours). The study reports receptor fluid concentration was less than 10% of measured saturation quantities.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Low	The study did not measure skin integrity by any an acceptable measure (checking electrical resistance; checking trans-epidermal water loss is in normal range; or measuring penetration characteristics of a reference material). The standard deviation between the 4-donor measure for permeability measurements was 27%. (0.259 +/-0.070 cm/h). From each donor, 3 skin disks were studied. The study does not provide data on the variance between the 3 disks from the same donor.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	Solubility in the receptor fluid was not demonstrated, however study does state the concentration in the receptor fluid was less than 10% of saturated concentration, therefore is in not likely to be an issue.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Statistical methods were clearly described. The study calculated Kp and lag time (τ) using a mathematical equation. The study states "Use of equation 1 is mathematically equivalent to calculating kp from the slope of the steady-state accumulation curve and τ as the intercept of this asymptote with the time axis." The CV for the overall Kp was slightly low but close to 25%; the lag time CV was 42% for human skin.
	Metric 20:	Data interpretation	High	Data were interpreted correctly. Permeability (Kp) was calculated using infinite concentration.
	Metric 21:	Reporting of data	Medium	Study reports calculated permeability (kp) and lag time but does not provide any raw data. Information on variance between donors is reported, however variance between experiments within the same donor are not reported (4 donors, 3 skin disks from each donor were tested). Data is presented as mean +/- SD of the four donors.

Overall Quality Determination Uninformative

Study Citation:	Frasch, H. F., Barbero, A. M. (2009). A paired comparison between human skin and hairless guinea pig skin in vitro permeability and lag time measurements for 6 industrial chemicals. Cutaneous and Ocular Toxicology 28(3):107-113.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	734137
Unique ID:	Permeability coefficient (kp) in hairless guinea pig skin

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified as 1,2-dichloroethane with CAS No. 107-06-2.
	Metric 2:	Test substance source	High	The source of the test substance was Sigma-Aldrich (St. Louis, MO, USA). Lot or batch number were not provided, but not required for a rating of high.
	Metric 3:	Test substance purity	High	The purity of the test substance was reported to be ≥99.8%.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	A concurrent reference compound was not tested along with the test substance. The study also tested and report data for 5 other chemical (aniline, benzene, diethyl phthalate, naphthalene, and tetrachloroethylene); however, these are not considered reference compounds.
	Metric 5:	Assay procedures	Low	The assay procedure was partially described. The study used a vertical static diffusion set up. The temperature of the skin surface was maintained at 32oC; humidity was not reported. The donor compartment was filled with 0.5 ml of saturated donor solution, the receptor compartment was filled with 5 ml of warmed HEPES-buffered Hanks' balanced salt solution. The test substance is non-polar and lipophilic, therefore there is the potential for inadequate solubility in receptor fluid. To address this the study should have added a modifier to the solution (6% polyethylene glycol 20 oleyl ether or 5% bovine serum albumin as described in OECD guidance document 28). The study did not report if the receptor compartment fluid was stirred constantly (OECD guidelines recommends constant stirring of receptor fluid). The exposed skin surface area was 9mm. The donor compartment was covered with parafilm, donor solutions were replaced periodically to maintain "infinite" dose conditions. Abdominal skin was harvested and used the same day.
	Metric 6:	Standards for tests	Low	Abdominal skin from hairless guinea pigs was harvested and used the same day. Since the skin was not stored, determining integrity by electrical resistance, trans-epidermal water loss or use of a reference material is not required. A dissecting microscope was used to visually inspect the skin for obvious defects (holes). The coefficient of variance for permeability (kp) was 32%.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of test substance is adequately reported. Saturated solutions were made by adding excess test chemical to buffer and vortexing overnight at room temperature, and then warming solution to 32oC. When added to donor cell, a small excess of chemical remained to maintain saturation. The storage conditions were not reported. It is not clear if test solutions were prepared immediately before each exposure test or if solutions were stored. Given that the test solution was a saturated solution, with small excess in donor cells, lack of storage information is unlikely to substantially impact results.

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Study Citation: Frasch, H. F., Barbero, A. M. (2009). A paired comparison between human skin and hairless guinea pig skin in vitro permeability and lag time measurements for 6 industrial chemicals. Cutaneous and Ocular Toxicology 28(3):107-113.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 734137
Unique ID: Permeability coefficient (kp) in hairless guinea pig skin

Domain	Metric		Rating	Comments
	Metric 8:	Consistency of exposure administration	Low	The diameter of skin studied was consistent (9mm) and volume of donor and receptor compartments were consistent. The study did not report the thickness of the skin. It states the epidermis was teased from the dermis using cotton swabs but does not report the thickness. Therefore, it is not known how identical each of the samples were. Permeability and lag time are reported with variance. Coefficient of variation was 32% for permeability and 67% for lag time suggesting substantial variation between donors. It is difficult to know if this is due to lack of consistency in preparation of skin samples.
	Metric 9:	Reporting of concentrations	High	The concentration in the donor solution was sampled in triplicate from each experiment and analyzed using gas chromatography. Concentration is presented with standard deviation.
	Metric 10:	Exposure frequency	High	The exposure duration of 2 hours was appropriate for outcome of interest (Kp/flux and lag time).
	Metric 11:	Number of exposure groups and concentration spacing	High	The number of exposure groups was appropriate for study design. An infinite dose was studied to determine Kp, in agreement with OECD guidelines.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	Abdominal skin from hairless guinea pigs was harvested and used the same day. Heat separated epiderma membranes were used. Skin disks were visually inspected with a dissecting microscope for obvious defects. The thickness of the skin was not reported.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates/group (n=4) and concentration studies (infinite) were appropriate according to OECD guidelines.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	Outcome assessment methodology was appropriate. 0.5 ml of an infinite dose was added to the donor compartment. The diameter of the exposed skin was 9mm. The area of the skin was calculated by the reviewer to be 0.63 cm2, therefore a 793 uL/cm2 of saturated solution was studied and in line with guidance. The timing of sampling the receptor compartment (0.25, 0.5, 0.75, 1.0, 1.5 and 2.0 hours) was appropriate.
	Metric 15:	Consistency of outcome assessment	High	The outcome assessment was carried out consistently across study groups. 0.2 ml samples were taken from the receptor compartment at specified and consistent timepoints. Receptor volume was replaced with the same volume of buffer. Assessment of concentration in receptor fluid was analyzed consistently with gas chromatography.
	Metric 16:	Sampling adequacy and sensitivity	High	The sampling intervals were adequate (0.25, 0.5, 0.75, 1.0, 1.5, and 2.0 hours). The study reports receptor fluid concentration was less than 10% of measured saturation quantities.
Domain 6: Confounding/Variable Control				

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Study Citation: Frasch, H. F., Barbero, A. M. (2009). A paired comparison between human skin and hairless guinea pig skin in vitro permeability and lag time measurements for 6 industrial chemicals. Cutaneous and Ocular Toxicology 28(3):107-113.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 734137
Unique ID: Permeability coefficient (kp) in hairless guinea pig skin

Domain	Metric		Rating	Comments
	Metric 17:	Confounding variables in test design and procedures	Low	The thickness of the skin was not reported. Although not required, since skin was used the same day as harvest, integrity was not measured. The coefficient of variation between the 4-donor permeability measurements was 32% (0.295 +/- 0.093 cm/h). From each donor, 3 skin disks were studied. The study does not provide data on the variance between the 3 disks from the same donor.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	Solubility in the receptor fluid was not demonstrated, however study does state the concentration in the receptor fluid was less than 10% of saturated concentration, therefore is in not likely to be an issue.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Statistical methods were clearly described. The study calculated Kp and lag time (τ) using a mathematical equation. The study states "Use of equation 1 is mathematically equivalent to calculating kp from the slope of the steady-state accumulation curve and τ as the intercept of this asymptote with the time axis." The CV was greater than 25% for main result - the Kp value. (Lag time CV was 66%.)
	Metric 20:	Data interpretation	High	Data were interpreted correctly. Permeability (Kp) was calculated using infinite concentration.
	Metric 21:	Reporting of data	Medium	Study reports calculated permeability (kp) and lag time but does not provide any raw data. Information on variance between donors is reported, however variance between experiments within the same donor are not reported (4 donors, 3 skin disks from each donor were tested). Data is presented as mean +/- SD of the four donors.

Overall Quality Determination Medium

Study Citation:	Frasch, H. F., Barbero, A. M., Alachkar, H., Mcdougal, J. N. (2007). Skin penetration and lag times of neat and aqueous diethyl phthalate, 1,2-dichloroethane and naphthalene. Cutaneous and Ocular Toxicology 26(2):147-160.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	1313327
Unique ID:	Aqueous from the Frasch lab

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substance was identified as 1,2-dichloroethane; CAS RN 107-06-2.
	Metric 2:	Test substance source	High	The source of the test substance was Sigma-Aldrich (St. Louis, MO, USA). Lot or batch number were not provided, but this is not required for a rating of high.
	Metric 3:	Test substance purity	High	The purity of the test substance was reported to be 99.8%.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	A concurrent reference compound was not tested along with the test substance.
	Metric 5:	Assay procedures	Medium	The assay procedure was partially described. The study used a Franz static water-jetted cell apparatus with a 9 mm diameter opening for the skin (0.636 cm2 exposure area). The temperature of the receptor compartment was maintained at 37oC, and the donor compartment at 32oC; humidity was not reported. The donor compartment was 0.5 ml of saturated solution (in a HEPES-buffered Hanks' balanced salt solution). The receptor compartment was filled with 5 ml HEPES-buffered Hanks' balanced salt solution. The test substance is non-polar and lipophilic, therefore there is the potential for inadequate solubility in receptor fluid. To address this the study should have added a modifier to the solution (6% polyethylene glycol 20 oleyl ether or 5% bovine serum albumin as described in OECD guidance document 28). The receptor compartment fluid was stirred at ~1000 rpm. The donor compartment was covered with parafilm, donor solutions were replaced periodically to maintain "infinite" dose conditions. Concentration in receptor fluid was analyzed using gas chromatography and method adequately reported. Although not explicitly stated, from methods it can be inferred harvested skin was studied the same day.
	Metric 6:	Standards for tests	Low	Harvested skin was not stored and used the same day. The integrity of the skin was not tested prior to testing (via electrical resistance, trans-epidermal water loss is in normal range, or tritiated water). The Coefficient of variation was <25%.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Saturated aqueous solutions were made fresh prior to the experiment. Excess chemical was added to HBSS buffer and vortexed for approximately 24 hours at room temperature before being centrifuged for 30 minutes at 4,000 rpms. Storage conditions of stock solution was not reported, however since excess chemical was added to buffer, any evaporation of stock solution that may have occurred is not likely to impact results.
	Metric 8:	Consistency of exposure administration	Medium	The diameter of skin studied was consistent (9mm) and volume of donor and receptor compartments were consistent. Dorsal skin dermatoned at 315 um (after the removal of underlying muscle and fat). Coefficient of variation was <25% for permeability.
	Metric 9:	Reporting of concentrations	Medium	The donor solution is a saturated solution. The study does not measure the concentration, rather uses the measured a measured solubility in buffer (5,347 ug/ml) as the assumed concentration for calculations.

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Study Citation: Frasch, H. F., Barbero, A. M., Alachkar, H., Mcdougal, J. N. (2007). Skin penetration and lag times of neat and aqueous diethyl phthalate, 1,2-dichloroethane and naphthalene. Cutaneous and Ocular Toxicology 26(2):147-160.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 1313327
Unique ID: Aqueous from the Frasch lab

Domain	Metric		Rating	Comments
	Metric 10:	Exposure frequency	Low	The duration of 1.5 hours was much shorter than typical occupational exposure scenarios and may be too short to establish a reliable steady-state flux, although the shallow absorption curve does appear relatively linear by visual inspection.
	Metric 11:	Number of exposure groups and concentration spacing	High	The number of exposure groups was appropriate for study design. An infinite dose was studied to determine Kp, in agreement with OECD guidelines.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	Dorsal skin from a hairless guinea pig skin was harvested, dermatomed to 315 um and used directly. Skin integrity was not measured. The model and skin thickness were appropriate. Lack of measuring integrity could impact results.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates/group (n=8) and concentration studies (infinite) were appropriate according to OECD guidelines.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	The aqueous saturated solution did not meet the definition of infinite dose. Based on solubility, the concentration was calculated as only 0.5% 1,2DCE, which results in only 2.5ul of 1,2DCE from the 500ul dosed saturated solution. For 0.636 cm2 surface area, this results in loading of only 3.9 ul/cm2, which is well below the recommended loading of 100 ul/cm2. This metric was not scored as unacceptable because a steady-state dose was able to be derived based on regression analysis, however it was nonlinear regression and the absorption curve is very shallow which makes visual inspection difficult.The timing of sampling the receptor compartment (0, 10, 20, 30, 45, 60, and 90 minutes) was appropriate based on the absorption curve, although longer duration would be preferred to establish steady-state. 100 uL of receptor solution was removed and replaced with the same volume fresh buffer and aqueous donor solution was replaced every 15 minutes. .
	Metric 15:	Consistency of outcome assessment	High	The outcome assessment was carried out consistently across study groups. 100 ul samples were taken from the receptor compartment at specified and consistent timepoints. Receptor volume was replaced with the same volume of buffer. Assessment of concentration in receptor fluid was analyzed consistently with gas chromatography.
	Metric 16:	Sampling adequacy and sensitivity	High	The sampling intervals were adequate to allow for accurate graphical representation of results (0, 10, 20, 30, 45, 60, and 90 minutes).
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Low	The thickness of the skin was consistent. The study did not measure skin integrity by any acceptable measure (checking electrical resistance; checking trans-epidermal water loss is in normal range; or measure penetration characteristics of a reference material).
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	Solubility in the receptor fluid was not expected to substantially impact results. The receptor compartment volume was 5 ml and the donor compartment volume was 0.5 ml. The solubility is reported to be 5,347 ug/ml at 22oC (determined by this lab), therefore is in not likely to be a limiting factor in the receptor fluid.

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Study Citation: Frasch, H. F., Barbero, A. M., Alachkar, H., Mcdougal, J. N. (2007). Skin penetration and lag times of neat and aqueous diethyl phthalate, 1,2-dichloroethane and naphthalene. Cutaneous and Ocular Toxicology 26(2):147-160.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 1313327
Unique ID: Aqueous from the Frasch lab

Domain	Metric	Rating	Comments
Domain 7: Data Presentation and Analysis			
	Metric 19: Data analysis	High	Statistical methods and data analysis were clearly described. CV below 25%.
	Metric 20: Data interpretation	Low	Permeability (Kp) was calculated using less-than infinite concentration, and a non-linear regression was used for deriving Kp/flux values. The study also does not report what timepoints were used for Kp/flux calculation, although presumably it was the timepoints beginning from the end of lag time through the end of the experiment.
	Metric 21: Reporting of data	High	Study reports calculated permeability (kp), steady state flux, and lag time. Mass accumulation vs time plots are shown. Data is presented as mean +/- SD (n=8).

Overall Quality Determination Medium

Study Citation:	Frasch, H. F., Barbero, A. M., Alachkar, H., Mcdougal, J. N. (2007). Skin penetration and lag times of neat and aqueous diethyl phthalate, 1,2-dichloroethane and naphthalene. Cutaneous and Ocular Toxicology 26(2):147-160.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	1313327
Unique ID:	Neat from the Frasch lab

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substance was identified as 1,2-dichloroethane; CAS RN 107-06-2.
	Metric 2:	Test substance source	High	The source of the test substance was Sigma-Aldrich (St. Louis, MO, USA). Lot or batch number were not provided, but this is not required for a rating of high.
	Metric 3:	Test substance purity	High	The purity of the test substance was reported to be 99.8%.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	A concurrent reference compound was not tested along with the test substance.
	Metric 5:	Assay procedures	Medium	The assay procedure was partially described. The study used a Franz static water-jetted cell apparatus with a 9 mm diameter opening for the skin (0.636 cm2 exposure area). The temperature of the receptor compartment was maintained at 37oC, and the donor compartment at 32oC; humidity was not reported. The donor compartment was 0.5 ml of neat solution. The receptor compartment was filled with 5 ml HEPES-buffered Hanks' balanced salt solution). The test substance is non-polar and lipophilic, therefore there is the potential for inadequate solubility in receptor fluid. To address this the study should have added a modifier to the solution (6% polyethylene glycol 20 oleyl ether or 5% bovine serum albumin as described in OECD guidance document 28). The receptor compartment fluid was stirred at ~1000 rpm. The donor compartment was covered with parafilm, donor solutions were replaced periodically to maintain "infinite" dose conditions. Concentration in receptor fluid was analyzed using gas chromatography and method adequately reported. Although not explicitly stated, from methods it can be inferred harvested skin was studied the same day.
	Metric 6:	Standards for tests	Low	Harvested skin was not stored and used the same day. The integrity of the skin was not tested prior to testing (via electrical resistance, trans-epidermal water loss is in normal range, or tritiated water). The Coefficient of variation was <25%.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Neat test substance was added to the donor cell and covered with parafilm. Storage conditions of stock solution was not reported.
	Metric 8:	Consistency of exposure administration	Medium	The diameter of skin studied was consistent (9mm) and volume of donor and receptor compartments were consistent. Dorsal skin dermatoned at 315 um (after the removal of underlying muscle and fat). Coefficient of variation was <25% for permeability.
	Metric 9:	Reporting of concentrations	Medium	The concentration of neat test substance is not measured, rather the study uses the density of the substance (1.235 ug/cm3) for calculations. Since the test substance is used neat this is unlikely to substantially impact results.
	Metric 10:	Exposure frequency	Low	The duration of 1.5 hours was much shorter than typical occupational exposure scenarios and may be too short to establish a reliable steady-state flux, although the shallow absorption curve does appear relatively linear by visual inspection.
	Metric 11:	Number of exposure groups and concentration spacing	High	The number of exposure groups was appropriate for study design. An infinite dose was studied to determine Kp, in agreement with OECD guidelines.

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Study Citation:	Frasch, H. F., Barbero, A. M., Alachkar, H., Mcdougal, J. N. (2007). Skin penetration and lag times of neat and aqueous diethyl phthalate, 1,2-dichloroethane and naphthalene. Cutaneous and Ocular Toxicology 26(2):147-160.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	1313327
Unique ID:	Neat from the Frasch lab

Domain	Metric		Rating	Comments
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	Dorsal skin from a hairless guinea pig skin was harvested, dermatomed to 315 um and used directly. Skin integrity was not measured. The model and skin thickness were appropriate. Lack of measuring integrity could impact results.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates/group (n=8) and concentration studies (infinite) were appropriate according to OECD guidelines.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	Outcome assessment methodology was appropriate. 0.5 ml of an infinite dose was added to the donor compartment. The diameter of the exposed skin was 9mm. The area of the skin was calculated by the reviewer to be 0.636 cm2, therefore a 786 uL/cm2 of saturated solution was studied and in line with guidance. The timing of sampling the receptor compartment (0, 10, 20, 30, 45, 60, and 90 minutes) was appropriate. 100 uL of receptor solution was removed and replaced with the same volume fresh buffer.
	Metric 15:	Consistency of outcome assessment	High	The outcome assessment was carried out consistently across study groups. 100 ul samples were taken from the receptor compartment at specified and consistent timepoints. Receptor volume was replaced with the same volume of buffer. Assessment of concentration in receptor fluid was analyzed consistently with gas chromatography.
	Metric 16:	Sampling adequacy and sensitivity	High	The sampling intervals were adequate to allow for accurate graphical representation of results (0, 10, 20, 30, 45, 60, and 90 minutes).
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Low	The thickness of the skin was consistent. The study did not measure skin integrity by any acceptable measure (checking electrical resistance; checking trans-epidermal water loss is in normal range; or measure penetration characteristics of a reference material).
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	Solubility in the receptor fluid was not expected to substantially impact results. The receptor compartment volume was 5 ml and the donor compartment volume was 0.5 ml. The solubility is reported to be 5,347 ug/ml at 22oC (determined by this lab), therefore is in not likely to be a limiting factor in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	High	Statistical methods and data analysis were clearly described. CV below 25%.
	Metric 20:	Data interpretation	Medium	Permeability (Kp) was calculated using infinite concentration, however a non-linear regression was used for deriving Kp/flux values. The study also does not report what timepoints were used for Kp/flux calculation, although presumably it was the timepoints beginning from the end of lag time through the end of the experiment.
	Metric 21:	Reporting of data	High	Study reports calculated permeability (kp), steady state flux, and lag time. Mass accumulation vs time plots are shown. Data is presented as mean +/- SD (n=8).

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Study Citation:	Frasch, H. F., Barbero, A. M., Alachkar, H., Mcdougal, J. N. (2007). Skin penetration and lag times of neat and aqueous diethyl phthalate, 1,2-dichloroethane and naphthalene. Cutaneous and Ocular Toxicology 26(2):147-160.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	1313327
Unique ID:	Neat from the Frasch lab

Domain	Metric	Rating	Comments
Overall Quality Determination		**Medium**	

Study Citation:	Frasch, H. F., Barbero, A. M., Alachkar, H., Mcdougal, J. N. (2007). Skin penetration and lag times of neat and aqueous diethyl phthalate, 1,2-dichloroethane and naphthalene. Cutaneous and Ocular Toxicology 26(2):147-160.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	1313327
Unique ID:	Neat from the McDougal lab

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substance was identified as 1,2-dichloroethane; CAS RN 107-06-2.
	Metric 2:	Test substance source	High	The source of the test substance was Sigma-Aldrich (St. Louis, MO, USA). Lot or batch number were not provided, but this is not required for a rating of high.
	Metric 3:	Test substance purity	High	The purity of the test substance was reported to be 99.5%.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	A concurrent reference compound was not tested along with the test substance.
	Metric 5:	Assay procedures	Medium	The assay procedure was partially described. The study used a Franz static water-jetted cell apparatus with a 11.28 mm diameter opening for the skin (1.0 cm2 exposure area). The temperature of the receptor compartment was maintained at 37oC, and the donor compartment at 32oC; humidity was not reported. The donor compartment was 1 ml of neat solution. The receptor compartment was filled with 8 ml HEPES-buffered Hanks' balanced salt solution. The test substance is non-polar and lipophilic, therefore there is the potential for inadequate solubility in receptor fluid. To address this the study should have added a modifier to the solution (6% polyethylene glycol 20 oleyl ether or 5% bovine serum albumin as described in OECD guidance document 28). The receptor compartment fluid was stirred at ~800 rpm. The donor compartment was covered with parafilm, donor solutions were replaced periodically to maintain "infinite" dose conditions. Concentration in receptor fluid was analyzed using gas chromatography and method adequately reported. Although not explicitly stated, from methods it can be inferred harvested skin was studied the same day.
	Metric 6:	Standards for tests	Low	Harvested skin was not stored and used the same day. The integrity of the skin was not tested prior to testing (via electrical resistance, trans-epidermal water loss is in normal range, or tritiated water). The Coefficient of variation was <25%.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Neat test substance was added to the donor cell and covered with parafilm. Storage conditions of stock solution was not reported.
	Metric 8:	Consistency of exposure administration	Medium	The diameter of skin studied was consistent (11.28 mm) and volume of donor and receptor compartments were consistent. Skin from the midscapular area of the guinea pigs back was excised and dermatomed to 350 um. Coefficient of variation was <25% for permeability.
	Metric 9:	Reporting of concentrations	Medium	The concentration of neat test substance is not measured, rather the study uses the density of the substance (1.235 ug/cm3) for calculations. Since the test substance is used neat this is unlikely to substantially impact results.
	Metric 10:	Exposure frequency	Low	The duration of 2 hours was much shorter than typical occupational exposure scenarios and may be too short to establish a reliable steady-state flux, although the shallow absorption curve does appear relatively linear by visual inspection.
	Metric 11:	Number of exposure groups and concentration spacing	High	The number of exposure groups was appropriate for study design. An infinite dose was studied to determine Kp, in agreement with OECD guidelines.

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Study Citation: Frasch, H. F., Barbero, A. M., Alachkar, H., Mcdougal, J. N. (2007). Skin penetration and lag times of neat and aqueous diethyl phthalate, 1,2-dichloroethane and naphthalene. Cutaneous and Ocular Toxicology 26(2):147-160.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 1313327
Unique ID: Neat from the McDougal lab

Domain	Metric		Rating	Comments
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	Skin from the midscapular area from a hairless guinea pig skin was harvested, dermatomed to 350 um and used directly. Skin integrity was not measured. The model and skin thickness were appropriate. Lack of measuring integrity could impact results.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates/group (n=8) and concentration studies (infinite) were appropriate according to OECD guidelines.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	Outcome assessment methodology was appropriate. 1.0 ml of an infinite dose was added to the donor compartment. The diameter of the exposed skin was 11.28 mm. The area of the skin was calculated by the reviewer to be 1.0 cm2, therefore a 1000 uL/cm2 of saturated solution was studied and in line with guidance. 20uL of receptor volume was removed at 15–30-minute intervals for 4-6 hours and replaced with fresh buffer. “The solubility of each chemical in HBSS was determined to assure that was not a limiting factor in the flux experiment”.
	Metric 15:	Consistency of outcome assessment	High	The outcome assessment was carried out consistently across study groups. 20 ul samples were taken from the receptor compartment at specified and consistent timepoints. Receptor volume was replaced with the same volume of buffer. Assessment of concentration in receptor fluid was analyzed consistently with gas chromatography.
	Metric 16:	Sampling adequacy and sensitivity	High	The sampling intervals were adequate to allow for accurate graphical representation of results (15-30 minutes).
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Low	The thickness of the skin was consistent. The study did not measure skin integrity by any acceptable measure (checking electrical resistance; checking trans-epidermal water loss is in normal range; or measure penetration characteristics of a reference material).
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	The study authors states “The solubility of each chemical in HBSS was determined to assure that was not a limiting factor in the flux experiment.” The solubility at 20oC in buffer was reported to be 87,000 ug/ml (determined by this lab)..
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	High	Statistical methods and data analysis were clearly described. CV less than 25%.
	Metric 20:	Data interpretation	Medium	Permeability (Kp) was calculated using infinite concentration, however a non-linear regression was used for deriving Kp/flux values. The study also does not report what timepoints were used for Kp/flux calculation, although presumably it was the timepoints beginning from the end of lag time through the end of the experiment.

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Study Citation: Frasch, H. F., Barbero, A. M., Alachkar, H., Mcdougal, J. N. (2007). Skin penetration and lag times of neat and aqueous diethyl phthalate, 1,2-dichloroethane and naphthalene. Cutaneous and Ocular Toxicology 26(2):147-160.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 1313327
Unique ID: Neat from the McDougal lab

Domain	Metric	Rating	Comments
	Metric 21: Reporting of data	Medium	Study reports calculated permeability (kp), steady state flux, and lag time. Mass accumulation vs time plots are shown. Data is presented as mean +/- SD (n=8). Methods state samples were collected for 4-6 hours, however data is only presented for 2 hours, without an explanation.

Overall Quality Determination Medium

Study Citation:	Gajjar, R. M., Kasting, G. B. (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicology and Applied Pharmacology 281(1):109-117.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	4141541
Unique ID:	7.9 mg/m2 group

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	The test substance was identified as 1,2-dichloroethane (radiolabeled 14C-1,2-DCE). The test substance is sold in liquid form (as per supplier websites). The radiolabeled test substance was a neat liquid in break seal or ethanol solvent. The location of the radiolabel within the substance was not reported; ideally the radiolabel should be in a metabolically stable position. An unlabeled neat test substance was also mentioned in the methods but was not mentioned further.
	Metric 2:	Test substance source	High	The sources of the test substance were clearly reported although batch/lot numbers were not provided. The radiolabeled test substance was purchased from American Radiolabeled. The unlabeled test substance was purchased from Sigma Aldrich.
	Metric 3:	Test substance purity	High	The purity of the radiolabeled chemical was 99.0%. It is not clear which unlabeled product was purchased from Sigma-Aldrich, so the purity cannot be definitively determined. Because the study did not specify further use of the unlabeled material, this is not considered to be relevant.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	The study did not include any of the specified concurrent controls (caffeine, testosterone, or benzoic acid). The study did cite other publications on their diffusion skin model, but it is not known whether they previously performed skin absorption studies. Other solvents including ethanol, acetone, and benzene were also tested in this study.
	Metric 5:	Assay procedures	Low	The study adequately described the diffusion cell setup. The receptor fluid was PBS which is acceptable for a non-lipophilic compound; however, 1,2-DCE is lipophilic, and the use of a saline solution may not be appropriate (OECD No. 156 Guidance, 2019). It is unclear what effect this may have on the study results. Upon collection, the receptor fluid was immediately placed into scintillation vials to minimize loss and radioactivity was measured within an hour. The temperature was reported and was appropriate (32 degrees C); humidity was not specified. The study was conducted in a fume hood; therefore, the humidity was likely low. A wind velocity was 0.92 m/s was reported. The static set-up was continuously stirred with a magnetic stir bar. The glass tops were non-occluded. The doses per skin surface area were clearly reported. The volumes applied, up to 40 ul per 0.79 cm2 cell, were higher than recommended (up to 10 uL/cm2). The volume of the receptor fluid was not reported. Receptor fluid was collected at 5, 10, 15, 20, and 40 minutes, and at 1, 2, 4, 8, and 24 hours post-dosing. The study did not use tape strips but measured the total amount of radioactivity in the tissue 24 hours after application. The skin was not washed, but due to evaporation, it is unlikely that there was any unabsorbed test material left on the skin surface.The study did indicate the use of a carbon trap filter for a volatile substance.

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Study Citation: Gajjar, R. M., Kasting, G. B. (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicology and Applied Pharmacology 281(1):109-117.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4141541
Unique ID: 7.9 mg/m2 group

Domain	Metric		Rating	Comments
	Metric 6:	Standards for tests	Low	The study did not conduct all of the recommended QC criteria. Skin integrity was assessed prior to the start of exposure; any samples with permeation values > 1.2uL/cm2 were discarded. The study did not explicitly report the overall percentage recovered. The cumulative permeated over 24 hours (ranging from 0.21% to 0.13%), as well as the amount of radioactivity remaining in the tissue (reported to be <0.08% -data not shown) was noted. The study authors did not justify why carbon filter traps were not utilized. Without complete measurements of recovery, it cannot be excluded that, for example, there wasn't loss due to absorbed material onto experimental equipment. CV values were not explicitly reported. Data were presented as means ± SE were reported for data from three donors (with an n = 2-7 per donor). All data were first averaged by dose for each donor, and the results represent the average across donors (indicating an n =3). Assuming an n of 3, CV values can be calculated; these values are > 25% for the 7.9, 15.8, and 31.5 mg/cm2 groups, but < 25% for the 63.1 mg/cm2 group. Further discussion of CVs is in Metric 19.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Details of the test solution preparation and storage of the volatile test substance were not provided. The stability and solubility of the test substance were not discussed, and the properties of the test substance (insoluble, lipophilic) suggest solubility may be poor. It is presumed that the substance was applied neat (no vehicle), but it is unclear whether the radiolabeled substance was diluted with the non-labelled substance. Long-term storage could have an impact on the specific activity; the specific activity of the radiolabeled test substance at purchase was reported. It is unclear if the reported specific activity at the time of dosing (0.05 uCi/uL) was measured in a scintillation counter or simply based on the activity at purchase (5.0 mCi/mmol).
	Metric 8:	Consistency of exposure administration	Low	Different volumes (ranging from 5 to 40 uL) were applied across groups to obtain different exposure concentrations. The different volumes applied likely had an impact on the study results. The skin thickness and area of the skin were uniform across groups.
	Metric 9:	Reporting of concentrations	Low	The exposure concentrations were clearly reported. Volumes of 5, 10, 20, and 40 uL of the radiolabeled test substance were added per 0.79 cm2 cell, with a specific activity of 0.05 uCi/uL, yielding concentrations of 7.9, 15.8, 31.5, and 63.1 mg/cm2. The concentrations were not analytically verified, and it was not reported whether the specific activity of the test solutions was measured.
	Metric 10:	Exposure frequency	High	The skin was exposed to a finite dose and receptor solutions were collected up to 24 hours post-dosing. The purpose of the study was to present a method for estimating the absorption of small doses of liquid VOCs that are splashed on the skin, so the finite dose and 24-hour post-exposure monitoring period were appropriate for the purposes of the study. However, due to the volatility of the test substance, there was clearly a significant amount of evaporation and essentially no test material was present in the receptor fluid after 1-hour post-exposure, and max absorption rates were obtained within 10-20 min. A shorter duration in this case may also have been appropriate.

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Study Citation: Gajjar, R. M., Kasting, G. B. (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicology and Applied Pharmacology 281(1):109-117.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4141541
Unique ID: 7.9 mg/m2 group

Domain	Metric		Rating	Comments
	Metric 11:	Number of exposure groups and concentration spacing	Low	The study tested 4 exposure concentrations. The concentrations and spacing were not explicitly justified by the study authors. The goal was to mimic small doses of liquid VOCs that are splashed on the skin, but it was not specified what those expected doses/volumes would be. The doses used exceeded the typically recommended dose for an in vitro dermal absorption test (1-5 mg/cm2 for finite dose experiments as per WHO2006, OECD TG 428 etc.,). An inverse dose-response (decreased absorption with increasing dose) was obtained. It is unclear if max absorption would be obtained at even lower concentrations not tested in this study.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test used dermatomed split-thickness human cadaver skin (~0.3 mm thick) either from the back, abdomen, or thigh. These are acceptable sites for skin samples. The source of the skin samples was provided. The skin came treated with a 10% glycerol solution and was stored at -80 degrees C. The skin samples were washed prior to use and cut into 1.5 cm x 1.5 cm squares that were mounted onto modified Franz diffusion cells. According to OECD No. 28, skin should not be stored at low temperatures because storage at -80 degrees C can enhance permeability. However, skin integrity was tested pre-study, and only samples with water permeation values less than 1.2 uL/cm2 were used.
	Metric 13:	Number/Replicates per group	Medium	Permeation experiments were done using skin from 3 donors with an n = 2-7 per donor. The text did indicate that in most cases, conditions were tested with 4-5 replicates for each of the 3 donors, yielding 12-15 replicates per dose. This meets or exceeds the guideline recommendation of 4 replicates per test preparation.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	The purpose of the study was to develop a methodology for estimating absorption from small doses of liquid VOCs. The model estimates were compared to experimental values generated by using human cadaver skin. The outcome methodology was generally appropriate for the purposes of the study; a skin surface of 0.79 cm2 was loaded with different volumes (5, 10, 20, and 40 uL) of the neat test material. The volumes applied at higher doses were greater than guideline recommendations (up to 10 ul/cm2). Cumulative skin permeation was determined by measuring radioactivity in receptor fluid over a 24-hour period and in the skin after 24 hours. Carbon traps were not used to capture the evaporation of a volatile chemical. The study was conducted in a fume hood rather than under ambient conditions, although the authors indicated fume hood was used for safety reasons. However, since most of the applied dose presumably evaporated from the skin surface, the higher airflow may not have been appropriate. The study authors often point to the higher airflow as justification for the low permeation percentages. Solubility in the receptor fluid was not tested. This is considered to be a significant flaw as PBS is not generally recommended for a lipophilic compound. The study did not wash the skin sample, which deviates from OECD TG 428 recommendations.

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Study Citation: Gajjar, R. M., Kasting, G. B. (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicology and Applied Pharmacology 281(1):109-117.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4141541
Unique ID: 7.9 mg/m2 group

Domain	Metric		Rating	Comments
	Metric 15:	Consistency of outcome assessment	High	Details of the outcome assessment protocol were reported, and the outcomes were consistently assessed across groups
	Metric 16:	Sampling adequacy and sensitivity	Medium	Limited details on scintillation counting were provided. Receptor fluid was poured into scintillation vials containing 12 mL of scintillation flued and vials were measured within 1 hour of collection. Skin samples were dissolved in Soluene and analyzed by LSC. The number of scintillation counts per sample, signal to noise ratio/background levels were not reported. It is not clear that any background measurements were taken. The number of evaluations per exposure group in the data table indicates 2-7 per donor per dose, and there were 3 donors.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Low	The skin batch/lot numbers were not reported. The number of skin samples per group varied (2-7 samples per donor, 3 donors/ group). Skin integrity was measured based on 3H20 permeation. It was specified that samples with water permeation $>$ 1.2 uL/cm2 were discarded, therefore there were no differences in the quality of the tissue. The results were not expressed as Kp values or % of the applied dose. Electrical resistance and TEWL measurements were not conducted. It is unknown whether the skin sample collection sites (back, abdomen, or shoulder) were consistent within or across groups. The distribution of the samples in each group was not specified, and this missing information is likely to have a significant impact on the study results.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Low	Solubility of the test substance in the receptor fluid is a potential concern. The test substance has low solubility in water (8.6 g/L) and is lipophilic. The receptor fluid (PBS) is generally appropriate for water soluble compounds but may not be appropriate for lipophilic compounds. The solubility of the test substance in the receptor fluid was not reported, and it is unclear if the permeation rate was influenced by solubility, and whether this had a confounding impact, particularly at the higher doses.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	The cumulative amount of permeated test substance was reported across time the data were reported as means donors $\pm$ SE. The percent of dose permeated was graphically displayed and reported numerically in the text. Data were first averaged by dose for each donor, and then averaged across donors to obtain the mean values. It is unknown whether the study accounted for any outliers. The study did not report the percentage absorbed, but this could be determined by dividing the cumulative amount permeated by the applied dose, although it should be taken into consideration that it is presumed that the majority of the applied dose evaporated. Based on the data provided for the cumulative amount permeated (at 24hrs), the standard deviations can first be determined (SD = SE x SQRT(n), where n =3). The CV values can then be calculated (SD relative to the mean). The calculated CV values are 35%, 44%, 27%, and 23%, for the 7.9, 15.8, 31.5, and 63.1 mg/cm2 groups, respectively. Only the high dose group had an acceptable CV ($<$25%); however, data are available for EPA to calculate an alternate (upper end) value to account for variability in the results.

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Study Citation: Gajjar, R. M., Kasting, G. B. (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicology and Applied Pharmacology 281(1):109-117.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4141541
Unique ID: 7.9 mg/m2 group

Domain	Metric		Rating	Comments
	Metric 20:	Data interpretation	Medium	The percent recovery of the applied test substance was not explicitly reported, although it is presumed to be low because the total cumulative penetration amount ranged from 0.21% to 0.13% of the applied dose. The study authors presumed the remainder evaporated; however, carbon traps were not used to definitively account for evaporated material. The skin was not washed (no measurements of washes), and no measurements of amounts in the donor chamber were collected. Only percentage absorption in the skin from a finite dose is reported and is not defined by dose group (quantitative values not reported). It is not specified whether the absorption estimates were normalized, but it is highly likely that the missing material evaporated and therefore, was unlikely to have been absorbed (under the conditions of this test); the inclusion of evaporated material may not be required. The study also reported the maximum flux of the VOC into the receptor solution. The study authors believed that the data implied that mild lipid barrier disruption likely occurred.
	Metric 21:	Reporting of data	Low	Overall cumulative absorption for each exposure group, at each collection point, was reported as Means ± SE, and the percentage of the applied dose was noted in the text for some, but not all exposure groups. These values presumably represent primarily the amounts measured in receptor fluid. The amount in the skin after 24 hours was simply reported to be less than 0.08% (presumably of the applied dose), and was not described by exposure group. It is not clear if this amount was included in the reported cumulative values. Separate measurements for receptor fluid alone were not reported.

Overall Quality Determination Low

Study Citation: Gajjar, R. M., Kasting, G. B. (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicology and Applied Pharmacology 281(1):109-117.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4141541
Unique ID: 15.8 mg/cm2 group

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	The test substance was identified as 1,2-dichloroethane (radiolabeled 14C-1,2-DCE). The test substance is sold in liquid form (as per supplier websites). The radiolabeled test substance was a neat liquid in break seal or ethanol solvent. The location of the radiolabel within the substance was not reported; ideally the radiolabel should be in a metabolically stable position. An unlabeled neat test substance was also mentioned in the methods but was not mentioned further.
	Metric 2:	Test substance source	High	The sources of the test substance were clearly reported although batch/lot numbers were not provided. The radiolabeled test substance was purchased from American Radiolabeled. The unlabeled test substance was purchased from Sigma Aldrich.
	Metric 3:	Test substance purity	High	The purity of the radiolabeled chemical was 99.0%. It is not clear which unlabeled product was purchased from Sigma-Aldrich, so the purity cannot be definitively determined. Because the study did not specify further use of the unlabeled material, this is not considered to be relevant.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	The study did not include any of the specified concurrent controls (caffeine, testosterone, or benzoic acid). The study did cite other publications on their diffusion skin model, but it is not known whether they previously performed skin absorption studies. Other solvents including ethanol, acetone, and benzene were also tested in this study.
	Metric 5:	Assay procedures	Low	The study adequately described the diffusion cell setup. The receptor fluid was PBS which is acceptable for a non-lipophilic compound; however, 1,2-DCE is lipophilic, and the use of a saline solution may not be appropriate (OECD No. 156 Guidance, 2019). It is unclear what effect this may have on the study results. Upon collection, the receptor fluid was immediately placed into scintillation vials to minimize loss and radioactivity was measured within an hour. The temperature was reported and was appropriate (32 degrees C); humidity was not specified. The study was conducted in a fume hood; therefore, the humidity was likely low. A wind velocity was 0.92 m/s was reported. The static set-up was continuously stirred with a magnetic stir bar. The glass tops were non-occluded. The doses per skin surface area were clearly reported. The volumes applied, up to 40 ul per 0.79 cm2 cell, were higher than recommended (up to 10 uL/cm2). The volume of the receptor fluid was not reported. Receptor fluid was collected at 5, 10, 15, 20, and 40 minutes, and at 1, 2, 4, 8, and 24 hours post-dosing. The study did not use tape strips but measured the total amount of radioactivity in the tissue 24 hours after application. The skin was not washed, but due to evaporation, it is unlikely that there was any unabsorbed test material left on the skin surface.The study did indicate the use of a carbon trap filter for a volatile substance.

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Study Citation: Gajjar, R. M., Kasting, G. B. (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicology and Applied Pharmacology 281(1):109-117.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4141541
Unique ID: 15.8 mg/cm2 group

Domain	Metric		Rating	Comments
	Metric 6:	Standards for tests	Low	The study did not conduct all of the recommended QC criteria. Skin integrity was assessed prior to the start of exposure; any samples with permeation values > 1.2uL/cm2 were discarded. The study did not explicitly report the overall percentage recovered. The cumulative permeated over 24 hours (ranging from 0.21% to 0.13%), as well as the amount of radioactivity remaining in the tissue (reported to be <0.08% -data not shown) was noted. The study authors did not justify why carbon filter traps were not utilized. Without complete measurements of recovery, it cannot be excluded that, for example, there wasn't loss due to absorbed material onto experimental equipment. CV values were not explicitly reported. Data were presented as means ± SE were reported for data from three donors (with an n = 2-7 per donor). All data were first averaged by dose for each donor, and the results represent the average across donors (indicating an n =3). Assuming an n of 3, CV values can be calculated; these values are > 25% for the 7.9, 15.8, and 31.5 mg/cm2 groups, but < 25% for the 63.1 mg/cm2 group. Further discussion of CVs is in Metric 19.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Details of the test solution preparation and storage of the volatile test substance were not provided. The stability and solubility of the test substance were not discussed, and the properties of the test substance (insoluble, lipophilic) suggest solubility may be poor. It is presumed that the substance was applied neat (no vehicle), but it is unclear whether the radiolabeled substance was diluted with the non-labelled substance. Long-term storage could have an impact on the specific activity; the specific activity of the radiolabeled test substance at purchase was reported. It is unclear if the reported specific activity at the time of dosing (0.05 uCi/uL) was measured in a scintillation counter or simply based on the activity at purchase (5.0 mCi/mmol).
	Metric 8:	Consistency of exposure administration	Low	Different volumes (ranging from 5 to 40 uL) were applied across groups to obtain different exposure concentrations. The different volumes applied likely had an impact on the study results. The skin thickness and area of the skin were uniform across groups.
	Metric 9:	Reporting of concentrations	Low	The exposure concentrations were clearly reported. Volumes of 5, 10, 20, and 40 uL of the radiolabeled test substance were added per 0.79 cm2 cell, with a specific activity of 0.05 uCi/uL, yielding concentrations of 7.9, 15.8, 31.5, and 63.1 mg/cm2. The concentrations were not analytically verified, and it was not reported whether the specific activity of the test solutions was measured.
	Metric 10:	Exposure frequency	High	The skin was exposed to a finite dose and receptor solutions were collected up to 24 hours post-dosing. The purpose of the study was to present a method for estimating the absorption of small doses of liquid VOCs that are splashed on the skin, so the finite dose and 24-hour post-exposure monitoring period were appropriate for the purposes of the study. However, due to the volatility of the test substance, there was clearly a significant amount of evaporation and essentially no test material was present in the receptor fluid after 1-hour post-exposure, and max absorption rates were obtained within 10-20 min. A shorter duration in this case may also have been appropriate.

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Study Citation: Gajjar, R. M., Kasting, G. B. (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicology and Applied Pharmacology 281(1):109-117.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4141541
Unique ID: 15.8 mg/cm2 group

Domain	Metric		Rating	Comments
	Metric 11:	Number of exposure groups and concentration spacing	Low	The study tested 4 exposure concentrations. The concentrations and spacing were not explicitly justified by the study authors. The goal was to mimic small doses of liquid VOCs that are splashed on the skin, but it was not specified what those expected doses/volumes would be. The doses used exceeded the typically recommended dose for an in vitro dermal absorption test (1-5 mg/cm2 for finite dose experiments as per WHO2006, OECD TG 428 etc.,). An inverse dose-response (decreased absorption with increasing dose) was obtained. It is unclear if max absorption would be obtained at even lower concentrations not tested in this study.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test used dermatomed split-thickness human cadaver skin (~0.3 mm thick) either from the back, abdomen, or thigh. These are acceptable sites for skin samples. The source of the skin samples was provided. The skin came treated with a 10% glycerol solution and was stored at -80 degrees C. The skin samples were washed prior to use and cut into 1.5 cm x 1.5 cm squares that were mounted onto modified Franz diffusion cells. According to OECD No. 28, skin should not be stored at low temperatures because storage at -80 degrees C can enhance permeability. However, skin integrity was tested pre-study, and only samples with water permeation values less than 1.2 uL/cm2 were used.
	Metric 13:	Number/Replicates per group	Medium	Permeation experiments were done using skin from 3 donors with an n = 2-7 per donor. The text did indicate that in most cases, conditions were tested with 4-5 replicates for each of the 3 donors, yielding 12-15 replicates per dose. This meets or exceeds the guideline recommendation of 4 replicates per test preparation.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	The purpose of the study was to develop a methodology for estimating absorption from small doses of liquid VOCs. The model estimates were compared to experimental values generated by using human cadaver skin. The outcome methodology was generally appropriate for the purposes of the study; a skin surface of 0.79 cm2 was loaded with different volumes (5, 10, 20, and 40 uL) of the neat test material. The volumes applied at higher doses were greater than guideline recommendations (up to 10 ul/cm2). Cumulative skin permeation was determined by measuring radioactivity in receptor fluid over a 24-hour period and in the skin after 24 hours. Carbon traps were not used to capture the evaporation of a volatile chemical. The study was conducted in a fume hood rather than under ambient conditions, although the authors indicated fume hood was used for safety reasons. However, since most of the applied dose presumably evaporated from the skin surface, the higher airflow may not have been appropriate. The study authors often point to the higher airflow as justification for the low permeation percentages. Solubility in the receptor fluid was not tested. This is considered to be a significant flaw as PBS is not generally recommended for a lipophilic compound. The study did not wash the skin sample, which deviates from OECD TG 428 recommendations.

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Study Citation: Gajjar, R. M., Kasting, G. B. (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicology and Applied Pharmacology 281(1):109-117.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4141541
Unique ID: 15.8 mg/cm2 group

Domain	Metric		Rating	Comments
	Metric 15:	Consistency of outcome assessment	High	Details of the outcome assessment protocol were reported, and the outcomes were consistently assessed across groups
	Metric 16:	Sampling adequacy and sensitivity	Medium	Limited details on scintillation counting were provided. Receptor fluid was poured into scintillation vials containing 12 mL of scintillation flued and vials were measured within 1 hour of collection. Skin samples were dissolved in Soluene and analyzed by LSC. The number of scintillation counts per sample, signal to noise ratio/background levels were not reported. It is not clear that any background measurements were taken. The number of evaluations per exposure group in the data table indicates 2-7 per donor per dose, and there were 3 donors.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Low	The skin batch/lot numbers were not reported. The number of skin samples per group varied (2-7 samples per donor, 3 donors/ group). Skin integrity was measured based on 3H20 permeation. It was specified that samples with water permeation $>$ 1.2 uL/cm2 were discarded, therefore there were no differences in the quality of the tissue. The results were not expressed as Kp values or % of the applied dose. Electrical resistance and TEWL measurements were not conducted. It is unknown whether the skin sample collection sites (back, abdomen, or shoulder) were consistent within or across groups. The distribution of the samples in each group was not specified, and this missing information is likely to have a significant impact on the study results.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Low	Solubility of the test substance in the receptor fluid is a potential concern. The test substance has low solubility in water (8.6 g/L) and is lipophilic. The receptor fluid (PBS) is generally appropriate for water soluble compounds but may not be appropriate for lipophilic compounds. The solubility of the test substance in the receptor fluid was not reported, and it is unclear if the permeation rate was influenced by solubility, and whether this had a confounding impact, particularly at the higher doses.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	The cumulative amount of permeated test substance was reported across time the data were reported as means donors $\pm$ SE. The percent of dose permeated was graphically displayed and reported numerically in the text. Data were first averaged by dose for each donor, and then averaged across donors to obtain the mean values. It is unknown whether the study accounted for any outliers. The study did not report the percentage absorbed, but this could be determined by dividing the cumulative amount permeated by the applied dose, although it should be taken into consideration that it is presumed that the majority of the applied dose evaporated. Based on the data provided for the cumulative amount permeated (at 24hrs), the standard deviations can first be determined (SD = SE x SQRT(n), where n =3). The CV values can then be calculated (SD relative to the mean). The calculated CV values are 35%, 44%, 27%, and 23%, for the 7.9, 15.8, 31.5, and 63.1 mg/cm2 groups, respectively. Only the high dose group had an acceptable CV ($<$25%); however, data are available for EPA to calculate an alternate (upper end) value to account for variability in the results.

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Study Citation: Gajjar, R. M., Kasting, G. B. (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicology and Applied Pharmacology 281(1):109-117.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4141541
Unique ID: 15.8 mg/cm2 group

Domain	Metric		Rating	Comments
	Metric 20:	Data interpretation	Medium	The percent recovery of the applied test substance was not explicitly reported, although it is presumed to be low because the total cumulative penetration amount ranged from 0.21% to 0.13% of the applied dose. The study authors presumed the remainder evaporated; however, carbon traps were not used to definitively account for evaporated material. The skin was not washed (no measurements of washes), and no measurements of amounts in the donor chamber were collected. Only percentage absorption in the skin from a finite dose is reported and is not defined by dose group (quantitative values not reported). It is not specified whether the absorption estimates were normalized, but it is highly likely that the missing material evaporated and therefore, was unlikely to have been absorbed (under the conditions of this test); the inclusion of evaporated material may not be required. The study also reported the maximum flux of the VOC into the receptor solution. The study authors believed that the data implied that mild lipid barrier disruption likely occurred.
	Metric 21:	Reporting of data	Low	Overall cumulative absorption for each exposure group, at each collection point, was reported as Means $\pm$ SE, and the percentage of the applied dose was noted in the text for some, but not all exposure groups. These values presumably represent primarily the amounts measured in receptor fluid. The amount in the skin after 24 hours was simply reported to be less than 0.08% (presumably of the applied dose), and was not described by exposure group. It is not clear if this amount was included in the reported cumulative values. Separate measurements for receptor fluid alone were not reported.

Overall Quality Determination Low

Study Citation: Gajjar, R. M., Kasting, G. B. (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicology and Applied Pharmacology 281(1):109-117.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4141541
Unique ID: 31.5 mg/cm2 group

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	The test substance was identified as 1,2-dichloroethane (radiolabeled 14C-1,2-DCE). The test substance is sold in liquid form (as per supplier websites). The radiolabeled test substance was a neat liquid in break seal or ethanol solvent. The location of the radiolabel within the substance was not reported; ideally the radiolabel should be in a metabolically stable position. An unlabeled neat test substance was also mentioned in the methods but was not mentioned further.
	Metric 2:	Test substance source	High	The sources of the test substance were clearly reported although batch/lot numbers were not provided. The radiolabeled test substance was purchased from American Radiolabeled. The unlabeled test substance was purchased from Sigma Aldrich.
	Metric 3:	Test substance purity	High	The purity of the radiolabeled chemical was 99.0%. It is not clear which unlabeled product was purchased from Sigma-Aldrich, so the purity cannot be definitively determined. Because the study did not specify further use of the unlabeled material, this is not considered to be relevant.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	The study did not include any of the specified concurrent controls (caffeine, testosterone, or benzoic acid). The study did cite other publications on their diffusion skin model, but it is not known whether they previously performed skin absorption studies. Other solvents including ethanol, acetone, and benzene were also tested in this study.
	Metric 5:	Assay procedures	Low	The study adequately described the diffusion cell setup. The receptor fluid was PBS which is acceptable for a non-lipophilic compound; however, 1,2-DCE is lipophilic, and the use of a saline solution may not be appropriate (OECD No. 156 Guidance, 2019). It is unclear what effect this may have on the study results. Upon collection, the receptor fluid was immediately placed into scintillation vials to minimize loss and radioactivity was measured within an hour. The temperature was reported and was appropriate (32 degrees C); humidity was not specified. The study was conducted in a fume hood; therefore, the humidity was likely low. A wind velocity was 0.92 m/s was reported. The static set-up was continuously stirred with a magnetic stir bar. The glass tops were non-occluded. The doses per skin surface area were clearly reported. The volumes applied, up to 40 ul per 0.79 cm2 cell, were higher than recommended (up to 10 uL/cm2). The volume of the receptor fluid was not reported. Receptor fluid was collected at 5, 10, 15, 20, and 40 minutes, and at 1, 2, 4, 8, and 24 hours post-dosing. The study did not use tape strips but measured the total amount of radioactivity in the tissue 24 hours after application. The skin was not washed, but due to evaporation, it is unlikely that there was any unabsorbed test material left on the skin surface.The study did indicate the use of a carbon trap filter for a volatile substance.

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Study Citation: Gajjar, R. M., Kasting, G. B. (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicology and Applied Pharmacology 281(1):109-117.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4141541
Unique ID: 31.5 mg/cm2 group

Domain	Metric		Rating	Comments
	Metric 6:	Standards for tests	Low	The study did not conduct all of the recommended QC criteria. Skin integrity was assessed prior to the start of exposure; any samples with permeation values > 1.2uL/cm2 were discarded. The study did not explicitly report the overall percentage recovered. The cumulative permeated over 24 hours (ranging from 0.21% to 0.13%), as well as the amount of radioactivity remaining in the tissue (reported to be <0.08% -data not shown) was noted. The study authors did not justify why carbon filter traps were not utilized. Without complete measurements of recovery, it cannot be excluded that, for example, there wasn't loss due to absorbed material onto experimental equipment. CV values were not explicitly reported. Data were presented as means ± SE were reported for data from three donors (with an n = 2-7 per donor). All data were first averaged by dose for each donor, and the results represent the average across donors (indicating an n =3). Assuming an n of 3, CV values can be calculated; these values are > 25% for the 7.9, 15.8, and 31.5 mg/cm2 groups, but < 25% for the 63.1 mg/cm2 group. Further discussion of CVs is in Metric 19.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Details of the test solution preparation and storage of the volatile test substance were not provided. The stability and solubility of the test substance were not discussed, and the properties of the test substance (insoluble, lipophilic) suggest solubility may be poor. It is presumed that the substance was applied neat (no vehicle), but it is unclear whether the radiolabeled substance was diluted with the non-labelled substance. Long-term storage could have an impact on the specific activity; the specific activity of the radiolabeled test substance at purchase was reported. It is unclear if the reported specific activity at the time of dosing (0.05 uCi/uL) was measured in a scintillation counter or simply based on the activity at purchase (5.0 mCi/mmol).
	Metric 8:	Consistency of exposure administration	Low	Different volumes (ranging from 5 to 40 uL) were applied across groups to obtain different exposure concentrations. The different volumes applied likely had an impact on the study results. The skin thickness and area of the skin were uniform across groups.
	Metric 9:	Reporting of concentrations	Low	The exposure concentrations were clearly reported. Volumes of 5, 10, 20, and 40 uL of the radiolabeled test substance were added per 0.79 cm2 cell, with a specific activity of 0.05 uCi/uL, yielding concentrations of 7.9, 15.8, 31.5, and 63.1 mg/cm2. The concentrations were not analytically verified, and it was not reported whether the specific activity of the test solutions was measured.
	Metric 10:	Exposure frequency	High	The skin was exposed to a finite dose and receptor solutions were collected up to 24 hours post-dosing. The purpose of the study was to present a method for estimating the absorption of small doses of liquid VOCs that are splashed on the skin, so the finite dose and 24-hour post-exposure monitoring period were appropriate for the purposes of the study. However, due to the volatility of the test substance, there was clearly a significant amount of evaporation and essentially no test material was present in the receptor fluid after 1-hour post-exposure, and max absorption rates were obtained within 10-20 min. A shorter duration in this case may also have been appropriate.

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Study Citation:	Gajjar, R. M., Kasting, G. B. (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicology and Applied Pharmacology 281(1):109-117.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	4141541
Unique ID:	31.5 mg/cm2 group

Domain	Metric		Rating	Comments
	Metric 11:	Number of exposure groups and concentration spacing	Low	The study tested 4 exposure concentrations. The concentrations and spacing were not explicitly justified by the study authors. The goal was to mimic small doses of liquid VOCs that are splashed on the skin, but it was not specified what those expected doses/volumes would be. The doses used exceeded the typically recommended dose for an in vitro dermal absorption test (1-5 mg/cm2 for finite dose experiments as per WHO2006, OECD TG 428 etc.,). An inverse dose-response (decreased absorption with increasing dose) was obtained. It is unclear if max absorption would be obtained at even lower concentrations not tested in this study.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test used dermatomed split-thickness human cadaver skin (~0.3 mm thick) either from the back, abdomen, or thigh. These are acceptable sites for skin samples. The source of the skin samples was provided. The skin came treated with a 10% glycerol solution and was stored at -80 degrees C. The skin samples were washed prior to use and cut into 1.5 cm x 1.5 cm squares that were mounted onto modified Franz diffusion cells. According to OECD No. 28, skin should not be stored at low temperatures because storage at -80 degrees C can enhance permeability. However, skin integrity was tested pre-study, and only samples with water permeation values less than 1.2 uL/cm2 were used.
	Metric 13:	Number/Replicates per group	Medium	Permeation experiments were done using skin from 3 donors with an n = 2-7 per donor. The text did indicate that in most cases, conditions were tested with 4-5 replicates for each of the 3 donors, yielding 12-15 replicates per dose. This meets or exceeds the guideline recommendation of 4 replicates per test preparation.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	The purpose of the study was to develop a methodology for estimating absorption from small doses of liquid VOCs. The model estimates were compared to experimental values generated by using human cadaver skin. The outcome methodology was generally appropriate for the purposes of the study; a skin surface of 0.79 cm2 was loaded with different volumes (5, 10, 20, and 40 uL) of the neat test material. The volumes applied at higher doses were greater than guideline recommendations (up to 10 ul/cm2). Cumulative skin permeation was determined by measuring radioactivity in receptor fluid over a 24-hour period and in the skin after 24 hours. Carbon traps were not used to capture the evaporation of a volatile chemical. The study was conducted in a fume hood rather than under ambient conditions, although the authors indicated fume hood was used for safety reasons. However, since most of the applied dose presumably evaporated from the skin surface, the higher airflow may not have been appropriate. The study authors often point to the higher airflow as justification for the low permeation percentages. Solubility in the receptor fluid was not tested. This is considered to be a significant flaw as PBS is not generally recommended for a lipophilic compound. The study did not wash the skin sample, which deviates from OECD TG 428 recommendations.

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Study Citation: Gajjar, R. M., Kasting, G. B. (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicology and Applied Pharmacology 281(1):109-117.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4141541
Unique ID: 31.5 mg/cm2 group

Domain	Metric		Rating	Comments
	Metric 15:	Consistency of outcome assessment	High	Details of the outcome assessment protocol were reported, and the outcomes were consistently assessed across groups
	Metric 16:	Sampling adequacy and sensitivity	Medium	Limited details on scintillation counting were provided. Receptor fluid was poured into scintillation vials containing 12 mL of scintillation flued and vials were measured within 1 hour of collection. Skin samples were dissolved in Soluene and analyzed by LSC. The number of scintillation counts per sample, signal to noise ratio/background levels were not reported. It is not clear that any background measurements were taken. The number of evaluations per exposure group in the data table indicates 2-7 per donor per dose, and there were 3 donors.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Low	The skin batch/lot numbers were not reported. The number of skin samples per group varied (2-7 samples per donor, 3 donors/ group). Skin integrity was measured based on 3H20 permeation. It was specified that samples with water permeation $>$ 1.2 uL/cm2 were discarded, therefore there were no differences in the quality of the tissue. The results were not expressed as Kp values or % of the applied dose. Electrical resistance and TEWL measurements were not conducted. It is unknown whether the skin sample collection sites (back, abdomen, or shoulder) were consistent within or across groups. The distribution of the samples in each group was not specified, and this missing information is likely to have a significant impact on the study results.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Low	Solubility of the test substance in the receptor fluid is a potential concern. The test substance has low solubility in water (8.6 g/L) and is lipophilic. The receptor fluid (PBS) is generally appropriate for water soluble compounds but may not be appropriate for lipophilic compounds. The solubility of the test substance in the receptor fluid was not reported, and it is unclear if the permeation rate was influenced by solubility, and whether this had a confounding impact, particularly at the higher doses.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	The cumulative amount of permeated test substance was reported across time the data were reported as means donors $\pm$ SE. The percent of dose permeated was graphically displayed and reported numerically in the text. Data were first averaged by dose for each donor, and then averaged across donors to obtain the mean values. It is unknown whether the study accounted for any outliers. The study did not report the percentage absorbed, but this could be determined by dividing the cumulative amount permeated by the applied dose, although it should be taken into consideration that it is presumed that the majority of the applied dose evaporated. Based on the data provided for the cumulative amount permeated (at 24hrs), the standard deviations can first be determined (SD = SE x SQRT(n), where n =3). The CV values can then be calculated (SD relative to the mean). The calculated CV values are 35%, 44%, 27%, and 23%, for the 7.9, 15.8, 31.5, and 63.1 mg/cm2 groups, respectively. Only the high dose group had an acceptable CV ($<$25%); however, data are available for EPA to calculate an alternate (upper end) value to account for variability in the results.

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Study Citation: Gajjar, R. M., Kasting, G. B. (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicology and Applied Pharmacology 281(1):109-117.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4141541
Unique ID: 31.5 mg/cm2 group

Domain	Metric		Rating	Comments
	Metric 20:	Data interpretation	Medium	The percent recovery of the applied test substance was not explicitly reported, although it is presumed to be low because the total cumulative penetration amount ranged from 0.21% to 0.13% of the applied dose. The study authors presumed the remainder evaporated; however, carbon traps were not used to definitively account for evaporated material. The skin was not washed (no measurements of washes), and no measurements of amounts in the donor chamber were collected. Only percentage absorption in the skin from a finite dose is reported and is not defined by dose group (quantitative values not reported). It is not specified whether the absorption estimates were normalized, but it is highly likely that the missing material evaporated and therefore, was unlikely to have been absorbed (under the conditions of this test); the inclusion of evaporated material may not be required. The study also reported the maximum flux of the VOC into the receptor solution. The study authors believed that the data implied that mild lipid barrier disruption likely occurred.
	Metric 21:	Reporting of data	Low	Overall cumulative absorption for each exposure group, at each collection point, was reported as Means ± SE, and the percentage of the applied dose was noted in the text for some, but not all exposure groups. These values presumably represent primarily the amounts measured in receptor fluid. The amount in the skin after 24 hours was simply reported to be less than 0.08% (presumably of the applied dose), and was not described by exposure group. It is not clear if this amount was included in the reported cumulative values. Separate measurements for receptor fluid alone were not reported.

Overall Quality Determination Low

Study Citation: Gajjar, R. M., Kasting, G. B. (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicology and Applied Pharmacology 281(1):109-117.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4141541
Unique ID: 63.1 mg/cm2 group

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	The test substance was identified as 1,2-dichloroethane (radiolabeled 14C-1,2-DCE). The test substance is sold in liquid form (as per supplier websites). The radiolabeled test substance was a neat liquid in break seal or ethanol solvent. The location of the radiolabel within the substance was not reported; ideally the radiolabel should be in a metabolically stable position. An unlabeled neat test substance was also mentioned in the methods but was not mentioned further.
	Metric 2:	Test substance source	High	The sources of the test substance were clearly reported although batch/lot numbers were not provided. The radiolabeled test substance was purchased from American Radiolabeled. The unlabeled test substance was purchased from Sigma Aldrich.
	Metric 3:	Test substance purity	High	The purity of the radiolabeled chemical was 99.0%. It is not clear which unlabeled product was purchased from Sigma-Aldrich, so the purity cannot be definitively determined. Because the study did not specify further use of the unlabeled material, this is not considered to be relevant.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	The study did not include any of the specified concurrent controls (caffeine, testosterone, or benzoic acid). The study did cite other publications on their diffusion skin model, but it is not known whether they previously performed skin absorption studies. Other solvents including ethanol, acetone, and benzene were also tested in this study.
	Metric 5:	Assay procedures	Low	The study adequately described the diffusion cell setup. The receptor fluid was PBS which is acceptable for a non-lipophilic compound; however, 1,2-DCE is lipophilic, and the use of a saline solution may not be appropriate (OECD No. 156 Guidance, 2019). It is unclear what effect this may have on the study results. Upon collection, the receptor fluid was immediately placed into scintillation vials to minimize loss and radioactivity was measured within an hour. The temperature was reported and was appropriate (32 degrees C); humidity was not specified. The study was conducted in a fume hood; therefore, the humidity was likely low. A wind velocity was 0.92 m/s was reported. The static set-up was continuously stirred with a magnetic stir bar. The glass tops were non-occluded. The doses per skin surface area were clearly reported. The volumes applied, up to 40 ul per 0.79 cm2 cell, were higher than recommended (up to 10 uL/cm2). The volume of the receptor fluid was not reported. Receptor fluid was collected at 5, 10, 15, 20, and 40 minutes, and at 1, 2, 4, 8, and 24 hours post-dosing. The study did not use tape strips but measured the total amount of radioactivity in the tissue 24 hours after application. The skin was not washed, but due to evaporation, it is unlikely that there was any unabsorbed test material left on the skin surface.The study did indicate the use of a carbon trap filter for a volatile substance.

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4141541
Unique ID: 63.1 mg/cm2 group

Domain	Metric		Rating	Comments
	Metric 6:	Standards for tests	Low	The study did not conduct all of the recommended QC criteria. Skin integrity was assessed prior to the start of exposure; any samples with permeation values > 1.2uL/cm2 were discarded. The study did not explicitly report the overall percentage recovered. The cumulative permeated over 24 hours (ranging from 0.21% to 0.13%), as well as the amount of radioactivity remaining in the tissue (reported to be <0.08% -data not shown) was noted. The study authors did not justify why carbon filter traps were not utilized. Without complete measurements of recovery, it cannot be excluded that, for example, there wasn't loss due to absorbed material onto experimental equipment. CV values were not explicitly reported. Data were presented as means ± SE were reported for data from three donors (with an n = 2-7 per donor). All data were first averaged by dose for each donor, and the results represent the average across donors (indicating an n =3). Assuming an n of 3, CV values can be calculated; these values are > 25% for the 7.9, 15.8, and 31.5 mg/cm2 groups, but < 25% for the 63.1 mg/cm2 group. Further discussion of CVs is in Metric 19.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Details of the test solution preparation and storage of the volatile test substance were not provided. The stability and solubility of the test substance were not discussed, and the properties of the test substance (insoluble, lipophilic) suggest solubility may be poor. It is presumed that the substance was applied neat (no vehicle), but it is unclear whether the radiolabeled substance was diluted with the non-labelled substance. Long-term storage could have an impact on the specific activity; the specific activity of the radiolabeled test substance at purchase was reported. It is unclear if the reported specific activity at the time of dosing (0.05 uCi/uL) was measured in a scintillation counter or simply based on the activity at purchase (5.0 mCi/mmol).
	Metric 8:	Consistency of exposure administration	Low	Different volumes (ranging from 5 to 40 uL) were applied across groups to obtain different exposure concentrations. The different volumes applied likely had an impact on the study results. The skin thickness and area of the skin were uniform across groups.
	Metric 9:	Reporting of concentrations	Low	The exposure concentrations were clearly reported. Volumes of 5, 10, 20, and 40 uL of the radiolabeled test substance were added per 0.79 cm2 cell, with a specific activity of 0.05 uCi/uL, yielding concentrations of 7.9, 15.8, 31.5, and 63.1 mg/cm2. The concentrations were not analytically verified, and it was not reported whether the specific activity of the test solutions was measured.
	Metric 10:	Exposure frequency	High	The skin was exposed to a finite dose and receptor solutions were collected up to 24 hours post-dosing. The purpose of the study was to present a method for estimating the absorption of small doses of liquid VOCs that are splashed on the skin, so the finite dose and 24-hour post-exposure monitoring period were appropriate for the purposes of the study. However, due to the volatility of the test substance, there was clearly a significant amount of evaporation and essentially no test material was present in the receptor fluid after 1-hour post-exposure, and max absorption rates were obtained within 10-20 min. A shorter duration in this case may also have been appropriate.

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Study Citation: Gajjar, R. M., Kasting, G. B. (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicology and Applied Pharmacology 281(1):109-117.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4141541
Unique ID: 63.1 mg/cm2 group

Domain	Metric		Rating	Comments
	Metric 11:	Number of exposure groups and concentration spacing	Low	The study tested 4 exposure concentrations. The concentrations and spacing were not explicitly justified by the study authors. The goal was to mimic small doses of liquid VOCs that are splashed on the skin, but it was not specified what those expected doses/volumes would be. The doses used exceeded the typically recommended dose for an in vitro dermal absorption test (1-5 mg/cm2 for finite dose experiments as per WHO2006, OECD TG 428 etc.,). An inverse dose-response (decreased absorption with increasing dose) was obtained. It is unclear if max absorption would be obtained at even lower concentrations not tested in this study.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test used dermatomed split-thickness human cadaver skin (~0.3 mm thick) either from the back, abdomen, or thigh. These are acceptable sites for skin samples. The source of the skin samples was provided. The skin came treated with a 10% glycerol solution and was stored at -80 degrees C. The skin samples were washed prior to use and cut into 1.5 cm x 1.5 cm squares that were mounted onto modified Franz diffusion cells. According to OECD No. 28, skin should not be stored at low temperatures because storage at -80 degrees C can enhance permeability. However, skin integrity was tested pre-study, and only samples with water permeation values less than 1.2 uL/cm2 were used.
	Metric 13:	Number/Replicates per group	Medium	Permeation experiments were done using skin from 3 donors with an n = 2-7 per donor. The text did indicate that in most cases, conditions were tested with 4-5 replicates for each of the 3 donors, yielding 12-15 replicates per dose. This meets or exceeds the guideline recommendation of 4 replicates per test preparation.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	The purpose of the study was to develop a methodology for estimating absorption from small doses of liquid VOCs. The model estimates were compared to experimental values generated by using human cadaver skin. The outcome methodology was generally appropriate for the purposes of the study; a skin surface of 0.79 cm2 was loaded with different volumes (5, 10, 20, and 40 uL) of the neat test material. The volumes applied at higher doses were greater than guideline recommendations (up to 10 ul/cm2). Cumulative skin permeation was determined by measuring radioactivity in receptor fluid over a 24-hour period and in the skin after 24 hours. Carbon traps were not used to capture the evaporation of a volatile chemical. The study was conducted in a fume hood rather than under ambient conditions, although the authors indicated fume hood was used for safety reasons. However, since most of the applied dose presumably evaporated from the skin surface, the higher airflow may not have been appropriate. The study authors often point to the higher airflow as justification for the low permeation percentages. Solubility in the receptor fluid was not tested. This is considered to be a significant flaw as PBS is not generally recommended for a lipophilic compound. The study did not wash the skin sample, which deviates from OECD TG 428 recommendations.

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4141541
Unique ID: 63.1 mg/cm2 group

Domain	Metric		Rating	Comments
	Metric 15:	Consistency of outcome assessment	High	Details of the outcome assessment protocol were reported, and the outcomes were consistently assessed across groups
	Metric 16:	Sampling adequacy and sensitivity	Medium	Limited details on scintillation counting were provided. Receptor fluid was poured into scintillation vials containing 12 mL of scintillation flued and vials were measured within 1 hour of collection. Skin samples were dissolved in Soluene and analyzed by LSC. The number of scintillation counts per sample, signal to noise ratio/background levels were not reported. It is not clear that any background measurements were taken. The number of evaluations per exposure group in the data table indicates 2-7 per donor per dose, and there were 3 donors.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Low	The skin batch/lot numbers were not reported. The number of skin samples per group varied (2-7 samples per donor, 3 donors/ group). Skin integrity was measured based on 3H20 permeation. It was specified that samples with water permeation $>$ 1.2 uL/cm2 were discarded, therefore there were no differences in the quality of the tissue. The results were not expressed as Kp values or % of the applied dose. Electrical resistance and TEWL measurements were not conducted. It is unknown whether the skin sample collection sites (back, abdomen, or shoulder) were consistent within or across groups. The distribution of the samples in each group was not specified, and this missing information is likely to have a significant impact on the study results.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Low	Solubility of the test substance in the receptor fluid is a potential concern. The test substance has low solubility in water (8.6 g/L) and is lipophilic. The receptor fluid (PBS) is generally appropriate for water soluble compounds but may not be appropriate for lipophilic compounds. The solubility of the test substance in the receptor fluid was not reported, and it is unclear if the permeation rate was influenced by solubility, and whether this had a confounding impact, particularly at the higher doses.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	The cumulative amount of permeated test substance was reported across time the data were reported as means donors $\pm$ SE. The percent of dose permeated was graphically displayed and reported numerically in the text. Data were first averaged by dose for each donor, and then averaged across donors to obtain the mean values. It is unknown whether the study accounted for any outliers. The study did not report the percentage absorbed, but this could be determined by dividing the cumulative amount permeated by the applied dose, although it should be taken into consideration that it is presumed that the majority of the applied dose evaporated. Based on the data provided for the cumulative amount permeated (at 24hrs), the standard deviations can first be determined (SD = SE x SQRT(n), where n =3). The CV values can then be calculated (SD relative to the mean). The calculated CV values are 35%, 44%, 27%, and 23%, for the 7.9, 15.8, 31.5, and 63.1 mg/cm2 groups, respectively. Only the high dose group had an acceptable CV ($<$25%); however, data are available for EPA to calculate an alternate (upper end) value to account for variability in the results.

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4141541
Unique ID: 63.1 mg/cm2 group

Domain	Metric		Rating	Comments
	Metric 20:	Data interpretation	Medium	The percent recovery of the applied test substance was not explicitly reported, although it is presumed to be low because the total cumulative penetration amount ranged from 0.21% to 0.13% of the applied dose. The study authors presumed the remainder evaporated; however, carbon traps were not used to definitively account for evaporated material. The skin was not washed (no measurements of washes), and no measurements of amounts in the donor chamber were collected. Only percentage absorption in the skin from a finite dose is reported and is not defined by dose group (quantitative values not reported). It is not specified whether the absorption estimates were normalized, but it is highly likely that the missing material evaporated and therefore, was unlikely to have been absorbed (under the conditions of this test); the inclusion of evaporated material may not be required. The study also reported the maximum flux of the VOC into the receptor solution. The study authors believed that the data implied that mild lipid barrier disruption likely occurred.
	Metric 21:	Reporting of data	Low	Overall cumulative absorption for each exposure group, at each collection point, was reported as Means ± SE, and the percentage of the applied dose was noted in the text for some, but not all exposure groups. These values presumably represent primarily the amounts measured in receptor fluid. The amount in the skin after 24 hours was simply reported to be less than 0.08% (presumably of the applied dose), and was not described by exposure group. It is not clear if this amount was included in the reported cumulative values. Separate measurements for receptor fluid alone were not reported.

Overall Quality Determination Low

Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: Neat - Infinite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled 1,2-dichloroethane and radiolabeled [14C]-1,2-dichlorethane, CAS number: 107-06-2. The structure was reported for the radiolabeled substance noting the location of the radiolabel within the structure.
	Metric 2:	Test substance source	High	The non-radiolabeled, 1,2-dichloroethane was sourced from LGC standards; the radio-labeled 1,2-dichloroethane was sourced from American Radiolabeled Chemicals, Inc, St. Louis, MO. The study included certificates of analyses that included lot numbers and HPLC outputs.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the radiolabeled test substance was reported to be ≥97.6 by HPLC. The purity of the non-radiolabeled substance was 98.87% by GC/FID. Impurities were not reported. Radiochemical purities of prepared solutions were determined by study authors using HPLC prior to application; all were ≥97.6%, and impurities were not reported.
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	Testosterone (non-labelled and radiolabeled) was used as a reference compound in a finite exposure scenario in accordance with OECD 28 guidelines. Data are fully reported for testosterone studies. 1 mg/ml was administered to the skin (0.012 mg/cm2); n=4. Study authors report a mean mass balance of 93.47% (CV = 1.46), total absorbed dose (receptor fluids and receptor camber) 11.71% (CV=50.47), and maximum absorption rats as 0.2146 ug/cm2/hr (CV=26.6076).“The absorption profiles and distribution of radioactivity obtained from this experiment showed the expected trends and the data was comparable with results obtained in the multi-center comparison study conducted by Van de Sandt et al, 2004.”

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: Neat - Infinite

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428, and OECD 28, The assay procedures specified in the report were described in detail, although some information was missing. The flow through diffusion set-up is sufficiently reported including a schematic drawing. The study does not report if there was an equilibration period after the skin was placed into the chamber (guidelines recommend a 30-minute equilibrium period). An infinite dose of 1,2-dichloroethane (neat, 50%, or 10% dissolved in either isopropyl myristate or 1,1,2-trichloroethane) was applied to human skin (at least 5 replicates; surface area of 0.64 cm2). Volume applied (125 – 1250 uL) was necessary achieve desired application rate of 195 uL/cm2. Human skin samples were dermatomed; samples contained epidermis and some dermis. The thickness of skin samples ranged from 200 to 400 um, exact thickness was not reported. Skin was exposed to the test substance under occluded conditions (PTFE screw lid) for 24 hours. The receptor solution (water fortified with 6% polyethoxyoleate 20 oleyl ether) was appropriate for this lipophilic chemical. The solubility of 1,2-dichloroethane was tested in the receptor fluid prior to the study and determined dissolution of 1,2-dichloroethane was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity ranged from 30-70%. Flow rate of receptor fluid was 1.5 mL/hour. It was not specified whether the receptor fluid was continuously stirred as per OECD 428 guidelines. Receptor fluid samples (volume not reported) were collected at 10 minutes, 30 minutes, 1 hour, 2 hours, and every 2 hours henceforth for 24 hours (16 samples) post-application and analyzed for radioactivity. Radioactivity was measured using a liquid scintillation counter. “Radioactivity in gross amounts less than twice the background level was considered to be below the limit of accurate determination.” A steady state was reached.
	Metric 6:	Standards for tests	Medium	The integrity of the skin was determined by stable trans epidermal water loss (TEWL) prior to dose application and at the end of the experiment. A TWEL of $\leq$ 13 gm-2h-1 was considered acceptable. This is a slight deviation from guidelines which suggest viable skin has a TEWL reading of less than 10 grams/m2/hour. Skin that did not meet the criteria was allowed to dry and TEWL was remeasured. Skins that failed to meet the criteria were not included in the analysis. TEWL readings were reported. The percentage of recovered test substance was not reported. However, recovery determination is not generally relevant for studies only determining a Kp. Coefficients of variation (CV) values were not reported but could be determined based on the SD relative to the mean.

Domain 3: Exposure Characterization

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: Neat - Infinite

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of the test substance was partially reported. The volume of radiolabeled, non-radiolabeled and diluent used for each dose solution was reported in a table. Dilutions were magnetically stirred if deemed necessary by study authors (criteria not reported). The activity and homogeneity of the diluted doses were assessed from the top, middle, and bottom of the solution. All doses were considered homogenous (data not shown). Storage conditions of stock radiolabeled and non-radiolabeled 1,2-dichloroethane were reported. It is unclear how far in advance the dilutions were made; however, the study does state that the radiochemical content and homogeneity were measured prior to dosing. The solubility of the test substance in the receptor fluid was determined to be 19.1 mg/ml. This was deemed appropriate (>60-fold higher than maximum cumulative absorption); solubility in receptor solution was not considered to be rate-limiting.
	Metric 8:	Consistency of exposure administration	Low	The study did not use the same volume across all samples (ranging from 64ul – 640ul) however this was done in order to maintain a constant application rate and is not expected to substantially impact the study results. The skin surface area of 0.64 cm2 was consistent across groups. However, the skin thickness was reported as a range (200 to 400 uM). It is unclear if the variation in thicknesses was consistent across groups, and this may have contributed to some of the endpoint variations (and subsequently high CVs) observed.
	Metric 9:	Reporting of concentrations	High	The applied dose is reported as dpm, mg, and mg/cm2. Individual cells are reported independently. Nominal and analytical doses are reported.
	Metric 10:	Exposure frequency	High	Exposure duration (24-hours) was reported and was appropriate for Kp determination. A steady state flux was obtained.
	Metric 11:	Number of exposure groups and concentration spacing	High	There were 3 dose groups tested in a wide range of concentrations (neat, 50%, and 10%). Dilutions of test substance was performed in two different vehicles (isopropyl myristate or 1,1,2-trichloroethane). Justification for dose selection is provided by authors.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Samples of full-thickness skin samples were obtained from 1 male and 13 female donors following elective surgery. Abdominal skin samples from 14 people (race not reported) ranging in age from 31-70 years old were studied. The samples were stored frozen at -20 degrees C +/- 10 degrees C. Prior to use, the skin samples were thawed, wiped to remove residual fat and blood, re-hydrated in purified water, and dermatomed using a mini-dermatome. The thickness ranged from 200 to 400 uM. The skin contained epidermis and some dermis. These methods were in agreement with OECD guidelines which state split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring transepidermal water loss prior to/and upon completion of the experiment.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates was appropriate as per OECD 428. Guidelines recommend a minimum of 4 replicates per test preparation. This study examined 5-10 replicates/dose.
Domain 5: Outcome Assessment				

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: Neat - Infinite

Domain	Metric		Rating	Comments
	Metric 14:	Outcome assessment methodology	High	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28. Measurement techniques and timing were reported and appropriate. An infinite dose of the test substance was used to determine the Kp and maximum absorption rate. An application rate of 195 uL/cm2 was used, which is in agreement with OECD guideline of using >100 uL/cm2 for infinite exposures.
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assess consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period was consistent across replicates.
	Metric 16:	Sampling adequacy and sensitivity	Medium	The study reported adequate sampling for the outcomes of interest; measurement sensitivity was sufficient. The sampling intervals were adequate to allow for a steady-state portion of the absorption profile to be obtained. Methods for the determination of radioactivity are reported. "Radioactivity in gross amounts of less than twice the background level was considered to be below the limit of accurate determination." Scintillation counts were not shown. Graphical representations of absorption over time are shown.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study used a single batch of radiolabeled 1,2-dichloroethane. Human abdominal skin was obtained from 14 donors, male and female, ranging in age from 31 to 70 years old. The large age range and sex differences may influence results. The split-thickness was reported as a range (200-400 um). This variation in skin thickness may result in inconsistencies between samples. Skin integrity was confirmed by TEWL both pre and post-exposure. Only skin meeting inclusion criteria ($\leq$ 13 grams/m2/hour) at both time points were included in the analysis. This is a slight deviation from OECD 428 and 156 which suggests viable skin have a TEWL reading of less than 10 grams/m2/hour. All TEWL measurements are reported. The majority are $\leq$10 grams/m2/hour.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Means and standard deviations were calculated and reported. Mathematical calculations used to determine Kp are reported and were appropriate. The Kp was based on the steady-state part of the absorption curve. CV values were not reported for Kp/flux measurements and maximum absorption rate, however the study provided sufficient data to independently calculate themCalculated CV for Kp and maximum flux are >50%, but sufficient data are available for EPA to calculate an alternate value.
	Metric 20:	Data interpretation	Medium	The Kp and mean maximum absorption rate was derived from an appropriate exposure condition (infinite dose). The author states that "data indicates that true sink conditions were not maintained for some replicates. . . due to the volatility of the test item". Despite this, they do conclude that sufficient data were obtained to calculate Kp over the steady state portion of the absorption profile. Recovery was not reported but this determination is not relevant for infinite dose applications.

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Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	Neat - Infinite

Domain	Metric		Rating	Comments
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means ± SD. Individual replicate data were provided.

Overall Quality Determination High

Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	50% in 1,1,2-trichloroethane- infinite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled 1,2-dichloroethane and radiolabeled [14C]-1,2-dichlorethane, CAS number: 107-06-2. The structure was reported for the radiolabeled substance noting the location of the radiolabel within the structure.
	Metric 2:	Test substance source	High	The non-radiolabeled, 1,2-dichloroethane was sourced from LGC standards; the radio-labeled 1,2-dichloroethane was sourced from American Radiolabeled Chemicals, Inc, St. Louis, MO. The study included certificates of analyses that included lot numbers and HPLC outputs.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the radiolabeled test substance was reported to be ≥97.6 by HPLC. The purity of the non-radiolabeled substance was 98.87% by GC/FID. Impurities were not reported. Radiochemical purities of prepared solutions were determined by study authors using HPLC prior to application; all were ≥97.6%, and impurities were not reported.
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	Testosterone (non-labelled and radiolabeled) was used as a reference compound in a finite exposure scenario in accordance with OECD 28 guidelines. Data are fully reported for testosterone studies. 1 mg/ml was administered to the skin (0.012 mg/cm2); n=4. Study authors report a mean mass balance of 93.47% (CV = 1.46), total absorbed dose (receptor fluids and receptor camber) 11.71% (CV=50.47), and maximum absorption rats as 0.2146 ug/cm2/hr (CV=26.6076).“The absorption profiles and distribution of radioactivity obtained from this experiment showed the expected trends and the data was comparable with results obtained in the multi-center comparison study conducted by Van de Sandt et al, 2004.”

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Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	50% in 1,1,2-trichloroethane- infinite

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428, and OECD 28, The assay procedures specified in the report were described in detail, although some information was missing. The flow through diffusion set-up is sufficiently reported including a schematic drawing. The study does not report if there was an equilibration period after the skin was placed into the chamber (guidelines recommend a 30-minute equilibrium period). An infinite dose of 1,2-dichloroethane (neat, 50%, or 10% dissolved in either isopropyl myristate or 1,1,2-trichloroethane) was applied to human skin (at least 5 replicates; surface area of 0.64 cm2). Volume applied (125 – 1250 uL) was necessary achieve desired application rate of 195 uL/cm2. Human skin samples were dermatomed; samples contained epidermis and some dermis. The thickness of skin samples ranged from 200 to 400 um, exact thickness was not reported. Skin was exposed to the test substance under occluded conditions (PTFE screw lid) for 24 hours. The receptor solution (water fortified with 6% polyethoxyoleate 20 oleyl ether) was appropriate for this lipophilic chemical. The solubility of 1,2-dichloroethane was tested in the receptor fluid prior to the study and determined dissolution of 1,2-dichloroethane was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity ranged from 30-70%. Flow rate of receptor fluid was 1.5 mL/hour. It was not specified whether the receptor fluid was continuously stirred as per OECD 428 guidelines. Receptor fluid samples (volume not reported) were collected at 10 minutes, 30 minutes, 1 hour, 2 hours, and every 2 hours henceforth for 24 hours (16 samples) post-application and analyzed for radioactivity. Radioactivity was measured using a liquid scintillation counter. “Radioactivity in gross amounts less than twice the background level was considered to be below the limit of accurate determination.” A steady state was reached.
	Metric 6:	Standards for tests	Medium	The integrity of the skin was determined by stable trans epidermal water loss (TEWL) prior to dose application and at the end of the experiment. A TWEL of $\leq$ 13 gm-2h-1 was considered acceptable. This is a slight deviation from guidelines which suggest viable skin has a TEWL reading of less than 10 grams/m2/hour. Skin that did not meet the criteria was allowed to dry and TEWL was remeasured. Skins that failed to meet the criteria were not included in the analysis. TEWL readings were reported. The percentage of recovered test substance was not reported. However, recovery determination is not generally relevant for studies only determining a Kp. Coefficients of variation (CV) values were not reported but could be determined based on the SD relative to the mean.

Domain 3: Exposure Characterization

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 50% in 1,1,2-trichloroethane- infinite

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of the test substance was partially reported. The volume of radiolabeled, non-radiolabeled and diluent used for each dose solution was reported in a table. Dilutions were magnetically stirred if deemed necessary by study authors (criteria not reported). The activity and homogeneity of the diluted doses were assessed from the top, middle, and bottom of the solution. All doses were considered homogenous (data not shown). Storage conditions of stock radiolabeled and non-radiolabeled 1,2-dichloroethane were reported. It is unclear how far in advance the dilutions were made; however, the study does state that the radiochemical content and homogeneity were measured prior to dosing. The solubility of the test substance in the receptor fluid was determined to be 19.1 mg/ml. This was deemed appropriate (>60-fold higher than maximum cumulative absorption); solubility in receptor solution was not considered to be rate-limiting.
	Metric 8:	Consistency of exposure administration	Low	The study did not use the same volume across all samples (ranging from 64ul – 640ul) however this was done in order to maintain a constant application rate and is not expected to substantially impact the study results. The skin surface area of 0.64 cm2 was consistent across groups. However, the skin thickness was reported as a range (200 to 400 uM). It is unclear if the variation in thicknesses was consistent across groups, and this may have contributed to some of the endpoint variations (and subsequently high CVs) observed.
	Metric 9:	Reporting of concentrations	High	The applied dose is reported as dpm, mg, and mg/cm2. Individual cells are reported independently. Nominal and analytical doses are reported.
	Metric 10:	Exposure frequency	High	Exposure duration (24-hours) was reported and was appropriate for Kp determination. A steady state flux was obtained.
	Metric 11:	Number of exposure groups and concentration spacing	High	There were 3 dose groups tested in a wide range of concentrations (neat, 50%, and 10%). Dilutions of test substance was performed in two different vehicles (isopropyl myristate or 1,1,2-trichloroethane). Justification for dose selection is provided by authors.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Samples of full-thickness skin samples were obtained from 1 male and 13 female donors following elective surgery. Abdominal skin samples from 14 people (race not reported) ranging in age from 31-70 years old were studied. The samples were stored frozen at -20 degrees C +/- 10 degrees C. Prior to use, the skin samples were thawed, wiped to remove residual fat and blood, re-hydrated in purified water, and dermatomed using a mini-dermatome. The thickness ranged from 200 to 400 uM. The skin contained epidermis and some dermis. These methods were in agreement with OECD guidelines which state split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring transepidermal water loss prior to/and upon completion of the experiment.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates was appropriate as per OECD 428. Guidelines recommend a minimum of 4 replicates per test preparation. This study examined 5-10 replicates/dose.
Domain 5: Outcome Assessment				

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 50% in 1,1,2-trichloroethane- infinite

Domain	Metric		Rating	Comments
	Metric 14:	Outcome assessment methodology	High	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28. Measurement techniques and timing were reported and appropriate. An infinite dose of the test substance was used to determine the Kp and maximum absorption rate. An application rate of 195 uL/cm2 was used, which is in agreement with OECD guideline of using >100 uL/cm2 for infinite exposures.
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assess consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period was consistent across replicates.
	Metric 16:	Sampling adequacy and sensitivity	Medium	The study reported adequate sampling for the outcomes of interest; measurement sensitivity was sufficient. The sampling intervals were adequate to allow for a steady-state portion of the absorption profile to be obtained. Methods for the determination of radioactivity are reported. "Radioactivity in gross amounts of less than twice the background level was considered to be below the limit of accurate determination." Scintillation counts were not shown. Graphical representations of absorption over time are shown.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study used a single batch of radiolabeled 1,2-dichloroethane. Human abdominal skin was obtained from 14 donors, male and female, ranging in age from 31 to 70 years old. The large age range and sex differences may influence results. The split-thickness was reported as a range (200-400 um). This variation in skin thickness may result in inconsistencies between samples. Skin integrity was confirmed by TEWL both pre and post-exposure. Only skin meeting inclusion criteria ($\leq$ 13 grams/m2/hour) at both time points were included in the analysis. This is a slight deviation from OECD 428 and 156 which suggests viable skin have a TEWL reading of less than 10 grams/m2/hour. All TEWL measurements are reported. The majority are $\leq$10 grams/m2/hour.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Means and standard deviations were calculated and reported. Mathematical calculations used to determine Kp are reported and were appropriate. The Kp was based on the steady-state part of the absorption curve. CV values were not reported for Kp/flux measurements and maximum absorption rate, however the study provided sufficient data to independently calculate themCalculated CV for Kp and maximum flux are >50%, but sufficient data are available for EPA to calculate an alternate value.
	Metric 20:	Data interpretation	Medium	The Kp and mean maximum absorption rate was derived from an appropriate exposure condition (infinite dose). The author states that "data indicates that true sink conditions were not maintained for some replicates. . . due to the volatility of the test item". Despite this, they do conclude that sufficient data were obtained to calculate Kp over the steady state portion of the absorption profile. Recovery was not reported but this determination is not relevant for infinite dose applications.

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Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	50% in 1,1,2-trichloroethane- infinite

Domain	Metric		Rating	Comments
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means ± SD. Individual replicate data were provided.

Overall Quality Determination High

Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	50% in IPM - infinite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled 1,2-dichloroethane and radiolabeled [14C]-1,2-dichlorethane, CAS number: 107-06-2. The structure was reported for the radiolabeled substance noting the location of the radiolabel within the structure.
	Metric 2:	Test substance source	High	The non-radiolabeled, 1,2-dichloroethane was sourced from LGC standards; the radiolabeled 1,2-dichloroethane was sourced from American Radiolabeled Chemicals, Inc, St. Louis, MO. The study included certificates of analyses that included lot numbers and HPLC outputs.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the radiolabeled test substance was reported to be ≥97.6 by HPLC. The purity of the non-radiolabeled substance was 98.87% by GC/FID. Impurities were not reported. Radiochemical purities of prepared solutions were determined by study authors using HPLC prior to application; all were ≥97.6%, and impurities were not reported.
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	Testosterone (non-labelled and radiolabeled) was used as a reference compound in a finite exposure scenario in accordance with OECD 28 guidelines. Data are fully reported for testosterone studies. 1 mg/ml was administered to the skin (0.012 mg/cm2); n=4. Study authors report a mean mass balance of 93.47% (CV = 1.46), total absorbed dose (receptor fluids and receptor camber) 11.71% (CV=50.47), and maximum absorption rats as 0.2146 ug/cm2/hr (CV=26.6076).“The absorption profiles and distribution of radioactivity obtained from this experiment showed the expected trends and the data was comparable with results obtained in the multi-center comparison study conducted by Van de Sandt et al, 2004.”

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 50% in IPM - infinite

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428, and OECD 28, The assay procedures specified in the report were described in detail, although some information was missing. The flow through diffusion set-up is sufficiently reported including a schematic drawing. The study does not report if there was an equilibration period after the skin was placed into the chamber (guidelines recommend a 30-minute equilibrium period). An infinite dose of 1,2-dichloroethane (neat, 50%, or 10% dissolved in either isopropyl myristate or 1,1,2-trichloroethane) was applied to human skin (at least 5 replicates; surface area of 0.64 cm2). Volume applied (125 – 1250 uL) was necessary achieve desired application rate of 195 uL/cm2. Human skin samples were dermatomed; samples contained epidermis and some dermis. The thickness of skin samples ranged from 200 to 400 um, exact thickness was not reported. Skin was exposed to the test substance under occluded conditions (PTFE screw lid) for 24 hours. The receptor solution (water fortified with 6% polyethoxyoleate 20 oleyl ether) was appropriate for this lipophilic chemical. The solubility of 1,2-dichloroethane was tested in the receptor fluid prior to the study and determined dissolution of 1,2-dichloroethane was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity ranged from 30-70%. Flow rate of receptor fluid was 1.5 mL/hour. It was not specified whether the receptor fluid was continuously stirred as per OECD 428 guidelines. Receptor fluid samples (volume not reported) were collected at 10 minutes, 30 minutes, 1 hour, 2 hours, and every 2 hours henceforth for 24 hours (16 samples) post-application and analyzed for radioactivity. Radioactivity was measured using a liquid scintillation counter. “Radioactivity in gross amounts less than twice the background level was considered to be below the limit of accurate determination.” A steady state was reached.
	Metric 6:	Standards for tests	Medium	The integrity of the skin was determined by stable trans epidermal water loss (TEWL) prior to dose application and at the end of the experiment. A TWEL of $\leq$ 13 gm-2h-1 was considered acceptable. This is a slight deviation from guidelines which suggest viable skin has a TEWL reading of less than 10 grams/m2/hour. Skin that did not meet the criteria was allowed to dry and TEWL was remeasured. Skins that failed to meet the criteria were not included in the analysis. TEWL readings were reported. The percentage of recovered test substance was not reported. However, recovery determination is not generally relevant for studies only determining a Kp. Coefficients of variation (CV) values were not reported but could be determined based on the SD relative to the mean.

Domain 3: Exposure Characterization

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 50% in IPM - infinite

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of the test substance was partially reported. The volume of radiolabeled, non-radiolabeled and diluent used for each dose solution was reported in a table. Dilutions were magnetically stirred if deemed necessary by study authors (criteria not reported). The activity and homogeneity of the diluted doses were assessed from the top, middle, and bottom of the solution. All doses were considered homogenous (data not shown). Storage conditions of stock radiolabeled and non-radiolabeled 1,2-dichloroethane were reported. It is unclear how far in advance the dilutions were made; however, the study does state that the radiochemical content and homogeneity were measured prior to dosing. The solubility of the test substance in the receptor fluid was determined to be 19.1 mg/ml. This was deemed appropriate (>60-fold higher than maximum cumulative absorption); solubility in receptor solution was not considered to be rate-limiting.
	Metric 8:	Consistency of exposure administration	Low	The study did not use the same volume across all samples (ranging from 64ul – 640ul) however this was done in order to maintain a constant application rate and is not expected to substantially impact the study results. The skin surface area of 0.64 cm2 was consistent across groups. However, the skin thickness was reported as a range (200 to 400 uM). It is unclear if the variation in thicknesses was consistent across groups, and this may have contributed to some of the endpoint variations (and subsequently high CVs) observed.
	Metric 9:	Reporting of concentrations	High	The applied dose is reported as dpm, mg, and mg/cm2. Individual cells are reported independently. Nominal and analytical doses are reported.
	Metric 10:	Exposure frequency	High	Exposure duration (24-hours) was reported and was appropriate for Kp determination. A steady state flux was obtained.
	Metric 11:	Number of exposure groups and concentration spacing	High	There were 3 dose groups tested in a wide range of concentrations (neat, 50%, and 10%). Dilutions of test substance was performed in two different vehicles (isopropyl myristate or 1,1,2-trichloroethane). Justification for dose selection is provided by authors.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Samples of full-thickness skin samples were obtained from 1 male and 13 female donors following elective surgery. Abdominal skin samples from 14 people (race not reported) ranging in age from 31-70 years old were studied. The samples were stored frozen at -20 degrees C +/- 10 degrees C. Prior to use, the skin samples were thawed, wiped to remove residual fat and blood, re-hydrated in purified water, and dermatomed using a mini-dermatome. The thickness ranged from 200 to 400 uM. The skin contained epidermis and some dermis. These methods were in agreement with OECD guidelines which state split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring transepidermal water loss prior to/and upon completion of the experiment.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates was appropriate as per OECD 428. Guidelines recommend a minimum of 4 replicates per test preparation. This study examined 5-10 replicates/dose.
Domain 5: Outcome Assessment				

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 50% in IPM - infinite

Domain	Metric		Rating	Comments
	Metric 14:	Outcome assessment methodology	High	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28. Measurement techniques and timing were reported and appropriate. An infinite dose of the test substance was used to determine the Kp and maximum absorption rate. An application rate of 195 uL/cm2 was used, which is in agreement with OECD guideline of using >100 uL/cm2 for infinite exposures.
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assess consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period was consistent across replicates.
	Metric 16:	Sampling adequacy and sensitivity	Medium	The study reported adequate sampling for the outcomes of interest; measurement sensitivity was sufficient. The sampling intervals were adequate to allow for a steady-state portion of the absorption profile to be obtained. Methods for the determination of radioactivity are reported. "Radioactivity in gross amounts of less than twice the background level was considered to be below the limit of accurate determination." Scintillation counts were not shown. Graphical representations of absorption over time are shown.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study used a single batch of radiolabeled 1,2-dichloroethane. Human abdominal skin was obtained from 14 donors, male and female, ranging in age from 31 to 70 years old. The large age range and sex differences may influence results. The split-thickness was reported as a range (200-400 um). This variation in skin thickness may result in inconsistencies between samples. Skin integrity was confirmed by TEWL both pre and post-exposure. Only skin meeting inclusion criteria ($\leq$ 13 grams/m2/hour) at both time points were included in the analysis. This is a slight deviation from OECD 428 and 156 which suggests viable skin have a TEWL reading of less than 10 grams/m2/hour. All TEWL measurements are reported. The majority are $\leq$10 grams/m2/hour.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Means and standard deviations were calculated and reported. Mathematical calculations used to determine Kp are reported and were appropriate. The Kp was based on the steady-state part of the absorption curve. CV values were not reported for Kp/flux measurements and maximum absorption rate, however the study provided sufficient data to independently calculate themCalculated CV for Kp and maximum flux are >50%, but sufficient data are available for EPA to calculate an alternate value.
	Metric 20:	Data interpretation	High	The Kp and mean maximum absorption rate was derived from an appropriate exposure condition (infinite dose). Recovery was not reported but this determination is not relevant for infinite dose applications.
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means $\pm$ SD. Individual replicate data were provided.

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Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	50% in IPM - infinite

Domain	Metric	Rating	Comments
Overall Quality Determination		**High**	

Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	10% in IPM - infinite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled 1,2-dichloroethane and radiolabeled [14C]-1,2-dichlorethane, CAS number: 107-06-2. The structure was reported for the radiolabeled substance noting the location of the radiolabel within the structure.
	Metric 2:	Test substance source	High	The non-radiolabeled, 1,2-dichloroethane was sourced from LGC standards; the radiolabeled 1,2-dichloroethane was sourced from American Radiolabeled Chemicals, Inc, St. Louis, MO. The study included certificates of analyses that included lot numbers and HPLC outputs.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the radiolabeled test substance was reported to be ≥97.6 by HPLC. The purity of the non-radiolabeled substance was 98.87% by GC/FID. Impurities were not reported. Radiochemical purities of prepared solutions were determined by study authors using HPLC prior to application; all were ≥97.6%, and impurities were not reported.
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	Testosterone (non-labelled and radiolabeled) was used as a reference compound in a finite exposure scenario in accordance with OECD 28 guidelines. Data are fully reported for testosterone studies. 1 mg/ml was administered to the skin (0.012 mg/cm2); n=4. Study authors report a mean mass balance of 93.47% (CV = 1.46), total absorbed dose (receptor fluids and receptor camber) 11.71% (CV=50.47), and maximum absorption rats as 0.2146 ug/cm2/hr (CV=26.6076).“The absorption profiles and distribution of radioactivity obtained from this experiment showed the expected trends and the data was comparable with results obtained in the multi-center comparison study conducted by Van de Sandt et al, 2004.”

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 10% in IPM - infinite

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428, and OECD 28, The assay procedures specified in the report were described in detail, although some information was missing. The flow through diffusion set-up is sufficiently reported including a schematic drawing. The study does not report if there was an equilibration period after the skin was placed into the chamber (guidelines recommend a 30-minute equilibrium period). An infinite dose of 1,2-dichloroethane (neat, 50%, or 10% dissolved in either isopropyl myristate or 1,1,2-trichloroethane) was applied to human skin (at least 5 replicates; surface area of 0.64 cm2). Volume applied (125 – 1250 uL) was necessary achieve desired application rate of 195 uL/cm2. Human skin samples were dermatomed; samples contained epidermis and some dermis. The thickness of skin samples ranged from 200 to 400 um, exact thickness was not reported. Skin was exposed to the test substance under occluded conditions (PTFE screw lid) for 24 hours. The receptor solution (water fortified with 6% polyethoxyoleate 20 oleyl ether) was appropriate for this lipophilic chemical. The solubility of 1,2-dichloroethane was tested in the receptor fluid prior to the study and determined dissolution of 1,2-dichloroethane was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity ranged from 30-70%. Flow rate of receptor fluid was 1.5 mL/hour. It was not specified whether the receptor fluid was continuously stirred as per OECD 428 guidelines. Receptor fluid samples (volume not reported) were collected at 10 minutes, 30 minutes, 1 hour, 2 hours, and every 2 hours henceforth for 24 hours (16 samples) post-application and analyzed for radioactivity. Radioactivity was measured using a liquid scintillation counter. “Radioactivity in gross amounts less than twice the background level was considered to be below the limit of accurate determination.” A steady state was reached.
	Metric 6:	Standards for tests	Medium	The integrity of the skin was determined by stable trans epidermal water loss (TEWL) prior to dose application and at the end of the experiment. A TWEL of $\leq$ 13 gm-2h-1 was considered acceptable. This is a slight deviation from guidelines which suggest viable skin has a TEWL reading of less than 10 grams/m2/hour. Skin that did not meet the criteria was allowed to dry and TEWL was remeasured. Skins that failed to meet the criteria were not included in the analysis. TEWL readings were reported. The percentage of recovered test substance was not reported. However, recovery determination is not generally relevant for studies only determining a Kp. Coefficients of variation (CV) values were not reported but could be determined based on the SD relative to the mean.

Domain 3: Exposure Characterization

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 10% in IPM - infinite

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of the test substance was partially reported. The volume of radiolabeled, non-radiolabeled and diluent used for each dose solution was reported in a table. Dilutions were magnetically stirred if deemed necessary by study authors (criteria not reported). The activity and homogeneity of the diluted doses were assessed from the top, middle, and bottom of the solution. All doses were considered homogenous (data not shown). Storage conditions of stock radiolabeled and non-radiolabeled 1,2-dichloroethane were reported. It is unclear how far in advance the dilutions were made; however, the study does state that the radiochemical content and homogeneity were measured prior to dosing. The solubility of the test substance in the receptor fluid was determined to be 19.1 mg/ml. This was deemed appropriate (>60-fold higher than maximum cumulative absorption); solubility in receptor solution was not considered to be rate-limiting.
	Metric 8:	Consistency of exposure administration	Low	The study did not use the same volume across all samples (ranging from 64ul – 640ul) however this was done in order to maintain a constant application rate and is not expected to substantially impact the study results. The skin surface area of 0.64 cm2 was consistent across groups. However, the skin thickness was reported as a range (200 to 400 uM). It is unclear if the variation in thicknesses was consistent across groups, and this may have contributed to some of the endpoint variations (and subsequently high CVs) observed.
	Metric 9:	Reporting of concentrations	High	The applied dose is reported as dpm, mg, and mg/cm2. Individual cells are reported independently. Nominal and analytical doses are reported.
	Metric 10:	Exposure frequency	High	Exposure duration (24-hours) was reported and was appropriate for Kp determination. A steady state flux was obtained.
	Metric 11:	Number of exposure groups and concentration spacing	High	There were 3 dose groups tested in a wide range of concentrations (neat, 50%, and 10%). Dilutions of test substance was performed in two different vehicles (isopropyl myristate or 1,1,2-trichloroethane). Justification for dose selection is provided by authors.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Samples of full-thickness skin samples were obtained from 1 male and 13 female donors following elective surgery. Abdominal skin samples from 14 people (race not reported) ranging in age from 31-70 years old were studied. The samples were stored frozen at -20 degrees C +/- 10 degrees C. Prior to use, the skin samples were thawed, wiped to remove residual fat and blood, re-hydrated in purified water, and dermatomed using a mini-dermatome. The thickness ranged from 200 to 400 uM. The skin contained epidermis and some dermis. These methods were in agreement with OECD guidelines which state split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring transepidermal water loss prior to/and upon completion of the experiment.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates was appropriate as per OECD 428. Guidelines recommend a minimum of 4 replicates per test preparation. This study examined 5-10 replicates/dose.
Domain 5: Outcome Assessment				

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 10% in IPM - infinite

Domain	Metric		Rating	Comments
	Metric 14:	Outcome assessment methodology	High	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28. Measurement techniques and timing were reported and appropriate. An infinite dose of the test substance was used to determine the Kp and maximum absorption rate. An application rate of 195 uL/cm2 was used, which is in agreement with OECD guideline of using >100 uL/cm2 for infinite exposures.
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assess consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period was consistent across replicates.
	Metric 16:	Sampling adequacy and sensitivity	Medium	The study reported adequate sampling for the outcomes of interest; measurement sensitivity was sufficient. The sampling intervals were adequate to allow for a steady-state portion of the absorption profile to be obtained. Methods for the determination of radioactivity are reported. "Radioactivity in gross amounts of less than twice the background level was considered to be below the limit of accurate determination." Scintillation counts were not shown. Graphical representations of absorption over time are shown.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study used a single batch of radiolabeled 1,2-dichloroethane. Human abdominal skin was obtained from 14 donors, male and female, ranging in age from 31 to 70 years old. The large age range and sex differences may influence results. The split-thickness was reported as a range (200-400 um). This variation in skin thickness may result in inconsistencies between samples. Skin integrity was confirmed by TEWL both pre and post-exposure. Only skin meeting inclusion criteria ($\leq$ 13 grams/m2/hour) at both time points were included in the analysis. This is a slight deviation from OECD 428 and 156 which suggests viable skin have a TEWL reading of less than 10 grams/m2/hour. All TEWL measurements are reported. The majority are $\leq$10 grams/m2/hour.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Means and standard deviations were calculated and reported. Mathematical calculations used to determine Kp are reported and were appropriate. The Kp was based on the steady-state part of the absorption curve. CV values were not reported for Kp/flux measurements and maximum absorption rate, however the study provided sufficient data to independently calculate themCalculated CV for Kp and maximum flux are >50%, but sufficient data are available for EPA to calculate an alternate value.
	Metric 20:	Data interpretation	High	The Kp and mean maximum absorption rate was derived from an appropriate exposure condition (infinite dose). Recovery was not reported but this determination is not relevant for infinite dose applications.
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means $\pm$ SD. Individual replicate data were provided.

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Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	10% in IPM - infinite

Domain	Metric	Rating	Comments
Overall Quality Determination		**High**	

Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	10% in 1,1,2-trichloroethane- infinite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled 1,2-dichloroethane and radiolabeled [14C]-1,2-dichlorethane, CAS number: 107-06-2. The structure was reported for the radiolabeled substance noting the location of the radiolabel within the structure.
	Metric 2:	Test substance source	High	The non-radiolabeled, 1,2-dichloroethane was sourced from LGC standards; the radiolabeled 1,2-dichloroethane was sourced from American Radiolabeled Chemicals, Inc, St. Louis, MO. The study included certificates of analyses that included lot numbers and HPLC outputs.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the radiolabeled test substance was reported to be ≥97.6 by HPLC. The purity of the non-radiolabeled substance was 98.87% by GC/FID. Impurities were not reported. Radiochemical purities of prepared solutions were determined by study authors using HPLC prior to application; all were ≥97.6%, and impurities were not reported.
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	Testosterone (non-labelled and radiolabeled) was used as a reference compound in a finite exposure scenario in accordance with OECD 28 guidelines. Data are fully reported for testosterone studies. 1 mg/ml was administered to the skin (0.012 mg/cm2); n=4. Study authors report a mean mass balance of 93.47% (CV = 1.46), total absorbed dose (receptor fluids and receptor camber) 11.71% (CV=50.47), and maximum absorption rats as 0.2146 ug/cm2/hr (CV=26.6076).“The absorption profiles and distribution of radioactivity obtained from this experiment showed the expected trends and the data was comparable with results obtained in the multi-center comparison study conducted by Van de Sandt et al, 2004.”

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 10% in 1,1,2-trichloroethane- infinite

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428, and OECD 28, The assay procedures specified in the report were described in detail, although some information was missing. The flow through diffusion set-up is sufficiently reported including a schematic drawing. The study does not report if there was an equilibration period after the skin was placed into the chamber (guidelines recommend a 30-minute equilibrium period). An infinite dose of 1,2-dichloroethane (neat, 50%, or 10% dissolved in either isopropyl myristate or 1,1,2-trichloroethane) was applied to human skin (at least 5 replicates; surface area of 0.64 cm2). Volume applied (125 – 1250 uL) was necessary achieve desired application rate of 195 uL/cm2. Human skin samples were dermatomed; samples contained epidermis and some dermis. The thickness of skin samples ranged from 200 to 400 um, exact thickness was not reported. Skin was exposed to the test substance under occluded conditions (PTFE screw lid) for 24 hours. The receptor solution (water fortified with 6% polyethoxyoleate 20 oleyl ether) was appropriate for this lipophilic chemical. The solubility of 1,2-dichloroethane was tested in the receptor fluid prior to the study and determined dissolution of 1,2-dichloroethane was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity ranged from 30-70%. Flow rate of receptor fluid was 1.5 mL/hour. It was not specified whether the receptor fluid was continuously stirred as per OECD 428 guidelines. Receptor fluid samples (volume not reported) were collected at 10 minutes, 30 minutes, 1 hour, 2 hours, and every 2 hours henceforth for 24 hours (16 samples) post-application and analyzed for radioactivity. Radioactivity was measured using a liquid scintillation counter. “Radioactivity in gross amounts less than twice the background level was considered to be below the limit of accurate determination.” A steady state was reached.
	Metric 6:	Standards for tests	Medium	The integrity of the skin was determined by stable trans epidermal water loss (TEWL) prior to dose application and at the end of the experiment. A TWEL of $\leq$ 13 gm-2h-1 was considered acceptable. This is a slight deviation from guidelines which suggest viable skin has a TEWL reading of less than 10 grams/m2/hour. Skin that did not meet the criteria was allowed to dry and TEWL was remeasured. Skins that failed to meet the criteria were not included in the analysis. TEWL readings were reported. The percentage of recovered test substance was not reported. However, recovery determination is not generally relevant for studies only determining a Kp. Coefficients of variation (CV) values were not reported but could be determined based on the SD relative to the mean.

Domain 3: Exposure Characterization

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 10% in 1,1,2-trichloroethane- infinite

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of the test substance was partially reported. The volume of radiolabeled, non-radiolabeled and diluent used for each dose solution was reported in a table. Dilutions were magnetically stirred if deemed necessary by study authors (criteria not reported). The activity and homogeneity of the diluted doses were assessed from the top, middle, and bottom of the solution. All doses were considered homogenous (data not shown). Storage conditions of stock radiolabeled and non-radiolabeled 1,2-dichloroethane were reported. It is unclear how far in advance the dilutions were made; however, the study does state that the radiochemical content and homogeneity were measured prior to dosing. The solubility of the test substance in the receptor fluid was determined to be 19.1 mg/ml. This was deemed appropriate (>60-fold higher than maximum cumulative absorption); solubility in receptor solution was not considered to be rate-limiting.
	Metric 8:	Consistency of exposure administration	Low	The study did not use the same volume across all samples (ranging from 64ul – 640ul) however this was done in order to maintain a constant application rate and is not expected to substantially impact the study results. The skin surface area of 0.64 cm2 was consistent across groups. However, the skin thickness was reported as a range (200 to 400 uM). It is unclear if the variation in thicknesses was consistent across groups, and this may have contributed to some of the endpoint variations (and subsequently high CVs) observed.
	Metric 9:	Reporting of concentrations	High	The applied dose is reported as dpm, mg, and mg/cm2. Individual cells are reported independently. Nominal and analytical doses are reported.
	Metric 10:	Exposure frequency	High	Exposure duration (24-hours) was reported and was appropriate for Kp determination. A steady state flux was obtained.
	Metric 11:	Number of exposure groups and concentration spacing	High	There were 3 dose groups tested in a wide range of concentrations (neat, 50%, and 10%). Dilutions of test substance was performed in two different vehicles (isopropyl myristate or 1,1,2-trichloroethane). Justification for dose selection is provided by authors.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Samples of full-thickness skin samples were obtained from 1 male and 13 female donors following elective surgery. Abdominal skin samples from 14 people (race not reported) ranging in age from 31-70 years old were studied. The samples were stored frozen at -20 degrees C +/- 10 degrees C. Prior to use, the skin samples were thawed, wiped to remove residual fat and blood, re-hydrated in purified water, and dermatomed using a mini-dermatome. The thickness ranged from 200 to 400 uM. The skin contained epidermis and some dermis. These methods were in agreement with OECD guidelines which state split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring transepidermal water loss prior to/and upon completion of the experiment.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates was appropriate as per OECD 428. Guidelines recommend a minimum of 4 replicates per test preparation. This study examined 5-10 replicates/dose.
Domain 5: Outcome Assessment				

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 10% in 1,1,2-trichloroethane- infinite

Domain	Metric		Rating	Comments
	Metric 14:	Outcome assessment methodology	High	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28. Measurement techniques and timing were reported and appropriate. An infinite dose of the test substance was used to determine the Kp and maximum absorption rate. An application rate of 195 uL/cm2 was used, which is in agreement with OECD guideline of using >100 uL/cm2 for infinite exposures.
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assess consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period was consistent across replicates.
	Metric 16:	Sampling adequacy and sensitivity	Medium	The study reported adequate sampling for the outcomes of interest; measurement sensitivity was sufficient. The sampling intervals were adequate to allow for a steady-state portion of the absorption profile to be obtained. Methods for the determination of radioactivity are reported. "Radioactivity in gross amounts of less than twice the background level was considered to be below the limit of accurate determination." Scintillation counts were not shown. Graphical representations of absorption over time are shown.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study used a single batch of radiolabeled 1,2-dichloroethane. Human abdominal skin was obtained from 14 donors, male and female, ranging in age from 31 to 70 years old. The large age range and sex differences may influence results. The split-thickness was reported as a range (200-400 um). This variation in skin thickness may result in inconsistencies between samples. Skin integrity was confirmed by TEWL both pre and post-exposure. Only skin meeting inclusion criteria ($\leq$ 13 grams/m2/hour) at both time points were included in the analysis. This is a slight deviation from OECD 428 and 156 which suggests viable skin have a TEWL reading of less than 10 grams/m2/hour. All TEWL measurements are reported. The majority are $\leq$10 grams/m2/hour.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Means and standard deviations were calculated and reported. Mathematical calculations used to determine Kp are reported and were appropriate. The Kp was based on the steady-state part of the absorption curve. CV values were not reported for Kp/flux measurements and maximum absorption rate, however the study provided sufficient data to independently calculate themCalculated CV for Kp and maximum flux are >50%, but sufficient data are available for EPA to calculate an alternate value.
	Metric 20:	Data interpretation	High	The Kp and mean maximum absorption rate was derived from an appropriate exposure condition (infinite dose). Recovery was not reported but this determination is not relevant for infinite dose applications.
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means $\pm$ SD. Individual replicate data were provided.

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Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	10% in 1,1,2-trichloroethane- infinite

Domain	Metric	Rating	Comments
Overall Quality Determination		**High**	

Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	Neat - finite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled 1,2-dichloroethane and radiolabeled [14C]-1,2-dichlorethane, CAS number: 107-06-2. The structure was reported for the radiolabeled substance noting the location of the radiolabel within the structure.
	Metric 2:	Test substance source	High	The non-radiolabeled, 1,2-dichloroethane was sourced from LGC standards; the radiolabeled 1,2-dichloroethane was sourced from American Radiolabeled Chemicals, Inc, St. Louis, MO. The study included certificates of analyses that included lot numbers and HPLC outputs.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the radiolabeled test substance was reported to be ≥97.6 by HPLC. The purity of the non-radiolabeled substance was 98.87% by GC/FID. Impurities were not reported. Radiochemical purities of prepared solutions were determined by study authors using HPLC prior to application; all were ≥97.6%, and impurities were not reported.
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	Testosterone (non-labelled and radiolabeled) was used as a reference compound in a finite exposure scenario in accordance with OECD 28 guidelines. Data are fully reported for testosterone studies. 1 mg/ml was administered to the skin (0.012 mg/cm2); n=4. Study authors report a mean mass balance of 93.47% (CV = 1.46), total absorbed dose (receptor fluids and receptor camber) 11.71% (CV=50.47), and maximum absorption rats as 0.2146 ug/cm2/hr (CV=26.6076).“The absorption profiles and distribution of radioactivity obtained from this experiment showed the expected trends and the data was comparable with results obtained in the multi-center comparison study conducted by Van de Sandt et al, 2004.”

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: Neat - finite

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428, and OECD 28, The assay procedures specified in the report were described in detail, although some information was missing. The flow through diffusion set-up is sufficiently reported including a schematic drawing. The study does not report if there was an equilibration period after the skin was placed into the chamber (guidelines recommend a 30-minute equilibrium period). Finite doses of 1,2-dichloroethane (neat, 50%, 10%, and 1% dissolved in either isopropyl myristate or 1,1,2-trichloroethane) were applied to human skin (at least 5 replicates; surface area of 0.64 cm2). The test substance was applied to the skin at an application rate of approximately 10 uL/cm2 (6.4 uL dose). This is in agreement with OECD guidelines. The cells were semi-occluded by charcoal filters in the neck of the donor cell. The thickness of skin samples ranged from 200 to 400 um, the exact thickness was not reported. The receptor solution was water fortified with 6% polyethoxyoleate 20 oleyl ether. OECD 156 guidelines recommend <6% polyoxyethelene (20) oleyl ether in water for lipophilic compounds. The solubility of 1,2-dichloroethane was tested in the receptor fluid prior to the start of the study and the observed dissolution of 1,2-dichloroethane was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity ranged from 30-70%. The flow rate of receptor fluid was 1.5 mL/hour. After 8 hours skin was washed. "The surface of the membrane was rinsed three times (3 x 0.5 mL) with a mild solution of Dove™ soap in water (ca. 1%). The skin surface was swabbed twice with cotton buds soaked with the liquid soap solution. Finally, the membrane was rinsed with a small volume (0.5 mL) of water and a further cotton bud was used to swab the surface of the membrane until dry". Charcoal filters were collected at 4-, 8-, and 24-hours post-dosing. Receptor fluid samples (volume not reported) were collected for one hour pre-dose and post-dose at 10 minutes, 30 minutes, 1 hour, 2 hours and every 2 hours henceforth for 24 hours (16 samples) and analyzed for radioactivity. After 24 hours, skin was tap-stripped up to 5 times. "Radioactivity in gross amounts less than twice the background level was considered to be below the limit of accurate determination."
	Metric 6:	Standards for tests	Medium	The integrity of the skin was determined by stable trans epidermal water loss (TEWL) prior to dose application and at the end of the experiment. A TWEL of $\leq$ 13 gm-2h-1 was considered acceptable. This is a slight deviation from guidelines which suggest viable skin has a TEWL reading of less than 10 grams/m2/hour. Skin that did not meet the criteria was allowed to dry and TEWL was remeasured. Skins that failed to meet the criteria were not included in the analysis. TEWL readings were reported. Coefficients of variation (CV) values were reported. Further discussion of the CVs is provided in Metric 19. The percent recovery was 89.04% (neat), 94.36% (50% in IPM) , 89.81% (10% in IPM), 91.27% (1% in IPM), 87.63% (50% in 1,1,2-TCE), 88.40 (10% in 1,1,2-TCE), and 87.59% (1% in 1,1,2-TCE).

Domain 3: Exposure Characterization

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: Neat - finite

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of the test substance was partially reported. The volume of radiolabeled, non-radiolabeled and diluent used for each dose solution was reported in a table. Dilutions were magnetically stirred if deemed necessary by study authors (criteria not reported). The activity and homogeneity of the diluted doses were assessed from the top, middle, and bottom of the solution. All doses were considered homogenous (data not shown). Storage conditions of stock radiolabeled and non-radiolabeled 1,2-dichloroethane were reported. It is unclear how far in advance the dilutions were made; however, the study does state that the radiochemical content and homogeneity were measured prior to dosing. The solubility of the test substance in the receptor fluid was determined to be 19.1 mg/ml. This was deemed appropriate (>60-fold higher than maximum cumulative absorption); solubility in receptor solution was not considered to be rate-limiting.
	Metric 8:	Consistency of exposure administration	Low	The application rate (10 uL/cm3) and volume (6.4 uL) were delivered consistently across study groups to exposed skin. This is in agreement with OECD guidelines. The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was reported as a range (200 to 400 uM). It is unclear if the variation in thicknesses was consistent across groups, and this may have contributed to some of the endpoint variations (and subsequently high CVs) observed.
	Metric 9:	Reporting of concentrations	High	The applied dose is reported as dpm, mg, and mg/cm2. Individual cells are reported independently. Nominal and analytical doses are reported.
	Metric 10:	Exposure frequency	High	Exposure duration was reported and appropriate for determining absorption. The test substance was in contact with the skin for 8 hours prior to washing. Samples of receptor fluid were collected for a total of 24 hours. An 8-hour exposure period has been selected to represent the average length of the working day."
	Metric 11:	Number of exposure groups and concentration spacing	High	There were 3 dose groups tested in a wide range of concentrations (neat, 50%, and 10%). Dilutions of test substance was performed in two different vehicles (isopropyl myristate or 1,1,2-trichloroethane). Justification for dose selection is provided by authors.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Samples of full-thickness skin samples were obtained from 1 male and 13 female donors following elective surgery. Abdominal skin samples from 14 people (race not reported) ranging in age from 31-70 years old were studied. The samples were stored frozen at -20 degrees C +/- 10 degrees C. Prior to use, the skin samples were thawed, wiped to remove residual fat and blood, re-hydrated in purified water, and dermatomed using a mini-dermatome. The thickness ranged from 200 to 400 uM. The skin contained epidermis and some dermis. These methods were in agreement with OECD guidelines which state split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring transepidermal water loss prior to/and upon completion of the experiment.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates was appropriate as per OECD 428. Guidelines recommend a minimum of 4 replicates per test preparation. This study examined 6 replicates/dose.

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: Neat - finite

Domain	Metric		Rating	Comments
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28. An application rate of 10 uL/cm2 was applied to skin samples which is appropriate for finite conditions. Measurement techniques and timing were reported and appropriate. A finite dose was used to determine absorption.
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assess consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period was consistent across replicates.
	Metric 16:	Sampling adequacy and sensitivity	Medium	The study reported adequate sampling for the outcomes of interest; measurement sensitivity was sufficient. Methods for the determination of radioactivity are reported. "Radioactivity in gross amounts of less than twice the background level was considered to be below the limit of accurate determination." Scintillation counts were not shown. Graphical representation of absorption over time is shown.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study used a single batch of radiolabeled 1,2-dichloroethane. Human abdominal skin was obtained from 14 donors, male and female, ranging in age from 31 to 70 years old. The large age range and sex differences may influence results. The split-thickness was reported as a range (200-400 um). This variation in skin thickness may result in inconsistencies between samples. Skin integrity was confirmed by TEWL both pre and post-exposure. Only skin meeting inclusion criteria ($\leq$ 13 grams/m2/hour) at both time points were included in the analysis. This is a slight deviation from OECD 428 and 156 which suggests viable skin have a TEWL reading of less than 10 grams/m2/hour. All TEWL measurements are reported. The majority are $\leq$10 grams/m2/hour.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	All statistical methods were described and were appropriate. Absorption estimates were based on appropriate measurements. Half or more than half of the CV values within an individual scenario were either >25% and <50%, or were >50%; however, standard deviations were provided which will allow for EPA to calculate an alternate upper-end value to account for variability in the results.
	Metric 20:	Data interpretation	High	Absorption estimates were calculated appropriately and included dislodegeable doses from two skin washes, tape stripping, unexposed skin, total unabsorbed, exposed skin, receptor fluid, and receptor chamber fluid. Recovery of the applied test substance was adequate given its volatility (>87%).
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means $\pm$ SD. Individual replicate data were provided.

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Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	Neat - finite

Domain	Metric	Rating	Comments
Overall Quality Determination		**High**	

Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	50% in IPM - finite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled 1,2-dichloroethane and radiolabeled [14C]-1,2-dichlorethane, CAS number: 107-06-2. The structure was reported for the radiolabeled substance noting the location of the radiolabel within the structure.
	Metric 2:	Test substance source	High	The non-radiolabeled, 1,2-dichloroethane was sourced from LGC standards; the radiolabeled 1,2-dichloroethane was sourced from American Radiolabeled Chemicals, Inc, St. Louis, MO. The study included certificates of analyses that included lot numbers and HPLC outputs.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the radiolabeled test substance was reported to be ≥97.6 by HPLC. The purity of the non-radiolabeled substance was 98.87% by GC/FID. Impurities were not reported. Radiochemical purities of prepared solutions were determined by study authors using HPLC prior to application; all were ≥97.6%, and impurities were not reported.
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	Testosterone (non-labelled and radiolabeled) was used as a reference compound in a finite exposure scenario in accordance with OECD 28 guidelines. Data are fully reported for testosterone studies. 1 mg/ml was administered to the skin (0.012 mg/cm2); n=4. Study authors report a mean mass balance of 93.47% (CV = 1.46), total absorbed dose (receptor fluids and receptor camber) 11.71% (CV=50.47), and maximum absorption rats as 0.2146 ug/cm2/hr (CV=26.6076).“The absorption profiles and distribution of radioactivity obtained from this experiment showed the expected trends and the data was comparable with results obtained in the multi-center comparison study conducted by Van de Sandt et al, 2004.”

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 50% in IPM - finite

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428, and OECD 28, The assay procedures specified in the report were described in detail, although some information was missing. The flow through diffusion set-up is sufficiently reported including a schematic drawing. The study does not report if there was an equilibration period after the skin was placed into the chamber (guidelines recommend a 30-minute equilibrium period). Finite doses of 1,2-dichloroethane (neat, 50%, 10%, and 1% dissolved in either isopropyl myristate or 1,1,2-trichloroethane) were applied to human skin (at least 5 replicates; surface area of 0.64 cm2). The test substance was applied to the skin at an application rate of approximately 10 uL/cm2 (6.4 uL dose). This is in agreement with OECD guidelines. The cells were semi-occluded by charcoal filters in the neck of the donor cell. The thickness of skin samples ranged from 200 to 400 um, the exact thickness was not reported. The receptor solution was water fortified with 6% polyethoxyoleate 20 oleyl ether. OECD 156 guidelines recommend <6% polyoxyethelene (20) oleyl ether in water for lipophilic compounds. The solubility of 1,2-dichloroethane was tested in the receptor fluid prior to the start of the study and the observed dissolution of 1,2-dichloroethane was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity ranged from 30-70%. The flow rate of receptor fluid was 1.5 mL/hour. After 8 hours skin was washed. "The surface of the membrane was rinsed three times (3 x 0.5 mL) with a mild solution of Dove™ soap in water (ca. 1%). The skin surface was swabbed twice with cotton buds soaked with the liquid soap solution. Finally, the membrane was rinsed with a small volume (0.5 mL) of water and a further cotton bud was used to swab the surface of the membrane until dry". Charcoal filters were collected at 4-, 8-, and 24-hours post-dosing. Receptor fluid samples (volume not reported) were collected for one hour pre-dose and post-dose at 10 minutes, 30 minutes, 1 hour, 2 hours and every 2 hours henceforth for 24 hours (16 samples) and analyzed for radioactivity. After 24 hours, skin was tap-stripped up to 5 times. "Radioactivity in gross amounts less than twice the background level was considered to be below the limit of accurate determination."
	Metric 6:	Standards for tests	Medium	The integrity of the skin was determined by stable trans epidermal water loss (TEWL) prior to dose application and at the end of the experiment. A TWEL of $\leq$ 13 gm-2h-1 was considered acceptable. This is a slight deviation from guidelines which suggest viable skin has a TEWL reading of less than 10 grams/m2/hour. Skin that did not meet the criteria was allowed to dry and TEWL was remeasured. Skins that failed to meet the criteria were not included in the analysis. TEWL readings were reported. Coefficients of variation (CV) values were reported. Further discussion of the CVs is provided in Metric 19. The percent recovery was 89.04% (neat), 94.36% (50% in IPM) , 89.81% (10% in IPM), 91.27% (1% in IPM), 87.63% (50% in 1,1,2-TCE), 88.40 (10% in 1,1,2-TCE), and 87.59% (1% in 1,1,2-TCE).

Domain 3: Exposure Characterization

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 50% in IPM - finite

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of the test substance was partially reported. The volume of radiolabeled, non-radiolabeled and diluent used for each dose solution was reported in a table. Dilutions were magnetically stirred if deemed necessary by study authors (criteria not reported). The activity and homogeneity of the diluted doses were assessed from the top, middle, and bottom of the solution. All doses were considered homogenous (data not shown). Storage conditions of stock radiolabeled and non-radiolabeled 1,2-dichloroethane were reported. It is unclear how far in advance the dilutions were made; however, the study does state that the radiochemical content and homogeneity were measured prior to dosing. The solubility of the test substance in the receptor fluid was determined to be 19.1 mg/ml. This was deemed appropriate (>60-fold higher than maximum cumulative absorption); solubility in receptor solution was not considered to be rate-limiting.
	Metric 8:	Consistency of exposure administration	Low	The application rate (10 uL/cm3) and volume (6.4 uL) were delivered consistently across study groups to exposed skin. This is in agreement with OECD guidelines. The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was reported as a range (200 to 400 uM). It is unclear if the variation in thicknesses was consistent across groups, and this may have contributed to some of the endpoint variations (and subsequently high CVs) observed.
	Metric 9:	Reporting of concentrations	High	The applied dose is reported as dpm, mg, and mg/cm2. Individual cells are reported independently. Nominal and analytical doses are reported.
	Metric 10:	Exposure frequency	High	Exposure duration was reported and appropriate for determining absorption. The test substance was in contact with the skin for 8 hours prior to washing. Samples of receptor fluid were collected for a total of 24 hours. An 8-hour exposure period has been selected to represent the average length of the working day."
	Metric 11:	Number of exposure groups and concentration spacing	High	There were 3 dose groups tested in a wide range of concentrations (neat, 50%, and 10%). Dilutions of test substance was performed in two different vehicles (isopropyl myristate or 1,1,2-trichloroethane). Justification for dose selection is provided by authors.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Samples of full-thickness skin samples were obtained from 1 male and 13 female donors following elective surgery. Abdominal skin samples from 14 people (race not reported) ranging in age from 31-70 years old were studied. The samples were stored frozen at -20 degrees C +/- 10 degrees C. Prior to use, the skin samples were thawed, wiped to remove residual fat and blood, re-hydrated in purified water, and dermatomed using a mini-dermatome. The thickness ranged from 200 to 400 uM. The skin contained epidermis and some dermis. These methods were in agreement with OECD guidelines which state split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring transepidermal water loss prior to/and upon completion of the experiment.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates was appropriate as per OECD 428. Guidelines recommend a minimum of 4 replicates per test preparation. This study examined 6 replicates/dose.

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 50% in IPM - finite

Domain	Metric		Rating	Comments
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28. An application rate of 10 uL/cm2 was applied to skin samples which is appropriate for finite conditions. Measurement techniques and timing were reported and appropriate. A finite dose was used to determine absorption.
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assess consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period was consistent across replicates.
	Metric 16:	Sampling adequacy and sensitivity	Medium	The study reported adequate sampling for the outcomes of interest; measurement sensitivity was sufficient. Methods for the determination of radioactivity are reported. "Radioactivity in gross amounts of less than twice the background level was considered to be below the limit of accurate determination." Scintillation counts were not shown. Graphical representation of absorption over time is shown.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study used a single batch of radiolabeled 1,2-dichloroethane. Human abdominal skin was obtained from 14 donors, male and female, ranging in age from 31 to 70 years old. The large age range and sex differences may influence results. The split-thickness was reported as a range (200-400 um). This variation in skin thickness may result in inconsistencies between samples. Skin integrity was confirmed by TEWL both pre and post-exposure. Only skin meeting inclusion criteria ($\leq$ 13 grams/m2/hour) at both time points were included in the analysis. This is a slight deviation from OECD 428 and 156 which suggests viable skin have a TEWL reading of less than 10 grams/m2/hour. All TEWL measurements are reported. The majority are $\leq$10 grams/m2/hour.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	All statistical methods were described and were appropriate. Absorption estimates were based on appropriate measurements. Half or more than half of the CV values within an individual scenario were either >25% and <50%, or were >50%; however, standard deviations were provided which will allow for EPA to calculate an alternate upper-end value to account for variability in the results.
	Metric 20:	Data interpretation	High	Absorption estimates were calculated appropriately and included dislodegeable doses from two skin washes, tape stripping, unexposed skin, total unabsorbed, exposed skin, receptor fluid, and receptor chamber fluid. Recovery of the applied test substance was adequate given its volatility (>87%).
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means $\pm$ SD. Individual replicate data were provided.

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Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	50% in IPM - finite

Domain	Metric	Rating	Comments
Overall Quality Determination		**High**	

Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	10% in IPM - finite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled 1,2-dichloroethane and radiolabeled [14C]-1,2-dichlorethane, CAS number: 107-06-2. The structure was reported for the radiolabeled substance noting the location of the radiolabel within the structure.
	Metric 2:	Test substance source	High	The non-radiolabeled, 1,2-dichloroethane was sourced from LGC standards; the radiolabeled 1,2-dichloroethane was sourced from American Radiolabeled Chemicals, Inc, St. Louis, MO. The study included certificates of analyses that included lot numbers and HPLC outputs.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the radiolabeled test substance was reported to be ≥97.6 by HPLC. The purity of the non-radiolabeled substance was 98.87% by GC/FID. Impurities were not reported. Radiochemical purities of prepared solutions were determined by study authors using HPLC prior to application; all were ≥97.6%, and impurities were not reported.
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	Testosterone (non-labelled and radiolabeled) was used as a reference compound in a finite exposure scenario in accordance with OECD 28 guidelines. Data are fully reported for testosterone studies. 1 mg/ml was administered to the skin (0.012 mg/cm2); n=4. Study authors report a mean mass balance of 93.47% (CV = 1.46), total absorbed dose (receptor fluids and receptor camber) 11.71% (CV=50.47), and maximum absorption rats as 0.2146 ug/cm2/hr (CV=26.6076).“The absorption profiles and distribution of radioactivity obtained from this experiment showed the expected trends and the data was comparable with results obtained in the multi-center comparison study conducted by Van de Sandt et al, 2004.”

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 10% in IPM - finite

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428, and OECD 28, The assay procedures specified in the report were described in detail, although some information was missing. The flow through diffusion set-up is sufficiently reported including a schematic drawing. The study does not report if there was an equilibration period after the skin was placed into the chamber (guidelines recommend a 30-minute equilibrium period). Finite doses of 1,2-dichloroethane (neat, 50%, 10%, and 1% dissolved in either isopropyl myristate or 1,1,2-trichloroethane) were applied to human skin (at least 5 replicates; surface area of 0.64 cm2). The test substance was applied to the skin at an application rate of approximately 10 uL/cm2 (6.4 uL dose). This is in agreement with OECD guidelines. The cells were semi-occluded by charcoal filters in the neck of the donor cell. The thickness of skin samples ranged from 200 to 400 um, the exact thickness was not reported. The receptor solution was water fortified with 6% polyethoxyoleate 20 oleyl ether. OECD 156 guidelines recommend <6% polyoxyethelene (20) oleyl ether in water for lipophilic compounds. The solubility of 1,2-dichloroethane was tested in the receptor fluid prior to the start of the study and the observed dissolution of 1,2-dichloroethane was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity ranged from 30-70%. The flow rate of receptor fluid was 1.5 mL/hour. After 8 hours skin was washed. "The surface of the membrane was rinsed three times (3 x 0.5 mL) with a mild solution of Dove™ soap in water (ca. 1%). The skin surface was swabbed twice with cotton buds soaked with the liquid soap solution. Finally, the membrane was rinsed with a small volume (0.5 mL) of water and a further cotton bud was used to swab the surface of the membrane until dry". Charcoal filters were collected at 4-, 8-, and 24-hours post-dosing. Receptor fluid samples (volume not reported) were collected for one hour pre-dose and post-dose at 10 minutes, 30 minutes, 1 hour, 2 hours and every 2 hours henceforth for 24 hours (16 samples) and analyzed for radioactivity. After 24 hours, skin was tap-stripped up to 5 times. "Radioactivity in gross amounts less than twice the background level was considered to be below the limit of accurate determination."
	Metric 6:	Standards for tests	Medium	The integrity of the skin was determined by stable trans epidermal water loss (TEWL) prior to dose application and at the end of the experiment. A TWEL of $\leq$ 13 gm-2h-1 was considered acceptable. This is a slight deviation from guidelines which suggest viable skin has a TEWL reading of less than 10 grams/m2/hour. Skin that did not meet the criteria was allowed to dry and TEWL was remeasured. Skins that failed to meet the criteria were not included in the analysis. TEWL readings were reported. Coefficients of variation (CV) values were reported. Further discussion of the CVs is provided in Metric 19. The percent recovery was 89.04% (neat), 94.36% (50% in IPM) , 89.81% (10% in IPM), 91.27% (1% in IPM), 87.63% (50% in 1,1,2-TCE), 88.40 (10% in 1,1,2-TCE), and 87.59% (1% in 1,1,2-TCE).

Domain 3: Exposure Characterization

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 10% in IPM - finite

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of the test substance was partially reported. The volume of radiolabeled, non-radiolabeled and diluent used for each dose solution was reported in a table. Dilutions were magnetically stirred if deemed necessary by study authors (criteria not reported). The activity and homogeneity of the diluted doses were assessed from the top, middle, and bottom of the solution. All doses were considered homogenous (data not shown). Storage conditions of stock radiolabeled and non-radiolabeled 1,2-dichloroethane were reported. It is unclear how far in advance the dilutions were made; however, the study does state that the radiochemical content and homogeneity were measured prior to dosing. The solubility of the test substance in the receptor fluid was determined to be 19.1 mg/ml. This was deemed appropriate (>60-fold higher than maximum cumulative absorption); solubility in receptor solution was not considered to be rate-limiting.
	Metric 8:	Consistency of exposure administration	Low	The application rate (10 uL/cm3) and volume (6.4 uL) were delivered consistently across study groups to exposed skin. This is in agreement with OECD guidelines. The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was reported as a range (200 to 400 uM). It is unclear if the variation in thicknesses was consistent across groups, and this may have contributed to some of the endpoint variations (and subsequently high CVs) observed.
	Metric 9:	Reporting of concentrations	High	The applied dose is reported as dpm, mg, and mg/cm2. Individual cells are reported independently. Nominal and analytical doses are reported.
	Metric 10:	Exposure frequency	High	Exposure duration was reported and appropriate for determining absorption. The test substance was in contact with the skin for 8 hours prior to washing. Samples of receptor fluid were collected for a total of 24 hours. An 8-hour exposure period has been selected to represent the average length of the working day."
	Metric 11:	Number of exposure groups and concentration spacing	High	There were 3 dose groups tested in a wide range of concentrations (neat, 50%, and 10%). Dilutions of test substance was performed in two different vehicles (isopropyl myristate or 1,1,2-trichloroethane). Justification for dose selection is provided by authors.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Samples of full-thickness skin samples were obtained from 1 male and 13 female donors following elective surgery. Abdominal skin samples from 14 people (race not reported) ranging in age from 31-70 years old were studied. The samples were stored frozen at -20 degrees C +/- 10 degrees C. Prior to use, the skin samples were thawed, wiped to remove residual fat and blood, re-hydrated in purified water, and dermatomed using a mini-dermatome. The thickness ranged from 200 to 400 uM. The skin contained epidermis and some dermis. These methods were in agreement with OECD guidelines which state split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring transepidermal water loss prior to/and upon completion of the experiment.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates was appropriate as per OECD 428. Guidelines recommend a minimum of 4 replicates per test preparation. This study examined 6 replicates/dose.

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 10% in IPM - finite

Domain	Metric		Rating	Comments
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28. An application rate of 10 uL/cm2 was applied to skin samples which is appropriate for finite conditions. Measurement techniques and timing were reported and appropriate. A finite dose was used to determine absorption.
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assess consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period was consistent across replicates.
	Metric 16:	Sampling adequacy and sensitivity	Medium	The study reported adequate sampling for the outcomes of interest; measurement sensitivity was sufficient. Methods for the determination of radioactivity are reported. "Radioactivity in gross amounts of less than twice the background level was considered to be below the limit of accurate determination." Scintillation counts were not shown. Graphical representation of absorption over time is shown.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study used a single batch of radiolabeled 1,2-dichloroethane. Human abdominal skin was obtained from 14 donors, male and female, ranging in age from 31 to 70 years old. The large age range and sex differences may influence results. The split-thickness was reported as a range (200-400 um). This variation in skin thickness may result in inconsistencies between samples. Skin integrity was confirmed by TEWL both pre and post-exposure. Only skin meeting inclusion criteria ($\leq$ 13 grams/m2/hour) at both time points were included in the analysis. This is a slight deviation from OECD 428 and 156 which suggests viable skin have a TEWL reading of less than 10 grams/m2/hour. All TEWL measurements are reported. The majority are $\leq$10 grams/m2/hour.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	All statistical methods were described and were appropriate. Absorption estimates were based on appropriate measurements. Half or more than half of the CV values within an individual scenario were either >25% and <50%, or were >50%; however, standard deviations were provided which will allow for EPA to calculate an alternate upper-end value to account for variability in the results.
	Metric 20:	Data interpretation	High	Absorption estimates were calculated appropriately and included dislodegeable doses from two skin washes, tape stripping, unexposed skin, total unabsorbed, exposed skin, receptor fluid, and receptor chamber fluid. Recovery of the applied test substance was adequate given its volatility (>87%).
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means $\pm$ SD. Individual replicate data were provided.

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Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	10% in IPM - finite

Domain	Metric	Rating	Comments
Overall Quality Determination		**High**	

Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	1% in IPM - finite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled 1,2-dichloroethane and radiolabeled [14C]-1,2-dichlorethane, CAS number: 107-06-2. The structure was reported for the radiolabeled substance noting the location of the radiolabel within the structure.
	Metric 2:	Test substance source	High	The non-radiolabeled, 1,2-dichloroethane was sourced from LGC standards; the radiolabeled 1,2-dichloroethane was sourced from American Radiolabeled Chemicals, Inc, St. Louis, MO. The study included certificates of analyses that included lot numbers and HPLC outputs.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the radiolabeled test substance was reported to be ≥97.6 by HPLC. The purity of the non-radiolabeled substance was 98.87% by GC/FID. Impurities were not reported. Radiochemical purities of prepared solutions were determined by study authors using HPLC prior to application; all were ≥97.6%, and impurities were not reported.
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	Testosterone (non-labelled and radiolabeled) was used as a reference compound in a finite exposure scenario in accordance with OECD 28 guidelines. Data are fully reported for testosterone studies. 1 mg/ml was administered to the skin (0.012 mg/cm2); n=4. Study authors report a mean mass balance of 93.47% (CV = 1.46), total absorbed dose (receptor fluids and receptor camber) 11.71% (CV=50.47), and maximum absorption rats as 0.2146 ug/cm2/hr (CV=26.6076).“The absorption profiles and distribution of radioactivity obtained from this experiment showed the expected trends and the data was comparable with results obtained in the multi-center comparison study conducted by Van de Sandt et al, 2004.”

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 1% in IPM - finite

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428, and OECD 28, The assay procedures specified in the report were described in detail, although some information was missing. The flow through diffusion set-up is sufficiently reported including a schematic drawing. The study does not report if there was an equilibration period after the skin was placed into the chamber (guidelines recommend a 30-minute equilibrium period). Finite doses of 1,2-dichloroethane (neat, 50%, 10%, and 1% dissolved in either isopropyl myristate or 1,1,2-trichloroethane) were applied to human skin (at least 5 replicates; surface area of 0.64 cm2). The test substance was applied to the skin at an application rate of approximately 10 uL/cm2 (6.4 uL dose). This is in agreement with OECD guidelines. The cells were semi-occluded by charcoal filters in the neck of the donor cell. The thickness of skin samples ranged from 200 to 400 um, the exact thickness was not reported. The receptor solution was water fortified with 6% polyethoxyoleate 20 oleyl ether. OECD 156 guidelines recommend <6% polyoxyethelene (20) oleyl ether in water for lipophilic compounds. The solubility of 1,2-dichloroethane was tested in the receptor fluid prior to the start of the study and the observed dissolution of 1,2-dichloroethane was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity ranged from 30-70%. The flow rate of receptor fluid was 1.5 mL/hour. After 8 hours skin was washed. "The surface of the membrane was rinsed three times (3 x 0.5 mL) with a mild solution of Dove™ soap in water (ca. 1%). The skin surface was swabbed twice with cotton buds soaked with the liquid soap solution. Finally, the membrane was rinsed with a small volume (0.5 mL) of water and a further cotton bud was used to swab the surface of the membrane until dry". Charcoal filters were collected at 4-, 8-, and 24-hours post-dosing. Receptor fluid samples (volume not reported) were collected for one hour pre-dose and post-dose at 10 minutes, 30 minutes, 1 hour, 2 hours and every 2 hours henceforth for 24 hours (16 samples) and analyzed for radioactivity. After 24 hours, skin was tap-stripped up to 5 times. "Radioactivity in gross amounts less than twice the background level was considered to be below the limit of accurate determination."
	Metric 6:	Standards for tests	Medium	The integrity of the skin was determined by stable trans epidermal water loss (TEWL) prior to dose application and at the end of the experiment. A TWEL of $\leq$ 13 gm-2h-1 was considered acceptable. This is a slight deviation from guidelines which suggest viable skin has a TEWL reading of less than 10 grams/m2/hour. Skin that did not meet the criteria was allowed to dry and TEWL was remeasured. Skins that failed to meet the criteria were not included in the analysis. TEWL readings were reported. Coefficients of variation (CV) values were reported. Further discussion of the CVs is provided in Metric 19. The percent recovery was 89.04% (neat), 94.36% (50% in IPM) , 89.81% (10% in IPM), 91.27% (1% in IPM), 87.63% (50% in 1,1,2-TCE), 88.40 (10% in 1,1,2-TCE), and 87.59% (1% in 1,1,2-TCE).

Domain 3: Exposure Characterization

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 1% in IPM - finite

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of the test substance was partially reported. The volume of radiolabeled, non-radiolabeled and diluent used for each dose solution was reported in a table. Dilutions were magnetically stirred if deemed necessary by study authors (criteria not reported). The activity and homogeneity of the diluted doses were assessed from the top, middle, and bottom of the solution. All doses were considered homogenous (data not shown). Storage conditions of stock radiolabeled and non-radiolabeled 1,2-dichloroethane were reported. It is unclear how far in advance the dilutions were made; however, the study does state that the radiochemical content and homogeneity were measured prior to dosing. The solubility of the test substance in the receptor fluid was determined to be 19.1 mg/ml. This was deemed appropriate (>60-fold higher than maximum cumulative absorption); solubility in receptor solution was not considered to be rate-limiting.
	Metric 8:	Consistency of exposure administration	Low	The application rate (10 uL/cm3) and volume (6.4 uL) were delivered consistently across study groups to exposed skin. This is in agreement with OECD guidelines. The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was reported as a range (200 to 400 uM). It is unclear if the variation in thicknesses was consistent across groups, and this may have contributed to some of the endpoint variations (and subsequently high CVs) observed.
	Metric 9:	Reporting of concentrations	High	The applied dose is reported as dpm, mg, and mg/cm2. Individual cells are reported independently. Nominal and analytical doses are reported.
	Metric 10:	Exposure frequency	High	Exposure duration was reported and appropriate for determining absorption. The test substance was in contact with the skin for 8 hours prior to washing. Samples of receptor fluid were collected for a total of 24 hours. An 8-hour exposure period has been selected to represent the average length of the working day."
	Metric 11:	Number of exposure groups and concentration spacing	High	There were 3 dose groups tested in a wide range of concentrations (neat, 50%, and 10%). Dilutions of test substance was performed in two different vehicles (isopropyl myristate or 1,1,2-trichloroethane). Justification for dose selection is provided by authors.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Samples of full-thickness skin samples were obtained from 1 male and 13 female donors following elective surgery. Abdominal skin samples from 14 people (race not reported) ranging in age from 31-70 years old were studied. The samples were stored frozen at -20 degrees C +/- 10 degrees C. Prior to use, the skin samples were thawed, wiped to remove residual fat and blood, re-hydrated in purified water, and dermatomed using a mini-dermatome. The thickness ranged from 200 to 400 uM. The skin contained epidermis and some dermis. These methods were in agreement with OECD guidelines which state split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring transepidermal water loss prior to/and upon completion of the experiment.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates was appropriate as per OECD 428. Guidelines recommend a minimum of 4 replicates per test preparation. This study examined 6 replicates/dose.

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 1% in IPM - finite

Domain	Metric		Rating	Comments
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28. An application rate of 10 uL/cm2 was applied to skin samples which is appropriate for finite conditions. Measurement techniques and timing were reported and appropriate. A finite dose was used to determine absorption.
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assess consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period was consistent across replicates.
	Metric 16:	Sampling adequacy and sensitivity	Medium	The study reported adequate sampling for the outcomes of interest; measurement sensitivity was sufficient. Methods for the determination of radioactivity are reported. "Radioactivity in gross amounts of less than twice the background level was considered to be below the limit of accurate determination." Scintillation counts were not shown. Graphical representation of absorption over time is shown.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study used a single batch of radiolabeled 1,2-dichloroethane. Human abdominal skin was obtained from 14 donors, male and female, ranging in age from 31 to 70 years old. The large age range and sex differences may influence results. The split-thickness was reported as a range (200-400 um). This variation in skin thickness may result in inconsistencies between samples. Skin integrity was confirmed by TEWL both pre and post-exposure. Only skin meeting inclusion criteria ($\leq$ 13 grams/m2/hour) at both time points were included in the analysis. This is a slight deviation from OECD 428 and 156 which suggests viable skin have a TEWL reading of less than 10 grams/m2/hour. All TEWL measurements are reported. The majority are $\leq$10 grams/m2/hour.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	All statistical methods were described and were appropriate. Absorption estimates were based on appropriate measurements. Half or more than half of the CV values within an individual scenario were either >25% and <50%, or were >50%; however, standard deviations were provided which will allow for EPA to calculate an alternate upper-end value to account for variability in the results.
	Metric 20:	Data interpretation	High	Absorption estimates were calculated appropriately and included dislodegeable doses from two skin washes, tape stripping, unexposed skin, total unabsorbed, exposed skin, receptor fluid, and receptor chamber fluid. Recovery of the applied test substance was adequate given its volatility (>87%).
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means $\pm$ SD. Individual replicate data were provided.

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Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	1% in IPM - finite

Domain	Metric	Rating	Comments
Overall Quality Determination		**High**	

Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	50% in 1,1,2-trichloroethane - finite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled 1,2-dichloroethane and radiolabeled [14C]-1,2-dichlorethane, CAS number: 107-06-2. The structure was reported for the radiolabeled substance noting the location of the radiolabel within the structure.
	Metric 2:	Test substance source	High	The non-radiolabeled, 1,2-dichloroethane was sourced from LGC standards; the radiolabeled 1,2-dichloroethane was sourced from American Radiolabeled Chemicals, Inc, St. Louis, MO. The study included certificates of analyses that included lot numbers and HPLC outputs.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the radiolabeled test substance was reported to be ≥97.6 by HPLC. The purity of the non-radiolabeled substance was 98.87% by GC/FID. Impurities were not reported. Radiochemical purities of prepared solutions were determined by study authors using HPLC prior to application; all were ≥97.6%, and impurities were not reported.
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	Testosterone (non-labelled and radiolabeled) was used as a reference compound in a finite exposure scenario in accordance with OECD 28 guidelines. Data are fully reported for testosterone studies. 1 mg/ml was administered to the skin (0.012 mg/cm2); n=4. Study authors report a mean mass balance of 93.47% (CV = 1.46), total absorbed dose (receptor fluids and receptor camber) 11.71% (CV=50.47), and maximum absorption rats as 0.2146 ug/cm2/hr (CV=26.6076).“The absorption profiles and distribution of radioactivity obtained from this experiment showed the expected trends and the data was comparable with results obtained in the multi-center comparison study conducted by Van de Sandt et al, 2004.”

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 50% in 1,1,2-trichloroethane - finite

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428, and OECD 28, The assay procedures specified in the report were described in detail, although some information was missing. The flow through diffusion set-up is sufficiently reported including a schematic drawing. The study does not report if there was an equilibration period after the skin was placed into the chamber (guidelines recommend a 30-minute equilibrium period). Finite doses of 1,2-dichloroethane (neat, 50%, 10%, and 1% dissolved in either isopropyl myristate or 1,1,2-trichloroethane) were applied to human skin (at least 5 replicates; surface area of 0.64 cm2). The test substance was applied to the skin at an application rate of approximately 10 uL/cm2 (6.4 uL dose). This is in agreement with OECD guidelines. The cells were semi-occluded by charcoal filters in the neck of the donor cell. The thickness of skin samples ranged from 200 to 400 um, the exact thickness was not reported. The receptor solution was water fortified with 6% polyethoxyoleate 20 oleyl ether. OECD 156 guidelines recommend <6% polyoxyethelene (20) oleyl ether in water for lipophilic compounds. The solubility of 1,2-dichloroethane was tested in the receptor fluid prior to the start of the study and the observed dissolution of 1,2-dichloroethane was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity ranged from 30-70%. The flow rate of receptor fluid was 1.5 mL/hour. After 8 hours skin was washed. "The surface of the membrane was rinsed three times (3 x 0.5 mL) with a mild solution of Dove™ soap in water (ca. 1%). The skin surface was swabbed twice with cotton buds soaked with the liquid soap solution. Finally, the membrane was rinsed with a small volume (0.5 mL) of water and a further cotton bud was used to swab the surface of the membrane until dry". Charcoal filters were collected at 4-, 8-, and 24-hours post-dosing. Receptor fluid samples (volume not reported) were collected for one hour pre-dose and post-dose at 10 minutes, 30 minutes, 1 hour, 2 hours and every 2 hours henceforth for 24 hours (16 samples) and analyzed for radioactivity. After 24 hours, skin was tap-stripped up to 5 times. "Radioactivity in gross amounts less than twice the background level was considered to be below the limit of accurate determination."
	Metric 6:	Standards for tests	Medium	The integrity of the skin was determined by stable trans epidermal water loss (TEWL) prior to dose application and at the end of the experiment. A TWEL of $\leq$ 13 gm-2h-1 was considered acceptable. This is a slight deviation from guidelines which suggest viable skin has a TEWL reading of less than 10 grams/m2/hour. Skin that did not meet the criteria was allowed to dry and TEWL was remeasured. Skins that failed to meet the criteria were not included in the analysis. TEWL readings were reported. Coefficients of variation (CV) values were reported. Further discussion of the CVs is provided in Metric 19. The percent recovery was 89.04% (neat), 94.36% (50% in IPM) , 89.81% (10% in IPM), 91.27% (1% in IPM), 87.63% (50% in 1,1,2-TCE), 88.40 (10% in 1,1,2-TCE), and 87.59% (1% in 1,1,2-TCE).

Domain 3: Exposure Characterization

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 50% in 1,1,2-trichloroethane - finite

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of the test substance was partially reported. The volume of radiolabeled, non-radiolabeled and diluent used for each dose solution was reported in a table. Dilutions were magnetically stirred if deemed necessary by study authors (criteria not reported). The activity and homogeneity of the diluted doses were assessed from the top, middle, and bottom of the solution. All doses were considered homogenous (data not shown). Storage conditions of stock radiolabeled and non-radiolabeled 1,2-dichloroethane were reported. It is unclear how far in advance the dilutions were made; however, the study does state that the radiochemical content and homogeneity were measured prior to dosing. The solubility of the test substance in the receptor fluid was determined to be 19.1 mg/ml. This was deemed appropriate (>60-fold higher than maximum cumulative absorption); solubility in receptor solution was not considered to be rate-limiting.
	Metric 8:	Consistency of exposure administration	Low	The application rate (10 uL/cm3) and volume (6.4 uL) were delivered consistently across study groups to exposed skin. This is in agreement with OECD guidelines. The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was reported as a range (200 to 400 uM). It is unclear if the variation in thicknesses was consistent across groups, and this may have contributed to some of the endpoint variations (and subsequently high CVs) observed.
	Metric 9:	Reporting of concentrations	High	The applied dose is reported as dpm, mg, and mg/cm2. Individual cells are reported independently. Nominal and analytical doses are reported.
	Metric 10:	Exposure frequency	High	Exposure duration was reported and appropriate for determining absorption. The test substance was in contact with the skin for 8 hours prior to washing. Samples of receptor fluid were collected for a total of 24 hours. An 8-hour exposure period has been selected to represent the average length of the working day."
	Metric 11:	Number of exposure groups and concentration spacing	High	There were 3 dose groups tested in a wide range of concentrations (neat, 50%, and 10%). Dilutions of test substance was performed in two different vehicles (isopropyl myristate or 1,1,2-trichloroethane). Justification for dose selection is provided by authors.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Samples of full-thickness skin samples were obtained from 1 male and 13 female donors following elective surgery. Abdominal skin samples from 14 people (race not reported) ranging in age from 31-70 years old were studied. The samples were stored frozen at -20 degrees C +/- 10 degrees C. Prior to use, the skin samples were thawed, wiped to remove residual fat and blood, re-hydrated in purified water, and dermatomed using a mini-dermatome. The thickness ranged from 200 to 400 uM. The skin contained epidermis and some dermis. These methods were in agreement with OECD guidelines which state split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring transepidermal water loss prior to/and upon completion of the experiment.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates was appropriate as per OECD 428. Guidelines recommend a minimum of 4 replicates per test preparation. This study examined 6 replicates/dose.

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 50% in 1,1,2-trichloroethane - finite

Domain	Metric		Rating	Comments
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28. An application rate of 10 uL/cm2 was applied to skin samples which is appropriate for finite conditions. Measurement techniques and timing were reported and appropriate. A finite dose was used to determine absorption.
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assess consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period was consistent across replicates.
	Metric 16:	Sampling adequacy and sensitivity	Medium	The study reported adequate sampling for the outcomes of interest; measurement sensitivity was sufficient. Methods for the determination of radioactivity are reported. "Radioactivity in gross amounts of less than twice the background level was considered to be below the limit of accurate determination." Scintillation counts were not shown. Graphical representation of absorption over time is shown.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study used a single batch of radiolabeled 1,2-dichloroethane. Human abdominal skin was obtained from 14 donors, male and female, ranging in age from 31 to 70 years old. The large age range and sex differences may influence results. The split-thickness was reported as a range (200-400 um). This variation in skin thickness may result in inconsistencies between samples. Skin integrity was confirmed by TEWL both pre and post-exposure. Only skin meeting inclusion criteria ($\leq$ 13 grams/m2/hour) at both time points were included in the analysis. This is a slight deviation from OECD 428 and 156 which suggests viable skin have a TEWL reading of less than 10 grams/m2/hour. All TEWL measurements are reported. The majority are $\leq$10 grams/m2/hour.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	All statistical methods were described and were appropriate. Absorption estimates were based on appropriate measurements. Half or more than half of the CV values within an individual scenario were either >25% and <50%, or were >50%; however, standard deviations were provided which will allow for EPA to calculate an alternate upper-end value to account for variability in the results.
	Metric 20:	Data interpretation	High	Absorption estimates were calculated appropriately and included dislodegeable doses from two skin washes, tape stripping, unexposed skin, total unabsorbed, exposed skin, receptor fluid, and receptor chamber fluid. Recovery of the applied test substance was adequate given its volatility (>87%).
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means $\pm$ SD. Individual replicate data were provided.

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Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	50% in 1,1,2-trichloroethane - finite

Domain	Metric	Rating	Comments
Overall Quality Determination		**High**	

Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	10% in 1,1,2-trichloroethane - finite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled 1,2-dichloroethane and radiolabeled [14C]-1,2-dichlorethane, CAS number: 107-06-2. The structure was reported for the radiolabeled substance noting the location of the radiolabel within the structure.
	Metric 2:	Test substance source	High	The non-radiolabeled, 1,2-dichloroethane was sourced from LGC standards; the radiolabeled 1,2-dichloroethane was sourced from American Radiolabeled Chemicals, Inc, St. Louis, MO. The study included certificates of analyses that included lot numbers and HPLC outputs.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the radiolabeled test substance was reported to be ≥97.6 by HPLC. The purity of the non-radiolabeled substance was 98.87% by GC/FID. Impurities were not reported. Radiochemical purities of prepared solutions were determined by study authors using HPLC prior to application; all were ≥97.6%, and impurities were not reported.
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	Testosterone (non-labelled and radiolabeled) was used as a reference compound in a finite exposure scenario in accordance with OECD 28 guidelines. Data are fully reported for testosterone studies. 1 mg/ml was administered to the skin (0.012 mg/cm2); n=4. Study authors report a mean mass balance of 93.47% (CV = 1.46), total absorbed dose (receptor fluids and receptor camber) 11.71% (CV=50.47), and maximum absorption rats as 0.2146 ug/cm2/hr (CV=26.6076).“The absorption profiles and distribution of radioactivity obtained from this experiment showed the expected trends and the data was comparable with results obtained in the multi-center comparison study conducted by Van de Sandt et al, 2004.”

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 10% in 1,1,2-trichloroethane - finite

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428, and OECD 28, The assay procedures specified in the report were described in detail, although some information was missing. The flow through diffusion set-up is sufficiently reported including a schematic drawing. The study does not report if there was an equilibration period after the skin was placed into the chamber (guidelines recommend a 30-minute equilibrium period). Finite doses of 1,2-dichloroethane (neat, 50%, 10%, and 1% dissolved in either isopropyl myristate or 1,1,2-trichloroethane) were applied to human skin (at least 5 replicates; surface area of 0.64 cm2). The test substance was applied to the skin at an application rate of approximately 10 uL/cm2 (6.4 uL dose). This is in agreement with OECD guidelines. The cells were semi-occluded by charcoal filters in the neck of the donor cell. The thickness of skin samples ranged from 200 to 400 um, the exact thickness was not reported. The receptor solution was water fortified with 6% polyethoxyoleate 20 oleyl ether. OECD 156 guidelines recommend <6% polyoxyethelene (20) oleyl ether in water for lipophilic compounds. The solubility of 1,2-dichloroethane was tested in the receptor fluid prior to the start of the study and the observed dissolution of 1,2-dichloroethane was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity ranged from 30-70%. The flow rate of receptor fluid was 1.5 mL/hour. After 8 hours skin was washed. "The surface of the membrane was rinsed three times (3 x 0.5 mL) with a mild solution of Dove™ soap in water (ca. 1%). The skin surface was swabbed twice with cotton buds soaked with the liquid soap solution. Finally, the membrane was rinsed with a small volume (0.5 mL) of water and a further cotton bud was used to swab the surface of the membrane until dry". Charcoal filters were collected at 4-, 8-, and 24-hours post-dosing. Receptor fluid samples (volume not reported) were collected for one hour pre-dose and post-dose at 10 minutes, 30 minutes, 1 hour, 2 hours and every 2 hours henceforth for 24 hours (16 samples) and analyzed for radioactivity. After 24 hours, skin was tap-stripped up to 5 times. "Radioactivity in gross amounts less than twice the background level was considered to be below the limit of accurate determination."
	Metric 6:	Standards for tests	Medium	The integrity of the skin was determined by stable trans epidermal water loss (TEWL) prior to dose application and at the end of the experiment. A TWEL of $\leq$ 13 gm-2h-1 was considered acceptable. This is a slight deviation from guidelines which suggest viable skin has a TEWL reading of less than 10 grams/m2/hour. Skin that did not meet the criteria was allowed to dry and TEWL was remeasured. Skins that failed to meet the criteria were not included in the analysis. TEWL readings were reported. Coefficients of variation (CV) values were reported. Further discussion of the CVs is provided in Metric 19. The percent recovery was 89.04% (neat), 94.36% (50% in IPM) , 89.81% (10% in IPM), 91.27% (1% in IPM), 87.63% (50% in 1,1,2-TCE), 88.40 (10% in 1,1,2-TCE), and 87.59% (1% in 1,1,2-TCE).

Domain 3: Exposure Characterization

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 10% in 1,1,2-trichloroethane - finite

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of the test substance was partially reported. The volume of radiolabeled, non-radiolabeled and diluent used for each dose solution was reported in a table. Dilutions were magnetically stirred if deemed necessary by study authors (criteria not reported). The activity and homogeneity of the diluted doses were assessed from the top, middle, and bottom of the solution. All doses were considered homogenous (data not shown). Storage conditions of stock radiolabeled and non-radiolabeled 1,2-dichloroethane were reported. It is unclear how far in advance the dilutions were made; however, the study does state that the radiochemical content and homogeneity were measured prior to dosing. The solubility of the test substance in the receptor fluid was determined to be 19.1 mg/ml. This was deemed appropriate (>60-fold higher than maximum cumulative absorption); solubility in receptor solution was not considered to be rate-limiting.
	Metric 8:	Consistency of exposure administration	Low	The application rate (10 uL/cm3) and volume (6.4 uL) were delivered consistently across study groups to exposed skin. This is in agreement with OECD guidelines. The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was reported as a range (200 to 400 uM). It is unclear if the variation in thicknesses was consistent across groups, and this may have contributed to some of the endpoint variations (and subsequently high CVs) observed.
	Metric 9:	Reporting of concentrations	High	The applied dose is reported as dpm, mg, and mg/cm2. Individual cells are reported independently. Nominal and analytical doses are reported.
	Metric 10:	Exposure frequency	High	Exposure duration was reported and appropriate for determining absorption. The test substance was in contact with the skin for 8 hours prior to washing. Samples of receptor fluid were collected for a total of 24 hours. An 8-hour exposure period has been selected to represent the average length of the working day."
	Metric 11:	Number of exposure groups and concentration spacing	High	There were 3 dose groups tested in a wide range of concentrations (neat, 50%, and 10%). Dilutions of test substance was performed in two different vehicles (isopropyl myristate or 1,1,2-trichloroethane). Justification for dose selection is provided by authors.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Samples of full-thickness skin samples were obtained from 1 male and 13 female donors following elective surgery. Abdominal skin samples from 14 people (race not reported) ranging in age from 31-70 years old were studied. The samples were stored frozen at -20 degrees C +/- 10 degrees C. Prior to use, the skin samples were thawed, wiped to remove residual fat and blood, re-hydrated in purified water, and dermatomed using a mini-dermatome. The thickness ranged from 200 to 400 uM. The skin contained epidermis and some dermis. These methods were in agreement with OECD guidelines which state split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring transepidermal water loss prior to/and upon completion of the experiment.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates was appropriate as per OECD 428. Guidelines recommend a minimum of 4 replicates per test preparation. This study examined 6 replicates/dose.

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 10% in 1,1,2-trichloroethane - finite

Domain	Metric		Rating	Comments
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28. An application rate of 10 uL/cm2 was applied to skin samples which is appropriate for finite conditions. Measurement techniques and timing were reported and appropriate. A finite dose was used to determine absorption.
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assess consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period was consistent across replicates.
	Metric 16:	Sampling adequacy and sensitivity	Medium	The study reported adequate sampling for the outcomes of interest; measurement sensitivity was sufficient. Methods for the determination of radioactivity are reported. "Radioactivity in gross amounts of less than twice the background level was considered to be below the limit of accurate determination." Scintillation counts were not shown. Graphical representation of absorption over time is shown.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study used a single batch of radiolabeled 1,2-dichloroethane. Human abdominal skin was obtained from 14 donors, male and female, ranging in age from 31 to 70 years old. The large age range and sex differences may influence results. The split-thickness was reported as a range (200-400 um). This variation in skin thickness may result in inconsistencies between samples. Skin integrity was confirmed by TEWL both pre and post-exposure. Only skin meeting inclusion criteria ($\leq$ 13 grams/m2/hour) at both time points were included in the analysis. This is a slight deviation from OECD 428 and 156 which suggests viable skin have a TEWL reading of less than 10 grams/m2/hour. All TEWL measurements are reported. The majority are $\leq$10 grams/m2/hour.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	All statistical methods were described and were appropriate. Absorption estimates were based on appropriate measurements. Half or more than half of the CV values within an individual scenario were either >25% and <50%, or were >50%; however, standard deviations were provided which will allow for EPA to calculate an alternate upper-end value to account for variability in the results.
	Metric 20:	Data interpretation	High	Absorption estimates were calculated appropriately and included dislodegeable doses from two skin washes, tape stripping, unexposed skin, total unabsorbed, exposed skin, receptor fluid, and receptor chamber fluid. Recovery of the applied test substance was adequate given its volatility (>87%).
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means $\pm$ SD. Individual replicate data were provided.

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Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	10% in 1,1,2-trichloroethane - finite

Domain	Metric	Rating	Comments
Overall Quality Determination		**High**	

Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	1% in 1,1,2-trichloroethane - finite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled 1,2-dichloroethane and radiolabeled [14C]-1,2-dichlorethane, CAS number: 107-06-2. The structure was reported for the radiolabeled substance noting the location of the radiolabel within the structure.
	Metric 2:	Test substance source	High	The non-radiolabeled, 1,2-dichloroethane was sourced from LGC standards; the radiolabeled 1,2-dichloroethane was sourced from American Radiolabeled Chemicals, Inc, St. Louis, MO. The study included certificates of analyses that included lot numbers and HPLC outputs.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the radiolabeled test substance was reported to be ≥97.6 by HPLC. The purity of the non-radiolabeled substance was 98.87% by GC/FID. Impurities were not reported. Radiochemical purities of prepared solutions were determined by study authors using HPLC prior to application; all were ≥97.6%, and impurities were not reported.
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	Testosterone (non-labelled and radiolabeled) was used as a reference compound in a finite exposure scenario in accordance with OECD 28 guidelines. Data are fully reported for testosterone studies. 1 mg/ml was administered to the skin (0.012 mg/cm2); n=4. Study authors report a mean mass balance of 93.47% (CV = 1.46), total absorbed dose (receptor fluids and receptor camber) 11.71% (CV=50.47), and maximum absorption rats as 0.2146 ug/cm2/hr (CV=26.6076).“The absorption profiles and distribution of radioactivity obtained from this experiment showed the expected trends and the data was comparable with results obtained in the multi-center comparison study conducted by Van de Sandt et al, 2004.”

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 1% in 1,1,2-trichloroethane - finite

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428, and OECD 28, The assay procedures specified in the report were described in detail, although some information was missing. The flow through diffusion set-up is sufficiently reported including a schematic drawing. The study does not report if there was an equilibration period after the skin was placed into the chamber (guidelines recommend a 30-minute equilibrium period). Finite doses of 1,2-dichloroethane (neat, 50%, 10%, and 1% dissolved in either isopropyl myristate or 1,1,2-trichloroethane) were applied to human skin (at least 5 replicates; surface area of 0.64 cm2). The test substance was applied to the skin at an application rate of approximately 10 uL/cm2 (6.4 uL dose). This is in agreement with OECD guidelines. The cells were semi-occluded by charcoal filters in the neck of the donor cell. The thickness of skin samples ranged from 200 to 400 um, the exact thickness was not reported. The receptor solution was water fortified with 6% polyethoxyoleate 20 oleyl ether. OECD 156 guidelines recommend <6% polyoxyethelene (20) oleyl ether in water for lipophilic compounds. The solubility of 1,2-dichloroethane was tested in the receptor fluid prior to the start of the study and the observed dissolution of 1,2-dichloroethane was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity ranged from 30-70%. The flow rate of receptor fluid was 1.5 mL/hour. After 8 hours skin was washed. "The surface of the membrane was rinsed three times (3 x 0.5 mL) with a mild solution of Dove™ soap in water (ca. 1%). The skin surface was swabbed twice with cotton buds soaked with the liquid soap solution. Finally, the membrane was rinsed with a small volume (0.5 mL) of water and a further cotton bud was used to swab the surface of the membrane until dry". Charcoal filters were collected at 4-, 8-, and 24-hours post-dosing. Receptor fluid samples (volume not reported) were collected for one hour pre-dose and post-dose at 10 minutes, 30 minutes, 1 hour, 2 hours and every 2 hours henceforth for 24 hours (16 samples) and analyzed for radioactivity. After 24 hours, skin was tap-stripped up to 5 times. "Radioactivity in gross amounts less than twice the background level was considered to be below the limit of accurate determination."
	Metric 6:	Standards for tests	Medium	The integrity of the skin was determined by stable trans epidermal water loss (TEWL) prior to dose application and at the end of the experiment. A TWEL of $\leq$ 13 gm-2h-1 was considered acceptable. This is a slight deviation from guidelines which suggest viable skin has a TEWL reading of less than 10 grams/m2/hour. Skin that did not meet the criteria was allowed to dry and TEWL was remeasured. Skins that failed to meet the criteria were not included in the analysis. TEWL readings were reported. Coefficients of variation (CV) values were reported. Further discussion of the CVs is provided in Metric 19. The percent recovery was 89.04% (neat), 94.36% (50% in IPM) , 89.81% (10% in IPM), 91.27% (1% in IPM), 87.63% (50% in 1,1,2-TCE), 88.40 (10% in 1,1,2-TCE), and 87.59% (1% in 1,1,2-TCE).

Domain 3: Exposure Characterization

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 1% in 1,1,2-trichloroethane - finite

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of the test substance was partially reported. The volume of radiolabeled, non-radiolabeled and diluent used for each dose solution was reported in a table. Dilutions were magnetically stirred if deemed necessary by study authors (criteria not reported). The activity and homogeneity of the diluted doses were assessed from the top, middle, and bottom of the solution. All doses were considered homogenous (data not shown). Storage conditions of stock radiolabeled and non-radiolabeled 1,2-dichloroethane were reported. It is unclear how far in advance the dilutions were made; however, the study does state that the radiochemical content and homogeneity were measured prior to dosing. The solubility of the test substance in the receptor fluid was determined to be 19.1 mg/ml. This was deemed appropriate (>60-fold higher than maximum cumulative absorption); solubility in receptor solution was not considered to be rate-limiting.
	Metric 8:	Consistency of exposure administration	Low	The application rate (10 uL/cm3) and volume (6.4 uL) were delivered consistently across study groups to exposed skin. This is in agreement with OECD guidelines. The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was reported as a range (200 to 400 uM). It is unclear if the variation in thicknesses was consistent across groups, and this may have contributed to some of the endpoint variations (and subsequently high CVs) observed.
	Metric 9:	Reporting of concentrations	High	The applied dose is reported as dpm, mg, and mg/cm2. Individual cells are reported independently. Nominal and analytical doses are reported.
	Metric 10:	Exposure frequency	High	Exposure duration was reported and appropriate for determining absorption. The test substance was in contact with the skin for 8 hours prior to washing. Samples of receptor fluid were collected for a total of 24 hours. An 8-hour exposure period has been selected to represent the average length of the working day."
	Metric 11:	Number of exposure groups and concentration spacing	High	There were 3 dose groups tested in a wide range of concentrations (neat, 50%, and 10%). Dilutions of test substance was performed in two different vehicles (isopropyl myristate or 1,1,2-trichloroethane). Justification for dose selection is provided by authors.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Samples of full-thickness skin samples were obtained from 1 male and 13 female donors following elective surgery. Abdominal skin samples from 14 people (race not reported) ranging in age from 31-70 years old were studied. The samples were stored frozen at -20 degrees C +/- 10 degrees C. Prior to use, the skin samples were thawed, wiped to remove residual fat and blood, re-hydrated in purified water, and dermatomed using a mini-dermatome. The thickness ranged from 200 to 400 uM. The skin contained epidermis and some dermis. These methods were in agreement with OECD guidelines which state split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring transepidermal water loss prior to/and upon completion of the experiment.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates was appropriate as per OECD 428. Guidelines recommend a minimum of 4 replicates per test preparation. This study examined 6 replicates/dose.

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Study Citation: Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 11581118
Unique ID: 1% in 1,1,2-trichloroethane - finite

Domain	Metric		Rating	Comments
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28. An application rate of 10 uL/cm2 was applied to skin samples which is appropriate for finite conditions. Measurement techniques and timing were reported and appropriate. A finite dose was used to determine absorption.
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assess consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period was consistent across replicates.
	Metric 16:	Sampling adequacy and sensitivity	Medium	The study reported adequate sampling for the outcomes of interest; measurement sensitivity was sufficient. Methods for the determination of radioactivity are reported. "Radioactivity in gross amounts of less than twice the background level was considered to be below the limit of accurate determination." Scintillation counts were not shown. Graphical representation of absorption over time is shown.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study used a single batch of radiolabeled 1,2-dichloroethane. Human abdominal skin was obtained from 14 donors, male and female, ranging in age from 31 to 70 years old. The large age range and sex differences may influence results. The split-thickness was reported as a range (200-400 um). This variation in skin thickness may result in inconsistencies between samples. Skin integrity was confirmed by TEWL both pre and post-exposure. Only skin meeting inclusion criteria ($\leq$ 13 grams/m2/hour) at both time points were included in the analysis. This is a slight deviation from OECD 428 and 156 which suggests viable skin have a TEWL reading of less than 10 grams/m2/hour. All TEWL measurements are reported. The majority are $\leq$10 grams/m2/hour.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	All statistical methods were described and were appropriate. Absorption estimates were based on appropriate measurements. Half or more than half of the CV values within an individual scenario were either >25% and <50%, or were >50%; however, standard deviations were provided which will allow for EPA to calculate an alternate upper-end value to account for variability in the results.
	Metric 20:	Data interpretation	High	Absorption estimates were calculated appropriately and included dislodegeable doses from two skin washes, tape stripping, unexposed skin, total unabsorbed, exposed skin, receptor fluid, and receptor chamber fluid. Recovery of the applied test substance was adequate given its volatility (>87%).
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means $\pm$ SD. Individual replicate data were provided.

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Study Citation:	Labcorp Early Development, (2024). 1,2-Dichloroethane: Rates of penetration through human skin using a flow through in vitro system.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	11581118
Unique ID:	1% in 1,1,2-trichloroethane - finite

Domain	Metric	Rating	Comments
Overall Quality Determination		**High**	

Study Citation:	Schenk, L., Rauma, M., Fransson, M. N., Johanson, G. (2018). Percutaneous absorption of thirty-eight organic solvents in vitro using pig skin. PLoS ONE 13(10):e0205458.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	4940676
Unique ID:	nan

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was definitively identified by name and CASRN.
	Metric 2:	Test substance source	High	The source of the test substance was reported as a manufacturer (Fluka).
	Metric 3:	Test substance purity	High	The purity of the test substance was >/= 99.5%.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Medium	The study did not report use of a reference compound (or cite historical data for a reference compound like caffeine, benzoic acid, or testosterone); however, the study evaluated the dermal absorption of 36 compounds of different lipophilicity (including other compounds with similar lipophilicity as 1,2-DCA). The log P indicated for 1,2-DCA was 1.83 (cited to EPI Suite); note: the log P identified for 1,2-DCA in the TSCA Scoping Document was 1.48. The study also noted that the results that they obtained for some compounds were similar to results for the same compounds in other studies.
	Metric 5:	Assay procedures	Medium	Assay procedures specified in the study report included: diffusion cell set-up (static), temperature, identity of and rationale for using PBS as the receptor fluid, receptor volume (5.0-5.4 mL), volume of the test substance applied (i.e., excess chemical; dosing volume was specified as approximately 1 mL), and skin exposure area (0.64 cm2). The donor compartment was capped with a glass stopper (presumably to prevent evaporation); aliquots of receptor fluid were sampled regularly (every 10 min for the first hour, every 20 min in the second hour, and then every 30 minutes). Levels in the receptor fluid aliquots were determined via gas chromoatographic analysis and a standard curve. The limits of detection were reported. Any omissions (i.e., humidity only) are unlikely to substantially impact the study results.
	Metric 6:	Standards for tests	Low	The study indicated that the cut-off resistance for skin integrity was 50 ohms; that cut-off value was validated against in-house measurements of intact and damaged skin. The actual resistance values were not reported. The coefficient of variation (CV) for neat 1,2-DCA was reported (32%); no cut-off for acceptability was specified. The CV was 11% to 120% across the chemicals tested in the study (and below 75% in 29/36 cases); this was interpreted by the study authors as "low variability." Further discussion of CV is provided in Metric 19. Few QC criteria were provided to define the boundaries of the test.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Details regarding test substance preparation and storage were not provided.

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Study Citation: Schenk, L., Rauma, M., Fransson, M. N., Johanson, G. (2018). Percutaneous absorption of thirty-eight organic solvents in vitro using pig skin. PLoS ONE 13(10):e0205458.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4940676
Unique ID: nan

Domain	Metric		Rating	Comments
	Metric 8:	Consistency of exposure administration	Medium	The study authors suggested that consistency of exposure administration within and across chemicals was one of the strengths of their study. The same area of skin (same area of pig) was used for all experiments. The volume of chemical (1 mL neat) used in the test was reported. The study authors noted when dermatomed skin, rather than full thickness skin, was used. Although some samples used in the study were split skin whereas others were full thickness skin, both experiments that involved 1,2-DCA (this experiment and the one described on a separate evaluation form) used full thickness skin (i.e., this was consistent within the 1,2-DCA experiments).
	Metric 9:	Reporting of concentrations	Medium	The test chemical concentrations were reported without ambiguity (i.e., neat 1,2-DCA); nominal concentrations were used to determine the 'apparent' Kp.
	Metric 10:	Exposure frequency	Low	The study did not explicitly indicate the exposure duration for each chemical (only a range of 4 to 9 hours for experiments conducted using 36 solvents, including 1,2-DCA). OECD TG 28 indicated that longer exposure periods may be required for infinite dosing protocols; standard curves were established for each chemical, and these data were used to measure the apparent permeability coefficient (Kp). The test chemical is expected to be volatile. There was no definitive evidence based on the study details provided that the exposure duration was consistent across the two 1,2-DCA experiments (i.e., the experiment for neat 1,2-DCA evaluated on this form and the experiment for diluted 1,2-DCA evaluated on a separate form).
	Metric 11:	Number of exposure groups and concentration spacing	Low	Fewer than 3 concentrations were tested; the study evaluated permeability of the neat chemical (this evaluation form) and a 0.8% dilution of 1,2-DCA in water (on a separate evaluation form).
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	The test model and descriptive information were reported (i.e., skin from the back and the flank regions of newborn Duroc piglets that died of natural causes). Details regarding tissue storage and preparation were provided. A rationale for using this specific skin type was provided based on characteristics that make this model a suitable comparison to human skin (i.e., "pig skin is similar to human skin with respect to stratum corneum and epidermal thickness, as well as permeability" and similar flux values were observed using human and pig skin in other studies). Although human or animal skin can be used; viable skin is preferable for this study type. The study authors provided some indication that the skin samples used, from dead pigs, were viable (a requirement for skin resistance >50 ohms). As per applicable guidelines, full thickness may be used so long as excessive thickness is avoided; the thickness of the skin sample used for this experiment (and the experiment using diluted 1,2-DCA) was not explicitly specified.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates per group (n = 6) was reported and appropriate.
Domain 5: Outcome Assessment				

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Study Citation: Schenk, L., Rauma, M., Fransson, M. N., Johanson, G. (2018). Percutaneous absorption of thirty-eight organic solvents in vitro using pig skin. PLoS ONE 13(10):e0205458.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4940676
Unique ID: nan

Domain	Metric		Rating	Comments
	Metric 14:	Outcome assessment methodology	High	An infinite dose of the test substance was used to determine the Kp. It was indicated that about 1 mL was used for 0.64 cm2 of skin; this exceeds the requirement of at least 100 uL/cm2 for infinite dosing protocols as per OECD 28. The measurement technique and timing of measurements appeared appropriate.
	Metric 15:	Consistency of outcome assessment	High	Based on the information provided, it appeared that outcomes were assessed consistently across groups. The same receptor fluid was used, the same sampling times were evaluated, etc.
	Metric 16:	Sampling adequacy and sensitivity	Medium	The number of total samples per replicate was not explicitly specified; the study stated that (for all chemicals evaluated in the study), aliquots were collected every 10 min for the first hour, every 20 min for the second hours, and every 30 minutes thereafter, and that experiments ranged from 4-9 hours. However, based on the timing of sampling (and knowledge about the standard curve for 1,2-DCA), sampling appeared appropriate.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	No differences were reported with respect to the size or integrity of skin samples among groups (but it was not explicitly specified that there were no differences). Skin integrity was measured using a preferable method (i.e., electrical resistance) and the study criteria were met for all replicates (i.e., at least 50 ohms for each skin sample). The study did not indicate how the skin samples correlated to chemical testing (number of pigs from which skin samples were obtained to perform the experiments).
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	The study indicated that the maximum solubility of the receptor fluid was not exceeded for 1,2-DCA (or any of the chemicals tested). There was no evidence to suggest that the test material interfered with the assay conditions.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Calculation of the Kp was described adequately in the methods. Kp measurements were based on the linear/steady-state of the curve; pre- and post-steady-state values were excluded from analyses. [Correlations between Kp values and other factors (molecular weight, number of carbons) across chemicals were analyzed statistically]. However, the CV for Kp using neat 1,2-DCA was 32%, which is >25% and <50%. The correlation of experimental Kp values with predicted values (using EPI Suite) was generally poor for both neat (separate evaluation) and diluted (this evaluation) substances evaluated in this study (not just 1,2-DCA).
	Metric 20:	Data interpretation	High	An infinite dosing protocol was used to calculate permeability. Results were interpreted adequately based on the assay set-up/conditions.
	Metric 21:	Reporting of data	High	Data were reported by exposure group for all measured outcomes. Table 1 included data for the test substance (neat = this evaluation or diluted = evaluated on a separate form, molecular weight, log P), the skin used (full thickness for 1,2-DCA experiments), number of replicates (n = 6) as well values determined experimentally, including lag time, flux at steady state, and coefficients of variation.

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Study Citation:	Schenk, L., Rauma, M., Fransson, M. N., Johanson, G. (2018). Percutaneous absorption of thirty-eight organic solvents in vitro using pig skin. PLoS ONE 13(10):e0205458.
Chemical:	1,2-Dichloroethane
Exposure Type:	Parent compound
HERO ID:	4940676
Unique ID:	nan

Domain	Metric	Rating	Comments
Overall Quality Determination		**Medium**	

Study Citation: Schenk, L., Rauma, M., Fransson, M. N., Johanson, G. (2018). Percutaneous absorption of thirty-eight organic solvents in vitro using pig skin. PLoS ONE 13(10):e0205458.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4940676
Unique ID: nan

Domain		Metric	Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was definitively identified by name and CASRN.
	Metric 2:	Test substance source	High	The source of the test substance was reported as a manufacturer (Fluka).
	Metric 3:	Test substance purity	High	The purity of the test substance was >/= 99.5%.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Medium	The study did not report use of a reference compound (or cite historical data for a reference compound like caffeine, benzoic acid, or testosterone); however, the study evaluated the dermal absorption of 36 compounds of different lipophilicity (and including other compounds with similar lipophilicity as 1,2-DCA). The log P indicated for 1,2-DCA was 1.83 (cited to EPI Suite); note: the log P identified for 1,2-DCA in the TSCA Scoping Document was 1.48. The study also noted that the results that they obtained for some compounds were similar to results for the same compounds in other studies.
	Metric 5:	Assay procedures	Medium	Assay procedures specified in the study report included: diffusion cell set-up (static), temperature, identity of and rationale for using PBS as the receptor fluid, receptor volume (5.0-5.4 mL), volume of the test substance applied (i.e., excess chemical; dosing volume was specified as approximately 1 mL), and skin exposure area (0.64 cm2). The donor compartment was capped with a glass stopper (presumably to prevent evaporation); aliquots of receptor fluid were sampled regularly (every 10 min for the first hour, every 20 min in the second hour, and then every 30 minutes). Levels in the receptor fluid aliquots were determined via gas chromoatographic analysis and a standard curve. The limits of detection were reported. Any omissions (i.e., humidity only) are unlikely to substantially impact the study results.
	Metric 6:	Standards for tests	Low	The study indicated that the cut-off resistance for skin integrity was 50 ohms; that cut-off value was validated against in-house measurements of intact and damaged skin. The actual resistance values were not reported. The coefficient of variation (CV) for diluted 1,2-DCA was reported (24%); no cut-off for acceptability was specified. The CV was 11% to 120% across the chemicals tested in the study (and below 75% in 29/36 cases); this was interpreted by the study authors as "low variability." Further discussion of CV is provided in Metric 19. Few QC criteria were provided to define the boundaries of the test.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Details regarding test substance preparation and storage were not provided.

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Study Citation: Schenk, L., Rauma, M., Fransson, M. N., Johanson, G. (2018). Percutaneous absorption of thirty-eight organic solvents in vitro using pig skin. PLoS ONE 13(10):e0205458.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4940676
Unique ID: nan

Domain	Metric		Rating	Comments
	Metric 8:	Consistency of exposure administration	Medium	The study authors suggested that consistency of exposure administration within and across chemicals was one of the strengths of their study. The same area of skin (same area of pig) was used for all experiments. The volume of chemical (1 mL of 0.8% 1,2-DCA) used in the test was reported. The study authors noted when dermatomed skin, rather than full thickness skin, was used. Although some samples used in the study were split skin whereas others were full thickness skin, both experiments that involved 1,2-DCA (this experiment and the one described on a separate evaluation form) used full thickness skin (i.e., this was consistent within the 1,2-DCA experiments). In addition, although most of the chemicals evaluated in the study were diluted in water, a few (that were not miscible in water) were diluted in PBS. This would not affect findings for 1,2-DCA because only the neat chemical (evaluated in a separate evaluation) or the diluted chemical (0.8% 1,2-DCA in water, this evaluation) were used; there was no inconsistency with respect to the 1,2-DCA experiments.
	Metric 9:	Reporting of concentrations	Medium	The test chemical concentrations were reported without ambiguity (i.e., 0.8% 1,2-DCA diluted in water); nominal concentrations were used to determine the 'apparent' Kp.
	Metric 10:	Exposure frequency	Low	The study did not explicitly indicate the exposure duration for each chemical (only a range of 4 to 9 hours for experiments conducted using 36 solvents, including 1,2-DCA). OECD TG 28 indicated that longer exposure periods may be required for infinite dosing protocols; standard curves were established for each chemical, and these data were used to measure the apparent permeability coefficient (Kp). The test chemical is expected to be volatile. There was no definitive evidence based on the study details provided that the exposure duration was consistent across the two 1,2-DCA experiments (i.e., the experiment for neat 1,2-DCA evaluated on a separate form and the experiment for diluted 1,2-DCA evaluated on this form).
	Metric 11:	Number of exposure groups and concentration spacing	Low	Fewer than 3 concentrations were tested; the study evaluated permeability of the neat chemical (evaluated on a separate form) and a 0.8% dilution of 1,2-DCA in water (evaluated on this form).
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	The test model and descriptive information were reported (i.e., skin from the back and the flank regions of newborn Duroc piglets that died of natural causes). Details regarding tissue storage and preparation were provided. A rationale for using this specific skin type was provided based on characteristics that make this model a suitable comparison to human skin (i.e., "pig skin is similar to human skin with respect to stratum corneum and epidermal thickness, as well as permeability" and similar flux values were observed using human and pig skin in other studies). Although human or animal skin can be used; viable skin is preferable for this study type. The study authors provided some indication that the skin samples used, from dead pigs, were viable (a requirement for skin resistance >50 ohms). As per applicable guidelines, full thickness may be used so long as excessive thickness is avoided; the thickness of the skin sample used for this experiment (and the experiment using neat 1,2-DCA) was not explicitly specified.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates per group (n = 6) was reported and appropriate.

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Study Citation: Schenk, L., Rauma, M., Fransson, M. N., Johanson, G. (2018). Percutaneous absorption of thirty-eight organic solvents in vitro using pig skin. PLoS ONE 13(10):e0205458.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4940676
Unique ID: nan

Domain	Metric		Rating	Comments
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	An infinite dose of the test substance was used to determine the Kp. It was indicated that about 1 mL was used for 0.64 cm2 of skin; this exceeds the requirement of at least 100 uL/cm2 for infinite dosing protocols as per OECD 28. The measurement technique and timing of measurements appeared appropriate.
	Metric 15:	Consistency of outcome assessment	High	Based on the information provided, it appeared that outcomes were assessed consistently across groups. The same receptor fluid was used, the same sampling times were evaluated, etc.).
	Metric 16:	Sampling adequacy and sensitivity	Medium	The number of total samples per replicate was not explicitly specified; the study stated that (for all chemicals evaluated in the study), aliquots were collected every 10 min for the first hour, every 20 min for the second hours, and every 30 minutes thereafter, and that experiments ranged from 4-9 hours. However, based on the timing of sampling (and knowledge about the standard curve for 1,2-DCA), sampling appeared appropriate.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	No differences were reported with respect to the size or integrity of skin samples among groups (but it was not explicitly specified that there were no differences). Skin integrity was measured using a preferable method (i.e., electrical resistance) and the study criteria were met for all replicates (i.e., at least 50 ohms for each skin sample). The study did not indicate how the skin samples correlated to chemical testing (number of pigs from which skin samples were obtained to perform the experiments).
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	The study indicated that the maximum solubility of the receptor fluid was not exceeded for 1,2-DCA (or any of the chemicals tested). There was no evidence to suggest that the test material interfered with the assay conditions.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	High	Calculation of the Kp was described adequately in the methods. Kp measurements were based on the linear/steady-state of the curve; pre- and post-steady-state values were excluded from analyses. [Correlations between Kp values and other factors (molecular weight, number of carbons) across chemicals were analyzed statistically.] The CV using diluted 1,2-DCA was 24%, which is within the range for acceptability (according to OECD 156, a CV of <25% indicates that variability is relatively low, while a CV equal or greater than 25% indicates that variability is high). The correlation of experimental Kp values with predicted values (using EPI Suite) was generally poor for both neat (separate evaluation) and diluted (this evaluation) substances evaluated in this study (not just 1,2-DCA).
	Metric 20:	Data interpretation	High	An infinite dosing protocol was used to calculate permeability. Results were interpreted adequately based on the assay set-up/conditions.

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Study Citation: Schenk, L., Rauma, M., Fransson, M. N., Johanson, G. (2018). Percutaneous absorption of thirty-eight organic solvents in vitro using pig skin. PLoS ONE 13(10):e0205458.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 4940676
Unique ID: nan

Domain	Metric		Rating	Comments
	Metric 21:	Reporting of data	High	Data were reported by exposure group for all measured outcomes. Table 1 included data for the test substance (diluted = this evaluation or neat = evaluated on a separate form, molecular weight, log P), the skin used (full thickness for 1,2-DCA experiments), number of replicates (n = 6) as well values determined experimentally, including lag time, flux at steady state, and coefficients of variation.

Overall Quality Determination Medium

Study Citation: Jakobson, I., Wahlberg, J. E., Holmberg, B., Johansson, G. (1982). Uptake via the blood and elimination of 10 organic solvents following epicutaneous exposure of anesthetized guinea pigs. Toxicology and Applied Pharmacology 63(2):181-187.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 94881
Unique ID: 1,2-DCE - uptake

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified definitively as 1, 2-dichloroethane. The form (liquid or solid) of the test substance was not specified. It was not radiolabeled.
	Metric 2:	Test substance source	Low	The test material was sourced from Merck, A.G., Darmstadt, West Germany. A batch or lot number was not specified. Certification was not provided. The exact material purchased from the supplier could not be determined (multiple products listed), therefore, the chemical could not be verified on the supplier's website.
	Metric 3:	Test substance purity	Medium	The test material was reported to be spectroscopic grade, an actual purity was not reported, but chemicals of this grade are generally highly pure.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Low	The study did not specify whether animals were randomized.
	Metric 5:	Standards for Tests	Uninformative	The study authors did not report whether the test met any pre-established criteria. This study did not employ the use of metabolism cages. Percutaneous uptake over time in an infinite exposure model was evaluated by measuring concentrations of the test substance in the blood. The study did not calculate or determine percent recovery. Graphs, presumably showing mean blood concentrations over time did not include any measures of variance. Measures of variance also were not provided in a table reporting quantitative values. This lack of data prevents the ability to determine the variance across means making it impossible to determine the validity of the test.
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	Low	Details of the test substance preparation and storage were not provided. No dilutions or use of vehicles were mentioned, so it is assumed that the materials were applied neat. Storage conditions of the purchased material were not reported, and the test material is a volatile chemical.
	Metric 7:	Consistency of exposure administration	High	Details of exposure administration were reported and based on the information provided, exposures were administered consistently across study groups. Glass rings (area 3.1 cm2) were glued onto the clipped skin on the backs of guinea pigs. A cover glass with a central hole was attached, and 1 mL of the test material was injected. The holes were covered to prevent leakage or evaporation.
	Metric 8:	Reporting of concentrations	Medium	The study reported the volume applied (1mL per depot) and the skin surface area (3.1 cm2); equivalent to 0.322 mL/cm2. Using the density of the test material (1.25 g/mL), a dose in mg/cm2 can be determined. (1.25 g/mL) x 0.322 mL/cm2) = 0.403 g/cm2 (or 403 mg/cm2). There is no indication that the purchased test material was analytically verified, but because the material was applied neat, and had spectral grade purity, the lack of measurement is not expected to have a significant impact on the study results.

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Study Citation: Jakobson, I., Wahlberg, J. E., Holmberg, B., Johansson, G. (1982). Uptake via the blood and elimination of 10 organic solvents following epicutaneous exposure of anesthetized guinea pigs. Toxicology and Applied Pharmacology 63(2):181-187.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 94881
Unique ID: 1,2-DCE - uptake

Domain	Metric		Rating	Comments
	Metric 9:	Exposure duration	High	Based on Figure 3 in the results, the exposure duration was 12 hours. The study authors did not provide justification for the duration of an uptake experiment, However, the purpose of the study was simply to measure concentrations in blood during exposure, and the authors did note (based on unpublished data) that "the concentration might eventually become fatal if the exposure is extended."
	Metric 10:	Number of exposure groups and concentration spacing	Low	The study included two groups. One group of animals had a single skin depot with 1 mL of the test substance; the other group had two skin depots, each containing 1 mL of the test substance. Separate groups of animals were used for elimination experiments (separate form). OECD TG 427 only specifies that a study will "normally involve several groups;" therefore, the number of groups in this study seems to be appropriate. It is unclear whether the concentrations/dosing was appropriate. Exposure should mimic potential human exposure, which is typically up to 10 uL/cm2 for a liquid. This study used 1 mL/3.1 cm2, or 322.5 uL/cm2 which is significantly higher than recommended in OECD 427.
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	Low	The study used male and female guinea pigs (distribution within groups not specified) with starting body weights ranging between 600 and 1,000 g (a mean weight was not reported), and it is not known whether the weights of the animals within a group were within 20% of the mean weight. The animal strain, age, and source were not reported. Guinea pigs are an appropriate model as per OECD 427, although rats are more commonly used.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	Low	No animal husbandry details were provided.
	Metric 13:	Number of animals per group	Low	The study used a total of 4 animals per group. The methods indicated that both males and females were used, but the number of each sex/group was not specified. OECD TG 427 indicates that at least 4 animals of a single-sex should be used.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Uninformative	The outcome assessment methodology deviated significantly from OECD 427 guidelines. Based on the information provided (volume applied and surface area), a dose of 700 mg/cm2 was determined using a test substance density of 2.17 g/mL, indicating infinite dosing. The surface area (3.1 cm2) is lower than the guideline recommendations and does not cover 10% of the animal surface area. The study did not evaluate anything other than the presence of the chemical in blood. It did not evaluate 1,2-DCA remaining in the excreta, carcass, skin, skin wash, or exhaled air. Therefore it cannot be used to determine skin absorption.
	Metric 15:	Consistency of outcome assessment	Medium	The outcome assessment methodology was reported, and based on the available information was mostly consistent across groups. There was one animal that was not anaesthetized; however, this animal showed a similar uptake curve, and the difference is not expected to have a significant impact on results.

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Study Citation: Jakobson, I., Wahlberg, J. E., Holmberg, B., Johansson, G. (1982). Uptake via the blood and elimination of 10 organic solvents following epicutaneous exposure of anesthetized guinea pigs. Toxicology and Applied Pharmacology 63(2):181-187.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 94881
Unique ID: 1,2-DCE - uptake

Domain	Metric		Rating	Comments
	Metric 16:	Sampling adequacy and sensitivity	Medium	None of the figures or data tables reported an "n." It is assumed that the data were generated from all 4 animals per group, but this was not explicitly stated. It is unclear if the frequency of blood collection is appropriate because it necessitated replacement with Marcodex.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study did not report all information to determine whether confounding bias occurred (test substance batch, body weight changes, or body weight variations greater than 20%, compared to the mean). Animals were anaesthetized throughout the experiment. Based on the results with one animal that was not anaesthetized, it was determined that the injection of pentobarbital (anaesthesia) did not significantly change the concentration of the test material in the blood.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition, health outcomes unrelated to exposure, or solubility that could influence the outcome assessment.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Uninformative	This study did not determine absorption estimates. The only results were blood concentrations over time and these data were not statistically analyzed.
	Metric 20:	Data interpretation	Uninformative	The study described the observed absorption pattern for the test material in blood but is inadequate for quantitatively determining skin absorption. Concentrations in the blood increased throughout the entire exposure, except for a short dip at 1 hr. In animals with a single skin depot, the maximum concentration in blood (at 12 hours) was approximately 20 ug/mL. This study did not calculate the amount of test substance the chemical absorbed per cm2 of skin over time. It is unclear how useful this study is due to significant deviations from standard guidelines.
	Metric 21:	Reporting of Data	Uninformative	The data for some, but not all specified outcomes were presented. The plot of blood concentrations by time for the group of animals exposed to 2 skin depots was not provided. Only concentrations at 0.5 and 6 hours was provided in table format. None of the data provided in the study included measures of variance. Data were inadequate for evaluating the fraction of the chemical absorbed through skin.

Overall Quality Determination Uninformative

Study Citation: Jakobson, I., Wahlberg, J. E., Holmberg, B., Johansson, G. (1982). Uptake via the blood and elimination of 10 organic solvents following epicutaneous exposure of anesthetized guinea pigs. Toxicology and Applied Pharmacology 63(2):181-187.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 94881
Unique ID: 1,2-DCE - Elimination

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified definitively as 1, 2-dichloroethane. The form (liquid or solid) of the test substance was not specified. It was not radiolabeled.
	Metric 2:	Test substance source	Low	The test material was sourced from Merck, A.G., Darmstadt, West Germany. A batch or lot number was not specified. Certification was not provided. The exact material purchased from the supplier could not be determined (multiple products listed), therefore, the chemical could not be verified on the supplier's website.
	Metric 3:	Test substance purity	Medium	The test material was reported to be spectroscopic grade, an actual purity was not reported, but chemicals of this grade are generally highly pure.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Low	The study did not specify whether animals were randomized.
	Metric 5:	Standards for Tests	Uninformative	The study authors did not report whether the test met any pre-established criteria. This study did not employ the use of metabolism cages. Percutaneous uptake over time in an infinite exposure model was evaluated by measuring concentrations of the test substance in the blood. The study did not calculate or determine percent recovery. Graphs, presumably showing mean blood concentrations over time did not include any measures of variance. Measures of variance also were not provided in a table reporting quantitative values. This lack of data prevents the ability to determine the variance across means making it impossible to determine the validity of the test.
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	Low	Details of the test substance preparation and storage were not provided. No dilutions or use of vehicles were mentioned, so it is assumed that the materials were applied neat. Storage conditions of the purchased material were not reported, and the test material is a volatile chemical.
	Metric 7:	Consistency of exposure administration	High	Details of exposure administration were reported and based on the information provided, exposures were administered consistently across study groups. Glass rings (area 3.1 cm2) were glued onto the clipped skin on the backs of guinea pigs. A cover glass with a central hole was attached, and 1 mL of the test material was injected. During elimination experiments, the seal was broken and the excess solvent was aspirated and the skin was dried with compressed air.
	Metric 8:	Reporting of concentrations	Medium	The study reported the volume applied (1mL per depot) and the skin surface area (3.1 cm2); equivalent to 0.322 mL/cm2. Using the density of the test material (1.25 g/mL), a dose in mg/cm2 can be determined. (1.25 g/mL) x 0.322 mL/cm2) = 0.403 g/cm2 (or 403 mg/cm2). There is no indication that the purchased test material was analytically verified, but because the material was applied neat, and had spectral grade purity, the lack of measurement is not expected to have a significant impact on the study results.
	Metric 9:	Exposure duration	High	For the elimination part of the study, animals were percutaneously exposed for 4 hours. Blood samples were then taken during the following 2 hours. The duration was not justified but seemed to be appropriate for this part of the test.

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 94881
Unique ID: 1,2-DCE - Elimination

Domain	Metric		Rating	Comments
	Metric 10:	Number of exposure groups and concentration spacing	Low	Elimination experiments (this form) were only done with animals exposed to one skin depot. OECD TG 427 only specifies that a study will "normally involve several groups;" therefore, the number of groups in this study seems to be appropriate. It is unclear whether the concentrations/dosing was appropriate. Exposure should mimic potential human exposure, which is typically up to 10 uL/cm2 for a liquid. This study used 1 mL/3.1 cm2, or 322.5 uL/cm2 which is significantly higher than recommended in OECD 427.
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	Low	The study used male and female guinea pigs (distribution within groups not specified) with starting body weights ranging between 600 and 1,000 g (a mean weight was not reported), and it is not known whether the weights of the animals within a group were within 20% of the mean weight. The animal strain, age, and source were not reported. Guinea pigs are an appropriate model as per OECD 427, although rats are more commonly used. .
	Metric 12:	Adequacy and consistency of animal husbandry conditions	Low	No animal husbandry details were provided.
	Metric 13:	Number of animals per group	Low	The number of animals per group was not specified in the methods. A table suggests 4 animals per group, but this table is reporting results from the uptake experiment. It is unclear if the same number of animals were used for the elimination experiments. The methods indicated that both males and females were used, but the number of each sex/group was not specified. OECD TG 427 indicates that at least 4 animals of a single-sex should be used.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Uninformative	The outcome assessment methodology deviated significantly from OECD 427 guidelines. Based on the information provided (volume applied and surface area), a dose of 403 mg/cm2 was determined using a test substance density of 1.25 g/mL, indicating infinite dosing. The surface area (3.1 cm2) is lower than the guideline recommendations and does not cover 10% of the animal surface area. The study did not evaluate anything other than the presence of the chemical in blood. It did not evaluate the chemical remaining in the excreta, carcass, skin, skin wash, or exhaled air. Therefore it cannot be used to determine skin absorption.
	Metric 15:	Consistency of outcome assessment	High	The outcome assessment methodology was reported, and, based on the available information was consistent across groups.
	Metric 16:	Sampling adequacy and sensitivity	Medium	None of the figures or data tables reported an "n." It is assumed that the data were generated from all 4 animals per group, but this was not explicitly stated. It is unclear if the frequency of blood collection is appropriate because it necessitated replacement with Marcodex.
Domain 6: Confounding/Variable Control				

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 94881
Unique ID: 1,2-DCE - Elimination

Domain	Metric		Rating	Comments
	Metric 17:	Confounding variables in test design and procedures	Medium	The study did not report all information to determine whether confounding bias occurred (test substance batch, body weight changes, or body weight variations greater than 20%, compared to the mean). Animals were anaesthetized throughout the experiment.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition, health outcomes unrelated to exposure, or solubility that could influence the outcome assessment.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Uninformative	Data analysis methods were described. Nonlinear regression analysis was conducted on values obtained for the concentration of the test material in the blood. The study referenced Holmberg et al. 1977 for additional details (open access, reviewed for this assessment). This cited reference did not provide a significant amount of additional details. The data were fitted to an equation representing a simplified two-compartment kinetic model (Snyder et al. 1981). The study, however, cannot be used to measure absorption based on a lack of appropriate information.
	Metric 20:	Data interpretation	Uninformative	The study specified studying elimination, but only measured concentrations in blood for 2 hours post-exposure, and not measure concentrations in other excreta. The study also did not calculate clearance from plasma, or report any elimination kinetics. This part of the study does not provide any useful information on absorption,.
	Metric 21:	Reporting of Data	Uninformative	A figure shows elimination curves from blood drawn according to a two-compartment model. The ”n” was not reported and the data points had no measures of variance. Data were inadequate for evaluating the fraction of the chemical absorbed through skin.

Overall Quality Determination Uninformative

Study Citation: Morgan, D. L., Cooper, S. W., Carlock, D. L., Sykora, J. J., Sutton, B., Mattie, D. R., McDougal, J. N. (1991). Dermal absorption of neat and aqueous volatile organic chemicals in the Fischer 344 rat. Environmental Research 55(1):51-63.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 200487; Linked HERO ID(s): 200487, 1070095
Unique ID: 1,2-Dichloroethane - Neat

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	The test substance was identified as unlabeled 1,2-dichloroethane, stabilized with 0.05% low alkyl epoxides. The CASRN and structure and chemical properties were not specified in the report. This information may be on the supplier's website, but no catalogue number was specified.
	Metric 2:	Test substance source	High	The test substance was obtained from Aldrich Chemical Co. The manufacturer, batch or lot number was not specified. The chemical purity was confirmed by gas chromatography by the performing laboratory.
	Metric 3:	Test substance purity	High	A purity of >99% was confirmed using gas chromatography.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Medium	The method of animal allocation was not specified. Still, it was indicated that some normalization to body weight occurred (body weights of rats within the same dose group were all within a 10 g range).
	Metric 5:	Standards for Tests	Low	The study authors did not report whether the test met any pre-established criteria. This study did not employ the use of metabolism cages. Percutaneous uptake over time in an intended infinite exposure model was evaluated by measuring concentrations of the test substance in the blood. The study did not calculate or determine percent recovery. It was mentioned that there was no loss to head space in the exposure cells, or to evaporation. The study did not explicitly report coefficients of variance. Figures showing mean ± SEM blood concentrations over time that could be extracted. The "n" was reported as a range (n = 6-10); however, a later data table (Table 3) reports the actual number of animals per group. CVs for the volume of the chemical solution absorbed could easily be calculated based on the data provided. These CV values (calculated for this review and noted in Metric 19) were >25%.
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	High	No preparation of the neat chemical was required. Saturated aqueous solutions were prepared by mixing 10-20 mL of neat chemical with 200 mL of HPLC-grade water. Details of mixing and removal of any remaining immiscible chemicals were provided. The samples were stored at 5-10 degrees C in zero head-space vials for 24 -48 hours prior to use. The study text suggests that stability tests were performed, and the solutions were stable for at least three weeks. The saturated solutions were diluted with HPLC-grade water.
	Metric 7:	Consistency of exposure administration	High	All animals were consistently exposed using the same protocol. Briefly, glass exposure cells (20 mm diameter, skin area 3.1 cm2) were attached to the shaved backs of rats the day before exposure. 2 mL volumes of the test solution were added to each cell under occlusive conditions (2 mL/3.1 cm2 or 0.645 mL/cm2), and animals were exposed for 24 hours.

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Study Citation: Morgan, D. L., Cooper, S. W., Carlock, D. L., Sykora, J. J., Sutton, B., Mattie, D. R., McDougal, J. N. (1991). Dermal absorption of neat and aqueous volatile organic chemicals in the Fischer 344 rat. Environmental Research 55(1):51-63.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 200487; Linked HERO ID(s): 200487, 1070095
Unique ID: 1,2-Dichloroethane - Neat

Domain	Metric		Rating	Comments
	Metric 8:	Reporting of concentrations	High	Animals were exposed to neat, 1/3 saturated (2,270 ug/mL), 2/3 saturated (4,290 ug/mL), or saturated (6,738 ug/mL) aqueous solutions. Saturated solutions were analyzed by GC to ensure that the concentrations were in the range of literature values. The volume applied (2 mL) and skin surface area (3.1 cm2 dorsal skin) were reported.
	Metric 9:	Exposure duration	High	Animals were exposed for 24 hours, which is consistent with OECD 427 guidelines.
	Metric 10:	Number of exposure groups and concentration spacing	High	The study included 4 exposure groups. The concentration spacing was not explicitly justified, but the study wanted to determine if there were differences in the volume absorbed and in blood concentrations attained from different dilutions. The concentrations of the chemical in surface or groundwater were reported to be magnitudes lower than those used in this study.
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	Medium	The study used male Fisher 344 rats sourced from Charles River Breeding Laboratories. An initial body weight range (at purchase) was reported to be 201-215g. Animals were acclimated for a week. Body weights prior to exposure were reported to be between 215 and 300 g, with all rats within one dose group within a 10g range. The variation between groups is not clear. Animal age was not reported.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	Medium	Housing, animals per cage, and food and water availability were reported. Additional animal husbandry details (e.g., temperature, humidity) were not specified.
	Metric 13:	Number of animals per group	Medium	The number of animals per group was not specified in the methods. Based on the data tables, the sample size ranged from 6 to 10. It is unclear whether all groups initially had 10 animals per group, or if the number per group was a range from 6-10 animals. OECD guidelines only require 4 animals per group, so overall, the number was more than required.
Domain 5: Outcome Assessment				

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 200487; Linked HERO ID(s): 200487, 1070095
Unique ID: 1,2-Dichloroethane - Neat

Domain	Metric		Rating	Comments
	Metric 14:	Outcome assessment methodology	Low	The outcome assessment methodology was sufficient to address the intentions of this non-guideline study but deviated from a traditional dermal absorption study as per OECD 427. In brief, this study attempted infinite exposure under occlusion. The mass per area was >10 mg/cm2 for all exposure groups; however, exposure was only about 1% of the total rat skin surface area, which is less than the suggested 5-10% (OECD 28). The report also indicated that in most cases, "levels in the blood rapidly decreased to near control levels by 24 hrs, probably due to depletion of chemical from the exposure cell," although this was not seen with neat levels. Blood samples were collected during exposure at times 0, 0.5, 1, 2, 4, 8, and 24 hours. The collection vials were sealed and stored at 5 degrees until GC analysis. They were stable for at least 3 weeks. At the end of exposure, the volume of test solution remaining in the exposure cell was measured. The remaining volume was subtracted from the initial 2 mL used to obtain the volume absorbed. The methods suggest that these samples were stored for GC analysis, but no results reporting concentrations of the test substance in the unabsorbed fraction were reported. This study did not determine the % recovery or the percent absorbed, but these were not intended endpoints for this study. The study did not conduct any skin washes or a wash of the dermal cell. Concentrations in the skin, other bodily fluids, or in exhaled air were not analyzed. The sampling sizes were not specified in the methods but were provided in the data tables and figures. The figures reported sample sizes "n" as a range from 6-10. For the volume of aqueous chemical absorbed endpoint, the data table indicated exact sample sizes. It was noted that animals also absorbed ~0.18 mL of water during the 24-hour exposure period. It is unclear whether water in the aqueous solutions increased skin permeability.
	Metric 15:	Consistency of outcome assessment	Medium	Blood samples were collected during exposure at times 0, 0.5, 1, 2, 4, 8, and 24 hours from 6-10 animals per group. Sample volumes were reported to be 50 or 100 uL; it is unclear if different volumes were collected from animals within a group, or across groups for a single chemical. This inconsistency could have an impact on the study results. Other aspects of outcome assessment (e.g., the timing of blood collection and study termination) were consistent across groups. The volume of aqueous solution remaining in the exposure cells at the end of the experiment was also measured from each replicate.
	Metric 16:	Sampling adequacy and sensitivity	High	Details of sampling were reported; VOC concentrations in blood were measured using GC with flame ionization for halogenated VOCs and electron capture for nonhalogenated VOCs from three repetitive samplings from each collection. Samples were stable for 3 weeks under the storage conditions specified. The sampling was appropriate for the endpoint of interest.

Domain 6: Confounding/Variable Control

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 200487; Linked HERO ID(s): 200487, 1070095
Unique ID: 1,2-Dichloroethane - Neat

Domain	Metric		Rating	Comments
	Metric 17:	Confounding variables in test design and procedures	Medium	Animal body weights at the start of exposure remained within 10 g within a group. Overall, weights ranged from 215-300 g. A mean was not specified, so it is not known if these ranges fall within 20% of the mean. It was noted that some exposure cells with low volumes of neat test chemicals were assumed to have leaked. The study tested multiple chemicals and did not specify what chemicals or how many samples were affected by this. It was noted that these cells were not used in the calculation of the mean absorption volume. The text also indicated that there was a small amount of headspace in the exposure cells; however, the authors said the headspace was too small to lower the exposure concentration. They confirmed this by exposing one group of rats to saturated 1,1,1-trichloroethane using a cell completely filled (no headspace). After 24 hours, the concentration of 1,1,1-trichloroethane was still depleted to an amount similar to samples that had a headspace, indicating no loss to headspace occurred.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition, health outcomes unrelated to exposure, or solubility that could influence the outcome assessment. Solubility was noted as a factor affecting absorption, where absorption of neat chemicals decreased as their water solubility decreased, but this was not a confounding factor.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	The coefficient of variation could only be easily determined for the volume of chemical solution absorbed (mL). The study authors noted a significant amount of variation, and the CVs (calculated for this review) were 26%, 76%, 33%, and 31% for the neat, saturated, 2/3 saturated, and 1/3 saturated solutions, respectively. Sufficient information (mean, SD and sample size) is provided for EPA to calculate an alternate upper-end value to account for variability in the results. Levels in blood over time were graphically displayed showing means ± SEM. The figures report n as a range (6-10), but exact n values can be obtained from another data table. No statistical analysis was conducted.
	Metric 20:	Data interpretation	Low	This study was not conducted according to OECD 427, or in a manner allowing the determination of recovery or the calculation of absorption estimates. The only tissue compartment analyzed was blood/plasma. Absorption volumes were also determined, but not the total percent absorbed. The authors found no correlation between blood levels and absorption volumes. Although the authors intended to create an infinite exposure scenario, less than 1% of the initial concentration was purportedly present in the exposure cells after 24 hours (chemical-specific quantitative values were not provided). This indicated rapid absorption and depletion from the aqueous solutions. The authors believed evaporation of the chemical was unlikely because the exposure cells were sealed, and the Teflon-coated caps were found not to absorb the test chemicals. The usefulness of this study is limited to demonstrating absorption through the skin occurs upon exposure to lower dilutions in aqueous solutions.

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 200487; Linked HERO ID(s): 200487, 1070095
Unique ID: 1,2-Dichloroethane - Neat

Domain	Metric	Rating	Comments
	Metric 21: Reporting of Data	Medium	Data were reported for all of the outcomes specified in the methods and included concentrations in blood over time and volume of test solution absorbed for each group. Data were presented as means ± either SE or SD. The number of samples was provided either as a range, or a specific numerical value. Individual animal data were not provided. Because a range was reported for some data (blood concentrations), CV values could not be calculated for those endpoints, which significantly reduces the ability to interpret the data.

Overall Quality Determination Medium

Study Citation: Morgan, D. L., Cooper, S. W., Carlock, D. L., Sykora, J. J., Sutton, B., Mattie, D. R., McDougal, J. N. (1991). Dermal absorption of neat and aqueous volatile organic chemicals in the Fischer 344 rat. Environmental Research 55(1):51-63.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 200487; Linked HERO ID(s): 200487, 1070095
Unique ID: 1,2-Dichloroethane - Saturated

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	The test substance was identified as unlabeled 1,2-dichloroethane, stabilized with 0.05% low alkyl epoxides. The CASRN and structure and chemical properties were not specified in the report. This information may be on the supplier's website, but no catalogue number was specified.
	Metric 2:	Test substance source	High	The test substance was obtained from Aldrich Chemical Co. The manufacturer, batch or lot number was not specified. The chemical purity was confirmed by gas chromatography by the performing laboratory.
	Metric 3:	Test substance purity	High	A purity of >99% was confirmed using gas chromatography.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Medium	The method of animal allocation was not specified. Still, it was indicated that some normalization to body weight occurred (body weights of rats within the same dose group were all within a 10 g range).
	Metric 5:	Standards for Tests	Low	The study authors did not report whether the test met any pre-established criteria. This study did not employ the use of metabolism cages. Percutaneous uptake over time in an intended infinite exposure model was evaluated by measuring concentrations of the test substance in the blood. The study did not calculate or determine percent recovery. It was mentioned that there was no loss to head space in the exposure cells, or to evaporation. The study did not explicitly report coefficients of variance. Figures showing mean ± SEM blood concentrations over time that could be extracted. The "n" was reported as a range (n = 6-10); however, a later data table (Table 3) reports the actual number of animals per group. CVs for the volume of the chemical solution absorbed could easily be calculated based on the data provided. These CV values (calculated for this review and noted in Metric 19) were >25%.
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	High	No preparation of the neat chemical was required. Saturated aqueous solutions were prepared by mixing 10-20 mL of neat chemical with 200 mL of HPLC-grade water. Details of mixing and removal of any remaining immiscible chemicals were provided. The samples were stored at 5-10 degrees C in zero head-space vials for 24 -48 hours prior to use. The study text suggests that stability tests were performed, and the solutions were stable for at least three weeks. The saturated solutions were diluted with HPLC-grade water.
	Metric 7:	Consistency of exposure administration	High	All animals were consistently exposed using the same protocol. Briefly, glass exposure cells (20 mm diameter, skin area 3.1 cm2) were attached to the shaved backs of rats the day before exposure. 2 mL volumes of the test solution were added to each cell under occlusive conditions (2 mL/3.1 cm2 or 0.645 mL/cm2), and animals were exposed for 24 hours.

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Chemical: 1,2-Dichloroethane
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HERO ID: 200487; Linked HERO ID(s): 200487, 1070095
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Domain	Metric		Rating	Comments
	Metric 8:	Reporting of concentrations	High	Animals were exposed to neat, 1/3 saturated (2,270 ug/mL), 2/3 saturated (4,290 ug/mL), or saturated (6,738 ug/mL) aqueous solutions. Saturated solutions were analyzed by GC to ensure that the concentrations were in the range of literature values. The volume applied (2 mL) and skin surface area (3.1 cm2 dorsal skin) were reported.
	Metric 9:	Exposure duration	High	Animals were exposed for 24 hours, which is consistent with OECD 427 guidelines.
	Metric 10:	Number of exposure groups and concentration spacing	High	The study included 4 exposure groups. The concentration spacing was not explicitly justified, but the study wanted to determine if there were differences in the volume absorbed and in blood concentrations attained from different dilutions. The concentrations of the chemical in surface or groundwater were reported to be magnitudes lower than those used in this study.
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	Medium	The study used male Fisher 344 rats sourced from Charles River Breeding Laboratories. An initial body weight range (at purchase) was reported to be 201-215g. Animals were acclimated for a week. Body weights prior to exposure were reported to be between 215 and 300 g, with all rats within one dose group within a 10g range. The variation between groups is not clear. Animal age was not reported.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	Medium	Housing, animals per cage, and food and water availability were reported. Additional animal husbandry details (e.g., temperature, humidity) were not specified.
	Metric 13:	Number of animals per group	Medium	The number of animals per group was not specified in the methods. Based on the data tables, the sample size ranged from 6 to 10. It is unclear whether all groups initially had 10 animals per group, or if the number per group was a range from 6-10 animals. OECD guidelines only require 4 animals per group, so overall, the number was more than required.
Domain 5: Outcome Assessment				

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Chemical: 1,2-Dichloroethane
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Unique ID: 1,2-Dichloroethane - Saturated

Domain	Metric		Rating	Comments
	Metric 14:	Outcome assessment methodology	Low	The outcome assessment methodology was sufficient to address the intentions of this non-guideline study but deviated from a traditional dermal absorption study as per OECD 427. In brief, this study attempted infinite exposure under occlusion. The mass per area was >10 mg/cm2 for all exposure groups; however, exposure was only about 1% of the total rat skin surface area, which is less than the suggested 5-10% (OECD 28). The report also indicated that in most cases, "levels in the blood rapidly decreased to near control levels by 24 hrs, probably due to depletion of chemical from the exposure cell," although this was not seen with neat levels. Blood samples were collected during exposure at times 0, 0.5, 1, 2, 4, 8, and 24 hours. The collection vials were sealed and stored at 5 degrees until GC analysis. They were stable for at least 3 weeks. At the end of exposure, the volume of test solution remaining in the exposure cell was measured. The remaining volume was subtracted from the initial 2 mL used to obtain the volume absorbed. The methods suggest that these samples were stored for GC analysis, but no results reporting concentrations of the test substance in the unabsorbed fraction were reported. This study did not determine the % recovery or the percent absorbed, but these were not intended endpoints for this study. The study did not conduct any skin washes or a wash of the dermal cell. Concentrations in the skin, other bodily fluids, or in exhaled air were not analyzed. The sampling sizes were not specified in the methods but were provided in the data tables and figures. The figures reported sample sizes "n" as a range from 6-10. For the volume of aqueous chemical absorbed endpoint, the data table indicated exact sample sizes. It was noted that animals also absorbed ~0.18 mL of water during the 24-hour exposure period. It is unclear whether water in the aqueous solutions increased skin permeability.
	Metric 15:	Consistency of outcome assessment	Medium	Blood samples were collected during exposure at times 0, 0.5, 1, 2, 4, 8, and 24 hours from 6-10 animals per group. Sample volumes were reported to be 50 or 100 uL; it is unclear if different volumes were collected from animals within a group, or across groups for a single chemical. This inconsistency could have an impact on the study results. Other aspects of outcome assessment (e.g., the timing of blood collection and study termination) were consistent across groups. The volume of aqueous solution remaining in the exposure cells at the end of the experiment was also measured from each replicate.
	Metric 16:	Sampling adequacy and sensitivity	High	Details of sampling were reported; VOC concentrations in blood were measured using GC with flame ionization for halogenated VOCs and electron capture for nonhalogenated VOCs from three repetitive samplings from each collection. Samples were stable for 3 weeks under the storage conditions specified. The sampling was appropriate for the endpoint of interest.

Domain 6: Confounding/Variable Control

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 200487; Linked HERO ID(s): 200487, 1070095
Unique ID: 1,2-Dichloroethane - Saturated

Domain	Metric		Rating	Comments
	Metric 17:	Confounding variables in test design and procedures	Medium	Animal body weights at the start of exposure remained within 10 g within a group. Overall, weights ranged from 215-300 g. A mean was not specified, so it is not known if these ranges fall within 20% of the mean. It was noted that some exposure cells with low volumes of neat test chemicals were assumed to have leaked. The study tested multiple chemicals and did not specify what chemicals or how many samples were affected by this. It was noted that these cells were not used in the calculation of the mean absorption volume. The text also indicated that there was a small amount of headspace in the exposure cells; however, the authors said the headspace was too small to lower the exposure concentration. They confirmed this by exposing one group of rats to saturated 1,1,1-trichloroethane using a cell completely filled (no headspace). After 24 hours, the concentration of 1,1,1-trichloroethane was still depleted to an amount similar to samples that had a headspace, indicating no loss to headspace occurred.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition, health outcomes unrelated to exposure, or solubility that could influence the outcome assessment. Solubility was noted as a factor affecting absorption, where absorption of neat chemicals decreased as their water solubility decreased, but this was not a confounding factor.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	The coefficient of variation could only be easily determined for the volume of chemical solution absorbed (mL). The study authors noted a significant amount of variation, and the CVs (calculated for this review) were 26%, 76%, 33%, and 31% for the neat, saturated, 2/3 saturated, and 1/3 saturated solutions, respectively. Sufficient information (mean, SD and sample size) is provided for EPA to calculate an alternate upper-end value to account for variability in the results. Levels in blood over time were graphically displayed showing means ± SEM. The figures report n as a range (6-10), but exact n values can be obtained from another data table. No statistical analysis was conducted.
	Metric 20:	Data interpretation	Low	This study was not conducted according to OECD 427, or in a manner allowing the determination of recovery or the calculation of absorption estimates. The only tissue compartment analyzed was blood/plasma. Absorption volumes were also determined, but not the total percent absorbed. The authors found no correlation between blood levels and absorption volumes. Although the authors intended to create an infinite exposure scenario, less than 1% of the initial concentration was purportedly present in the exposure cells after 24 hours (chemical-specific quantitative values were not provided). This indicated rapid absorption and depletion from the aqueous solutions. The authors believed evaporation of the chemical was unlikely because the exposure cells were sealed, and the Teflon-coated caps were found not to absorb the test chemicals. The usefulness of this study is limited to demonstrating absorption through the skin occurs upon exposure to lower dilutions in aqueous solutions.

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HERO ID: 200487; Linked HERO ID(s): 200487, 1070095
Unique ID: 1,2-Dichloroethane - Saturated

Domain	Metric	Rating	Comments
	Metric 21: Reporting of Data	Medium	Data were reported for all of the outcomes specified in the methods and included concentrations in blood over time and volume of test solution absorbed for each group. Data were presented as means ± either SE or SD. The number of samples was provided either as a range, or a specific numerical value. Individual animal data were not provided. Because a range was reported for some data (blood concentrations), CV values could not be calculated for those endpoints, which significantly reduces the ability to interpret the data.

Overall Quality Determination Medium

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 200487; Linked HERO ID(s): 200487, 1070095
Unique ID: 1,2-Dichloroethane - 2/3 Saturated

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	The test substance was identified as unlabeled 1,2-dichloroethane, stabilized with 0.05% low alkyl epoxides. The CASRN and structure and chemical properties were not specified in the report. This information may be on the supplier's website, but no catalogue number was specified.
	Metric 2:	Test substance source	High	The test substance was obtained from Aldrich Chemical Co. The manufacturer, batch or lot number was not specified. The chemical purity was confirmed by gas chromatography by the performing laboratory.
	Metric 3:	Test substance purity	High	A purity of >99% was confirmed using gas chromatography.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Medium	The method of animal allocation was not specified. Still, it was indicated that some normalization to body weight occurred (body weights of rats within the same dose group were all within a 10 g range).
	Metric 5:	Standards for Tests	Low	The study authors did not report whether the test met any pre-established criteria. This study did not employ the use of metabolism cages. Percutaneous uptake over time in an intended infinite exposure model was evaluated by measuring concentrations of the test substance in the blood. The study did not calculate or determine percent recovery. It was mentioned that there was no loss to head space in the exposure cells, or to evaporation. The study did not explicitly report coefficients of variance. Figures showing mean ± SEM blood concentrations over time that could be extracted. The "n" was reported as a range (n = 6-10); however, a later data table (Table 3) reports the actual number of animals per group. CVs for the volume of the chemical solution absorbed could easily be calculated based on the data provided. These CV values (calculated for this review and noted in Metric 19) were >25%.
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	High	No preparation of the neat chemical was required. Saturated aqueous solutions were prepared by mixing 10-20 mL of neat chemical with 200 mL of HPLC-grade water. Details of mixing and removal of any remaining immiscible chemicals were provided. The samples were stored at 5-10 degrees C in zero head-space vials for 24 -48 hours prior to use. The study text suggests that stability tests were performed, and the solutions were stable for at least three weeks. The saturated solutions were diluted with HPLC-grade water.
	Metric 7:	Consistency of exposure administration	High	All animals were consistently exposed using the same protocol. Briefly, glass exposure cells (20 mm diameter, skin area 3.1 cm2) were attached to the shaved backs of rats the day before exposure. 2 mL volumes of the test solution were added to each cell under occlusive conditions (2 mL/3.1 cm2 or 0.645 mL/cm2), and animals were exposed for 24 hours.

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Domain	Metric		Rating	Comments
	Metric 8:	Reporting of concentrations	High	Animals were exposed to neat, 1/3 saturated (2,270 ug/mL), 2/3 saturated (4,290 ug/mL), or saturated (6,738 ug/mL) aqueous solutions. Saturated solutions were analyzed by GC to ensure that the concentrations were in the range of literature values. The volume applied (2 mL) and skin surface area (3.1 cm2 dorsal skin) were reported.
	Metric 9:	Exposure duration	High	Animals were exposed for 24 hours, which is consistent with OECD 427 guidelines.
	Metric 10:	Number of exposure groups and concentration spacing	High	The study included 4 exposure groups. The concentration spacing was not explicitly justified, but the study wanted to determine if there were differences in the volume absorbed and in blood concentrations attained from different dilutions. The concentrations of the chemical in surface or groundwater were reported to be magnitudes lower than those used in this study.
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	Medium	The study used male Fisher 344 rats sourced from Charles River Breeding Laboratories. An initial body weight range (at purchase) was reported to be 201-215g. Animals were acclimated for a week. Body weights prior to exposure were reported to be between 215 and 300 g, with all rats within one dose group within a 10g range. The variation between groups is not clear. Animal age was not reported.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	Medium	Housing, animals per cage, and food and water availability were reported. Additional animal husbandry details (e.g., temperature, humidity) were not specified.
	Metric 13:	Number of animals per group	Medium	The number of animals per group was not specified in the methods. Based on the data tables, the sample size ranged from 6 to 10. It is unclear whether all groups initially had 10 animals per group, or if the number per group was a range from 6-10 animals. OECD guidelines only require 4 animals per group, so overall, the number was more than required.
Domain 5: Outcome Assessment				

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 200487; Linked HERO ID(s): 200487, 1070095
Unique ID: 1,2-Dichloroethane - 2/3 Saturated

Domain	Metric		Rating	Comments
	Metric 14:	Outcome assessment methodology	Low	The outcome assessment methodology was sufficient to address the intentions of this non-guideline study but deviated from a traditional dermal absorption study as per OECD 427. In brief, this study attempted infinite exposure under occlusion. The mass per area was >10 mg/cm2 for all exposure groups; however, exposure was only about 1% of the total rat skin surface area, which is less than the suggested 5-10% (OECD 28). The report also indicated that in most cases, "levels in the blood rapidly decreased to near control levels by 24 hrs, probably due to depletion of chemical from the exposure cell," although this was not seen with neat levels. Blood samples were collected during exposure at times 0, 0.5, 1, 2, 4, 8, and 24 hours. The collection vials were sealed and stored at 5 degrees until GC analysis. They were stable for at least 3 weeks. At the end of exposure, the volume of test solution remaining in the exposure cell was measured. The remaining volume was subtracted from the initial 2 mL used to obtain the volume absorbed. The methods suggest that these samples were stored for GC analysis, but no results reporting concentrations of the test substance in the unabsorbed fraction were reported. This study did not determine the % recovery or the percent absorbed, but these were not intended endpoints for this study. The study did not conduct any skin washes or a wash of the dermal cell. Concentrations in the skin, other bodily fluids, or in exhaled air were not analyzed. The sampling sizes were not specified in the methods but were provided in the data tables and figures. The figures reported sample sizes "n" as a range from 6-10. For the volume of aqueous chemical absorbed endpoint, the data table indicated exact sample sizes. It was noted that animals also absorbed ~0.18 mL of water during the 24-hour exposure period. It is unclear whether water in the aqueous solutions increased skin permeability.
	Metric 15:	Consistency of outcome assessment	Medium	Blood samples were collected during exposure at times 0, 0.5, 1, 2, 4, 8, and 24 hours from 6-10 animals per group. Sample volumes were reported to be 50 or 100 uL; it is unclear if different volumes were collected from animals within a group, or across groups for a single chemical. This inconsistency could have an impact on the study results. Other aspects of outcome assessment (e.g., the timing of blood collection and study termination) were consistent across groups. The volume of aqueous solution remaining in the exposure cells at the end of the experiment was also measured from each replicate.
	Metric 16:	Sampling adequacy and sensitivity	High	Details of sampling were reported; VOC concentrations in blood were measured using GC with flame ionization for halogenated VOCs and electron capture for nonhalogenated VOCs from three repetitive samplings from each collection. Samples were stable for 3 weeks under the storage conditions specified. The sampling was appropriate for the endpoint of interest.

Domain 6: Confounding/Variable Control

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HERO ID: 200487; Linked HERO ID(s): 200487, 1070095
Unique ID: 1,2-Dichloroethane - 2/3 Saturated

Domain	Metric		Rating	Comments
	Metric 17:	Confounding variables in test design and procedures	Medium	Animal body weights at the start of exposure remained within 10 g within a group. Overall, weights ranged from 215-300 g. A mean was not specified, so it is not known if these ranges fall within 20% of the mean. It was noted that some exposure cells with low volumes of neat test chemicals were assumed to have leaked. The study tested multiple chemicals and did not specify what chemicals or how many samples were affected by this. It was noted that these cells were not used in the calculation of the mean absorption volume. The text also indicated that there was a small amount of headspace in the exposure cells; however, the authors said the headspace was too small to lower the exposure concentration. They confirmed this by exposing one group of rats to saturated 1,1,1-trichloroethane using a cell completely filled (no headspace). After 24 hours, the concentration of 1,1,1-trichloroethane was still depleted to an amount similar to samples that had a headspace, indicating no loss to headspace occurred.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition, health outcomes unrelated to exposure, or solubility that could influence the outcome assessment. Solubility was noted as a factor affecting absorption, where absorption of neat chemicals decreased as their water solubility decreased, but this was not a confounding factor.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	The coefficient of variation could only be easily determined for the volume of chemical solution absorbed (mL). The study authors noted a significant amount of variation, and the CVs (calculated for this review) were 26%, 76%, 33%, and 31% for the neat, saturated, 2/3 saturated, and 1/3 saturated solutions, respectively. Sufficient information (mean, SD and sample size) is provided for EPA to calculate an alternate upper-end value to account for variability in the results. Levels in blood over time were graphically displayed showing means ± SEM. The figures report n as a range (6-10), but exact n values can be obtained from another data table. No statistical analysis was conducted.
	Metric 20:	Data interpretation	Low	This study was not conducted according to OECD 427, or in a manner allowing the determination of recovery or the calculation of absorption estimates. The only tissue compartment analyzed was blood/plasma. Absorption volumes were also determined, but not the total percent absorbed. The authors found no correlation between blood levels and absorption volumes. Although the authors intended to create an infinite exposure scenario, less than 1% of the initial concentration was purportedly present in the exposure cells after 24 hours (chemical-specific quantitative values were not provided). This indicated rapid absorption and depletion from the aqueous solutions. The authors believed evaporation of the chemical was unlikely because the exposure cells were sealed, and the Teflon-coated caps were found not to absorb the test chemicals. The usefulness of this study is limited to demonstrating absorption through the skin occurs upon exposure to lower dilutions in aqueous solutions.

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Domain	Metric	Rating	Comments
	Metric 21: Reporting of Data	Medium	Data were reported for all of the outcomes specified in the methods and included concentrations in blood over time and volume of test solution absorbed for each group. Data were presented as means ± either SE or SD. The number of samples was provided either as a range, or a specific numerical value. Individual animal data were not provided. Because a range was reported for some data (blood concentrations), CV values could not be calculated for those endpoints, which significantly reduces the ability to interpret the data.

Overall Quality Determination Medium

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Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 200487; Linked HERO ID(s): 200487, 1070095
Unique ID: 1,2-Dichloroethane - 1/3 Saturated

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	The test substance was identified as unlabeled 1,2-dichloroethane, stabilized with 0.05% low alkyl epoxides. The CASRN and structure and chemical properties were not specified in the report. This information may be on the supplier's website, but no catalogue number was specified.
	Metric 2:	Test substance source	High	The test substance was obtained from Aldrich Chemical Co. The manufacturer, batch or lot number was not specified. The chemical purity was confirmed by gas chromatography by the performing laboratory.
	Metric 3:	Test substance purity	High	A purity of >99% was confirmed using gas chromatography.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Medium	The method of animal allocation was not specified. Still, it was indicated that some normalization to body weight occurred (body weights of rats within the same dose group were all within a 10 g range).
	Metric 5:	Standards for Tests	Low	The study authors did not report whether the test met any pre-established criteria. This study did not employ the use of metabolism cages. Percutaneous uptake over time in an intended infinite exposure model was evaluated by measuring concentrations of the test substance in the blood. The study did not calculate or determine percent recovery. It was mentioned that there was no loss to head space in the exposure cells, or to evaporation. The study did not explicitly report coefficients of variance. Figures showing mean ± SEM blood concentrations over time that could be extracted. The "n" was reported as a range (n = 6-10); however, a later data table (Table 3) reports the actual number of animals per group. CVs for the volume of the chemical solution absorbed could easily be calculated based on the data provided. These CV values (calculated for this review and noted in Metric 19) were >25%.
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	High	No preparation of the neat chemical was required. Saturated aqueous solutions were prepared by mixing 10-20 mL of neat chemical with 200 mL of HPLC-grade water. Details of mixing and removal of any remaining immiscible chemicals were provided. The samples were stored at 5-10 degrees C in zero head-space vials for 24 -48 hours prior to use. The study text suggests that stability tests were performed, and the solutions were stable for at least three weeks. The saturated solutions were diluted with HPLC-grade water.
	Metric 7:	Consistency of exposure administration	High	All animals were consistently exposed using the same protocol. Briefly, glass exposure cells (20 mm diameter, skin area 3.1 cm2) were attached to the shaved backs of rats the day before exposure. 2 mL volumes of the test solution were added to each cell under occlusive conditions (2 mL/3.1 cm2 or 0.645 mL/cm2), and animals were exposed for 24 hours.

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Domain	Metric		Rating	Comments
	Metric 8:	Reporting of concentrations	High	Animals were exposed to neat, 1/3 saturated (2,270 ug/mL), 2/3 saturated (4,290 ug/mL), or saturated (6,738 ug/mL) aqueous solutions. Saturated solutions were analyzed by GC to ensure that the concentrations were in the range of literature values. The volume applied (2 mL) and skin surface area (3.1 cm2 dorsal skin) were reported.
	Metric 9:	Exposure duration	High	Animals were exposed for 24 hours, which is consistent with OECD 427 guidelines.
	Metric 10:	Number of exposure groups and concentration spacing	High	The study included 4 exposure groups. The concentration spacing was not explicitly justified, but the study wanted to determine if there were differences in the volume absorbed and in blood concentrations attained from different dilutions. The concentrations of the chemical in surface or groundwater were reported to be magnitudes lower than those used in this study.
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	Medium	The study used male Fisher 344 rats sourced from Charles River Breeding Laboratories. An initial body weight range (at purchase) was reported to be 201-215g. Animals were acclimated for a week. Body weights prior to exposure were reported to be between 215 and 300 g, with all rats within one dose group within a 10g range. The variation between groups is not clear. Animal age was not reported.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	Medium	Housing, animals per cage, and food and water availability were reported. Additional animal husbandry details (e.g., temperature, humidity) were not specified.
	Metric 13:	Number of animals per group	Medium	The number of animals per group was not specified in the methods. Based on the data tables, the sample size ranged from 6 to 10. It is unclear whether all groups initially had 10 animals per group, or if the number per group was a range from 6-10 animals. OECD guidelines only require 4 animals per group, so overall, the number was more than required.
Domain 5: Outcome Assessment				

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Domain	Metric		Rating	Comments
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	Metric 16:	Sampling adequacy and sensitivity	High	Details of sampling were reported; VOC concentrations in blood were measured using GC with flame ionization for halogenated VOCs and electron capture for nonhalogenated VOCs from three repetitive samplings from each collection. Samples were stable for 3 weeks under the storage conditions specified. The sampling was appropriate for the endpoint of interest.

Domain 6: Confounding/Variable Control

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Domain	Metric		Rating	Comments
	Metric 17:	Confounding variables in test design and procedures	Medium	Animal body weights at the start of exposure remained within 10 g within a group. Overall, weights ranged from 215-300 g. A mean was not specified, so it is not known if these ranges fall within 20% of the mean. It was noted that some exposure cells with low volumes of neat test chemicals were assumed to have leaked. The study tested multiple chemicals and did not specify what chemicals or how many samples were affected by this. It was noted that these cells were not used in the calculation of the mean absorption volume. The text also indicated that there was a small amount of headspace in the exposure cells; however, the authors said the headspace was too small to lower the exposure concentration. They confirmed this by exposing one group of rats to saturated 1,1,1-trichloroethane using a cell completely filled (no headspace). After 24 hours, the concentration of 1,1,1-trichloroethane was still depleted to an amount similar to samples that had a headspace, indicating no loss to headspace occurred.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition, health outcomes unrelated to exposure, or solubility that could influence the outcome assessment. Solubility was noted as a factor affecting absorption, where absorption of neat chemicals decreased as their water solubility decreased, but this was not a confounding factor.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	The coefficient of variation could only be easily determined for the volume of chemical solution absorbed (mL). The study authors noted a significant amount of variation, and the CVs (calculated for this review) were 26%, 76%, 33%, and 31% for the neat, saturated, 2/3 saturated, and 1/3 saturated solutions, respectively. Sufficient information (mean, SD and sample size) is provided for EPA to calculate an alternate upper-end value to account for variability in the results. Levels in blood over time were graphically displayed showing means ± SEM. The figures report n as a range (6-10), but exact n values can be obtained from another data table. No statistical analysis was conducted.
	Metric 20:	Data interpretation	Low	This study was not conducted according to OECD 427, or in a manner allowing the determination of recovery or the calculation of absorption estimates. The only tissue compartment analyzed was blood/plasma. Absorption volumes were also determined, but not the total percent absorbed. The authors found no correlation between blood levels and absorption volumes. Although the authors intended to create an infinite exposure scenario, less than 1% of the initial concentration was purportedly present in the exposure cells after 24 hours (chemical-specific quantitative values were not provided). This indicated rapid absorption and depletion from the aqueous solutions. The authors believed evaporation of the chemical was unlikely because the exposure cells were sealed, and the Teflon-coated caps were found not to absorb the test chemicals. The usefulness of this study is limited to demonstrating absorption through the skin occurs upon exposure to lower dilutions in aqueous solutions.

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Study Citation: Morgan, D. L., Cooper, S. W., Carlock, D. L., Sykora, J. J., Sutton, B., Mattie, D. R., McDougal, J. N. (1991). Dermal absorption of neat and aqueous volatile organic chemicals in the Fischer 344 rat. Environmental Research 55(1):51-63.
Chemical: 1,2-Dichloroethane
Exposure Type: Parent compound
HERO ID: 200487; Linked HERO ID(s): 200487, 1070095
Unique ID: 1,2-Dichloroethane - 1/3 Saturated

Domain	Metric	Rating	Comments
	Metric 21: Reporting of Data	Medium	Data were reported for all of the outcomes specified in the methods and included concentrations in blood over time and volume of test solution absorbed for each group. Data were presented as means ± either SE or SD. The number of samples was provided either as a range, or a specific numerical value. Individual animal data were not provided. Because a range was reported for some data (blood concentrations), CV values could not be calculated for those endpoints, which significantly reduces the ability to interpret the data.

Overall Quality Determination Medium