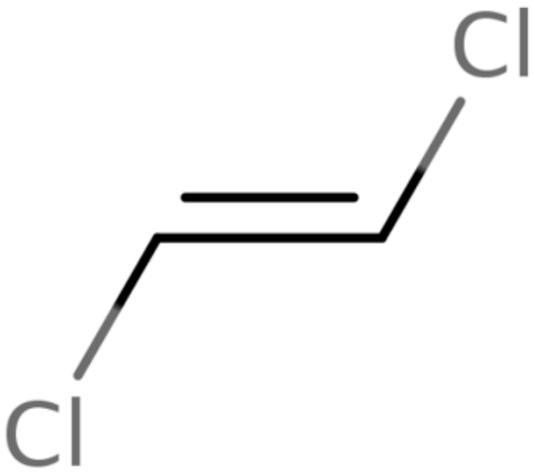
United States
Environmental Protection Agency

June 2026
Office of Chemical Safety and
Pollution Prevention

Draft Data Quality Evaluation Information for Dermal Absorption for *trans*-1,2-Dichloroethylene

Systematic Review Support Document for the Draft Risk Evaluation

CASRN: 156-60-5



June 2026

This supplemental file contains information regarding the data evaluation results for data sources that met the PECO screening criteria for the *Draft Risk Evaluation for trans-1,2-Dichloroethylene* and were used to characterize dermal absorption. EPA conducted data quality evaluation based on author-reported descriptions and results; additional analyses (*e.g.*, statistical analyses performed during data integration into the risk evaluation) potentially conducted by EPA are not contained in this supplemental file. Key parameters and corresponding data for each condition were not extracted from the reference. EPA used the TSCA systematic review process described in the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (also referred to as the '2021 Draft Systematic Review Protocol'). Any updated steps in the systematic review process since the publication of the 2021 Draft Systematic Review Protocol are described in the *Draft Systematic Review Protocol for trans-1,2-Dichloroethylene*.

To evaluate dermal absorption references, EPA consulted several OECD documents when considering quality rankings for individual metrics. Each condition (*e.g.*, individual concentrations tested or different experimental designs) is evaluated independently within a given reference, therefore each reference may have more than one overall quality determination (OQD) to more appropriately reflect the quality of each condition. No OQD is determined for each reference as a whole, if it contains data from more than one condition. A single reference may evaluate only a limited number of conditions (*e.g.*, use of only the neat compound). If all other methods and results are adequate, the study may be considered acceptable for certain conditions of use. However, the study may still be limited for use in the risk evaluation because it may not address other uses (*e.g.*, lower concentrations, certain solvents/diluents).

Table of Contents

Study Citation:	TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical:	trans-1,2-Dichloroethylene
Exposure Type:	Parent compound
HERO ID:	11523429
Unique ID:	Infinite- Neat

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled trans-1,2-dichloroethylene and radiolabeled [1,2-14C2]trans-1,2-dichloroethylene, CAS number: 156-60-5. 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, trans-1,2-dichloroethylene was sourced from Sigma-Aldrich; the source of the radiolabeled trans-1,2-dichloroethylene was redacted from the study. The study included certificates of analyses that reported lot/batch numbers. The radiolabeled test substance was verified by HPLC.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the initial radiolabeled test substance was determined to be ≥95.6% % by HPLC. The purity of the non-radiolabeled substance was reported to be 99.7%. Impurities were not reported. Post-dose radiochemical purity was also determined (>95%).
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No appropriate reference compound was studied. The study authors do not report their familiarity with performing this type of study.

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Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
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Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428, OECD 28, EPA guidelines for dermal studies and the European Commissions Guidance on Dermal Absorption. The assay procedures specified in the report were described in detail, although some information was missing. The static diffusion cell set up is sufficiently reported including a photograph. The study reported an equilibration period after the skin was placed into the chamber of 30 minutes, which is agreement with guidelines recommendations. An infinite dose of trans-1,2-dichloroethylene (neat) was applied to human skin (7-8 replicates; surface area of 0.64 cm2). The stability of the test substance over the course of the study was confirmed by HPLC. The study authors state "All test preparation were applied at an application rate of 100 uL/cm2 of TDCE, as directed by the EPA". The volume applied ranged from 64 uL. Due to the high volatility of the test substance, a larger application volume (>1 ml) would have been more appropriate. Full thickness human skin samples were thawed and dermatomed to create split-thickness membranes. Membranes were then refrozen (up to 2 months). Thickness of skin sample ranged from 380 to 400 um. Skin was exposed to test substance under occluded conditions (cap and wrapped in Parafilm®) for 8 hours. The receptor solution (PBS with 6% polyethoxyoleate 20 oleyl ether) was appropriate for this lipophilic chemical. The solubility of trans-1,2-dichloroethylene was tested in the receptor fluid prior to the study and determined solubility of the test substance was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity was monitored but not reported here. The receptor fluid (5 mL) was continuously stirred as per OECD 428 guidelines. Receptor fluid samples (300 uL) were collected at 0, 15, 30, 45 and 60 minutes, 2, 3, 4, 6, 8 hours post-application and analyzed for radioactivity. The study does not report if they added additional receptor fluid to the receptor chamber after each sampling in order to maintain 5 mL of receptor fluid. Radioactivity was measured with a representative blank sample subtracted from count rates. A limit of reliable measurement of 30 d.p.m. over background was determined.
	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. The authors did not specify inclusion criteria for this measurement; but full results were reported. The electrical resistance of the skin was measured following TEWL assessment using low voltage alternating current (100 Hz with a maximum of 300 mV). All samples had a resistance greater than 7.7 kilo ohms, the author-reported criteria for inclusion. 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 and insufficient information was provided to allow for independent determinations.

Domain 3: Exposure Characterization

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Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Infinite- Neat

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of test substance is described in detail. Dilutions were vortexed and magnetically stirred. The activity and homogeneity of the diluted doses were assessed. Test substance concentration and target concentration are reported with CV. After dosing, the test preparation was analyzed for stability. Storage conditions of test substances were reported and appropriate.
	Metric 8:	Consistency of exposure administration	Medium	The same volume across all samples (64ul; 100 uL/cm2 (per instructions given to study authors from EPA). The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was measured and reported (varying from 380-400 uM between samples); these slight variations were not likely to substantially impact results.
	Metric 9:	Reporting of concentrations	High	The applied mass is reported as mg equiv/cm2. Nominal and analytical doses are reported with CV.
	Metric 10:	Exposure frequency	High	Exposure duration (8 hours) was appropriate for Kp determination given the volatility of the test substance. 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, 10%, and 50%). Dilutions of test substance were performed in two different vehicles (isopropyl myristate or receptor fluid). Justification for dose selection was not provided.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Full thickness skin samples were obtained from males and females. Abdominal skin samples from 20 people (race not reported) ranging in age from 25-66 years old were studied. The samples arrived deep frozen on dry ice were stored frozen at -20 degrees C. The skin samples were thawed and dermatomed using an electric dermatome. The split-thickness samples were measured using a micrometer and ranged from 380 to 400 uM. The OECD guidelines indicate split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring trans epidermal water loss prior to/and upon completion of the experiment. Electrical resistance of skin was also determined as a measure of integrity. All samples had resistance >7.7 kilo ohms.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates/doses were reported and appropriate per OECD 428. The study used 7-8 replicates/dose from 4 donors.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	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 intended to determine the Kp. The study authors indicated that the application rate 100 uL/cm2 was requested by the EPA, but in combination with the volatility of the test substance, infinite exposure may not have been maintained. The authors note that a larger excess volume would have been more appropriate.
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assessed consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period was consistent across replicates.

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Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Infinite- Neat

Domain	Metric		Rating	Comments
	Metric 16:	Sampling adequacy and sensitivity	Medium	The study reported adequate sampling for the outcomes of interest; measurement sensitivity was sufficient (30 d.p.m). The sampling intervals were adequate to allow for steady state portion of absorption profile to be obtained. Methods for determination of radioactivity are reported. Scintillation counts were not shown. Graphical representation of absorption over time is shown for each individual cell.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study used a single batch of radiolabeled TCDE. Human abdominal skin was obtained from 20 donors, male and female, ranging in age from 25 to 66 years old. The large age range and sex differences may influence results. The split-thickness was consistent across samples (380-400 um). Skin integrity was confirmed by TEWL and all samples had a resistance above 7.7 k´Ω which was the author specified cutoff; however, this is below guideline recommendations. Pre-exposure, mean TEWL values across replicates in each sample were <10 grams/m2/hour which is consistent with OECD 428 and 156; however, some (1-2) individual replicates within samples were above this cutoff. Skin integrity measurements at the end of the study period indicated some loss in integrity that was more pronounced for some samples than others. The authors did not apply any criteria or indicate whether the loss was acceptable. One replicate in the neat group was excluded as an outlier with suspected skin damage.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure. During a solubility test, 56.55% of the target concentration was accepted into the receptor fluid suggesting no issues with solubility.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Statistical methods were described and appropriate. Kp/flux measurements were based on the linear part of the absorption curve. The outliers identified and excluded were appropriate. CV values were not reported for Kp/flux measurements, and quantitative measures of variance were not provided, however, quantitative data was extracted from available figures showing cumulative absorption for each replicate and EPA was able to independently calculate standard deviations, and thus CV values. The Kp CV was >50%, but data are available for EPA to calculate an alternate upper-end value.
	Metric 20:	Data interpretation	Medium	Kp values were purportedly derived from infinite dosing; however, the authors noted that the study was conducted using 100 uL/cm2 as requested by EPA. This resulted in the addition of 64 uL. This small volumes in combination with the volatile nature of the test stances, resulted in depletion of the test fluid rather than there being a continuous excess of test preparation in the donor compartment. The reported Kp values however, were determined from the linear phase of absorption, so it is unclear whether there was any major effect on the study results. Recovery was not reported but this determination is not relevant for infinite dose applications.
	Metric 21:	Reporting of data	High	Data for exposure related findings were reported for all outcomes by exposure group as well as for individual cells Kp values were reported without measures of variance; however, sufficient data were provided to independently calculate standard deviations.

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Chemical:	trans-1,2-Dichloroethylene
Exposure Type:	Parent compound
HERO ID:	11523429
Unique ID:	Infinite- Neat

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

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Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Infinite- 50% in Receptor fluid

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled trans-1,2-dichloroethylene and radiolabeled [1,2-14C2]trans-1,2-dichloroethylene, CAS number: 156-60-5. 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, trans-1,2-dichloroethylene was sourced from Sigma-Aldrich; the source of the radiolabeled trans-1,2-dichloroethylene was redacted from the study. The study included certificates of analyses that reported lot/batch numbers. The radiolabeled test substance was verified by HPLC.
	Metric 3:	Test substance purity	Uninformative	The radiochemical purity of the radiolabeled test substance was determined to be ≥95.6% by HPLC. The purity of the non-radiolabeled substance was reported to be 99.7%. Impurities were not reported. Post-dose radiochemical purities were also determined. The post-dose purities of the 50% in receptor fluid samples were extremely low; 10.5%. It was determined that the test substance was dissociating in the receptor fluid (used as a dilution solvent) resulting in the low purity. Because of this effect, the solvent was switched to toluene for the finite experiments. The low-purity samples were still used for analysis and determination of Kp. It is unclear how the dissociation of the test substance may have influenced the results.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No appropriate reference compound was studied. The study authors do not report their familiarity with performing this type of study.

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Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
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Unique ID: Infinite- 50% in Receptor fluid

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428, OECD 28, EPA guidelines for dermal studies and the European Commissions Guidance on Dermal Absorption. The assay procedures specified in the report were described in detail, although some information was missing. The static diffusion cell set up is sufficiently reported including a photograph. The study reported an equilibration period after the skin was placed into the chamber of 30 minutes, which is agreement with guidelines recommendations. An infinite dose of trans-1,2-dichloroethylene (50%, in receptor fluid) was applied to human skin (8 replicates; surface area of 0.64 cm2). The stability of the test substance over the course of the study was confirmed by HPLC. The study authors state “All test preparation were applied at an application rate of 100 uL/cm2 of TDCE, as directed by the EPA”. The volume applied was 640 uL. Due to the high volatility of the test substance, a larger application volume (>1 ml) would have been more appropriate. Full thickness human skin samples were thawed and dermatomed to create split-thickness membranes. Membranes were then refrozen (up to 2 months). Thickness of skin sample ranged from 380 to 400 um. Skin was exposed to test substance under occluded conditions (cap and wrapped in Parafilm®) for 8 hours. The receptor solution (PBS with 6% polyethoxyoleate 20 oleyl ether) was appropriate for this lipophilic chemical. The solubility of trans-1,2-dichloroethylene was tested in the receptor fluid prior to the study and determined solubility of the test substance was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity was monitored but not reported here. The receptor fluid (5 mL) was continuously stirred as per OECD 428 guidelines. Receptor fluid samples (300 uL) were collected at 0, 15, 30, 45 and 60 minutes, 2, 3, 4, 6, 8 hours post-application and analyzed for radioactivity. The study does not report if they added additional receptor fluid to the receptor chamber after each sampling in order to maintain 5 mL of receptor fluid. Radioactivity was measured with a representative blank sample subtracted from count rates. A limit of reliable measurement of 30 d.p.m. over background was determined.
	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. The authors did not specify inclusion criteria for this measurement; but full results were reported. The electrical resistance of the skin was measured following TEWL assessment using low voltage alternating current (100 Hz with a maximum of 300 mV). All samples had a resistance greater than 7.7 kilo ohms, the author-reported criteria for inclusion. 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 and insufficient information was provided to allow for independent determinations.

Domain 3: Exposure Characterization

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Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Infinite- 50% in Receptor fluid

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of test substance is described in detail. Dilutions were vortexed and magnetically stirred. The activity and homogeneity of the diluted doses were assessed. Test substance concentration and target concentration are reported with CV. After dosing, the test preparation was analyzed for stability. Storage conditions of test substances were reported and appropriate.
	Metric 8:	Consistency of exposure administration	Medium	The same volume across was applied across all samples (640ul; 100 uL/cm2 (per instructions given to study authors from EPA). The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was measured and reported (varying from 380-400 uM between samples); these slight variations were not likely to substantially impact results.
	Metric 9:	Reporting of concentrations	High	The applied mass is reported as mg equiv/cm2. Nominal and analytical doses are reported with CV.
	Metric 10:	Exposure frequency	High	Exposure duration (8 hours) was appropriate for Kp determination given the volatility of the test substance. 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, 10%, and 50%). Dilutions of test substance were performed in two different vehicles (isopropyl myristate or receptor fluid). Justification for dose selection was not provided.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Full thickness skin samples were obtained from males and females. Abdominal skin samples from 20 people (race not reported) ranging in age from 25-66 years old were studied. The samples arrived deep frozen on dry ice were stored frozen at -20 degrees C. The skin samples were thawed and dermatomed using an electric dermatome. The split-thickness samples were measured using a micrometer and ranged from 380 to 400 uM. The OECD guidelines indicate split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring trans epidermal water loss prior to/and upon completion of the experiment. Electrical resistance of skin was also determined as a measure of integrity. All samples had resistance >7.7 kilo ohms.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates/doses were reported and appropriate per OECD 428. The study used 8 replicates/dose from 4 donors.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	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 intended to determine the Kp. The study authors indicated that the application rate 100 uL/cm2 was requested by the EPA, but in combination with the volatility of the test substance, infinite exposure may not have been maintained. The authors note that a larger excess volume would have been more appropriate.

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Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Infinite- 50% in Receptor fluid

Domain	Metric		Rating	Comments
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assessed consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period 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 (30 d.p.m). The sampling intervals were adequate to allow for steady state portion of absorption profile to be obtained. Methods for determination of radioactivity are reported. Scintillation counts were not shown. Graphical representation of absorption over time is shown for each individual cell.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study used a single batch of radiolabeled TCDE. Human abdominal skin was obtained from 20 donors, male and female, ranging in age from 25 to 66 years old. The large age range and sex differences may influence results. The split-thickness was consistent across samples (380-400 um). Skin integrity was confirmed by TEWL and all samples had a resistance above 7.7 k´Ω which was the author specified cutoff; however, this is below guideline recommendations. Pre-exposure, mean TEWL values across replicates in each sample were <10 grams/m2/hour which is consistent with OECD 428 and 156; however, some (1-2) individual replicates within samples were above this cut-off. Skin integrity measurements at the end of the study period indicated some loss in integrity that was more pronounced for some samples than others. The authors did not apply any criteria or indicate whether the loss was acceptable.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure. During a solubility test, 56.55% of the target concentration was accepted into the receptor fluid suggesting no issues with solubility.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Statistical methods were described and appropriate. Kp/flux measurements were based on the linear part of the absorption curve. The outliers identified and excluded were appropriate. CV values were not reported for Kp/flux measurements, and quantitative measures of variance were not provided, however, quantitative data was extracted from available figures showing cumulative absorption for each replicate and EPA was able to independently calculate standard deviations, and thus CV values. The CV value was >50%, but data are available for EPA to calculate an alternate upper-end value.

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Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Infinite- 50% in Receptor fluid

Domain	Metric		Rating	Comments
	Metric 20:	Data interpretation	Medium	Kp values were purportedly derived from infinite dosing; however, the authors noted that the study was conducted using 100 uL/cm2 as requested by EPA. This resulted in the addition of 64 to 640 uL depending on concentration. These small volumes in combination with the volatile nature of the test stances, resulted in depletion of the test fluid rather than there being a continuous excess of test preparation in the donor compartment. This was specifically noted for the neat sample, but it was not specified which other samples or replicates became depleted. The reported Kp values however, were determined from the linear phase of absorption, so it is unclear whether there was any major effect on the study results. Recovery was not reported but this determination is not relevant for infinite dose applications.
	Metric 21:	Reporting of data	High	Data for exposure related findings were reported for all outcomes by exposure group as well as for individual cells Kp values were reported without measures of variance; however, sufficient data were provided to independently calculate standard deviations.

Overall Quality Determination Uninformative

Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 10% IPM

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled trans-1,2-dichloroethylene and radiolabeled [1,2-14C2]trans-1,2-dichloroethylene, CAS number: 156-60-5. 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, trans-1,2-dichloroethylene was sourced from Sigma-Aldrich; the source of the radiolabeled trans-1,2-dichloroethylene was redacted from the study. The study included certificates of analyses that reported lot/batch numbers. The radiolabeled test substance was verified by HPLC.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the radiolabeled test substance was determined to be ≥95.6% by HPLC. The purity of the non-radiolabeled substance was reported to be 99.7%. Impurities were not reported. Post-dose radiochemical purities were also determined (≥94.8%).
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No appropriate reference compound was studied. The study authors do not report their familiarity with performing this type of study.

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Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 10% IPM

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Low	This study was conducted according to OECD TG 428, OECD 28, EPA guidelines for dermal studies and the European Commissions Guidance on Dermal Absorption. The assay procedures specified in the report were described in detail, although some information was missing. The static diffusion cell set up is sufficiently reported including a photograph. The study reported an equilibration period after the skin was placed into the chamber of 30 minutes, which is agreement with guidelines recommendations. Finite doses of trans-1,2-dichloroethylene (10%, 1%, and 0.1% dissolved in either isopropyl myristate or toluene) was applied to human skin (8 replicates; surface area of 0.64 cm2). An application rateof 100uL/cm2 was applied to skin surface; this is the same volume used in the infinite exposures and higher than the guideline recommendations of 10uL/cm2. The authors acknowledge the guidelines and recognize the applied quantity is greater than recommended, however EPA requested an application of 100 ul/cm2. Cells were occluded with traps containing carbon filters and Tenax®TA and completely sealed with a cap. Full thickness human skin samples were thawed and dermatomed to create split-thickness membranes. Membranes were then refrozen (up to 2 months). Thickness of skin sample ranged from 380 to 400 um. The receptor solution (PBS with 6% polyethoxyoleate 20 oleyl ether) was appropriate for this lipophilic chemical. The solubility of trans-1,2-dichloroethylene was tested in the receptor fluid prior to the study and determined solubility of the test substance was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity was monitored but not reported here. The receptor fluid (5 mL) was continuously stirred as per OECD 428 guidelines. Skin washed at 8 hours with 50 uL commercial hand wash soap, gently rubbed with a tissue swap, and rinsed with 5 mL of a 2% (v/v) commercial soap solution. The donor cell was re-occluded with new filter. Receptor fluid samples continued to be collected, up to 24 hours. Receptor fluid samples (300 uL) were collected at 10 min, 30 min, 1, 2, 4, 8, 12, 16, 20, and 24 hours and analyzed for radioactivity. The study does not report if they added additional receptor fluid to the receptor chamber after each sampling in order to maintain 5 mL of receptor fluid. After 24 hours, the skin was rewashed as described at 8 hours, and then tap-stripped 20 times. Radioactivity was measured with a representative blank sample subtracted from count rats. A limit of reliable measurement of 30 d.p.m. over background was determined.
	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 (before tape stripping). The authors did not specify inclusion criteria for this measurement; but full results were reported. The electrical resistance of the skin was measured following TEWL assessment using low voltage alternating current (100 Hz with a maximum of 300 mV). All samples had a resistance greater than 7.7 kilo ohms, the author stated criteria for inclusion. Based on reported data, coefficients of variation (CV) values were calculated. Low recoveries are most likely from the high volatility of the test substance.

Domain 3: Exposure Characterization

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Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 10% IPM

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of test substance is described in detail. Dilutions were vortexed and magnetically stirred. The activity and homogeneity of the diluted doses were assessed. Test substance concentration and target concentration are reported with CV. After dosing, the test preparation was analyzed for stability. Storage conditions of test substances were reported and appropriate.
	Metric 8:	Consistency of exposure administration	Medium	The study used the same volume across all samples (64ul). The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was measured and reported (varying from 380-400 uM between samples); these slight variations are not likely to substantially impact results
	Metric 9:	Reporting of concentrations	High	The applied mass is reported as mg equiv/cm2. Nominal and analytical doses are reported with CV.
	Metric 10:	Exposure frequency	High	Exposure duration was reported and appropriate for determining absorption. 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.
	Metric 11:	Number of exposure groups and concentration spacing	High	There were 3 dose groups tested in a wide range of concentrations (10%, 1%, and 0.1%). Dilutions of test substance were performed in two different vehicles (isopropyl myristate or toluene Justification for dose selection was not provided.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Full thickness skin samples were obtained from males and females. Abdominal skin samples from 20 people (race not reported) ranging in age from 25-66 years old were studied. The samples arrived deep frozen on dry ice were stored frozen at -20 degrees C. The skin samples were thawed and dermatomed using an electric dermatome. The split-thickness samples were measured using a micrometer and ranged from 380 to 400 uM. The OECD guidelines indicate split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring trans epidermal water loss prior to/and upon completion of the experiment. Electrical resistance of skin was also determined as a measure of integrity. All samples had resistance >7.7 kilo ohms.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates/doses were reported and appropriate per OECD 428. The study used 8 replicates/dose from 4 donors.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28 with some exceptions. Guidelines specify application for 10 uL/cm2 for finite dosing. The study authors indicated that 100 uL/cm2 of test substance was used as per requested by the EPA. This was the same dose volume used for the infinite exposures. It is not clearly stated whether these dose volumes were appropriate for a finite exposure scenario. Measurement techniques and timing were reported and appropriate. A finite dose was used to determine absorption.

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 10% IPM

Domain	Metric		Rating	Comments
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assessed consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period 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 (30 d.p.m). The sampling intervals were adequate. Methods for determination of radioactivity are reported. 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	Low	The study used a single batch of radiolabeled TCDE. Human abdominal skin was obtained from 20 donors, male and female, ranging in age from 25 to 66 years old. The large age range and sex differences may influence results. The split-thickness was consistent across samples (380-400 um). Skin integrity was confirmed by TEWL, and all samples had a resistance above 7.7 k´Ω which was the author-specified cutoff; however, this is below guideline recommendations. Pre-exposure, mean TEWL values across replicates in each sample were <10 grams/m2/hour, which is consistent with OECD 428 and 156. Despite the overall mean being acceptable, ≥50% of the individual replicates had TWEL values >10 grams/m2/hour. These were not removed or evaluated separately as outliers. These integrity issues significantly impact the ability to reliably determine absorption values.
	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. The authors noted significant issues with test substance volatility. Missing mass balance was attributed to loss to the atmosphere despite tests being conducted under occluded conditions.
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; however, 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	Medium	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 for all finite samples was low and large differences across replicates within a sample. The majority of sample was located in the filter, and the missing mass balance was presumed by the authors to be lost due to volatilization of the test substance despite conducting the experiments under occlusion. Sufficient data are provided for alternative calculations.
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means ± SD. Individual replicate data were provided.

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Study Citation:	TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical:	trans-1,2-Dichloroethylene
Exposure Type:	Parent compound
HERO ID:	11523429
Unique ID:	Finite- 10% IPM

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

Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 0.1% IPM

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled trans-1,2-dichloroethylene and radiolabeled [1,2-14C2]trans-1,2-dichloroethylene, CAS number: 156-60-5. 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, trans-1,2-dichloroethylene was sourced from Sigma-Aldrich; the source of the radiolabeled trans-1,2-dichloroethylene was redacted from the study. The study included certificates of analyses that reported lot/batch numbers. The radiolabeled test substance was verified by HPLC.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the radiolabeled test substance was determined to be ≥95.6% by HPLC. The purity of the non-radiolabeled substance was reported to be 99.7%. Impurities were not reported. Post-dose radiochemical purities were also determined (≥94.8%).
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No appropriate reference compound was studied. The study authors do not report their familiarity with performing this type of study.

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 0.1% IPM

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Low	This study was conducted according to OECD TG 428, OECD 28, EPA guidelines for dermal studies and the European Commissions Guidance on Dermal Absorption. The assay procedures specified in the report were described in detail, although some information was missing. The static diffusion cell set up is sufficiently reported including a photograph. The study reported an equilibration period after the skin was placed into the chamber of 30 minutes, which is agreement with guidelines recommendations. Finite doses of trans-1,2-dichloroethylene (10%, 1%, and 0.1% dissolved in either isopropyl myristate or toluene) was applied to human skin (8 replicates; surface area of 0.64 cm2). An application rateof 100uL/cm2 was applied to skin surface; this is the same volume used in the infinite exposures and higher than the guideline recommendations of 10uL/cm2. The authors acknowledge the guidelines and recognize the applied quantity is greater than recommended, however EPA requested an application of 100 ul/cm2. Cells were occluded with traps containing carbon filters and Tenax®TA and completely sealed with a cap. Full thickness human skin samples were thawed and dermatomed to create split-thickness membranes. Membranes were then refrozen (up to 2 months). Thickness of skin sample ranged from 380 to 400 um. The receptor solution (PBS with 6% polyethoxyoleate 20 oleyl ether) was appropriate for this lipophilic chemical. The solubility of trans-1,2-dichloroethylene was tested in the receptor fluid prior to the study and determined solubility of the test substance was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity was monitored but not reported here. The receptor fluid (5 mL) was continuously stirred as per OECD 428 guidelines. Skin washed at 8 hours with 50 uL commercial hand wash soap, gently rubbed with a tissue swap, and rinsed with 5 mL of a 2% (v/v) commercial soap solution. The donor cell was re-occluded with new filter. Receptor fluid samples continued to be collected, up to 24 hours. Receptor fluid samples (300 uL) were collected at 10 min, 30 min, 1, 2, 4, 8, 12, 16, 20, and 24 hours and analyzed for radioactivity. The study does not report if they added additional receptor fluid to the receptor chamber after each sampling in order to maintain 5 mL of receptor fluid. After 24 hours, the skin was rewashed as described at 8 hours, and then tap-stripped 20 times. Radioactivity was measured with a representative blank sample subtracted from count rats. A limit of reliable measurement of 30 d.p.m. over background was determined.
	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 (before tape stripping). The authors did not specify inclusion criteria for this measurement; but full results were reported. The electrical resistance of the skin was measured following TEWL assessment using low voltage alternating current (100 Hz with a maximum of 300 mV). All samples had a resistance greater than 7.7 kilo ohms, the author stated criteria for inclusion. Based on reported data, coefficients of variation (CV) values were calculated. Low recoveries are most likely from the high volatility of the test substance.

Domain 3: Exposure Characterization

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 0.1% IPM

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of test substance is described in detail. Dilutions were vortexed and magnetically stirred. The activity and homogeneity of the diluted doses were assessed. Test substance concentration and target concentration are reported with CV. After dosing, the test preparation was analyzed for stability. Storage conditions of test substances were reported and appropriate.
	Metric 8:	Consistency of exposure administration	Medium	The study used the same volume across all samples (64ul). The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was measured and reported (varying from 380-400 uM between samples); these slight variations are not likely to substantially impact results
	Metric 9:	Reporting of concentrations	High	The applied mass is reported as mg equiv/cm2. Nominal and analytical doses are reported with CV.
	Metric 10:	Exposure frequency	High	Exposure duration was reported and appropriate for determining absorption. 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.
	Metric 11:	Number of exposure groups and concentration spacing	High	There were 3 dose groups tested in a wide range of concentrations (10%, 1%, and 0.1%). Dilutions of test substance were performed in two different vehicles (isopropyl myristate or toluene Justification for dose selection was not provided.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Full thickness skin samples were obtained from males and females. Abdominal skin samples from 20 people (race not reported) ranging in age from 25-66 years old were studied. The samples arrived deep frozen on dry ice were stored frozen at -20 degrees C. The skin samples were thawed and dermatomed using an electric dermatome. The split-thickness samples were measured using a micrometer and ranged from 380 to 400 uM. The OECD guidelines indicate split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring trans epidermal water loss prior to/and upon completion of the experiment. Electrical resistance of skin was also determined as a measure of integrity. All samples had resistance >7.7 kilo ohms.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates/doses were reported and appropriate per OECD 428. The study used 8 replicates/dose from 4 donors.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28 with some exceptions. Guidelines specify application for 10 uL/cm2 for finite dosing. The study authors indicated that 100 uL/cm2 of test substance was used as per requested by the EPA. This was the same dose volume used for the infinite exposures. It is not clearly stated whether these dose volumes were appropriate for a finite exposure scenario. Measurement techniques and timing were reported and appropriate. A finite dose was used to determine absorption.

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 0.1% IPM

Domain	Metric		Rating	Comments
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assessed consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period 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 (30 d.p.m). The sampling intervals were adequate. Methods for determination of radioactivity are reported. 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	Low	The study used a single batch of radiolabeled TCDE. Human abdominal skin was obtained from 20 donors, male and female, ranging in age from 25 to 66 years old. The large age range and sex differences may influence results. The split-thickness was consistent across samples (380-400 um). Skin integrity was confirmed by TEWL, and all samples had a resistance above 7.7 k´Ω which was the author-specified cutoff; however, this is below guideline recommendations. Pre-exposure, mean TEWL values across replicates in each sample were <10 grams/m2/hour, which is consistent with OECD 428 and 156. Despite the overall mean being acceptable, ≥50% of the individual replicates had TWEL values >10 grams/m2/hour. These were not removed or evaluated separately as outliers. These integrity issues significantly impact the ability to reliably determine absorption values.
	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. The authors noted significant issues with test substance volatility. Missing mass balance was attributed to loss to the atmosphere despite tests being conducted under occluded conditions.
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; however, 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	Medium	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 for all finite samples was low and large differences across replicates within a sample. The majority of sample was located in the filter, and the missing mass balance was presumed by the authors to be lost due to volatilization of the test substance despite conducting the experiments under occlusion. Sufficient data are provided for alternative calculations.
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means ± SD. Individual replicate data were provided.

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Study Citation:	TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical:	trans-1,2-Dichloroethylene
Exposure Type:	Parent compound
HERO ID:	11523429
Unique ID:	Finite- 0.1% IPM

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

Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 1% in Toluene

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled trans-1,2-dichloroethylene and radiolabeled [1,2-14C2]trans-1,2-dichloroethylene, CAS number: 156-60-5. 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, trans-1,2-dichloroethylene was sourced from Sigma-Aldrich; the source of the radiolabeled trans-1,2-dichloroethylene was redacted from the study. The study included certificates of analyses that reported lot/batch numbers. The radiolabeled test substance was verified by HPLC.
	Metric 3:	Test substance purity	Low	The radiochemical purity of the radiolabeled test substance was determined to be ≥95.6% % by HPLC. The purity of the non-radiolabeled substance was reported to be 99.7%. Impurities were not reported. Post-dose radiochemical purities were attempted; however, the due to technical difficulties these values could not be obtained. Due to the low concentration, a higher volume of test preparation needed to be injected, this blocked the system and exhausted the sample. Due to the uncertainty of the radiochemical purity after dosing, this metric was scored low.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No appropriate reference compound was studied. The study authors do not report their familiarity with performing this type of study.

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 1% in Toluene

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Low	This study was conducted according to OECD TG 428, OECD 28, EPA guidelines for dermal studies and the European Commissions Guidance on Dermal Absorption. The assay procedures specified in the report were described in detail, although some information was missing. The static diffusion cell set up is sufficiently reported including a photograph. The study reported an equilibration period after the skin was placed into the chamber of 30 minutes, which is agreement with guidelines recommendations. Finite doses of trans-1,2-dichloroethylene (10%, 1%, and 0.1% dissolved in either isopropyl myristate or toluene) was applied to human skin (8 replicates; surface area of 0.64 cm2). An application rateof 100uL/cm2 was applied to skin surface; this is the same volume used in the infinite exposures and higher than the guideline recommendations of 10uL/cm2. The authors acknowledge the guidelines and recognize the applied quantity is greater than recommended, however EPA requested an application of 100 ul/cm2. Cells were occluded with traps containing carbon filters and Tenax®TA and completely sealed with a cap. Full thickness human skin samples were thawed and dermatomed to create split-thickness membranes. Membranes were then refrozen (up to 2 months). Thickness of skin sample ranged from 380 to 400 um. The receptor solution (PBS with 6% polyethoxyoleate 20 oleyl ether) was appropriate for this lipophilic chemical. The solubility of trans-1,2-dichloroethylene was tested in the receptor fluid prior to the study and determined solubility of the test substance was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity was monitored but not reported here. The receptor fluid (5 mL) was continuously stirred as per OECD 428 guidelines. Skin washed at 8 hours with 50 uL commercial hand wash soap, gently rubbed with a tissue swap, and rinsed with 5 mL of a 2% (v/v) commercial soap solution. The donor cell was re-occluded with new filter. Receptor fluid samples continued to be collected, up to 24 hours. Receptor fluid samples (300 uL) were collected at 10 min, 30 min, 1, 2, 4, 8, 12, 16, 20, and 24 hours and analyzed for radioactivity. The study does not report if they added additional receptor fluid to the receptor chamber after each sampling in order to maintain 5 mL of receptor fluid. After 24 hours, the skin was rewashed as described at 8 hours, and then tap-stripped 20 times. Radioactivity was measured with a representative blank sample subtracted from count rats. A limit of reliable measurement of 30 d.p.m. over background was determined.
	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 (before tape stripping). The authors did not specify inclusion criteria for this measurement; but full results were reported. The electrical resistance of the skin was measured following TEWL assessment using low voltage alternating current (100 Hz with a maximum of 300 mV). All samples had a resistance greater than 7.7 kilo ohms, the author stated criteria for inclusion. Based on reported data, coefficients of variation (CV) values were calculated. Low recoveries are most likely from the high volatility of the test substance.

Domain 3: Exposure Characterization

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 1% in Toluene

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of test substance is described in detail. Dilutions were vortexed and magnetically stirred. The activity and homogeneity of the diluted doses were assessed. Test substance concentration and target concentration are reported with CV. After dosing, the test preparation was analyzed for stability. Storage conditions of test substances were reported and appropriate.
	Metric 8:	Consistency of exposure administration	Medium	The study used the same volume across all samples (64ul). The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was measured and reported (varying from 380-400 uM between samples); these slight variations are not likely to substantially impact results
	Metric 9:	Reporting of concentrations	High	The applied mass is reported as mg equiv/cm2. Nominal and analytical doses are reported with CV.
	Metric 10:	Exposure frequency	High	Exposure duration was reported and appropriate for determining absorption. 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.
	Metric 11:	Number of exposure groups and concentration spacing	High	There were 3 dose groups tested in a wide range of concentrations (10%, 1%, and 0.1%). Dilutions of test substance were performed in two different vehicles (isopropyl myristate or toluene Justification for dose selection was not provided.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Full thickness skin samples were obtained from males and females. Abdominal skin samples from 20 people (race not reported) ranging in age from 25-66 years old were studied. The samples arrived deep frozen on dry ice were stored frozen at -20 degrees C. The skin samples were thawed and dermatomed using an electric dermatome. The split-thickness samples were measured using a micrometer and ranged from 380 to 400 uM. The OECD guidelines indicate split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring trans epidermal water loss prior to/and upon completion of the experiment. Electrical resistance of skin was also determined as a measure of integrity. All samples had resistance >7.7 kilo ohms.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates/doses were reported and appropriate per OECD 428. The study used 8 replicates/dose from 4 donors.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28 with some exceptions. Guidelines specify application for 10 uL/cm2 for finite dosing. The study authors indicated that 100 uL/cm2 of test substance was used as per requested by the EPA. This was the same dose volume used for the infinite exposures. It is not clearly stated whether these dose volumes were appropriate for a finite exposure scenario. Measurement techniques and timing were reported and appropriate. A finite dose was used to determine absorption.

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 1% in Toluene

Domain	Metric		Rating	Comments
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assessed consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period 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 (30 d.p.m). The sampling intervals were adequate. Methods for determination of radioactivity are reported. 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 TCDE. Human abdominal skin was obtained from 20 donors, male and female, ranging in age from 25 to 66 years old. The large age range and sex differences may influence results. The split-thickness was consistent across samples (380-400 um). Skin integrity was confirmed by TEWL and all samples had a resistance above 7.7 k´Ω which was the author specified cutoff; however, this is below guideline recommendations. Pre-exposure, mean TEWL values across replicates in each sample were <10 grams/m2/hour which is consistent with OECD 428 and 156; however, one replicate's TEWL value was above this cutoff. Skin integrity measurements at the end of the study period indicated some loss in integrity that was more pronounced for some samples than others. The authors did not apply any criteria or indicate whether the loss was acceptable. No exclusions were made based on loss of integrity
	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. The authors noted significant issues with test substance volatility. Missing mass balance was attributed to loss to the atmosphere despite tests being conducted under occluded conditions.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	High	All Statistical methods were described and were appropriate. Absorption estimates were based on appropriate measurements. More than half of the CV values (total recovery, % in skin and receptor fluid) were ≤25%. The CV for tape strips was 50%.
	Metric 20:	Data interpretation	Medium	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 for all finite samples was low with means ranging from 25.44% to 65.75% and large differences across replicates within a sample. The majority of sample was located in the filter, and the missing mass balance was presumed by the authors to be lost due to volatilization of the test substance despite conducting the experiments under occlusion. Sufficient data are provided for alternative calculations.
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means ± SD. Individual replicate data were provided.

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Study Citation:	TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical:	trans-1,2-Dichloroethylene
Exposure Type:	Parent compound
HERO ID:	11523429
Unique ID:	Finite- 1% in Toluene

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

Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Infinite- 10% in Receptor fluid

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled trans-1,2-dichloroethylene and radiolabeled [1,2-14C2]trans-1,2-dichloroethylene, CAS number: 156-60-5. 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, trans-1,2-dichloroethylene was sourced from Sigma-Aldrich; the source of the radiolabeled trans-1,2-dichloroethylene was redacted from the study. The study included certificates of analyses that reported lot/batch numbers. The radiolabeled test substance was verified by HPLC.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the initial radiolabeled test substance was determined to be ≥95.6% % by HPLC. The purity of the non-radiolabeled substance was reported to be 99.7%. Impurities were not reported. Post-dose radiochemical purities were also determined. The post-dose purities of the 10% in receptor fluid samples was low; 73.1%. It was determined that the test substance was dissociating in the receptor fluid (used as a dilution solvent) resulting in the low purity. This is acceptable for a medium score based on criteria (>70%).
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No appropriate reference compound was studied. The study authors do not report their familiarity with performing this type of study.

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Infinite- 10% in Receptor fluid

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428, OECD 28, EPA guidelines for dermal studies and the European Commissions Guidance on Dermal Absorption. The assay procedures specified in the report were described in detail, although some information was missing. The static diffusion cell set up is sufficiently reported including a photograph. The study reported an equilibration period after the skin was placed into the chamber of 30 minutes, which is agreement with guidelines recommendations. An infinite dose of trans-1,2-dichloroethylene (neat, 50%, or 10% dissolved in either isopropyl myristate or receptor fluid) was applied to human skin (7-8 replicates; surface area of 0.64 cm2). The stability of the test substance over the course of the study was confirmed by HPLC. The study authors state “All test preparation were applied at an application rate of 100 uL/cm2 of TDCE, as directed by the EPA”. The volume applied ranged from 64 – 640 uL. Due to the high volatility of the test substance, a larger application volume (>1 ml) would have been more appropriate. Full thickness human skin samples were thawed and dermatomed to create split-thickness membranes. Membranes were then re-frozen (up to 2 months). Thickness of skin sample ranged from 380 to 400 um. Skin was exposed to test substance under occluded conditions (cap and wrapped in Parafilm®) for 8 hours. The receptor solution (PBS with 6% polyethoxyoleate 20 oleyl ether) was appropriate for this lipophilic chemical. The solubility of trans-1,2-dichloroethylene was tested in the receptor fluid prior to the study and determined solubility of the test substance was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity was monitored but not reported here. The receptor fluid (5 mL) was continuously stirred as per OECD 428 guidelines. Receptor fluid samples (300 uL) were collected at 0, 15, 30, 45 and 60 minutes, 2, 3, 4, 6, 8 hours post-application and analyzed for radioactivity. The study does not report if they added additional receptor fluid to the receptor chamber after each sampling in order to maintain 5 mL of receptor fluid. Radioactivity was measured with a representative blank sample subtracted from count rates. A limit of reliable measurement of 30 d.p.m. over background was determined.
	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. The authors did not specify inclusion criteria for this measurement; but full results were reported. The electrical resistance of the skin was measured following TEWL assessment using low voltage alternating current (100 Hz with a maximum of 300 mV). All samples had a resistance greater than 7.7 kilo ohms, the author-reported criteria for inclusion. 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 and insufficient information was provided to allow for independent determinations.

Domain 3: Exposure Characterization

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Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Infinite- 10% in Receptor fluid

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of test substance is described in detail. Dilutions were vortexed and magnetically stirred. The activity and homogeneity of the diluted doses were assessed. Test substance concentration and target concentration are reported with CV. After dosing, the test preparation was analyzed for stability. Storage conditions of test substances were reported and appropriate.
	Metric 8:	Consistency of exposure administration	Medium	The same volume across all samples (128 ul to maintain a constant application rate of 100 uL/cm2 (per instructions given to study authors from EPA). The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was measured and reported (varying from 380-400 uM between samples); these slight variations were not likely to substantially impact results.
	Metric 9:	Reporting of concentrations	High	The applied mass is reported as mg equiv/cm2. Nominal and analytical doses are reported with CV.
	Metric 10:	Exposure frequency	High	Exposure duration (8 hours) was appropriate for Kp determination given the volatility of the test substance. 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, 10%, and 50%). Dilutions of test substance were performed in two different vehicles (isopropyl myristate or receptor fluid). Justification for dose selection was not provided.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Full thickness skin samples were obtained from males and females. Abdominal skin samples from 20 people (race not reported) ranging in age from 25-66 years old were studied. The samples arrived deep frozen on dry ice were stored frozen at -20 degrees C. The skin samples were thawed and dermatomed using an electric dermatome. The split-thickness samples were measured using a micrometer and ranged from 380 to 400 uM. The OECD guidelines indicate split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring trans epidermal water loss prior to/and upon completion of the experiment. Electrical resistance of skin was also determined as a measure of integrity. All samples had resistance >7.7 kilo ohms.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates/doses were reported and appropriate per OECD 428. The study used 7-8 replicates/dose from 4 donors.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	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 intended to determine the Kp. The study authors indicated that the application rate 100 uL/cm2 was requested by the EPA, but in combination with the volatility of the test substance, infinite exposure may not have been maintained. The authors note that a larger excess volume would have been more appropriate.

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Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Infinite- 10% in Receptor fluid

Domain	Metric		Rating	Comments
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assessed consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period 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 (30 d.p.m). The sampling intervals were adequate to allow for steady state portion of absorption profile to be obtained. Methods for determination of radioactivity are reported. Scintillation counts were not shown. Graphical representation of absorption over time is shown for each individual cell.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study used a single batch of radiolabeled TCDE. Human abdominal skin was obtained from 20 donors, male and female, ranging in age from 25 to 66 years old. The large age range and sex differences may influence results. The split-thickness was consistent across samples (380-400 um). Skin integrity was confirmed by TEWL and all samples had a resistance above 7.7 k´Ω which was the author specified cutoff; however, this is below guideline recommendations. Pre-exposure, mean TEWL values across replicates in each sample were <10 grams/m2/hour which is consistent with OECD 428 and 156; however, some (1-2) individual replicates within samples were above this cut-off. Skin integrity measurements at the end of the study period indicated some loss in integrity that was more pronounced for some samples than others. The authors did not apply any criteria or indicate whether the loss was acceptable. No exclusions were made based on loss of integrity except for replicate 8 in the Neat group), which was an outlier with suspected skin damage.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure. During a solubility test, 56.55% of the target concentration was accepted into the receptor fluid suggesting no issues with solubility.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	High	Statistical methods were described and appropriate. Kp/flux measurements were based on the linear part of the absorption curve. The outliers identified and excluded were appropriate. CV values were not reported for Kp/flux measurements, and quantitative measures of variance were not provided, however, quantitative data was extracted from available figures showing cumulative absorption for each replicate and EPA was able to independently calculate standard deviations, and thus CV values. The CV value for Kp was <25%, but data are available for EPA to calculate an alternate upper-end value.

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Infinite- 10% in Receptor fluid

Domain	Metric		Rating	Comments
	Metric 20:	Data interpretation	Medium	Kp values were purportedly derived from infinite dosing; however, the authors noted that the study was conducted using 100 uL/cm2 as requested by EPA. This resulted in the addition of 64 to 640 uL depending on concentration. These small volumes in combination with the volatile nature of the test stances, resulted in depletion of the test fluid rather than there being a continuous excess of test preparation in the donor compartment. This was specifically noted for the neat sample, but it was not specified which other samples or replicates became depleted. The reported Kp values however, were determined from the linear phase of absorption, so it is unclear whether there was any major effect on the study results. Recovery was not reported but this determination is not relevant for infinite dose applications.
	Metric 21:	Reporting of data	High	Data for exposure related findings were reported for all outcomes by exposure group as well as for individual cells Kp values were reported without measures of variance; however, sufficient data were provided to independently calculate standard deviations.

Overall Quality Determination High

Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Infinite- 50% in IPM

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled trans-1,2-dichloroethylene and radiolabeled [1,2-14C2]trans-1,2-dichloroethylene, CAS number: 156-60-5. 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, trans-1,2-dichloroethylene was sourced from Sigma-Aldrich; the source of the radiolabeled trans-1,2-dichloroethylene was redacted from the study. The study included certificates of analyses that reported lot/batch numbers. The radiolabeled test substance was verified by HPLC.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the initial radiolabeled test substance was determined to be ≥95.6% % by HPLC. The purity of the non-radiolabeled substance was reported to be 99.7%. Impurities were not reported. Post-dose radiochemical purities were also determined. All met the acceptance criterion of >95% the post-dose purities of the receptor fluid samples.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No appropriate reference compound was studied. The study authors do not report their familiarity with performing this type of study.

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Infinite- 50% in IPM

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428, OECD 28, EPA guidelines for dermal studies and the European Commissions Guidance on Dermal Absorption. The assay procedures specified in the report were described in detail, although some information was missing. The static diffusion cell set up is sufficiently reported including a photograph. The study reported an equilibration period after the skin was placed into the chamber of 30 minutes, which is agreement with guidelines recommendations. An infinite dose of trans-1,2-dichloroethylene (neat, 50%, or 10% dissolved in either isopropyl myristate or receptor fluid) was applied to human skin (7-8 replicates; surface area of 0.64 cm2). The stability of the test substance over the course of the study was confirmed by HPLC. The study authors state "All test preparation were applied at an application rate of 100 uL/cm2 of TDCE, as directed by the EPA". The volume applied ranged from 64 – 640 uL. Due to the high volatility of the test substance, a larger application volume (>1 ml) would have been more appropriate. Full thickness human skin samples were thawed and dermatomed to create split-thickness membranes. Membranes were then re-frozen (up to 2 months). Thickness of skin sample ranged from 380 to 400 um. Skin was exposed to test substance under occluded conditions (cap and wrapped in Parafilm®) for 8 hours. The receptor solution (PBS with 6% polyethoxyoleate 20 oleyl ether) was appropriate for this lipophilic chemical. The solubility of trans-1,2-dichloroethylene was tested in the receptor fluid prior to the study and determined solubility of the test substance was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity was monitored but not reported here. The receptor fluid (5 mL) was continuously stirred as per OECD 428 guidelines. Receptor fluid samples (300 uL) were collected at 0, 15, 30, 45 and 60 minutes, 2, 3, 4, 6, 8 hours post-application and analyzed for radioactivity. The study does not report if they added additional receptor fluid to the receptor chamber after each sampling in order to maintain 5 mL of receptor fluid. Radioactivity was measured with a representative blank sample subtracted from count rates. A limit of reliable measurement of 30 d.p.m. over background was determined.
	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. The authors did not specify inclusion criteria for this measurement; but full results were reported. The electrical resistance of the skin was measured following TEWL assessment using low voltage alternating current (100 Hz with a maximum of 300 mV). All samples had a resistance greater than 7.7 kilo ohms, the author-reported criteria for inclusion. 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 and insufficient information was provided to allow for independent determinations.

Domain 3: Exposure Characterization

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Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Infinite- 50% in IPM

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of test substance is described in detail. Dilutions were vortexed and magnetically stirred. The activity and homogeneity of the diluted doses were assessed. Test substance concentration and target concentration are reported with CV. After dosing, the test preparation was analyzed for stability. Storage conditions of test substances were reported and appropriate.
	Metric 8:	Consistency of exposure administration	Medium	The volume was applied consistently across samples to achieve 100 uL/cm2 (per instructions given to study authors from EPA). The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was measured and reported (varying from 380-400 uM between samples); these slight variations were not likely to substantially impact results.
	Metric 9:	Reporting of concentrations	High	The applied mass is reported as mg equiv/cm2. Nominal and analytical doses are reported with CV.
	Metric 10:	Exposure frequency	High	Exposure duration (8 hours) was appropriate for Kp determination given the volatility of the test substance. 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, 10%, and 50%). Dilutions of test substance were performed in two different vehicles (isopropyl myristate or receptor fluid). Justification for dose selection was not provided.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Full thickness skin samples were obtained from males and females. Abdominal skin samples from 20 people (race not reported) ranging in age from 25-66 years old were studied. The samples arrived deep frozen on dry ice were stored frozen at -20 degrees C. The skin samples were thawed and dermatomed using an electric dermatome. The split-thickness samples were measured using a micrometer and ranged from 380 to 400 uM. The OECD guidelines indicate split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring trans epidermal water loss prior to/and upon completion of the experiment. Electrical resistance of skin was also determined as a measure of integrity. All samples had resistance >7.7 kilo ohms.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates/doses were reported and appropriate per OECD 428. The study used 7-8 replicates/dose from 4 donors.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	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 intended to determine the Kp. The study authors indicated that the application rate 100 uL/cm2 was requested by the EPA, but in combination with the volatility of the test substance, infinite exposure may not have been maintained. The authors note that a larger excess volume would have been more appropriate.

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Infinite- 50% in IPM

Domain	Metric		Rating	Comments
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assessed consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period 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 (30 d.p.m). The sampling intervals were adequate to allow for steady state portion of absorption profile to be obtained. Methods for determination of radioactivity are reported. Scintillation counts were not shown. Graphical representation of absorption over time is shown for each individual cell.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study used a single batch of radiolabeled TCDE. Human abdominal skin was obtained from 20 donors, male and female, ranging in age from 25 to 66 years old. The large age range and sex differences may influence results. The split-thickness was consistent across samples (380-400 um). Skin integrity was confirmed by TEWL and all samples had a resistance above 7.7 k´Ω which was the author specified cutoff; however, this is below guideline recommendations. Pre-exposure, mean TEWL values across replicates in each sample were <10 grams/m2/hour which is consistent with OECD 428 and 156; however, some (1-2) individual replicates within samples were above this cutoff. Skin integrity measurements at the end of the study period indicated some loss in integrity that was more pronounced for some samples than others. The authors did not apply any criteria or indicate whether the loss was acceptable. No exclusions were made.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure. During a solubility test, 56.55% of the target concentration was accepted into the receptor fluid suggesting no issues with solubility.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Statistical methods were described and appropriate. Kp/flux measurements were based on the linear part of the absorption curve. The outliers identified and excluded were appropriate. CV values were not reported for Kp/flux measurements, and quantitative measures of variance were not provided, however, quantitative data was extracted from available figures showing cumulative absorption for each replicate and EPA was able to independently calculate standard deviations, and thus CV values. The Kp CV values were either >25% and < 50%, or >50%, but data are available for EPA to calculate an alternate upper-end value.

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Infinite- 50% in IPM

Domain	Metric		Rating	Comments
	Metric 20:	Data interpretation	Medium	Kp values were purportedly derived from infinite dosing; however, the authors noted that the study was conducted using 100 uL/cm2 as requested by EPA. This resulted in the addition of 64 to 640 uL depending on concentration. These small volumes in combination with the volatile nature of the test stances, resulted in depletion of the test fluid rather than there being a continuous excess of test preparation in the donor compartment. This was specifically noted for the neat sample, but it was not specified which other samples or replicates became depleted. The reported Kp values however, were determined from the linear phase of absorption, so it is unclear whether there was any major effect on the study results. Recovery was not reported but this determination is not relevant for infinite dose applications.
	Metric 21:	Reporting of data	High	Data for exposure related findings were reported for all outcomes by exposure group as well as for individual cells Kp values were reported without measures of variance; however, sufficient data were provided to independently calculate standard deviations.

Overall Quality Determination Medium

Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Infinite- 10% in IPM

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled trans-1,2-dichloroethylene and radiolabeled [1,2-14C2]trans-1,2-dichloroethylene, CAS number: 156-60-5. 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, trans-1,2-dichloroethylene was sourced from Sigma-Aldrich; the source of the radiolabeled trans-1,2-dichloroethylene was redacted from the study. The study included certificates of analyses that reported lot/batch numbers. The radiolabeled test substance was verified by HPLC.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the initial radiolabeled test substance was determined to be ≥95.6% % by HPLC. The purity of the non-radiolabeled substance was reported to be 99.7%. Impurities were not reported. Post-dose radiochemical purities were also determined. All met the acceptance criterion of >95% the post-dose purities of the receptor fluid samples.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No appropriate reference compound was studied. The study authors do not report their familiarity with performing this type of study.

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Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
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Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428, OECD 28, EPA guidelines for dermal studies and the European Commissions Guidance on Dermal Absorption. The assay procedures specified in the report were described in detail, although some information was missing. The static diffusion cell set up is sufficiently reported including a photograph. The study reported an equilibration period after the skin was placed into the chamber of 30 minutes, which is agreement with guidelines recommendations. An infinite dose of trans-1,2-dichloroethylene (neat, 50%, or 10% dissolved in either isopropyl myristate or receptor fluid) was applied to human skin (7-8 replicates; surface area of 0.64 cm2). The stability of the test substance over the course of the study was confirmed by HPLC. The study authors state "All test preparation were applied at an application rate of 100 uL/cm2 of TDCE, as directed by the EPA". The volume applied ranged from 64 – 640 uL. Due to the high volatility of the test substance, a larger application volume (>1 ml) would have been more appropriate. Full thickness human skin samples were thawed and dermatomed to create split-thickness membranes. Membranes were then re-frozen (up to 2 months). Thickness of skin sample ranged from 380 to 400 um. Skin was exposed to test substance under occluded conditions (cap and wrapped in Parafilm®) for 8 hours. The receptor solution (PBS with 6% polyethoxyoleate 20 oleyl ether) was appropriate for this lipophilic chemical. The solubility of trans-1,2-dichloroethylene was tested in the receptor fluid prior to the study and determined solubility of the test substance was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity was monitored but not reported here. The receptor fluid (5 mL) was continuously stirred as per OECD 428 guidelines. Receptor fluid samples (300 uL) were collected at 0, 15, 30, 45 and 60 minutes, 2, 3, 4, 6, 8 hours post-application and analyzed for radioactivity. The study does not report if they added additional receptor fluid to the receptor chamber after each sampling in order to maintain 5 mL of receptor fluid. Radioactivity was measured with a representative blank sample subtracted from count rates. A limit of reliable measurement of 30 d.p.m. over background was determined.
	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. The authors did not specify inclusion criteria for this measurement; but full results were reported. The electrical resistance of the skin was measured following TEWL assessment using low voltage alternating current (100 Hz with a maximum of 300 mV). All samples had a resistance greater than 7.7 kilo ohms, the author-reported criteria for inclusion. 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 and insufficient information was provided to allow for independent determinations.

Domain 3: Exposure Characterization

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Chemical: trans-1,2-Dichloroethylene
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Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of test substance is described in detail. Dilutions were vortexed and magnetically stirred. The activity and homogeneity of the diluted doses were assessed. Test substance concentration and target concentration are reported with CV. After dosing, the test preparation was analyzed for stability. Storage conditions of test substances were reported and appropriate.
	Metric 8:	Consistency of exposure administration	Medium	The volume was applied consistently across samples to achieve 100 uL/cm2 (per instructions given to study authors from EPA). The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was measured and reported (varying from 380-400 uM between samples); these slight variations were not likely to substantially impact results.
	Metric 9:	Reporting of concentrations	High	The applied mass is reported as mg equiv/cm2. Nominal and analytical doses are reported with CV.
	Metric 10:	Exposure frequency	High	Exposure duration (8 hours) was appropriate for Kp determination given the volatility of the test substance. 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, 10%, and 50%). Dilutions of test substance were performed in two different vehicles (isopropyl myristate or receptor fluid). Justification for dose selection was not provided.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Full thickness skin samples were obtained from males and females. Abdominal skin samples from 20 people (race not reported) ranging in age from 25-66 years old were studied. The samples arrived deep frozen on dry ice were stored frozen at -20 degrees C. The skin samples were thawed and dermatomed using an electric dermatome. The split-thickness samples were measured using a micrometer and ranged from 380 to 400 uM. The OECD guidelines indicate split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring trans epidermal water loss prior to/and upon completion of the experiment. Electrical resistance of skin was also determined as a measure of integrity. All samples had resistance >7.7 kilo ohms.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates/doses were reported and appropriate per OECD 428. The study used 7-8 replicates/dose from 4 donors.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	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 intended to determine the Kp. The study authors indicated that the application rate 100 uL/cm2 was requested by the EPA, but in combination with the volatility of the test substance, infinite exposure may not have been maintained. The authors note that a larger excess volume would have been more appropriate.

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Chemical: trans-1,2-Dichloroethylene
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Domain	Metric		Rating	Comments
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assessed consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period 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 (30 d.p.m). The sampling intervals were adequate to allow for steady state portion of absorption profile to be obtained. Methods for determination of radioactivity are reported. Scintillation counts were not shown. Graphical representation of absorption over time is shown for each individual cell.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study used a single batch of radiolabeled TCDE. Human abdominal skin was obtained from 20 donors, male and female, ranging in age from 25 to 66 years old. The large age range and sex differences may influence results. The split-thickness was consistent across samples (380-400 um). Skin integrity was confirmed by TEWL and all samples had a resistance above 7.7 k´Ω which was the author specified cutoff; however, this is below guideline recommendations. Pre-exposure, mean TEWL values across replicates in each sample were <10 grams/m2/hour which is consistent with OECD 428 and 156; however, some (1-2) individual replicates within samples were above this cutoff. Skin integrity measurements at the end of the study period indicated some loss in integrity that was more pronounced for some samples than others. The authors did not apply any criteria or indicate whether the loss was acceptable. No exclusions were made.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure. During a solubility test, 56.55% of the target concentration was accepted into the receptor fluid suggesting no issues with solubility.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Statistical methods were described and appropriate. Kp/flux measurements were based on the linear part of the absorption curve. The outliers identified and excluded were appropriate. CV values were not reported for Kp/flux measurements, and quantitative measures of variance were not provided, however, quantitative data was extracted from available figures showing cumulative absorption for each replicate and EPA was able to independently calculate standard deviations, and thus CV values. The Kp CV values were either >25% and < 50%, or >50%, but data are available for EPA to calculate an alternate upper-end value.

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Infinite- 10% in IPM

Domain	Metric		Rating	Comments
	Metric 20:	Data interpretation	Medium	Kp values were purportedly derived from infinite dosing; however, the authors noted that the study was conducted using 100 uL/cm2 as requested by EPA. This resulted in the addition of 64 to 640 uL depending on concentration. These small volumes in combination with the volatile nature of the test stances, resulted in depletion of the test fluid rather than there being a continuous excess of test preparation in the donor compartment. This was specifically noted for the neat sample, but it was not specified which other samples or replicates became depleted. The reported Kp values however, were determined from the linear phase of absorption, so it is unclear whether there was any major effect on the study results. Recovery was not reported but this determination is not relevant for infinite dose applications.
	Metric 21:	Reporting of data	High	Data for exposure related findings were reported for all outcomes by exposure group as well as for individual cells Kp values were reported without measures of variance; however, sufficient data were provided to independently calculate standard deviations.

Overall Quality Determination Medium

Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 10% in Toluene

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled trans-1,2-dichloroethylene and radiolabeled [1,2-14C2]trans-1,2-dichloroethylene, CAS number: 156-60-5. 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, trans-1,2-dichloroethylene was sourced from Sigma-Aldrich; the source of the radiolabeled trans-1,2-dichloroethylene was redacted from the study. The study included certificates of analyses that reported lot/batch numbers. The radiolabeled test substance was verified by HPLC.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the radiolabeled test substance was determined to be ≥95.6% by HPLC. The purity of the non-radiolabeled substance was reported to be 99.7%. Impurities were not reported. Post-dose radiochemical purities were also determined. All of the measurements met the acceptance criterion of >95%.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No appropriate reference compound was studied. The study authors do not report their familiarity with performing this type of study.

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 10% in Toluene

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Low	This study was conducted according to OECD TG 428, OECD 28, EPA guidelines for dermal studies and the European Commissions Guidance on Dermal Absorption. The assay procedures specified in the report were described in detail, although some information was missing. The static diffusion cell set up is sufficiently reported including a photograph. The study reported an equilibration period after the skin was placed into the chamber of 30 minutes, which is agreement with guidelines recommendations. Finite doses of trans-1,2-dichloroethylene (10%, 1%, and 0.1% dissolved in either isopropyl myristate or toluene) was applied to human skin (8 replicates; surface area of 0.64 cm2). An application rateof 100uL/cm2 was applied to skin surface; this is the same volume used in the infinite exposures and higher than the guideline recommendations of 10uL/cm2. The authors acknowledge the guidelines and recognize the applied quantity is greater than recommended, however EPA requested an application of 100 ul/cm2. Cells were occluded with traps containing carbon filters and Tenax®TA and completely sealed with a cap. Full thickness human skin samples were thawed and dermatomed to create split-thickness membranes. Membranes were then refrozen (up to 2 months). Thickness of skin sample ranged from 380 to 400 um. The receptor solution (PBS with 6% polyethoxyoleate 20 oleyl ether) was appropriate for this lipophilic chemical. The solubility of trans-1,2-dichloroethylene was tested in the receptor fluid prior to the study and determined solubility of the test substance was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity was monitored but not reported here. The receptor fluid (5 mL) was continuously stirred as per OECD 428 guidelines. Skin washed at 8 hours with 50 uL commercial hand wash soap, gently rubbed with a tissue swap, and rinsed with 5 mL of a 2% (v/v) commercial soap solution. The donor cell was re-occluded with new filter. Receptor fluid samples continued to be collected, up to 24 hours. Receptor fluid samples (300 uL) were collected at 10 min, 30 min, 1, 2, 4, 8, 12, 16, 20, and 24 hours and analyzed for radioactivity. The study does not report if they added additional receptor fluid to the receptor chamber after each sampling in order to maintain 5 mL of receptor fluid. After 24 hours, the skin was rewashed as described at 8 hours, and then tap-stripped 20 times. Radioactivity was measured with a representative blank sample subtracted from count rats. A limit of reliable measurement of 30 d.p.m. over background was determined.
	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 (before tape stripping). The authors did not specify inclusion criteria for this measurement; but full results were reported. The electrical resistance of the skin was measured following TEWL assessment using low voltage alternating current (100 Hz with a maximum of 300 mV). All samples had a resistance greater than 7.7 kilo ohms, the author stated criteria for inclusion. Based on reported data, coefficients of variation (CV) values were calculated. Low recoveries are most likely from the high volatility of the test substance.

Domain 3: Exposure Characterization

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 10% in Toluene

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of test substance is described in detail. Dilutions were vortexed and magnetically stirred. The activity and homogeneity of the diluted doses were assessed. Test substance concentration and target concentration are reported with CV. After dosing, the test preparation was analyzed for stability. Storage conditions of test substances were reported and appropriate.
	Metric 8:	Consistency of exposure administration	Medium	The study used the same volume across all samples (64ul). The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was measured and reported (varying from 380-400 uM between samples); these slight variations are not likely to substantially impact results
	Metric 9:	Reporting of concentrations	High	The applied mass is reported as mg equiv/cm2. Nominal and analytical doses are reported with CV.
	Metric 10:	Exposure frequency	High	Exposure duration was reported and appropriate for determining absorption. 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.
	Metric 11:	Number of exposure groups and concentration spacing	High	There were 3 dose groups tested in a wide range of concentrations (10%, 1%, and 0.1%). Dilutions of test substance were performed in two different vehicles (isopropyl myristate or toluene Justification for dose selection was not provided.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Full thickness skin samples were obtained from males and females. Abdominal skin samples from 20 people (race not reported) ranging in age from 25-66 years old were studied. The samples arrived deep frozen on dry ice were stored frozen at -20 degrees C. The skin samples were thawed and dermatomed using an electric dermatome. The split-thickness samples were measured using a micrometer and ranged from 380 to 400 uM. The OECD guidelines indicate split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring trans epidermal water loss prior to/and upon completion of the experiment. Electrical resistance of skin was also determined as a measure of integrity. All samples had resistance >7.7 kilo ohms.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates/doses were reported and appropriate per OECD 428. The study used 8 replicates/dose from 4 donors.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28 with some exceptions. Guidelines specify application for 10 uL/cm2 for finite dosing. The study authors indicated that 100 uL/cm2 of test substance was used as per requested by the EPA. This was the same dose volume used for the infinite exposures. It is not clearly stated whether these dose volumes were appropriate for a finite exposure scenario. Measurement techniques and timing were reported and appropriate. A finite dose was used to determine absorption.

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 10% in Toluene

Domain	Metric		Rating	Comments
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assessed consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period 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 (30 d.p.m). The sampling intervals were adequate. Methods for determination of radioactivity are reported. 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	Low	The study used a single batch of radiolabeled TCDE. Human abdominal skin was obtained from 20 donors, male and female, ranging in age from 25 to 66 years old. The large age range and sex differences may influence results. The split-thickness was consistent across samples (380-400 um). Skin integrity was confirmed by TEWL, and all samples had a resistance above 7.7 k´Ω which was the author-specified cutoff; however, this is below guideline recommendations. Pre-exposure, mean TEWL values across replicates in each sample were <10 grams/m2/hour, which is consistent with OECD 428 and 156. Despite the overall mean being acceptable, ≥50% of the individual replicates had TWEL values >10 grams/m2/hour. These were not removed or evaluated separately as outliers. These integrity issues significantly impact the ability to reliably determine absorption values.
	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. The authors noted significant issues with test substance volatility. Missing mass balance was attributed to loss to the atmosphere despite tests being conducted under occluded conditions.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	All Finite except one to right: LOW All Statistical methods were described and were appropriate. Absorption estimates were based on appropriate measurements; however, 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	Medium	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 for all finite samples was low with means and large differences across replicates within a sample. The majority of sample was located in the filter, and the missing mass balance was presumed by the authors to be lost due to volatilization of the test substance despite conducting the experiments under occlusion. Sufficient data are provided for alternative calculations.
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means ± SD. Individual replicate data were provided.

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Study Citation:	TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical:	trans-1,2-Dichloroethylene
Exposure Type:	Parent compound
HERO ID:	11523429
Unique ID:	Finite- 10% in Toluene

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

Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 1% in Toluene

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled trans-1,2-dichloroethylene and radiolabeled [1,2-14C2]trans-1,2-dichloroethylene, CAS number: 156-60-5. 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, trans-1,2-dichloroethylene was sourced from Sigma-Aldrich; the source of the radiolabeled trans-1,2-dichloroethylene was redacted from the study. The study included certificates of analyses that reported lot/batch numbers. The radiolabeled test substance was verified by HPLC.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the radiolabeled test substance was determined to be ≥95.6% by HPLC. The purity of the non-radiolabeled substance was reported to be 99.7%. Impurities were not reported. Post-dose radiochemical purities were also determined. All of the measurements met the acceptance criterion of >95%.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No appropriate reference compound was studied. The study authors do not report their familiarity with performing this type of study.

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 1% in Toluene

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Low	This study was conducted according to OECD TG 428, OECD 28, EPA guidelines for dermal studies and the European Commissions Guidance on Dermal Absorption. The assay procedures specified in the report were described in detail, although some information was missing. The static diffusion cell set up is sufficiently reported including a photograph. The study reported an equilibration period after the skin was placed into the chamber of 30 minutes, which is agreement with guidelines recommendations. Finite doses of trans-1,2-dichloroethylene (10%, 1%, and 0.1% dissolved in either isopropyl myristate or toluene) was applied to human skin (8 replicates; surface area of 0.64 cm2). An application rateof 100uL/cm2 was applied to skin surface; this is the same volume used in the infinite exposures and higher than the guideline recommendations of 10uL/cm2. The authors acknowledge the guidelines and recognize the applied quantity is greater than recommended, however EPA requested an application of 100 ul/cm2. Cells were occluded with traps containing carbon filters and Tenax®TA and completely sealed with a cap. Full thickness human skin samples were thawed and dermatomed to create split-thickness membranes. Membranes were then refrozen (up to 2 months). Thickness of skin sample ranged from 380 to 400 um. The receptor solution (PBS with 6% polyethoxyoleate 20 oleyl ether) was appropriate for this lipophilic chemical. The solubility of trans-1,2-dichloroethylene was tested in the receptor fluid prior to the study and determined solubility of the test substance was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity was monitored but not reported here. The receptor fluid (5 mL) was continuously stirred as per OECD 428 guidelines. Skin washed at 8 hours with 50 uL commercial hand wash soap, gently rubbed with a tissue swap, and rinsed with 5 mL of a 2% (v/v) commercial soap solution. The donor cell was re-occluded with new filter. Receptor fluid samples continued to be collected, up to 24 hours. Receptor fluid samples (300 uL) were collected at 10 min, 30 min, 1, 2, 4, 8, 12, 16, 20, and 24 hours and analyzed for radioactivity. The study does not report if they added additional receptor fluid to the receptor chamber after each sampling in order to maintain 5 mL of receptor fluid. After 24 hours, the skin was rewashed as described at 8 hours, and then tap-stripped 20 times. Radioactivity was measured with a representative blank sample subtracted from count rats. A limit of reliable measurement of 30 d.p.m. over background was determined.
	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 (before tape stripping). The authors did not specify inclusion criteria for this measurement; but full results were reported. The electrical resistance of the skin was measured following TEWL assessment using low voltage alternating current (100 Hz with a maximum of 300 mV). All samples had a resistance greater than 7.7 kilo ohms, the author stated criteria for inclusion. Based on reported data, coefficients of variation (CV) values were calculated. Low recoveries are most likely from the high volatility of the test substance.

Domain 3: Exposure Characterization

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 1% in Toluene

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of test substance is described in detail. Dilutions were vortexed and magnetically stirred. The activity and homogeneity of the diluted doses were assessed. Test substance concentration and target concentration are reported with CV. After dosing, the test preparation was analyzed for stability. Storage conditions of test substances were reported and appropriate.
	Metric 8:	Consistency of exposure administration	Medium	The study used the same volume across all samples (64ul). The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was measured and reported (varying from 380-400 uM between samples); these slight variations are not likely to substantially impact results
	Metric 9:	Reporting of concentrations	High	The applied mass is reported as mg equiv/cm2. Nominal and analytical doses are reported with CV.
	Metric 10:	Exposure frequency	High	Exposure duration was reported and appropriate for determining absorption. 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.
	Metric 11:	Number of exposure groups and concentration spacing	High	There were 3 dose groups tested in a wide range of concentrations (10%, 1%, and 0.1%). Dilutions of test substance were performed in two different vehicles (isopropyl myristate or toluene Justification for dose selection was not provided.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Full thickness skin samples were obtained from males and females. Abdominal skin samples from 20 people (race not reported) ranging in age from 25-66 years old were studied. The samples arrived deep frozen on dry ice were stored frozen at -20 degrees C. The skin samples were thawed and dermatomed using an electric dermatome. The split-thickness samples were measured using a micrometer and ranged from 380 to 400 uM. The OECD guidelines indicate split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring trans epidermal water loss prior to/and upon completion of the experiment. Electrical resistance of skin was also determined as a measure of integrity. All samples had resistance >7.7 kilo ohms.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates/doses were reported and appropriate per OECD 428. The study used 8 replicates/dose from 4 donors.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28 with some exceptions. Guidelines specify application for 10 uL/cm2 for finite dosing. The study authors indicated that 100 uL/cm2 of test substance was used as per requested by the EPA. This was the same dose volume used for the infinite exposures. It is not clearly stated whether these dose volumes were appropriate for a finite exposure scenario. Measurement techniques and timing were reported and appropriate. A finite dose was used to determine absorption.

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 1% in Toluene

Domain	Metric		Rating	Comments
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assessed consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period 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 (30 d.p.m). The sampling intervals were adequate. Methods for determination of radioactivity are reported. 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	Low	The study used a single batch of radiolabeled TCDE. Human abdominal skin was obtained from 20 donors, male and female, ranging in age from 25 to 66 years old. The large age range and sex differences may influence results. The split-thickness was consistent across samples (380-400 um). Skin integrity was confirmed by TEWL, and all samples had a resistance above 7.7 k´Ω which was the author-specified cutoff; however, this is below guideline recommendations. Pre-exposure, mean TEWL values across replicates in each sample were <10 grams/m2/hour, which is consistent with OECD 428 and 156. Despite the overall mean being acceptable, ≥50% of the individual replicates had TWEL values >10 grams/m2/hour. These were not removed or evaluated separately as outliers. These integrity issues significantly impact the ability to reliably determine absorption values.
	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. The authors noted significant issues with test substance volatility. Missing mass balance was attributed to loss to the atmosphere despite tests being conducted under occluded conditions.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	All Finite except one to right: LOW All Statistical methods were described and were appropriate. Absorption estimates were based on appropriate measurements; however, 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	Medium	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 for all finite samples was low with means and large differences across replicates within a sample. The majority of sample was located in the filter, and the missing mass balance was presumed by the authors to be lost due to volatilization of the test substance despite conducting the experiments under occlusion. Sufficient data are provided for alternative calculations.
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means ± SD. Individual replicate data were provided.

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Study Citation:	TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical:	trans-1,2-Dichloroethylene
Exposure Type:	Parent compound
HERO ID:	11523429
Unique ID:	Finite- 1% in Toluene

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

Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 0.1% in Toluene

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled trans-1,2-dichloroethylene and radiolabeled [1,2-14C2]trans-1,2-dichloroethylene, CAS number: 156-60-5. 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, trans-1,2-dichloroethylene was sourced from Sigma-Aldrich; the source of the radiolabeled trans-1,2-dichloroethylene was redacted from the study. The study included certificates of analyses that reported lot/batch numbers. The radiolabeled test substance was verified by HPLC.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of the radiolabeled test substance was determined to be ≥95.6% by HPLC. The purity of the non-radiolabeled substance was reported to be 99.7%. Impurities were not reported. Post-dose radiochemical purities were also determined. All of the measurements met the acceptance criterion of >95%.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No appropriate reference compound was studied. The study authors do not report their familiarity with performing this type of study.

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 0.1% in Toluene

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Low	This study was conducted according to OECD TG 428, OECD 28, EPA guidelines for dermal studies and the European Commissions Guidance on Dermal Absorption. The assay procedures specified in the report were described in detail, although some information was missing. The static diffusion cell set up is sufficiently reported including a photograph. The study reported an equilibration period after the skin was placed into the chamber of 30 minutes, which is agreement with guidelines recommendations. Finite doses of trans-1,2-dichloroethylene (10%, 1%, and 0.1% dissolved in either isopropyl myristate or toluene) was applied to human skin (8 replicates; surface area of 0.64 cm2). An application rateof 100uL/cm2 was applied to skin surface; this is the same volume used in the infinite exposures and higher than the guideline recommendations of 10uL/cm2. The authors acknowledge the guidelines and recognize the applied quantity is greater than recommended, however EPA requested an application of 100 ul/cm2. Cells were occluded with traps containing carbon filters and Tenax®TA and completely sealed with a cap. Full thickness human skin samples were thawed and dermatomed to create split-thickness membranes. Membranes were then refrozen (up to 2 months). Thickness of skin sample ranged from 380 to 400 um. The receptor solution (PBS with 6% polyethoxyoleate 20 oleyl ether) was appropriate for this lipophilic chemical. The solubility of trans-1,2-dichloroethylene was tested in the receptor fluid prior to the study and determined solubility of the test substance was not rate-limiting. The skin membranes were maintained at 32 degrees C; humidity was monitored but not reported here. The receptor fluid (5 mL) was continuously stirred as per OECD 428 guidelines. Skin washed at 8 hours with 50 uL commercial hand wash soap, gently rubbed with a tissue swap, and rinsed with 5 mL of a 2% (v/v) commercial soap solution. The donor cell was re-occluded with new filter. Receptor fluid samples continued to be collected, up to 24 hours. Receptor fluid samples (300 uL) were collected at 10 min, 30 min, 1, 2, 4, 8, 12, 16, 20, and 24 hours and analyzed for radioactivity. The study does not report if they added additional receptor fluid to the receptor chamber after each sampling in order to maintain 5 mL of receptor fluid. After 24 hours, the skin was rewashed as described at 8 hours, and then tap-stripped 20 times. Radioactivity was measured with a representative blank sample subtracted from count rats. A limit of reliable measurement of 30 d.p.m. over background was determined.
	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 (before tape stripping). The authors did not specify inclusion criteria for this measurement; but full results were reported. The electrical resistance of the skin was measured following TEWL assessment using low voltage alternating current (100 Hz with a maximum of 300 mV). All samples had a resistance greater than 7.7 kilo ohms, the author stated criteria for inclusion. Based on reported data, coefficients of variation (CV) values were calculated. Low recoveries are most likely from the high volatility of the test substance.

Domain 3: Exposure Characterization

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Study Citation: TDCE Consortium, (2023). The in vitro percutaneous absorption of a trans-1,2-dichloroethylene (TDCE) at three concentrations through human skin and determination of permeability constants. Final report.
Chemical: trans-1,2-Dichloroethylene
Exposure Type: Parent compound
HERO ID: 11523429
Unique ID: Finite- 0.1% in Toluene

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of test substance is described in detail. Dilutions were vortexed and magnetically stirred. The activity and homogeneity of the diluted doses were assessed. Test substance concentration and target concentration are reported with CV. After dosing, the test preparation was analyzed for stability. Storage conditions of test substances were reported and appropriate.
	Metric 8:	Consistency of exposure administration	Medium	The study used the same volume across all samples (64ul). The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was measured and reported (varying from 380-400 uM between samples); these slight variations are not likely to substantially impact results
	Metric 9:	Reporting of concentrations	High	The applied mass is reported as mg equiv/cm2. Nominal and analytical doses are reported with CV.
	Metric 10:	Exposure frequency	High	Exposure duration was reported and appropriate for determining absorption. 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.
	Metric 11:	Number of exposure groups and concentration spacing	High	There were 3 dose groups tested in a wide range of concentrations (10%, 1%, and 0.1%). Dilutions of test substance were performed in two different vehicles (isopropyl myristate or toluene Justification for dose selection was not provided.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Full thickness skin samples were obtained from males and females. Abdominal skin samples from 20 people (race not reported) ranging in age from 25-66 years old were studied. The samples arrived deep frozen on dry ice were stored frozen at -20 degrees C. The skin samples were thawed and dermatomed using an electric dermatome. The split-thickness samples were measured using a micrometer and ranged from 380 to 400 uM. The OECD guidelines indicate split thickness (dermatomed) skin is preferred. Membrane integrity was determined by measuring trans epidermal water loss prior to/and upon completion of the experiment. Electrical resistance of skin was also determined as a measure of integrity. All samples had resistance >7.7 kilo ohms.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates/doses were reported and appropriate per OECD 428. The study used 8 replicates/dose from 4 donors.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	The outcome assessment methodology addressed the intended outcome of interest and was sensitive for the outcome. The test followed OECD guidelines 428 and 28 with some exceptions. Guidelines specify application for 10 uL/cm2 for finite dosing. The study authors indicated that 100 uL/cm2 of test substance was used as per requested by the EPA. This was the same dose volume used for the infinite exposures. It is not clearly stated whether these dose volumes were appropriate for a finite exposure scenario. Measurement techniques and timing were reported and appropriate. A finite dose was used to determine absorption.

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Domain	Metric		Rating	Comments
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assessed consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period 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 (30 d.p.m). The sampling intervals were adequate. Methods for determination of radioactivity are reported. 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	Low	The study used a single batch of radiolabeled TCDE. Human abdominal skin was obtained from 20 donors, male and female, ranging in age from 25 to 66 years old. The large age range and sex differences may influence results. The split-thickness was consistent across samples (380-400 um). Skin integrity was confirmed by TEWL, and all samples had a resistance above 7.7 k´Ω which was the author-specified cutoff; however, this is below guideline recommendations. Pre-exposure, mean TEWL values across replicates in each sample were <10 grams/m2/hour, which is consistent with OECD 428 and 156. Despite the overall mean being acceptable, ≥50% of the individual replicates had TWEL values >10 grams/m2/hour. These were not removed or evaluated separately as outliers. These integrity issues significantly impact the ability to reliably determine absorption values.
	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. The authors noted significant issues with test substance volatility. Missing mass balance was attributed to loss to the atmosphere despite tests being conducted under occluded conditions.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	All Finite except one to right: LOW All Statistical methods were described and were appropriate. Absorption estimates were based on appropriate measurements; however, 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	Medium	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 for all finite samples was low with means and large differences across replicates within a sample. The majority of sample was located in the filter, and the missing mass balance was presumed by the authors to be lost due to volatilization of the test substance despite conducting the experiments under occlusion. Sufficient data are provided for alternative calculations.
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means ± SD. Individual replicate data were provided.

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Overall Quality Determination		**Medium**	