United States
Environmental Protection Agency

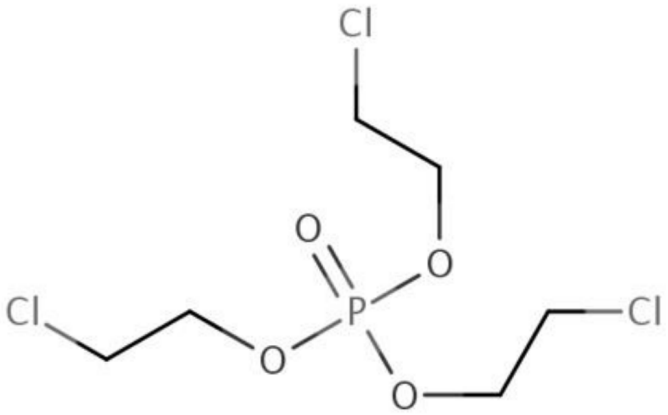
September 2024
Office of Chemical Safety and
Pollution Prevention

Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP)

Systematic Review Supplemental File:

Data Quality Evaluation and Data Extraction Information for Dermal Absorption

CASRN: 115-96-8



September 2024

This supplemental file contains information regarding the data extraction and evaluation results for data sources that met the PECO screening criteria for the *Draft Risk Evaluation for Tris(2-chloroethyl) phosphate* 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 extracted from the reference. EPA used the TSCA systematic review process described in the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (also referred to as the '2021 Draft Systematic Review Protocol'). Any updated steps in the systematic review process since the publication of the 2021 Draft Systematic Review Protocol are described in the *Systematic Review Protocol for the Draft Risk Evaluation for Tris(2-chloroethyl) phosphate*.

To evaluate dermal absorption references, EPA consulted several OECD documents when considering quality rankings for individual metrics. Each condition (*e.g.*, individual concentrations tested or different experimental designs) is evaluated independently within a given reference. Therefore each reference may have more than one overall quality determination (OQD) to more appropriately reflect the quality of each condition. No OQD is determined for each reference as a whole, if it contains data from more than condition. A single reference may evaluate only a limited number of conditions (*e.g.*, use of only the neat compound). If all other methods and results are adequate, the study may be considered acceptable for certain conditions of use. However, the study may still be limited for use in the risk evaluation because it may not address other uses (*e.g.*, lower concentrations, certain solvents/diluents). Within the contents of this document, tris(2-chloroethyl) phosphate may be referred to as the acronym TCEP.

Table of Contents

Study Citation: Abou-Elwafa Abdallah, M., Pawar, G., Harrad, S. (2016). Human dermal absorption of chlorinated organophosphate flame retardants; implications for human exposure. Toxicology and Applied Pharmacology 291:28-37.

HERO ID: 3120332

EXTRACTION

Parameter	Data
Extraction ID; Chemical:	Finite dose % absorp; Tris(2-chloroethyl) phosphate (TCEP)-Parent compound
Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type:	ex vivo human; Full thickness; Not Reported; Static; Notes: Not Reported
Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent):	Unoccluded; acetone; 0.005
Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin:	0.0005; 24 hrs; Not Reported
Duration of Absorbance Measured; Frequency of Samples:	24 hrs; Only evidence of measurement at 24hr; Notes: Not Reported
Time Skin was Washed and Method used; Radiolabel Presence:	Washed at 24 hrs with 1:1 hexane: ethyl acetate (repeated 5 x); No
Total Recovery (percent); Dose Type:	90; Finite
Percent Found in Skin Depot After Washing and Tape Stripping; Comments:	6.8; Notes: No tape stripping was used. There is significant uncertainty whether this value is 6.8 or 55.3 due to a reporting error between graph and table
Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments:	6.8; Notes: No tape stripping was used. There is significant uncertainty whether this value is 6.8 or 55.3 due to a reporting error between graph and table
Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments:	28.3; Notes: Not Reported
Total Percent Absorbed:	35
Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maxium Permeability Coefficient (Kp) (cm/hr); Maxium Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments):	Not Reported; Notes: Not presented; Not Reported; Notes: Not presented; Not Reported; Notes: Not presented; Not Reported; Notes: Not presented

EVALUATION

Domain		Metric	Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	Chemical name provided
	Metric 2:	Test substance source	High	Source (Sigma Aldrich) was identified and is available for purchase on website. No batch number provided but chemical not expected to vary in composition.
	Metric 3:	Test substance purity	High	$>$ 98%; test substance was unlabeled
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	Positive (labeled standard) and negative controls (solvent-only blank) were run and showed adequate results.

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EVALUATION

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	A static standard Franz diffusion cell was used (appropriate surface area assumed) with magnetic stirring; receptor fluid was appropriately maintained at 32 deg. C; DMEM-based culture medium was used for the receptor fluid with 5% bovine serum albumin - authors ensured solubility in the receptor fluid; only one time point of 24hr used, samples were taken and receptor fluid replaced; humidity was not reported; no information was provided on the seal for the diffusion cell. Tape stripping not performed but skin surface was wiped with cotton; no information was provided on occlusion.
	Metric 6:	Standards for tests	Low	Criteria were reported for obtained skin samples and calibration standards, but skin integrity of samples used in the study and coefficient of variation were not stated. Recovery was reported but not compared to any standard for acceptability.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	No storage details were provided (although TCEP is not very volatile). Limited preparation details were reported.
	Metric 8:	Consistency of exposure administration	Medium	Exposure details were reported, although due to the number of experiments with varying conditions the details were hard to follow. There was only a single study group for this experiment.
	Metric 9:	Reporting of concentrations	Medium	Concentrations were reported as nominal point estimates. They were also described confusingly in the text and not presented in a simple tabular format, making them difficult to interpret.
	Metric 10:	Exposure frequency	High	The duration of 24 hrs appears to have been chosen to mimic exposure to indoor dust. Including results from shorter timepoints would have been ideal but 24hr is fine.
	Metric 11:	Number of exposure groups and concentration spacing	Low	Only 1 dose group/concentration was tested (500 ng/cm2, 24hr).
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	Source, anatomical site, storage and preparation reported.
	Metric 13:	Number/Replicates per group	Low	The experiment was run in triplicate from three donors and it is unclear if the biological samples were also run as technical replicates or only 1 sample per donor. In the absence of confirmatory information it is assumed that only 3 replicates were run total.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	An appropriate vehicle was used for dermal absorption experiments (acetone). The finite dosing was appropriate (10 ul/cm2 of a dilute solution) for measures of percent absorption.
	Metric 15:	Consistency of outcome assessment	High	Only one study group to collect.
	Metric 16:	Sampling adequacy and sensitivity	Medium	Only tabular summary statistics were presented, and only for a single timepoint. Therefore the sensitivity cannot be fully determined.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Batches/lots as well as skin integrity was not reported, however the authors indicated that all tissues passed QA/QC. There is some uncertainty as to whether all tests were performed on skin tissue or only in vitro models.

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		EVALUATION		
Domain		Metric	Rating	Comments
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	Accuracy and precision of the analytical method appeared adequate and solubility of test substance in receptor fluid was adequate.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Statistical methods were described but absorption estimates were not presented across a time series. Standard deviation relative to mean was low for each compartment.
	Metric 20:	Data interpretation	Low	Recovery was ~ 90%, right at the recommended cutoff. Downgraded because tabular presentation of skin depot vs wash fractions are presumably switched, which makes overall interpretation of results uncertain. It is likely that the results are switched in Table 1 based on graphical results for other experiments,, but this uncertainty leads to a wide range of possible results.
	Metric 21:	Reporting of data	Medium	Results reported in a single table, however it is unclear if there were earlier timepoints sampled.

Overall Quality Determination Medium

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HERO ID: 3120332

EXTRACTION

Parameter	Data
Extraction ID; Chemical:	steady state flux/Kp; Tris(2-chloroethyl) phosphate (TCEP)-Parent compound
Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type:	ex vivo human; Full thickness; Not Reported; Static; Notes: Not Reported
Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent):	Unoccluded; acetone; 0.001
Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin:	0.001; 24 hrs; Not Reported
Duration of Absorbance Measured; Frequency of Samples:	24 hrs; 30 min, 45 min and 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 hrs + below; Notes: Not Reported
Time Skin was Washed and Method used; Radiolabel Presence:	Washed at 24 hrs with 1:1 hexane:ethylacetate (repeated 5 x).; No
Total Recovery (percent); Dose Type:	Not Reported; Infinite
Percent Found in Skin Depot After Washing and Tape Stripping; Comments:	Not Reported; Notes: Not stated for flux measurements
Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments:	Not Reported; Notes: Not stated for flux measurements
Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments:	Not Reported; Notes: Not stated for flux measurements
Total Percent Absorbed:	0
Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maxium Permeability Coefficient (Kp) (cm/hr); Maxium Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments):	0.022; Notes: Not infinite dose but based on linear part of dose-response curve; Not Reported; Notes: not measured at maximum acetone solubility; 0.0219; Notes: Not infinite dose but based on linear part of dose-response curve; Not Reported; Notes: not measured at maximum acetone solubility or neat

EVALUATION

Domain		Metric	Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	Chemical name provided
	Metric 2:	Test substance source	High	Source (Sigma Aldrich) was identified and is available for purchase on website. No batch number provided but chemical not expected to vary in composition.
	Metric 3:	Test substance purity	High	$>$ 98%; test substance was unlabeled
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	Positive (labeled standard) and negative controls (solvent-only blank) were run and showed adequate results.

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EVALUATION

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	A static standard Franz diffusion cell was used (appropriate surface area assumed) with magnetic stirring; receptor fluid was appropriately maintained at 32 deg. C; DMEM-based culture medium was used for the receptor fluid with 5% bovine serum albumin - authors ensured solubility in the receptor fluid; at fixed time points (estimated from graph as 30 min, 45 min, 1, 2,4,6,8,10,12,14,16,18,20,22,24 hrs+below), samples were taken and receptor fluid replaced; humidity was not reported; no information was provided on the seal for the diffusion cell. Tape stripping not performed but skin surface was wiped with cotton; no information was provided on occlusion.
	Metric 6:	Standards for tests	Low	Criteria were reported for obtained skin samples and calibration standards, but skin integrity of samples used in the study and coefficient of variation were not stated. Recovery was not reported or discussed for this assay.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	No storage details were provided (although TCEP is not very volatile). Limited preparation details were reported.
	Metric 8:	Consistency of exposure administration	Medium	There was only a single study group.
	Metric 9:	Reporting of concentrations	Medium	Concentrations were reported as nominal point estimates. They were also described confusingly in the text and not presented in a simple tabular format, making them difficult to interpret.
	Metric 10:	Exposure frequency	High	Measurements were taken at several timepoints through 24hr, with the duration approximating steady state identified within the curve.
	Metric 11:	Number of exposure groups and concentration spacing	Low	Only 1 dose group/concentration was tested for this assay (1000 mg/cm2). This concentration is orders of magnitude below infinite dose conditions and while the graph approximates steady state from 0.5-8hr, it is still not completely linear.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	Source, anatomical site, storage and preparation reported.
	Metric 13:	Number/Replicates per group	Low	The experiment was run in triplicate from three donors and it is unclear if the biological samples were also run as technical replicates or only 1 sample per donor. In the absence of confirmatory information it is assumed that only 3 replicates were run total.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	An appropriate vehicle was used (acetone). The infinite dosing experiments were not appropriate because even though the volume of 100 ul/cm2 was appropriate for the primary experiment, the test substance was applied as a dilute solution (whereas it should have been neat). The flux data can still be used over the duration of linearity which covers 8hr, however it cannot be extrapolated, and the flux curve is not precisely linear over the 8hr timeline.
	Metric 15:	Consistency of outcome assessment	High	Only one study group

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		EVALUATION		
Domain		Metric	Rating	Comments
	Metric 16:	Sampling adequacy and sensitivity	Medium	Graphical results indicate that the data was accurately detected enough for presentation, and timepoint durations were spaced sufficiently for defining ad discrete absorption curve. Measured via GC+spectrometry, so no scintillation counts required. Would have preferred more granularity in timepoints or sample size to better capture whether the less than infinite dose was non-depletable over the short-term.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Batches/lots as well as skin integrity was not reported, however the authors indicated that all tissues passed QA/QC. There is some uncertainty as to whether all tests were performed on skin tissue or only in vitro models. Error bars are relatively small across experimental groups, suggesting a major confounder is unlikely.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	Accuracy and precision of the analytical method appeared adequate and solubility of test substance in receptor fluid was adequate.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Coefficients of variation are difficult to determine given that the results were provided only graphically or with a single Jss/Kp reported. While linearity of the curve is only demonstrated by line of best fit, the results is clearly shown in supplemental files.
	Metric 20:	Data interpretation	Low	The authors didn't follow OECD guidance when considering conditions needed for infinite dosing (e.g., only relevant for neat or high concentration liquids). Kp was derived in situations that were finite dosing situations, although the range of linearity was provided which mitigates this issue. Recovery was not provided, although this is not typically calculated for permeability estimates.
	Metric 21:	Reporting of data	Medium	Findings reported graphically and summarized for linear part of curve in a table. Variability/error only shown as error bars in the graph but not summarized in a table.

Overall Quality Determination — Medium

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EXTRACTION

Parameter	Data
Extraction ID; Chemical:	wash vs no wash-6hr; Tris(2-chloroethyl) phosphate (TCEP)-Parent compound
Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type:	ex vivo human; Full thickness; Not Reported; Static; Notes: Not Reported
Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent):	Unoccluded; acetone; 0.005
Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin:	0.0005; 6 hrs; Not Reported
Duration of Absorbance Measured; Frequency of Samples:	24 hrs; 30 min, 45 min, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 hrs+ below; Notes: Not Reported
Time Skin was Washed and Method used; Radiolabel Presence:	At 6 hrs, with 1:1 hexane: ethyl acetate (repeated 5 x).; No
Total Recovery (percent); Dose Type:	Not Reported; Finite
Percent Found in Skin Depot After Washing and Tape Stripping; Comments:	Not Reported; Notes: not measured for washed sample and complicated to measure
Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments:	Not Reported; Notes: not measured for washed sample and complicated to measure
Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments:	13; Notes: approximately 65/500 absorbed at 6hr in washed sample
Total Percent Absorbed:	13
Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maxium Permeability Coefficient (Kp) (cm/hr); Maxium Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments):	Not Reported; Notes: Not stated; Not Reported; Notes: Not stated; Not Reported; Notes: Not stated; Not Reported; Notes: Not stated

EVALUATION

Domain		Metric	Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	Chemical name provided
	Metric 2:	Test substance source	High	Source (Sigma Aldrich) was identified and is available for purchase on website. No batch number provided but chemical not expected to vary in composition.
	Metric 3:	Test substance purity	High	> 98%; test substance was unlabeled
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	Positive (labeled standard) and negative controls (solvent-only blank) were run and showed adequate results.

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EVALUATION

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	A static standard Franz diffusion cell was used (appropriate surface area assumed) with magnetic stirring; receptor fluid was appropriately maintained at 32 deg. C; DMEM-based culture medium was used for the receptor fluid with 5% bovine serum albumin - authors ensured solubility in the receptor fluid; at fixed time points (estimated as 30 min, 45 min, 1, 2,4,6,8,10,12,14,16,18,20,22,24 hrs + below), samples were taken and receptor fluid replaced; humidity was not reported; no information was provided on the seal for the diffusion cell. Tape stripping not performed but skin surface was wiped with cotton; no information was provided on occlusion.
	Metric 6:	Standards for tests	Low	Criteria were reported for obtained skin samples and calibration standards, but skin integrity of samples used in the study and coefficient of variation were not stated as only a graph of results were shown. Recovery was not reported.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	No storage details were provided (although TCEP is not very volatile). Limited preparation details were reported.
	Metric 8:	Consistency of exposure administration	Medium	500 ng/cm2 used for wash comparison. Other than wash, other parameters appear to be the same between samples.
	Metric 9:	Reporting of concentrations	Medium	Concentrations were reported as nominal point estimates.
	Metric 10:	Exposure frequency	High	The duration of 24 hrs appears to have been chosen to mimic exposure to indoor dust, however the basis for a wash at 6hr is unclear and makes it difficult to interpret for occupational scenarios where an expected wash would be at either 4hr or 8hr. Nonetheless, it falls within the acceptable range for occupational scenarios.
	Metric 11:	Number of exposure groups and concentration spacing	Low	Only 1 dose group/concentration was tested.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	Source, anatomical site, storage and preparation reported.
	Metric 13:	Number/Replicates per group	Low	The experiment was run in triplicate from three donors and it is unclear if the biological samples were also run as technical replicates or only 1 sample per donor. In the absence of confirmatory information it is assumed that only 3 replicates were run total.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	An appropriate vehicle was used for dermal absorption experiments (acetone). A finite dose was used; absolute concentration was not measured but cumulative absorption over time was quantified graphically. The decision to wash at 6hr was not explained and makes interpretation a bit difficult, as occupational scenarios would typically wash at 4hr or 8hr.
	Metric 15:	Consistency of outcome assessment	High	Outcomes appear to have been assessed consistently (procedures the same; time of sample collection the same; samples collected at same time throughout experiment).
	Metric 16:	Sampling adequacy and sensitivity	High	Graphical results indicate that the data was accurately detected enough for presentation, and timepoint durations were spaced sufficiently for defining ad discrete absorption curve. Measured via GC+spectrometry, so no scintillation counts required.

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EVALUATION

Domain	Metric		Rating	Comments
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Batches/lots as well as skin integrity was not reported, however the authors indicated that all tissues passed QA/QC. There is some uncertainty as to whether all tests were performed on skin tissue or only in vitro models. Error bars are relatively small across experimental groups, suggesting a major confounder is unlikely.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	Accuracy and precision of the analytical method appeared adequate and solubility of test substance in receptor fluid was adequate.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Statistical methods were described but absorption estimates for each component (skin, receptor fluid, etc.) were not provided. Coefficients of variation were appropriate but were only shown graphically. There was a time series covering both pre and post-wash.
	Metric 20:	Data interpretation	Low	Only cumulative absorption reported (presumably based on receptor fluid). This requires independent data estimates to obtain the full absorbable dose at different timepoints.
	Metric 21:	Reporting of data	Low	Findings only reported graphically, without tick marks to more clearly indicate even major gridlines. Only cumulative absorbed dose reported.

Overall Quality Determination Medium

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EXTRACTION

Parameter	Data
Extraction ID; Chemical:	wash vs wash-24hr; Tris(2-chloroethyl) phosphate (TCEP)-Parent compound
Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type:	ex vivo human; Full thickness; Not Reported; Static; Notes: Not Reported
Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent):	Unoccluded; acetone; 0.005
Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin:	0.0005; 24 hrs; Not Reported
Duration of Absorbance Measured; Frequency of Samples:	24 hrs; 30 min, 45 min, 1,2,4,6,8,10,12,14,16,18,20,22,24 hrs + below; Notes: Not Reported
Time Skin was Washed and Method used; Radiolabel Presence:	Washed at 24 hrs with 1:1 hexane:ethyl acetate; No
Total Recovery (percent); Dose Type:	Not Reported; Finite
Percent Found in Skin Depot After Washing and Tape Stripping; Comments:	Not Reported; Notes: No information provided for this sample and hard to compare with other assay runs
Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments:	Not Reported; Notes: No information provided for this sample and hard to compare with other assay runs
Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments:	14; Notes: approximately 70/500 absorbed at 24hr in washed sample
Total Percent Absorbed:	14
Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maxium Permeability Coefficient (Kp) (cm/hr); Maxium Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments):	Not Reported; Notes: Not stated; Not Reported; Notes: Not stated; Not Reported; Notes: Not stated; Not Reported; Notes: Not stated

EVALUATION

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	Chemical name provided
	Metric 2:	Test substance source	High	Source (Sigma Aldrich) was identified and is available for purchase on website. No batch number provided but chemical not expected to vary in composition.
	Metric 3:	Test substance purity	High	> 98%; test substance was unlabeled
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	Positive (labeled standard) and negative controls (solvent-only blank) were run and showed adequate results.

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Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	A static standard Franz diffusion cell was used (appropriate surface area assumed) with magnetic stirring; receptor fluid was appropriately maintained at 32 deg. C; DMEM-based culture medium was used for the receptor fluid with 5% bovine serum albumin - authors ensured solubility in the receptor fluid; at fixed time points (estimated as 30 min, 45 min, 1, 2,4,6,8,10,12,14,16,18,20,22,24 hrs + below), samples were taken and receptor fluid replaced; humidity was not reported; no information was provided on the seal for the diffusion cell. Tape stripping not performed but skin surface was wiped with cotton; no information was provided on occlusion.
	Metric 6:	Standards for tests	Low	Criteria were reported for obtained skin samples and calibration standards, but skin integrity of samples used in the study and coefficient of variation were not stated as only a graph of results were shown. Recovery was not reported.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	No storage details were provided (although TCEP is not very volatile). Limited preparation details were reported.
	Metric 8:	Consistency of exposure administration	Medium	500 ng/cm2 used for wash comparison. Other than wash, other parameters appear to be the same between samples.
	Metric 9:	Reporting of concentrations	Medium	Concentrations were reported as nominal point estimates.
	Metric 10:	Exposure frequency	High	The duration of 24 hrs appears to have been chosen to mimic exposure to indoor dust, however the basis for a wash at 6hr is unclear and makes it difficult to interpret for occupational scenarios where an expected wash would be at either 4hr or 8hr. Nonetheless, it falls within the acceptable range for occupational scenarios.
	Metric 11:	Number of exposure groups and concentration spacing	Low	Only 1 dose group/concentration was tested.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	Source, anatomical site, storage and preparation reported.
	Metric 13:	Number/Replicates per group	Low	The experiment was run in triplicate from three donors and it is unclear if the biological samples were also run as technical replicates or only 1 sample per donor. In the absence of confirmatory information it is assumed that only 3 replicates were run total.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	An appropriate vehicle was used for dermal absorption experiments (acetone). A finite dose was used; absolute concentration was not measured but cumulative absorption over time was quantified graphically. The decision to wash at 6hr was not explained and makes interpretation a bit difficult, as occupational scenarios would typically wash at 4hr or 8hr.
	Metric 15:	Consistency of outcome assessment	High	Outcomes appear to have been assessed consistently (procedures the same; time of sample collection the same; samples collected at same time throughout experiment).
	Metric 16:	Sampling adequacy and sensitivity	High	Graphical results indicate that the data was accurately detected enough for presentation, and timepoint durations were spaced sufficiently for defining ad discrete absorption curve. Measured via GC+spectrometry, so no scintillation counts required.

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HERO ID: 3120332

EVALUATION

Domain	Metric		Rating	Comments
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Batches/lots as well as skin integrity was not reported, however the authors indicated that all tissues passed QA/QC. There is some uncertainty as to whether all tests were performed on skin tissue or only in vitro models. Error bars are relatively small across experimental groups, suggesting a major confounder is unlikely.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	Accuracy and precision of the analytical method appeared adequate and solubility of test substance in receptor fluid was adequate.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Statistical methods were described but absorption estimates for each component (skin, receptor fluid, etc.) were not provided. Coefficients of variation were appropriate but were only shown graphically. There was a time series covering both pre and post-wash.
	Metric 20:	Data interpretation	Low	Only cumulative absorption reported (presumably based on receptor fluid). This requires independent data estimates to obtain the full absorbable dose at different timepoints.
	Metric 21:	Reporting of data	Low	Findings only reported graphically, without tick marks to more clearly indicate even major gridlines. Only cumulative absorbed dose reported.

Overall Quality Determination Medium

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EXTRACTION

Parameter	Data
Extraction ID; Chemical:	solvent comparison-acetone; Tris(2-chloroethyl) phosphate (TCEP)-Parent compound
Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type:	ex vivo human; Full thickness; Not Reported; Static; Notes: Not Reported
Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent):	Unoccluded; acetone; 0.001
Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin:	0.0005; 24 hrs; Not Reported
Duration of Absorbance Measured; Frequency of Samples:	24 hrs; Only evidence of measurement at 24hr; Notes: Not Reported
Time Skin was Washed and Method used; Radiolabel Presence:	Washed at 24 hrs with 1:1 hexane: ethyl acetate; No
Total Recovery (percent); Dose Type:	88; Finite
Percent Found in Skin Depot After Washing and Tape Stripping; Comments:	8; Notes: Estimated from Figure 4: 40/500
Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments:	8; Notes: Estimated from Figure 4: 40/500
Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments:	27; Notes: Estimated from Figure 4: 135/500
Total Percent Absorbed:	35
Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maxium Permeability Coefficient (Kp) (cm/hr); Maxium Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments):	Not Reported; Notes: Not stated even though authors claim the dose is infinite; Not Reported; Notes: Not stated even though authors claim the dose is infinite; Not Reported; Notes: Not stated even though authors claim the dose is infinite; Not Reported; Notes: Not stated even though authors claim the dose is infinite

EVALUATION

Domain		Metric	Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	Chemical name provided
	Metric 2:	Test substance source	High	Source (Sigma Aldrich) was identified and is available for purchase on website. No batch number provided but chemical not expected to vary in composition.
	Metric 3:	Test substance purity	High	$>$ 98%; test substance was unlabeled
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	Positive (labeled standard) and negative controls (solvent-only blank) were run and showed adequate results.

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EVALUATION

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	A static standard Franz diffusion cell was used (appropriate surface area assumed) with magnetic stirring; receptor fluid was appropriately maintained at 32 deg. C; DMEM-based culture medium was used for the receptor fluid with 5% bovine serum albumin - authors ensured solubility in the receptor fluid; at single timepoint (24hr), samples were taken and receptor fluid replaced; humidity was not reported; no information was provided on the seal for the diffusion cell. Tape stripping not performed but skin surface was wiped with cotton; no information was provided on occlusion.
	Metric 6:	Standards for tests	Low	Criteria were reported for obtained skin samples and calibration standards, but skin integrity of samples used in the study and coefficient of variation were not stated as only a graph of results were shown. Recovery was not reported but can be estimated from the other reported values, although no comparison standard provided.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	No storage details were provided (although TCEP is not very volatile). Limited preparation details were reported.
	Metric 8:	Consistency of exposure administration	Medium	500 ng/cm2 used for solvent comparison. Other than solvent, other parameters appear to be the same between samples.
	Metric 9:	Reporting of concentrations	Medium	Concentrations were reported as nominal point estimates.
	Metric 10:	Exposure frequency	High	The duration of 24 hrs appears to have been chosen to mimic exposure to indoor dust. Including results from shorter timepoints would have been ideal but 24hr is fine.
	Metric 11:	Number of exposure groups and concentration spacing	Low	Only 1 dose group/concentration was tested.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	Source, anatomical site, storage and preparation reported.
	Metric 13:	Number/Replicates per group	Low	The experiment was run in triplicate from three donors and it is unclear if the biological samples were also run as technical replicates or only 1 sample per donor. In the absence of confirmatory information it is assumed that only 3 replicates were run total.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	An appropriate vehicle was used for dermal absorption experiments (acetone or Tween 80). A finite dose was used.
	Metric 15:	Consistency of outcome assessment	High	Outcomes appear to have been assessed consistently (procedures the same; time of sample collection the same; samples collected at same time throughout experiment).
	Metric 16:	Sampling adequacy and sensitivity	High	Graphical results indicate that the data was accurately detected enough for presentation, with relatively small error bars. Measured via GC+spectrometry, so no scintillation counts required.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Batches/lots as well as skin integrity was not reported, however the authors indicated that all tissues passed QA/QC. There is some uncertainty as to whether all tests were performed on skin tissue or only in vitro models. Error bars are relatively small across experimental groups, suggesting a major confounder is unlikely.

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		EVALUATION		
Domain		Metric	Rating	Comments
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	Accuracy and precision of the analytical method appeared adequate and solubility of test substance in receptor fluid was adequate.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Statistical methods were described and absorption estimates for each component (skin, receptor fluid, etc.) were provided. Coefficients of variation were appropriate but were only shown graphically. No time series, only a single 24hr timepoint.
	Metric 20:	Data interpretation	Low	All compartments measured in terms of absolute absorption but only reported graphically, and no recovery explicitly reported, although it can be estimated.
	Metric 21:	Reporting of data	Low	Findings only reported graphically without labels and as absolute absorption only. Percent absorption must be estimated and self-calculated.

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EXTRACTION

Parameter	Data
Extraction ID; Chemical:	solvent comparison-Tween; Tris(2-chloroethyl) phosphate (TCEP)-Parent compound
Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type:	ex vivo human; Full thickness; Not Reported; Static; Notes: Not Reported
Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent):	Unoccluded; 20% Tween 80 in water; 0.001
Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin:	0.0005; 24 hrs; Not Reported
Duration of Absorbance Measured; Frequency of Samples:	24 hrs; Only evidence of measurement at 24hr; Notes: Not Reported
Time Skin was Washed and Method used; Radiolabel Presence:	Skin washed at 24 hrs (1:1 hexane: ethyl acetate) (repeated 5 x).; No
Total Recovery (percent); Dose Type:	88; Finite
Percent Found in Skin Depot After Washing and Tape Stripping; Comments:	7; Notes: Estimated from Figure 4 : 35/500
Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments:	7; Notes: Estimated from Figure 4 : 35/500
Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments:	29; Notes: Estimated from Figure 4: 145/500
Total Percent Absorbed:	36
Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maxium Permeability Coefficient (Kp) (cm/hr); Maxium Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments):	Not Reported; Notes: Not stated even though authors claim the dose is infinite; Not Reported; Notes: Not stated even though authors claim the dose is infinite; Not Reported; Notes: Not stated even though authors claim the dose is infinite; Not Reported; Notes: Not stated even though authors claim the dose is infinite

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Domain		Metric	Rating	Comments
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Domain 2: Test Design				
	Metric 4:	Reference compounds	High	Positive (labeled standard) and negative controls (solvent-only blank) were run and showed adequate results.

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