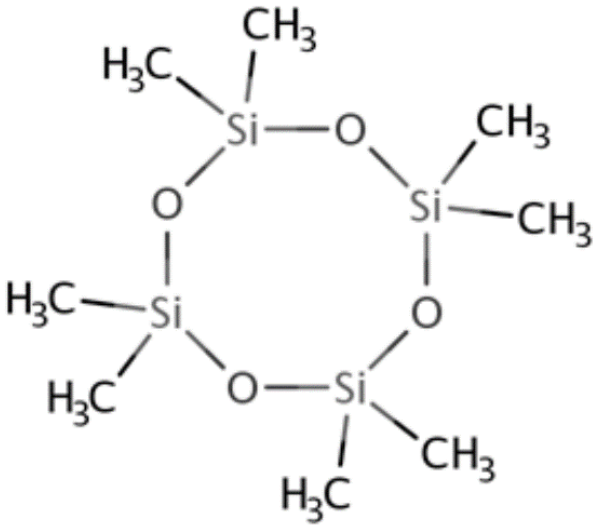
United States
Environmental Protection Agency

September 2025
Office of Chemical Safety and
Pollution Prevention

# Data Quality Evaluation and Data Extraction Information for Dermal Absorption for Octamethylcyclotetrasiloxane (D4)

# Systematic Review Support Document for the Draft Risk Evaluation

**CASRN: 556-67-2**



*September 2025*

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 Octamethylcyclotetrasiloxane (D4)* and were used to characterize dermal absorption. EPA conducted data quality evaluations based on author-reported descriptions and results; additional analyses (*e.g.*, statistical analyses performed during data integration for the risk evaluation) potentially conducted by EPA are not contained in this supplemental file. Key parameters and corresponding data for each condition were extracted from the reference. EPA used the TSCA systematic review process described in the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (also referred to as the '2021 Draft Systematic Review Protocol'). Any updated steps in the systematic review process since the publication of the 2021 Draft Systematic Review Protocol are described in the *Draft Systematic Review Protocol for Octamethylcyclotetrasiloxane (D4)*.

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 more appropriately. 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:** Dow Corning, (1991). Percutaneous absorption of D4 (octamethyltetrasiloxane).
**HERO ID:** 11438090

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Study 1 - 78 yr old female; D4; D4-Parent compound |
| Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type: | ex vivo human; Split thickness; 500; Flow-through; Notes: Not Reported |
| Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent): | Semi-occluded (e.g., vapor trap); No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin: | 0.44; 24 hrs; Not Reported |
| Duration of Absorbance Measured; Frequency of Samples: | 24 hrs; Receptor fluid fractions were collected at 1 hour intervals.; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | Skin was washed at the end of exposure (24hrs) once with 20% Ivory liquid soap, followed by two rinses with water.; Yes |
| Total Recovery (percent); Dose Type: | 38.6; Finite |
| Percent Found in Skin Depot After Washing and Tape Stripping; Comments: | 0.5; Notes: Reported as 0.45 $\pm$ 0.3% in Table 1 (CV = 67%) and 0.5 $\pm$ 0.1% (CV = 20) on pg. 43/108 |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments: | 0.5; Notes: Reported as 0.45 $\pm$ 0.3% in Table 1 (CV = 67%) and 0.5 $\pm$ 0.1% (CV = 20) on pg. 43/108 |
| Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments: | 4.1; Notes: Amount in receptor fluid: CV = 93% |
| Total Percent Absorbed: | 5 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maxium Permeability Coefficient (Kp) (cm/hr); Maxium Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments): | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as octamethylcyclotetrasiloxane (D4) CASRN 556-67-2 which was a pre-mixed mixture of unlabeled and labeled test substance. The chemical composition (25% perdeuterated D4, 74.3% nondeuterated D4 (predominantly 14C), 0.6% D5) was reported. No structure was provided, although physical-chemical properties were reported. The form and location of the radiolabel was not specified. |
| Metric 2: | Test substance source | High | The test substance was supplied by Dr. R.M.M. but was later reported to have been provided by Down Corning. A lot number and specific activity was provided. The chemical composition was certified by Dow Corning. |

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**Study Citation:** Dow Corning, (1991). Percutaneous absorption of D4 (octamethyltetrasiloxane).
**HERO ID:** 11438090

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 3: | Test substance purity | High | The test substance composition, purity, and activity were certified by Dow Corning; The purity was 99.3% |
| Domain 2: Test Design | | | | |
| | Metric 4: | Reference compounds | Low | The study did not include testing of a reference compound or indicate proficiency in conducting this study type. |
| | Metric 5: | Assay procedures | Medium | The study methods and procedures were mostly described. The study was conducted under dynamic conditions at 32 degrees C. using forced airflow through an Amberlite absorbent to trap volatiles. Humidity was not reported. The report indicates that variable and poor recovery was obtained using this set-up, and disruption of the seals and subsequent loss of the test material likely occurred due to packing of the absorbent material under the forced air flow. Exposures were conducted on human skin samples (n = 4 from the same donor) that were dermatomed to a thickness of 500 microns. A 5uL volume of the test substance was added to a 1cm2 area. The mass applied was not clearly reported. It was not specified whether there was any equilibration period prior to the start of the study. The receptor fluid was saline with 6% (w/v) Volpo 20 added as a surfactant. The flow rate was 3.2 mL/hour (one reservoir volume). Samples of the receptor fluid were collected at one-hour intervals throughout the 24-hour study period. Scintillation fluid was added to the receptor fluid samples after they had been collected. At the end of exposure, the skin was washed once with 20% Ivory liquid soap, followed by two rinses with water. No tape stripping was done. Radioactivity was measured in all samples collected including from the Amberlite trap, skin, skin washes, and receptor fluid. It was mentioned that a wash of the glass apparatus was conducted, but individual measurements for this were not provided. |
| | Metric 6: | Standards for tests | Medium | Visual inspections immediately prior to the start of the study were conducted to assess the integrity of the skin samples. No formal measurements of integrity were conducted. Additionally, a sample of each skin site was preserved for histopathological analysis, and no lesions or abnormalities were observed. Percent recovery was determined but was low (38.6%); see metric 20 for details on adequacy. Coefficients of variation were not reported but could be calculated using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 7: | Preparation and storage of test substance (chemical) | Medium | No preparation details were provided. The available information was suggestive that the test material was a pre-mixed mixture of labeled and unlabeled test substance which was applied without further dilutions. The test substance was stored frozen at 20 degrees C. The test substance is known to be extremely volatile. Stability was not tested. |
| | Metric 8: | Consistency of exposure administration | Medium | Exposures were consistent (same volume applied) within each group. Skin thicknesses were purportedly 500 um, the thicknesses of each replicate were not specified. The skin surface area (1cm2) was consistent across groups. |
| | Metric 9: | Reporting of concentrations | Medium | The dose was not clearly reported. The application rate was 5uL/cm2. 5 uL of a mixture containing 0.5 mg of labeled and 4.5 mg of unlabeled material was used. The mass applied was reported in the explanation of flux calculations (page 17) as ”assuming a dose” of 0.444mg. Given the surface area in 1 cm2, the mass applied would be 0.44 mg/cm2. The specific activity applied was 0.08uCi. No analytical measurements were noted. |

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**Study Citation:** Dow Corning, (1991). Percutaneous absorption of D4 (octamethyltetrasiloxane).
**HERO ID:** 11438090

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 10: | Exposure frequency | High | The 24 hour exposure duration was appropriate for the study type and the outcomes of interest. |
| | Metric 11: | Number of exposure groups and concentration spacing | Low | The study only tested the undiluted test substance. |
| Domain 4: Test Model | | | | |
| | Metric 12: | Test model (skin) | High | Details of the test model were reported. 4 autopsy skin samples (thigh) were obtained from a 78-yr old female. A lot number was provided. The unshaved skin was dermatomed to 500 microns. This is thicker than Guideline recommendations of 200-400 microns for split-thickness skin samples. Dermatomed skin was stored at 4 degrees C. in saline until use. The duration of storage was not specified. The available surface area after mounting was 1 cm2. Integrity was determined at the start of the study via visual inspection. After exposure the skin was histologically examined for integrity and no lesions or abnormalities were observed. The thickness of the stratum corneum was reported to be 28 microns and the thickness of the stratum Malpighii was 26 microns. |
| | Metric 13: | Number/Replicates per group | Medium | The study used 4 skin replicates from the same donor, which adheres to OECD guideline recommendations for number of replicates/group. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The outcome assessment methodology was sensitive and addressed the outcomes of interest. A finite dose was used to determine percent absorption. Although the exact dosing (mass applied) was not specified, based on the information available, it was <5mg and the volume applied was appropriate. The experiments only tested Neat test material, conditions of use were not discussed. |
| | Metric 15: | Consistency of outcome assessment | High | Details of the outcome assessment protocol were provided and were consistent across replicates. |
| | Metric 16: | Sampling adequacy and sensitivity | Low | Details of sampling (e.g., frequency and timing of collections) were specified. The volume of receptor fluid taken at each collection was not reported. No details of scintillation counting were provided including the number of counts/sample, or the level of background. It is unknown whether there was an appropriate signal-to-noise ratio. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Low | Skin replicates for one group were obtained from the same donor. No formal tests were conducted to determine skin integrity. There were large variations in results across replicates which could not be explained by the study authors. It is unclear whether there were differences in the quality of the replicate samples. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Low | The test substance was found to be extremely volatile and “difficult to control in the study.” The solubility of the test substance in the receptor fluid was not reported. The report indicates that variable and poor recovery was obtained using this set-up, and disruption of the seals and subsequent loss of the test material likely occurred due to packing of the absorbent material under the forced airflow. Humidity can influence absorbant retentivity, but humidity was not reported. |
| Domain 7: Data Presentation and Analysis | | | | |

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**HERO ID:** 11438090

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 19: | Data analysis | Low | Mass balance was done to maximize accountability of the dose. No results were clearly labeled mass balance, but Table 5 reports the % of dose recovered on skin, in skin, and in receptor fluid when only the dose not trapped in the absorbent was considered. Analysis of variance was done between different skin sources. Graphs showing absorption over time were reported. CV values for all endpoints were >50% but data enabling an independent analysis were provided.Details of flux calculations were reported. Regression analysis was performed on post-lag linear portions of the penetration curves. However, given uncertainty in the data flux calculations were not included in extraction. The authors raise these concerns in the discussion: "Hour-by-hour receptor recoveries are plotted in Figures 4, 5 and 6. The kinetics of absorption in different cells appears very different study-to-study (and even with skin from the same donor). Some of the curves in these figures are comparable to infinite dose curves, and some to finite dose plots (see Figure 2), but the small amounts of dose recovered in this compartment make definitive statements about the data unwise." |
| | Metric 20: | Data interpretation | Medium | Recovery of the test substance was inadequate (38.6%) and varied considerably across replicates; however, the authors acknowledged difficulties with volatility and issues with the experimental set-up (forced airflow). Despite the low recovery, the majority of the test substance was recovered in the absorbent trap and the authors concluded that "D4 evaporates too quickly to penetrate significantly" and this conclusion is consistent with the experimental data. Flux was reported for some replicates in a finite-dose experiment, which may not be appropriate. Data for all replicates and measurements are provided to allow for any alternative interpretations. |
| | Metric 21: | Reporting of data | High | Data for all specified outcomes were reported and individual replicate data were provided along with means ± SD. The results in Table 1 (pg. 29/108) are difficult to read in the available PDF, but most of these results were also reported elsewhere (pg. 43/108). |

## Overall Quality Determination — Medium

**Study Citation:** Dow Corning, (1991). Percutaneous absorption of D4 (octamethyltetrasiloxane).
**HERO ID:** 11438090

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Study 2- 58 yr old male; D4; D4-Parent compound |
| Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type: | ex vivo human; Split thickness; 500; Flow-through; Notes: Not Reported |
| Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent): | Semi-occluded (e.g., vapor trap); No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin: | 8.33; 24 hrs; Not Reported |
| Duration of Absorbance Measured; Frequency of Samples: | 24 hrs; Receptor fluid fractions were collected at 1 hour intervals.; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | Skin was washed at the end of exposure (24hrs) once with 20% Ivory liquid soap, followed by two rinses with water.; Yes |
| Total Recovery (percent); Dose Type: | 63.8; Finite |
| Percent Found in Skin Depot After Washing and Tape Stripping; Comments: | 0.26; Notes: CV = 92% |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments: | 0.26; Notes: CV = 92% |
| Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments: | 0.03; Notes: Amount in receptor fluid: CV = 33% |
| Total Percent Absorbed: | 0 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maxium Permeability Coefficient (Kp) (cm/hr); Maxium Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments): | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as octamethylcyclotetrasiloxane (D4) CASRN 556-67-2 which was a pre-mixed mixture of unlabeled and labeled test substance. The chemical composition (25% perdeuterated D4, 74.3% nondeuterated D4 (predominantly 14C), 0.6% D5) was reported. No structure was provided, although physical-chemical properties were reported. The form and location of the radiolabel was not specified. |
| Metric 2: | Test substance source | High | The test substance was supplied by Dr. R.M.M. but was later reported to have been provided by Down Corning. A sample order number and reference book number was reported along with the specific activity. The chemical composition was certified by Dow Corning. |
| Metric 3: | Test substance purity | High | The test substance composition, purity, and activity were certified by Dow Corning; The purity was 99.3% |

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**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| Domain 2: Test Design | | | | |
| | Metric 4: | Reference compounds | Low | The study did not include testing of a reference compound or indicate proficiency in conducting this study type. |
| | Metric 5: | Assay procedures | Medium | The study was conducted under dynamic conditions at 32 degrees C. Humidity was not reported. Exposures were conducted on human skin samples (n = 4 from the same donor) that were dermatomed to a thickness of 500 microns. An 8uL volume of the test substance was added to a 1cm2 area. The mass applied was not clearly reported. It was not specified whether there was any equilibration period prior to the start of the study. The receptor fluid was saline with 6% (w/v) Volpo 20 added as a surfactant. The flow rate was 3.2 mL/hour (one reservoir volume). Samples of the receptor fluid were collected at one-hour intervals throughout the 24-hour study period. Scintillation fluid was added to the receptor fluid samples after they had been collected. At the end of exposure, the skin was washed once with 20% Ivory liquid soap, followed by two rinses with water. No tape stripping was done. Radioactivity was measured in all samples collected including from the Amberlite trap, skin, skin washes, and receptor fluid. It was mentioned that a wash of the glass apparatus was conducted, but individual measurements for this were not provided. |
| | Metric 6: | Standards for tests | Medium | Visual inspections immediately prior to the start of the study were conducted to assess the integrity of the skin samples. No formal measurements of integrity were conducted. Additionally, a sample of each skin site was preserved for histopathological analysis, and no lesions or abnormalities were observed. Percent recovery was determined but was low (63.8%); see metric 20 for details on adequacy. Coefficients of variation were not reported but could be calculated using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 7: | Preparation and storage of test substance (chemical) | Medium | No preparation details were provided. The available information was suggestive that the test material was a pre-mixed mixture of labeled and unlabeled test substance which was applied without further dilutions. The test substance was stored frozen at 20 degrees C. The test substance is known to be extremely volatile. Stability was not tested. |
| | Metric 8: | Consistency of exposure administration | Medium | Exposures were consistent (same volume applied) within each group. Skin thicknesses were purportedly 500 um, the thicknesses of each replicate were not specified. The skin surface area (1cm2) was consistent across groups. |
| | Metric 9: | Reporting of concentrations | Medium | The dose was not clearly reported. The application rate was 8uL/cm2 where 8 uL of a mixture containing 0.5 mg of labeled and 4.5 mg of unlabeled material was used. A protocol deviation on pg. 85 indicates that the volume was 8 uL instead of 5 uL because the specific activity of the test substance was lower than anticipated and this was adjusted for. The specific activity applied was 1.48 uCi. The mass applied was reported in the explanation of flux calculations (page 17) as ”assuming a dose” of 8.333 mg. Given the surface area in 1 cm2, the mass applied would be 8.333 mg/cm2. |
| | Metric 10: | Exposure frequency | High | The 24 hour exposure duration was appropriate for the study type and the outcomes of interest. |
| | Metric 11: | Number of exposure groups and concentration spacing | Low | The study only tested the undiluted test substance. |
| Domain 4: Test Model | | | | |

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**Study Citation:** Dow Corning, (1991). Percutaneous absorption of D4 (octamethyltetrasiloxane).
**HERO ID:** 11438090

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 12: | Test model (skin) | High | 4 autopsy skin samples (thigh) were obtained from a 58-year-old male. The unshaved skin was dermatomed to 500 microns. This is thicker than the Guideline recommendation of 200-400 microns for split-thickness skin samples. Dermatomed skin was stored at 4 degrees C. in saline until use. The duration of storage was not specified. The available surface area after mounting was 1 cm2. Integrity was determined at the start of the study via visual inspection. After exposure the skin was histologically examined for integrity and no lesions or abnormalities were observed. The thickness of the stratum corneum was reported to be 35 microns and the thickness of the stratum Malpighii was ~25 microns. |
| | Metric 13: | Number/Replicates per group | Medium | The study used 4 skin replicates from the same donor, which adheres to OECD guideline recommendations for number of replicates/group. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The outcome assessment methodology was sensitive and addressed the outcomes of interest. A finite dose was used to determine percent absorption. Although the exact dosing (mass applied) was not specified, based on the information available, it was <5mg and the volume applied was appropriate. The experiments only tested Neat test material, conditions of use were not discussed. |
| | Metric 15: | Consistency of outcome assessment | High | Details of the outcome assessment protocol were provided and were consistent across replicates. |
| | Metric 16: | Sampling adequacy and sensitivity | Low | Details of sampling (e.g., frequency and timing of collections) were specified. The volume of receptor fluid taken at each collection was not reported. No details of scintillation counting were provided including the number of counts/sample, or the level of background. It is unknown whether there was an appropriate signal-to-noise ratio. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Low | Skin replicates for one group were obtained from the same donor. No formal tests were conducted to determine skin integrity. There were large variations in results across replicates which could not be explained by the study authors. It is unclear whether there were differences in the quality of the replicate samples. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Low | The test substance was found to be extremely volatile and “difficult to control in the study.” This resulted in large variability. The solubility of the test substance in the receptor fluid was not reported. |
| Domain 7: Data Presentation and Analysis | | | | |

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**HERO ID:** 11438090

| | | EVALUATION | | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 19: | Data analysis | Low | Mass balance was done to maximize accountability of the dose. No results were clearly labeled mass balance, but Table 5 reports the % of dose recovered on skin, in skin, and in receptor fluid when only the dose not trapped in the absorbent was considered. Analysis of variance was done between different skin sources. Graphs showing absorption over time were reported. CV values for all endpoints were >50% but data enabling an independent analysis were provided. Details of flux calculations were reported. Regression analysis was performed on post-lag linear portions of the penetration curves. However, given uncertainty in the data flux calculations were not included in extraction. The authors raise these concerns in the discussion: "Hour-by-hour receptor recoveries are plotted in Figures 4, 5 and 6. The kinetics of absorption in different cells appears very different study-to-study (and even with skin from the same donor). Some of the curves in these figures are comparable to infinite dose curves, and some to finite dose plots (see Figure 2), but the small amounts of dose recovered in this compartment make definitive statements about the data unwise." |
| | Metric 20: | Data interpretation | Medium | Recovery of the test substance was inadequate (63.8%) and varied considerably across replicates; however, the authors acknowledged difficulties with volatility and issues with the experimental set-up (forced airflow). Despite the low recovery, the majority of the test substance was recovered in the absorbent trap and the authors concluded that "D4 evaporates too quickly to penetrate significantly" and this conclusion is consistent with the experimental data. Flux was reported for some replicates in a finite-dose experiment, which may not be appropriate. Data for all replicates and measurements are provided to allow for any alternative interpretations. |
| | Metric 21: | Reporting of data | High | Data for all specified outcomes were reported and individual replicate data were provided along with means ± SD. The results in Table 1 (pg. 29/108) are difficult to read in the available PDF, but most of these results were also reported elsewhere (pg. 43/108). |

## Overall Quality Determination — Medium

**Study Citation:** Dow Corning, (1991). Percutaneous absorption of D4 (octamethyltetrasiloxane).
**HERO ID:** 11438090

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Study 3- 40 yr old male; D4; D4-Parent compound |
| Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type: | ex vivo human; Split thickness; 500; Flow-through; Notes: Not Reported |
| Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent): | Semi-occluded (e.g., vapor trap); No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin: | 8.33; 24 hrs; Not Reported |
| Duration of Absorbance Measured; Frequency of Samples: | 24 hrs; Receptor fluid fractions were collected at 1 hour intervals.; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | Skin was washed at the end of exposure (24hrs) once with 20% Ivory liquid soap, followed by two rinses with water.; Yes |
| Total Recovery (percent); Dose Type: | 51.1; Finite |
| Percent Found in Skin Depot After Washing and Tape Stripping; Comments: | 0.27; Notes: CV = 33% |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments: | 0.27; Notes: CV = 33% |
| Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments: | 0.05; Notes: Amount in receptor fluid: CV = 60% |
| Total Percent Absorbed: | 0 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maxium Permeability Coefficient (Kp) (cm/hr); Maxium Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments): | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as octamethylcyclotetrasiloxane (D4) CASRN 556-67-2 which was a pre-mixed mixture of unlabeled and labeled test substance. The chemical composition (25% perdeuterated D4, 74.3% nondeuterated D4 (predominantly 14C), 0.6% D5) was reported. No structure was provided, although physical-chemical properties were reported. The form and location of the radiolabel was not specified. |
| Metric 2: | Test substance source | High | The test substance was supplied by Dr. R.M.M. but was later reported to have been provided by Down Corning. A sample order number and reference book number was reported along with the specific activity. The chemical composition was certified by Dow Corning. |
| Metric 3: | Test substance purity | High | The test substance composition, purity, and activity were certified by Dow Corning; The purity was 99.3% |

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| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| Domain 2: Test Design | | | | |
| | Metric 4: | Reference compounds | Low | The study did not include testing of a reference compound or indicate proficiency in conducting this study type. |
| | Metric 5: | Assay procedures | Medium | The study was conducted under dynamic conditions at 32 degrees C. Humidity was not reported. Exposures were conducted on human skin samples (n = 4 from the same donor) that were dermatomed to a thickness of 500 microns. An 8uL volume of the test substance was added to a 1cm2 area. The mass applied was not clearly reported. It was not specified whether there was any equilibration period prior to the start of the study. The receptor fluid was saline with 6% (w/v) Volpo 20 added as a surfactant. The flow rate was 3.2 mL/hour (one reservoir volume). Samples of the receptor fluid were collected at one-hour intervals throughout the 24-hour study period. A scintillation cocktail was added to the vials prior to sample collection to ensure no loss of D4 by hypothetical evaporation from aqueous solutions. At the end of exposure, the skin was washed once with 20% Ivory liquid soap, followed by two rinses with water. No tape stripping was done. Radioactivity was measured in all samples collected including from the Amberlite trap, skin, skin washes, and receptor fluid. It was mentioned that a wash of the glass apparatus was conducted, but individual measurements for this were not provided. |
| | Metric 6: | Standards for tests | Medium | Visual inspections immediately prior to the start of the study were conducted to assess the integrity of the skin samples. No formal measurements of integrity were conducted. Additionally, a sample of each skin site was preserved for histopathological analysis, and no lesions or abnormalities were observed. Percent recovery was determined but was low (51.1%); see metric 20 for details on adequacy. Coefficients of variation were not reported but could be calculated using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 7: | Preparation and storage of test substance (chemical) | Medium | No preparation details were provided. The available information was suggestive that the test material was a pre-mixed mixture of labeled and unlabeled test substance which was applied without further dilutions. The test substance was stored frozen at 20 degrees C. The test substance is known to be extremely volatile. Stability was not tested. |
| | Metric 8: | Consistency of exposure administration | Medium | Exposures were consistent (same volume applied) within each group. Skin thicknesses were purportedly 500 um, the thicknesses of each replicate were not specified. The skin surface area (1cm2) was consistent across groups. |
| | Metric 9: | Reporting of concentrations | Medium | The dose was not clearly reported. The application rate was 8uL/cm2 where 8 uL of a mixture containing 0.5 mg of labeled and 4.5 mg of unlabeled material was used. A protocol deviation on pg. 85 indicates that the volume was 8 uL instead of 5 uL because the specific activity of the test substance was lower than anticipated and this was adjusted for. The specific activity applied was 1.48 uCi. The mass applied was reported in the explanation of flux calculations (page 17) as ”assuming a dose” of 8.333 mg. Given the surface area in 1 cm2, the mass applied would be 8.333 mg/cm2. |
| | Metric 10: | Exposure frequency | High | The 24 hour exposure duration was appropriate for the study type and the outcomes of interest. |
| | Metric 11: | Number of exposure groups and concentration spacing | Low | The study only tested the undiluted test substance. |

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**Study Citation:** Dow Corning, (1991). Percutaneous absorption of D4 (octamethyltetrasiloxane).
**HERO ID:** 11438090

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| Domain 4: Test Model | | | | |
| | Metric 12: | Test model (skin) | High | 4 autopsy skin samples (thigh) were obtained from a 40-year-old male. The unshaved skin was dermatomed to 500 microns. This is thicker than the Guideline recommendations of 200-400 microns for split-thickness skin samples. Dermatomed skin was stored at 4 degrees C. in saline until use. The duration of storage was not specified. The available surface area after mounting was 1 cm2. Integrity was determined at the start of the study via visual inspection. After exposure the skin was histologically examined for integrity and no lesions or abnormalities were observed. The thickness of the stratum corneum was reported to be 44 microns and the thickness of the stratum Malpighii was ~43 microns. |
| | Metric 13: | Number/Replicates per group | Medium | The study used 4 skin replicates from the same donor, which adheres to OECD guideline recommendations for number of replicates/group. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The outcome assessment methodology was sensitive and addressed the outcomes of interest. A finite dose was used to determine percent absorption. Although the exact dosing (mass applied) was not specified, based on the information available, it was <5mg and the volume applied was appropriate. The experiments only tested Neat test material, conditions of use were not discussed. |
| | Metric 15: | Consistency of outcome assessment | High | Details of the outcome assessment protocol were provided and were consistent across replicates. |
| | Metric 16: | Sampling adequacy and sensitivity | Low | Details of sampling (e.g., frequency and timing of collections) were specified. The volume of receptor fluid taken at each collection was not reported. No details of scintillation counting were provided including the number of counts/sample, or the level of background. It is unknown whether there was an appropriate signal-to-noise ratio. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Low | Skin replicates for one group were obtained from the same donor. No formal tests were conducted to determine skin integrity. There were large variations in results across replicates which could not be explained by the study authors. It is unclear whether there were differences in the quality of the replicate samples. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Low | The test substance was found to be extremely volatile and “difficult to control in the study.” This resulted in large variability. The solubility of the test substance in the receptor fluid was not reported. |
| Domain 7: Data Presentation and Analysis | | | | |

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**Study Citation:** Dow Corning, (1991). Percutaneous absorption of D4 (octamethyltetrasiloxane).
**HERO ID:** 11438090

| | | EVALUATION | | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 19: | Data analysis | Low | Mass balance was done to maximize accountability of the dose. No results were clearly labeled mass balance, but Table 5 reports the % of dose recovered on skin, in skin, and in receptor fluid when only the dose not trapped in the absorbent was considered. Analysis of variance was done between different skin sources. Graphs showing absorption over time were reported. CV values for all endpoints were >50% but data enabling an independent analysis were provided.Details of flux calculations were reported. Regression analysis was performed on post-lag linear portions of the penetration curves. However, given uncertainty in the data flux calculations were not included in extraction. The authors raise these concerns in the discussion: "Hour-by-hour receptor recoveries are plotted in Figures 4, 5 and 6. The kinetics of absorption in different cells appears very different study-to-study (and even with skin from the same donor). Some of the curves in these figures are comparable to infinite dose curves, and some to finite dose plots (see Figure 2), but the small amounts of dose recovered in this compartment make definitive statements about the data unwise." |
| | Metric 20: | Data interpretation | Medium | Recovery of the test substance was inadequate (51.1%) and varied considerably across replicates; however, the authors acknowledged difficulties with volatility and issues with the experimental set-up (forced airflow). Despite the low recovery, the majority of the test substance was recovered in the absorbent trap and the authors concluded that "D4 evaporates too quickly to penetrate significantly" and this conclusion is consistent with the experimental data. Flux was reported for some replicates in a finite-dose experiment, which may not be appropriate. Data for all replicates and measurements are provided to allow for any alternative interpretations. |
| | Metric 21: | Reporting of data | High | Data for all specified outcomes were reported and individual replicate data were provided along with means ± SD. The results in Table 1 (pg. 29/108) are difficult to read in the available PDF, but most of these results were also reported elsewhere (pg. 43/108). |

## Overall Quality Determination — Medium

**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Skin moisturizer - 5% D4; D4-Other (e.g., metabolite, degradant, mixture/product) (Skin moisturizer formulation) |
| Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type: | ex vivo pig; Split thickness; 500; Flow-through; Notes: Not Reported |
| Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent): | Semi-occluded (e.g., vapor trap); Skin moisturizer formulation; 4.97 |
| Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin: | 0.6; 24 hrs; Not Reported |
| Duration of Absorbance Measured; Frequency of Samples: | 24 hrs; 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | At the end of a 24-hr exposure period, skin was blotted using dry swabs, then with cotton applicators moistened with a 1% aqueous soap solution (3-4 times); Yes |
| Total Recovery (percent); Dose Type: | 91.16; Infinite |
| Percent Found in Skin Depot After Washing and Tape Stripping; Comments: | 0.007; Notes: CV = 29% |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments: | 0.007; Notes: CV = 29% |
| Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments: | 0.01; Notes: CV = 100%; includes receptor fluid, but not rinse. |
| 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): | 0.0000001; Notes: Not Reported; Not Reported; Notes: Not Reported; 0.005; Notes: Not Reported; Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as [14C] octamethylcyclotetrasiloxane (14C-D4). The position of the radiolabel was not specified. Unlabeled D4 was also used. The CASRN of D4 was provided. The unlabeled D4 was prepared into skin moisturizer formulations which was spiked with 14C-D4 to a desired specific activity. The other ingredients in the formulations were not provided. |
| Metric 2: | Test substance source | High | Dow Corning prepared the unlabeled formulations, and HES Chemistry group added the 14C-D4 to the formulations to achieve the target radioactivity concentration. The text also stated that the Dow Corning Life Sciences Innovation Team prepared the radiolabeled test chemical. |

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**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 3: | Test substance purity | High | The purities of unlabeled and radiolabeled D4 were 99.75% and 99.6%, respectively. The radiochemical purities of the formulations was tested using HPLC/RAD the day of dosing and were >99%. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Reference compounds | Low | A concurrent reference compound was not tested along with the test substance. The study text did not specify an established history of test performance in the performing laboratory. |
| | Metric 5: | Assay procedures | Medium | The assay methods and procedures were described and appropriate. The study used a Bronaugh flow-through diffusion cell system under dynamic, semi-occluded conditions. A charcoal basket was placed above the exposure site immediately after the application of the test formulations. The flow rate through the receptor compartment was reported. The receptor fluid was held at 37 ± 1 degree C, and the skin surface temperature was kept at 32 ± 1 degree C. Humidity was not reported. The receptor fluid was the physiological buffer, Hank's Balanced Salt Solution with additions (HEPES, Gentamicin, BSA), which was considered to be appropriate.Receptor fluid samples were collected at 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, and 24hrs. The volume collected was not specified. At the end of a 24-hour exposure period, the skin was blotted using dry swabs, then with cotton applicators moistened with a 1% aqueous soap solution (3-4 times). The skin was tape-stripped (10x). The charcoal baskets, holders, swaps, saran wrap, tape strips, flow-through cells, excised skin, and receptor fluid samples were measured for radioactivity using scintillation counting. The number of counts was specified and results were corrected for background radioactivity. |
| | Metric 6: | Standards for tests | Medium | Percent recovery was reported and was within 100 ± 10% of the radioactivity as stated in OECD 428. The skin integrity was tested prior to the application of the test substance using tritiated water. The study reported the following acceptance criteria for the skin integrity test 1) CV between replicates was less than 60% and 2) the average percent dose absorbed for each skin specimen was ≤0.21% which is acceptable. Coefficients of variation were either reported or they could be calculated for most datasets. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 7: | Preparation and storage of test substance (chemical) | Medium | The study described the preparation of the test formulations in detail and reported the formulations' storage conditions. Formulations were mixed by vortexing for 15 minutes, and skin moisturizer formulations were mixed mechanically with a spatula prior to homogeneity testing; the use of a centrifuge was not specified. Solubility in the receptor fluid used was demonstrated in a separate study and was appropriate. |
| | Metric 8: | Consistency of exposure administration | Low | The thickness of the skin samples ranged from 320-500 um, with most samples being >400 um. This is thicker than the recommended range of 200-400 um (OECD 428). |
| | Metric 9: | Reporting of concentrations | High | Dosing formulations were analyzed for D4 content by gas chromatography with flame ionization. The specific activities and homogeneity were determined using scintillation counting and were reported for each formulation. The target dose was 10 mg/cm2. Actual doses were determined gravimetrically by weighing the dosing pipette pre- and post-dosing and mean average doses were reported. Average doses (mg formulation/cm2 skin were 11.2 and 10.6 mg/cm2 and the doses (mg D4/cm2 skin) were 0.6 and 4.4 mg/cm2 for the low and high dose groups, respectively. |

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**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

| | | EVALUATION | | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 10: | Exposure frequency | High | The exposure duration was 24 hours, which is consistent with OECD guidelines. |
| | Metric 11: | Number of exposure groups and concentration spacing | Low | Two formulations containing 5.0% or 41.7% D4 were tested. These formulations were tested on separate days (2-days apart). |
| Domain 4: Test Model | | | | |
| | Metric 12: | Test model (skin) | High | Skin samples were prepared fresh from three Yucatan miniature swine sourced from Sinclair Research Center, Inc. The skin samples were received within 24 hours of harvest and were dermatomed to 320-500 um. Discs with a surface area of 0.64 cm2 were placed into the diffusion cells, and tested on the same day they were received (one concentration). The second concentration was tested on skin that had been stored at 4 degrees C for 2 days prior to use. The authors justified the use of swine skin. The integrity of each sample was tested prior to use, and any samples not meeting the criteria specified by the authors were excluded. |
| | Metric 13: | Number/Replicates per group | Medium | The study included 6 skin replicates per donor (3 swine) totaling 18 replicates per group, which exceeds minimum guideline recommendations. Replicates not meeting skin integrity criteria at the start of the study were excluded (1-2 per experiment). |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The study was conducted under infinite exposure conditions. The target dose was 10 mg of test formulation/cm2, and the measured doses were all 10 mg/cm2. The study did achieve a steady state and the steady state flux and Kp were reported. The study also reported % absorption, which may not be appropriate when using an infinite exposure scenario. However, although the test formulation was applied at >10 mg/cm2, the actual doses of D4 were <5 mg/cm2, which is more consistent with finite dosing. |
| | Metric 15: | Consistency of outcome assessment | Medium | Sufficient information was reported and the same protocol was used across replicates and dose groups. The duration of exposure was the same, and collections were taken at the same time points after the initiation of the study. Although the same protocols were used, the two exposure groups were tested 2-days apart. |
| | Metric 16: | Sampling adequacy and sensitivity | Medium | Sampling details were mostly reported, including handling of samples and any deviations. Each sample was assayed in duplicate. Results were corrected for background radioactivity with the level of detection set at 1x the background value. The number of counts and LOD were not specified. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | High | The skin samples used, including the size and number of samples per group were appropriate. Skin integrity was measured using a less desirable method (20-minute tritiated water test). Most results of the skin integrity testing were acceptable. Samples that did not meet the author-reported criteria were excluded. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | High | A separate cited study assessed the solubility of radiolabeled D4 in physiological buffer with 4% BSA. The solubility was determined to be greater than the reported aqueous solubility of the test chemical, and was "more than ten times higher than the expected amount of test article penetrated into the receptor fluid over 24 hr of skin exposure" - when making comparisons with in vitro penetration of neat material through human skin in vitro. |

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**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

| | | EVALUATION | |
|---|---|---|---|
| Domain | Metric | Rating | Comments |
| Domain 7: Data Presentation and Analysis | | | |
| Metric 19: | Data analysis | Low | The methods for calculating the Kp, steady-state flux, and percent absorbed were clearly reported along with statistical methods for comparing absorption between dose levels. Percent absorption estimates were presented across a time series for each compartment of the test system, and Kp/flux measurements were based on the linear/steady-state part of the absorption curve. The CV value for % absorbed was 50% for the low dose. Sufficient information was provided for alternate upper-end calculations to account for variability in the results. A CV could not be calculated for the high dose because the variance was 0. No CV values were provided for the KP and flux values, and these values were reported without measures of variance. |
| Metric 20: | Data interpretation | Medium | Recovery of the test substance was adequate; 91.16% and 90.52% for the low and high-dose, respectively. Absorption estimates were calculated from the skin and receptor fluid compartments. It also included recovery from saran wrap that the excised skin was laid on immediately after excision but the calculation did not include tape strips (minus the first two) and ten tape strips were conducted. Information for individual replicates for each compartment analyzed is provided. Kp and flux determinations were based on a steady-state, linear portion of the curve. The majority of the sample volatilized and was collected in the charcoal trap. |
| Metric 21: | Reporting of data | Medium | Most data were adequately reported and the report included individual replicate data for all compartments and time points. The data tables reporting the steady-state flux and estimated Kp values did not include measures of variance, however, individual cell data were included and could be used to do independent calculations. |

## Overall Quality Determination — Medium

**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Skin moisturizer - 41.7% D4; D4-Other (e.g., metabolite, degradant, mixture/product) (Skin moisturizer formulation) |
| Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type: | ex vivo pig; Split thickness; 500; Flow-through; Notes: Not Reported |
| Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent): | Semi-occluded (e.g., vapor trap); Skin moisturizer formulation; 41.7 |
| Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin: | 4.4; 24 hrs; Not Reported |
| Duration of Absorbance Measured; Frequency of Samples: | 24 hrs; 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | At the end of a 24-hr exposure period, skin was blotted using dry swabs, then with cotton applicators moistened with a 1% aqueous soap solution (3-4 times); Yes |
| Total Recovery (percent); Dose Type: | 90.52; Infinite |
| Percent Found in Skin Depot After Washing and Tape Stripping; Comments: | 0.01; Notes: CV = 20 |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments: | 0.01; Notes: CV = 20 |
| Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments: | 0.01; Notes: SD = 0; CV cannot be calculated. Includes receptor fluid, but not rinse. |
| 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): | 0.000000016; Notes: Not Reported; Not Reported; Notes: Not Reported; 0.0067; Notes: Not Reported; Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| Domain 1: Test Substance | | | | |
| | Metric 1: | Test substance identity | Medium | The test substance was identified as [14C] octamethylcyclotetrasiloxane (14C-D4). The position of the radiolabel was not specified. Unlabeled D4 was also used. The CASRN of D4 was provided. The unlabeled D4 was prepared into skin moisturizer formulations which was spiked with 14C-D4 to a desired specific activity. The other ingredients in the formulations were not provided. |
| | Metric 2: | Test substance source | High | Dow Corning prepared the unlabeled formulations, and HES Chemistry group added the 14C-D4 to the formulations to achieve the target radioactivity concentration. The text also stated that the Dow Corning Life Sciences Innovation Team prepared the radiolabeled test chemical. |

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**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 3: | Test substance purity | High | The purities of unlabeled and radiolabeled D4 were 99.75% and 99.6%, respectively. The radiochemical purities of the formulations was tested using HPLC/RAD the day of dosing and were >99%. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Reference compounds | Low | A concurrent reference compound was not tested along with the test substance. The study text did not specify an established history of test performance in the performing laboratory. |
| | Metric 5: | Assay procedures | Medium | The assay methods and procedures were described and appropriate. The study used a Bronaugh flow-through diffusion cell system under dynamic, semi-occluded conditions. A charcoal basket was placed above the exposure site immediately after the application of the test formulations. The flow rate through the receptor compartment was reported. The receptor fluid was held at 37 ± 1 degree C, and the skin surface temperature was kept at 32 ± 1 degree C. Humidity was not reported. The receptor fluid was the physiological buffer, Hank's Balanced Salt Solution with additions (HEPES, Gentamicin, BSA), which was considered to be appropriate.Receptor fluid samples were collected at 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, and 24hrs. The volume collected was not specified. At the end of a 24-hour exposure period, the skin was blotted using dry swabs, then with cotton applicators moistened with a 1% aqueous soap solution (3-4 times). The skin was tape-stripped (10x). The charcoal baskets, holders, swaps, saran wrap, tape strips, flow-through cells, excised skin, and receptor fluid samples were measured for radioactivity using scintillation counting. The number of counts was specified and results were corrected for background radioactivity. |
| | Metric 6: | Standards for tests | Medium | Percent recovery was reported and was within 100 ± 10% of the radioactivity as stated in OECD 428. The skin integrity was tested prior to the application of the test substance using tritiated water. The study reported the following acceptance criteria for the skin integrity test 1) CV between replicates was less than 60% and 2) the average percent dose absorbed for each skin specimen was ≤0.21% which is acceptable. Coefficients of variation were either reported or they could be calculated for most datasets. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 7: | Preparation and storage of test substance (chemical) | Medium | The study described the preparation of the test formulations in detail and reported the formulations' storage conditions. Formulations were mixed by vortexing for 15 minutes, and skin moisturizer formulations were mixed mechanically with a spatula prior to homogeneity testing; the use of a centrifuge was not specified. Solubility in the receptor fluid used was demonstrated in a separate study and was appropriate. |
| | Metric 8: | Consistency of exposure administration | Low | The thickness of the skin samples ranged from 320-500 um, with most samples being >400 um. This is thicker than the recommended range of 200-400 um (OECD 428). |
| | Metric 9: | Reporting of concentrations | High | Dosing formulations were analyzed for D4 content by gas chromatography with flame ionization. The specific activities and homogeneity were determined using scintillation counting and were reported for each formulation. The target dose was 10 mg/cm2. Actual doses were determined gravimetrically by weighing the dosing pipette pre- and post-dosing and mean average doses were reported. Average doses (mg formulation/cm2 skin were 11.2 and 10.6 mg/cm2 and the doses (mg D4/cm2 skin) were 0.6 and 4.4 mg/cm2 for the low and high dose groups, respectively. |

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**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 10: | Exposure frequency | High | The exposure duration was 24 hours, which is consistent with OECD guidelines. |
| | Metric 11: | Number of exposure groups and concentration spacing | Low | Two formulations containing 5.0% or 41.7% D4 were tested. These formulations were tested on separate days (2-days apart). |
| Domain 4: Test Model | | | | |
| | Metric 12: | Test model (skin) | High | Skin samples were prepared fresh from three Yucatan miniature swine sourced from Sinclair Research Center, Inc. The skin samples were received within 24 hours of harvest and were dermatomed to 320-500 um. Discs with a surface area of 0.64 cm2 were placed into the diffusion cells, and tested on the same day they were received (one concentration). The second concentration was tested on skin that had been stored at 4 degrees C for 2 days prior to use. The authors justified the use of swine skin. The integrity of each sample was tested prior to use, and any samples not meeting the criteria specified by the authors were excluded. |
| | Metric 13: | Number/Replicates per group | Medium | The study included 6 skin replicates per donor (3 swine) totaling 18 replicates per group, which exceeds minimum guideline recommendations. Replicates not meeting skin integrity criteria at the start of the study were excluded (1-2 per experiment). |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The study was conducted under infinite exposure conditions. The target dose was 10 mg of test formulation/cm2, and the measured doses were all 10 mg/cm2. The study did achieve a steady state and the steady state flux and Kp were reported. The study also reported % absorption, which may not be appropriate when using an infinite exposure scenario. However, although the test formulation was applied at >10 mg/cm2, the actual doses of D4 were <5 mg/cm2, which is more consistent with finite dosing. |
| | Metric 15: | Consistency of outcome assessment | Medium | Sufficient information was reported and the same protocol was used across replicates and dose groups. The duration of exposure was the same, and collections were taken at the same time points after the initiation of the study. Although the same protocols were used, the two exposure groups were tested 2-days apart. |
| | Metric 16: | Sampling adequacy and sensitivity | Medium | Sampling details were mostly reported, including handling of samples and any deviations. Each sample was assayed in duplicate. Results were corrected for background radioactivity with the level of detection set at 1x the background value. The number of counts and LOD were not specified. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | High | The skin samples used, including the size and number of samples per group were appropriate. Skin integrity was measured using a less desirable method (20-minute tritiated water test). Most results of the skin integrity testing were acceptable. Samples that did not meet the author-reported criteria were excluded. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | High | A separate cited study assessed the solubility of radiolabeled D4 in physiological buffer with 4% BSA. The solubility was determined to be greater than the reported aqueous solubility of the test chemical, and was "more than ten times higher than the expected amount of test article penetrated into the receptor fluid over 24 hr of skin exposure" - when making comparisons with in vitro penetration of neat material through human skin in vitro. |

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**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

| | | EVALUATION | |
|---|---|---|---|
| Domain | Metric | Rating | Comments |
| Domain 7: Data Presentation and Analysis | | | |
| Metric 19: | Data analysis | Low | The methods for calculating the Kp, steady-state flux, and percent absorbed were clearly reported along with statistical methods for comparing absorption between dose levels. Percent absorption estimates were presented across a time series for each compartment of the test system, and Kp/flux measurements were based on the linear/steady-state part of the absorption curve. The CV value for % absorbed was 50% for the low dose. Sufficient information was provided for alternate upper-end calculations to account for variability in the results. A CV could not be calculated for the high dose because the variance was 0. No CV values were provided for the KP and flux values, and these values were reported without measures of variance. |
| Metric 20: | Data interpretation | Medium | Recovery of the test substance was adequate; 91.16% and 90.52% for the low and high-dose, respectively. Absorption estimates were calculated from the skin and receptor fluid compartments. It also included recovery from saran wrap that the excised skin was laid on immediately after excision but the calculation did not include tape strips (minus the first two) and ten tape strips were conducted. Information for individual replicates for each compartment analyzed is provided. Kp and flux determinations were based on a steady-state, linear portion of the curve. The majority of the sample volatilized and was collected in the charcoal trap. |
| Metric 21: | Reporting of data | Medium | Most data were adequately reported and the report included individual replicate data for all compartments and time points. The data tables reporting the steady-state flux and estimated Kp values did not include measures of variance, however, individual cell data were included and could be used to do independent calculations. |

## Overall Quality Determination — Medium

**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Antiperspirant - 10.6% D4; D4-Other (e.g., metabolite, degradant, mixture/product) (Antiperspirant formula) |
| Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type: | ex vivo pig; Split thickness; 500; Flow-through; Notes: Not Reported |
| Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent): | Semi-occluded (e.g., vapor trap); Skin moisturizer formulation; 10.6 |
| Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin: | 1.1; 24 hrs; Not Reported |
| Duration of Absorbance Measured; Frequency of Samples: | 24 hrs; 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | At the end of a 24-hr exposure period, skin was blotted using dry swabs, then with cotton applicators moistened with a 1% aqueous soap solution (3-4 times); Yes |
| Total Recovery (percent); Dose Type: | 99; Infinite |
| Percent Found in Skin Depot After Washing and Tape Stripping; Comments: | 0.004; Notes: CV = 25% |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments: | 0.004; Notes: CV = 25% |
| Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments: | 0; Notes: includes receptor fluid, but not rinse. |
| 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): | 1.90E-09; Notes: Not Reported; Not Reported; Notes: Not Reported; 0.0002; Notes: Not Reported; Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as [14C] octamethylcyclotetrasiloxane (14C-D4). The position of the radiolabel was not specified. Unlabeled D4 was also used. The CASRN of D4 was provided. The unlabeled D4 was prepared into antiperspirant formulations which were spiked with 14C-D4 to a desired specific activity. The other ingredients in the formulations were not provided. |
| Metric 2: | Test substance source | High | Dow Corning prepared the unlabeled formulations, and HES Chemistry group added the 14C-D4 to the formulations to achieve the target radioactivity concentration. The text also stated that the Dow Corning Life Sciences Innovation Team prepared the radiolabeled test chemical. |

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**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 3: | Test substance purity | High | The purities of unlabeled and radiolabeled D4 were 99.75% and 99.6%, respectively. The radiochemical purities of the formulations was tested using HPLC/RAD the day of dosing and were >99%. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Reference compounds | Low | A concurrent reference compound was not tested along with the test substance. The study text did not specify an established history of test performance in the performing laboratory. |
| | Metric 5: | Assay procedures | Medium | The assay methods and procedures were described and appropriate. The study used a Bronaugh flow-through diffusion cell system under dynamic, semi-occluded conditions. A charcoal basket was placed above the exposure site immediately after the application of the test formulations. The flow rate through the receptor compartment was reported. The receptor fluid was held at 37 ± 1 degree C, and the skin surface temperature was kept at 32 ± 1 degree C. Humidity was not reported. The receptor fluid was the physiological buffer, Hank's Balanced Salt Solution with additions (HEPES, Gentamicin, BSA), which was considered to be appropriate.Receptor fluid samples were collected at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24hrs. The volume collected was not specified. At the end of a 24-hour exposure period, the skin was blotted using dry swabs, then with cotton applicators moistened with a 1% aqueous soap solution (3-4 times). The skin was tape-stripped (10x). The charcoal baskets, holders, swaps, saran wrap, tape strips, flow-through cells, excised skin, and receptor fluid samples were measured for radioactivity using scintillation counting. The number of counts was specified and results were corrected for background radioactivity. |
| | Metric 6: | Standards for tests | Medium | Percent recovery was reported and was within 100 ± 10% of the radioactivity as stated in OECD 428. The skin integrity was tested prior to the application of the test substance using tritiated water. The study reported the following acceptance criteria for the skin integrity test 1) CV between replicates was less than 60% and 2) the average percent dose absorbed for each skin specimen was ≤0.21% which is acceptable. Coefficients of variation were either reported or could be calculated for most datasets. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 7: | Preparation and storage of test substance (chemical) | Medium | The study described the preparation of the test formulations in detail and reported the formulations' storage conditions. Formulations were mixed by vortexing for 15 minutes, and skin moisturizer formulations were mixed mechanically with a spatula prior to homogeneity testing; the use of a centrifuge was not specified. Solubility in the receptor fluid used was demonstrated in a separate study and was appropriate. |
| | Metric 8: | Consistency of exposure administration | Low | The thickness of the skin samples ranged from 320-500 um, with most samples being >400 um. This is thicker than the recommended range of 200-400 um (OECD 428). |
| | Metric 9: | Reporting of concentrations | High | Dosing formulations were analyzed for D4 content by gas chromatography with flame ionization. The specific activities and homogeneity were determined using scintillation counting and were reported for each formulation. The target dose was 10 mg/cm2. Actual doses were determined gravimetrically by weighing the dosing pipette pre- and post-dosing and mean average doses were reported. Average doses (mg formulation/cm2 skin were 10.3 and 10.6 mg/cm2 and the doses (mg D4/cm2 skin) were 1.1 and 6.6 mg/cm2 for the low and high dose groups, respectively. |

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**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 10: | Exposure frequency | High | The exposure duration was 24 hours, which is consistent with OECD guidelines. |
| | Metric 11: | Number of exposure groups and concentration spacing | Low | Two formulations containing 10.6% or 62.2% D4 were tested. These formulations were tested on separate days (2 days apart). |
| Domain 4: Test Model | | | | |
| | Metric 12: | Test model (skin) | High | Skin samples were prepared fresh from three Yucatan miniature swine sourced from Sinclair Research Center, Inc. The skin samples were received within 24 hours of harvest and were dermatomed to 320-500 um. Discs with a surface area of 0.64 cm2 were placed into the diffusion cells, and tested on the same day they were received (one concentration). The second concentration was tested on skin that had been stored at 4 degrees C for 2 days prior to use. The authors justified the use of swine skin. The integrity of each sample was tested prior to use, and any samples not meeting the criteria specified by the authors were excluded. |
| | Metric 13: | Number/Replicates per group | Medium | The study included 6 skin replicates per donor (3 swine) totaling 18 replicates per group, which exceeds minimum guideline recommendations. Replicates not meeting skin integrity criteria at the start of the study were excluded (1-2 per experiment). |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The study was conducted under infinite exposure conditions. The target dose was 10 mg of test formulation/cm2, and the measured doses were all 10 mg/cm2. The study did achieve a steady state and the steady state flux and Kp were reported. The study also reported % absorption, which may not be appropriate when using an infinite exposure scenario. However, although the test formulation was applied at >10 mg/cm2, the actual doses of D4 were 1.1 and 6.6 mg/cm2, which is more consistent with finite dosing. |
| | Metric 15: | Consistency of outcome assessment | Medium | Sufficient information was reported and the same protocol was used across replicates and dose groups. The duration of exposure was the same, and collections were taken at the same time points after the initiation of the study. Although the same protocols were used, the two exposure groups were tested 2-days apart. |
| | Metric 16: | Sampling adequacy and sensitivity | Medium | Sampling details were mostly reported, including handling of samples and any deviations. Each sample was assayed in duplicate. Results were corrected for background radioactivity with the level of detection set at 1x the background value. The number of counts and LOD were not specified. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | High | The skin samples used, including the size and number of samples per group were appropriate. Skin integrity was measured using a less desirable method (20-minute tritiated water test). Most results of the skin integrity testing were acceptable. Samples that did not meet the author-reported criteria were excluded. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | High | A separate cited study assessed the solubility of radiolabeled D4 in physiological buffer with 4% BSA. The solubility was determined to be greater than the reported aqueous solubility of the test chemical, and was "more than ten times higher than the expected amount of test article penetrated into the receptor fluid over 24 hr of skin exposure" - when making comparisons with in vitro penetration of neat material through human skin in vitro. |

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**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

| | | **EVALUATION** | |
|---|---|---|---|
| Domain | Metric | Rating | Comments |
| Domain 7: Data Presentation and Analysis | | | |
| Metric 19: | Data analysis | Low | The methods for calculating the Kp, steady-state flux, and percent absorbed were clearly reported along with statistical methods for comparing absorption between dose levels. Percent absorption estimates were presented across a time series for each compartment of the test system, and Kp/flux measurements were based on the linear/steady-state part of the absorption curve. The CV values for % absorbed were <1 for both the low and high-dose groups. No CV values were provided for the KP and flux values, and these values were reported without measures of variance. |
| Metric 20: | Data interpretation | Medium | Recovery of the test substance was adequate; 99% and 95.18% for the low and high-dose, respectively. Absorption estimates were calculated from the skin and receptor fluid compartments. It also included recovery from saran wrap that the excised skin was laid on immediately after excision but the calculation did not include tape strips (minus the first two) and ten tape strips were conducted. Information for individual replicates for each compartment analyzed is provided. Kp and flux determinations were based on a steady-state, linear portion of the curve. The majority of the sample volatilized and was collected in the charcoal trap. |
| Metric 21: | Reporting of data | Medium | Most data were adequately reported and the report included individual replicate data for all compartments and time points. The data tables reporting the steady-state flux and estimated Kp values did not include measures of variance. |

## Overall Quality Determination — Medium

**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Antiperspirant - 62.2% D4; D4-Other (e.g., metabolite, degradant, mixture/product) (Antiperspirant formula) |
| Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type: | ex vivo pig; Split thickness; 500; Flow-through; Notes: Not Reported |
| Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent): | Semi-occluded (e.g., vapor trap); Skin moisturizer formulation; 62.2 |
| Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin: | 6.6; 24 hrs; Not Reported |
| Duration of Absorbance Measured; Frequency of Samples: | 24 hrs; 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | At the end of a 24-hr exposure period, skin was blotted using dry swabs, then with cotton applicators moistened with a 1% aqueous soap solution (3-4 times); Yes |
| Total Recovery (percent); Dose Type: | 95.18; Infinite |
| Percent Found in Skin Depot After Washing and Tape Stripping; Comments: | 0.01; Notes: CV = 90% |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments: | 0.01; Notes: CV = 90% |
| Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments: | 0.01; Notes: SD = 0; CV cannot be calculated. Includes receptor fluid, but not rinse. |
| 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): | 0.000000069; Notes: Not Reported; Not Reported; Notes: Not Reported; 0.0427; Notes: Not Reported; Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as [14C] octamethylcyclotetrasiloxane (14C-D4). The position of the radiolabel was not specified. Unlabeled D4 was also used. The CASRN of D4 was provided. The unlabeled D4 was prepared into antiperspirant formulations which were spiked with 14C-D4 to a desired specific activity. The other ingredients in the formulations were not provided. |
| Metric 2: | Test substance source | High | Dow Corning prepared the unlabeled formulations, and HES Chemistry group added the 14C-D4 to the formulations to achieve the target radioactivity concentration. The text also stated that the Dow Corning Life Sciences Innovation Team prepared the radiolabeled test chemical. |

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**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 3: | Test substance purity | High | The purities of unlabeled and radiolabeled D4 were 99.75% and 99.6%, respectively. The radiochemical purities of the formulations was tested using HPLC/RAD the day of dosing and were >99%. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Reference compounds | Low | A concurrent reference compound was not tested along with the test substance. The study text did not specify an established history of test performance in the performing laboratory. |
| | Metric 5: | Assay procedures | Medium | The assay methods and procedures were described and appropriate. The study used a Bronaugh flow-through diffusion cell system under dynamic, semi-occluded conditions. A charcoal basket was placed above the exposure site immediately after the application of the test formulations. The flow rate through the receptor compartment was reported. The receptor fluid was held at 37 ± 1 degree C, and the skin surface temperature was kept at 32 ± 1 degree C. Humidity was not reported. The receptor fluid was the physiological buffer, Hank's Balanced Salt Solution with additions (HEPES, Gentamicin, BSA), which was considered to be appropriate.Receptor fluid samples were collected at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24hrs. The volume collected was not specified. At the end of a 24-hour exposure period, the skin was blotted using dry swabs, then with cotton applicators moistened with a 1% aqueous soap solution (3-4 times). The skin was tape-stripped (10x). The charcoal baskets, holders, swaps, saran wrap, tape strips, flow-through cells, excised skin, and receptor fluid samples were measured for radioactivity using scintillation counting. The number of counts was specified and results were corrected for background radioactivity. |
| | Metric 6: | Standards for tests | Medium | Percent recovery was reported and was within 100 ± 10% of the radioactivity as stated in OECD 428. The skin integrity was tested prior to the application of the test substance using tritiated water. The study reported the following acceptance criteria for the skin integrity test 1) CV between replicates was less than 60% and 2) the average percent dose absorbed for each skin specimen was ≤0.21% which is acceptable. Coefficients of variation were either reported or could be calculated for most datasets. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 7: | Preparation and storage of test substance (chemical) | Medium | The study described the preparation of the test formulations in detail and reported the formulations' storage conditions. Formulations were mixed by vortexing for 15 minutes, and skin moisturizer formulations were mixed mechanically with a spatula prior to homogeneity testing; the use of a centrifuge was not specified. Solubility in the receptor fluid used was demonstrated in a separate study and was appropriate. |
| | Metric 8: | Consistency of exposure administration | Low | The thickness of the skin samples ranged from 320-500 um, with most samples being >400 um. This is thicker than the recommended range of 200-400 um (OECD 428). |
| | Metric 9: | Reporting of concentrations | High | Dosing formulations were analyzed for D4 content by gas chromatography with flame ionization. The specific activities and homogeneity were determined using scintillation counting and were reported for each formulation. The target dose was 10 mg/cm2. Actual doses were determined gravimetrically by weighing the dosing pipette pre- and post-dosing and mean average doses were reported. Average doses (mg formulation/cm2 skin were 10.3 and 10.6 mg/cm2 and the doses (mg D4/cm2 skin) were 1.1 and 6.6 mg/cm2 for the low and high dose groups, respectively. |

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**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

| Domain | | Metric | EVALUATION Rating | Comments |
|---|---|---|---|---|
| | Metric 10: | Exposure frequency | High | The exposure duration was 24 hours, which is consistent with OECD guidelines. |
| | Metric 11: | Number of exposure groups and concentration spacing | Low | Two formulations containing 10.6% or 62.2% D4 were tested. These formulations were tested on separate days (2 days apart). |
| Domain 4: Test Model | | | | |
| | Metric 12: | Test model (skin) | High | Skin samples were prepared fresh from three Yucatan miniature swine sourced from Sinclair Research Center, Inc. The skin samples were received within 24 hours of harvest and were dermatomed to 320-500 um. Discs with a surface area of 0.64 cm2 were placed into the diffusion cells, and tested on the same day they were received (one concentration). The second concentration was tested on skin that had been stored at 4 degrees C for 2 days prior to use. The authors justified the use of swine skin. The integrity of each sample was tested prior to use, and any samples not meeting the criteria specified by the authors were excluded. |
| | Metric 13: | Number/Replicates per group | Medium | The study included 6 skin replicates per donor (3 swine) totaling 18 replicates per group, which exceeds minimum guideline recommendations. Replicates not meeting skin integrity criteria at the start of the study were excluded (1-2 per experiment). |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The study was conducted under infinite exposure conditions. The target dose was 10 mg of test formulation/cm2, and the measured doses were all 10 mg/cm2. The study did achieve a steady state and the steady state flux and Kp were reported. The study also reported % absorption, which may not be appropriate when using an infinite exposure scenario. However, although the test formulation was applied at >10 mg/cm2, the actual doses of D4 were 1.1 and 6.6 mg/cm2, which is more consistent with finite dosing. |
| | Metric 15: | Consistency of outcome assessment | Medium | Sufficient information was reported and the same protocol was used across replicates and dose groups. The duration of exposure was the same, and collections were taken at the same time points after the initiation of the study. Although the same protocols were used, the two exposure groups were tested 2-days apart. |
| | Metric 16: | Sampling adequacy and sensitivity | Medium | Sampling details were mostly reported, including handling of samples and any deviations. Each sample was assayed in duplicate. Results were corrected for background radioactivity with the level of detection set at 1x the background value. The number of counts and LOD were not specified. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | High | The skin samples used, including the size and number of samples per group were appropriate. Skin integrity was measured using a less desirable method (20-minute tritiated water test). Most results of the skin integrity testing were acceptable. Samples that did not meet the author-reported criteria were excluded. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | High | A separate cited study assessed the solubility of radiolabeled D4 in physiological buffer with 4% BSA. The solubility was determined to be greater than the reported aqueous solubility of the test chemical, and was "more than ten times higher than the expected amount of test article penetrated into the receptor fluid over 24 hr of skin exposure" - when making comparisons with in vitro penetration of neat material through human skin in vitro. |

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**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

| | | **EVALUATION** | |
|---|---|---|---|
| Domain | Metric | Rating | Comments |
| Domain 7: Data Presentation and Analysis | | | |
| Metric 19: | Data analysis | Low | The methods for calculating the Kp, steady-state flux, and percent absorbed were clearly reported along with statistical methods for comparing absorption between dose levels. Percent absorption estimates were presented across a time series for each compartment of the test system, and Kp/flux measurements were based on the linear/steady-state part of the absorption curve. The CV values for % absorbed were <1 for both the low and high-dose groups. No CV values were provided for the KP and flux values, and these values were reported without measures of variance. |
| Metric 20: | Data interpretation | Medium | Recovery of the test substance was adequate; 99% and 95.18% for the low and high-dose, respectively. Absorption estimates were calculated from the skin and receptor fluid compartments. It also included recovery from saran wrap that the excised skin was laid on immediately after excision but the calculation did not include tape strips (minus the first two) and ten tape strips were conducted. Information for individual replicates for each compartment analyzed is provided. Kp and flux determinations were based on a steady-state, linear portion of the curve. The majority of the sample volatilized and was collected in the charcoal trap. |
| Metric 21: | Reporting of data | Medium | Most data were adequately reported and the report included individual replicate data for all compartments and time points. The data tables reporting the steady-state flux and estimated Kp values did not include measures of variance. |

## Overall Quality Determination — Medium

**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Cuticle coat - 51.6% D4; D4-Other (e.g., metabolite, degradant, mixture/product) (Cuticle coat formulation) |
| Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type: | ex vivo pig; Split thickness; 500; Flow-through; Notes: Not Reported |
| Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent): | Semi-occluded (e.g., vapor trap); Skin moisturizer formulation; 51.6 |
| Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin: | 6.3; 24 hrs; Not Reported |
| Duration of Absorbance Measured; Frequency of Samples: | 24 hrs; 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | At the end of a 24-hr exposure period, skin was blotted using dry swabs, then with cotton applicators moistened with a 1% aqueous soap solution (3-4 times); Yes |
| Total Recovery (percent); Dose Type: | 98.46; Infinite |
| Percent Found in Skin Depot After Washing and Tape Stripping; Comments: | 0.033; Notes: CV = 30% |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments: | 0.033; Notes: CV = 30% |
| Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments: | 0.01; Notes: CV = 100%. Includes receptor fluid, but not rinse. |
| 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): | 0.000000051; Notes: Not Reported; Not Reported; Notes: Not Reported; 0.0264; Notes: Not Reported; Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as [14C] octamethylcyclotetrasiloxane (14C-D4). The position of the radiolabel was not specified. Unlabeled D4 was also used. The CASRN of D4 was provided. The unlabeled D4 was prepared into cuticle coat formulations which were spiked with 14C-D4 to a desired specific activity. The other ingredients in the formulations were not provided. |
| Metric 2: | Test substance source | High | Dow Corning prepared the unlabeled formulations, and HES Chemistry group added the 14C-D4 to the formulations to achieve the target radioactivity concentration. The text also stated that the Dow Corning Life Sciences Innovation Team prepared the radiolabeled test chemical. |

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**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 3: | Test substance purity | High | The purities of unlabeled and radiolabeled D4 were 99.75% and 99.6%, respectively. The radiochemical purities of the formulations was tested using HPLC/RAD the day of dosing and were >99%. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Reference compounds | Low | A concurrent reference compound was not tested along with the test substance. The study text did not specify an established history of test performance in the performing laboratory. |
| | Metric 5: | Assay procedures | Medium | The assay methods and procedures were described and appropriate. The study used a Bronaugh flow-through diffusion cell system under dynamic, semi-occluded conditions. A charcoal basket was placed above the exposure site immediately after the application of the test formulations. The flow rate through the receptor compartment was reported. The receptor fluid was held at 37 ± 1 degree C, and the skin surface temperature was kept at 32 ± 1 degree C. Humidity was not reported. The receptor fluid was the physiological buffer, Hank's Balanced Salt Solution with additions (HEPES, Gentamicin, BSA), which was considered to be appropriate.Receptor fluid samples were collected at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24hrs. The volume collected was not specified. At the end of a 24-hour exposure period, the skin was blotted using dry swabs, then with cotton applicators moistened with a 1% aqueous soap solution (3-4 times). The skin was tape-stripped (10x). The charcoal baskets, holders, swaps, saran wrap, tape strips, flow-through cells, excised skin, and receptor fluid samples were measured for radioactivity using scintillation counting. The number of counts was specified and results were corrected for background radioactivity. |
| | Metric 6: | Standards for tests | Medium | Percent recovery was reported and was within 100 ± 10% of the radioactivity as stated in OECD 428. The skin integrity was tested prior to the application of the test substance using tritiated water. The study reported the following acceptance criteria for the skin integrity test 1) CV between replicates was less than 60% and 2) the average percent dose absorbed for each skin specimen was ≤0.21% which is acceptable. Coefficients of variation were either reported or could be calculated for most datasets. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 7: | Preparation and storage of test substance (chemical) | Medium | The study described the preparation of the test formulations in detail and reported the formulations' storage conditions. Formulations were mixed by vortexing for 15 minutes. The 90% D4 cuticle coat dose formulation had to be mixed by vial inversion and by repeatedly drawing and expelling the formulation with a pipet to obtain sufficienthomogeneity.; the use of a centrifuge was not specified. Solubility in the receptor fluid used was demonstrated in a separate study and was appropriate. |
| | Metric 8: | Consistency of exposure administration | Low | The thickness of the skin samples ranged from 320-500 um, with most samples being >400 um. This is thicker than the recommended range of 200-400 um (OECD 428). |

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**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 9: | Reporting of concentrations | High | Dosing formulations were analyzed for D4 content by gas chromatography with flame ionization. The specific activities and homogeneity were determined using scintillation counting and were reported for each formulation. The target dose was 10 mg/cm2. Actual doses were determined gravimetrically by weighing the dosing pipette pre- and post-dosing and mean average doses were reported. Average doses (mg formulation/cm2 skin were 12.1 and 10.5 mg/cm2 and the doses (mg D4/cm2 skin) were 6.3 and 10.0 mg/cm2 for the low and high dose groups, respectively. |
| | Metric 10: | Exposure frequency | High | The exposure duration was 24 hours, which is consistent with OECD guidelines. |
| | Metric 11: | Number of exposure groups and concentration spacing | Low | Two formulations containing 51.6% or 95.8% D4 were tested. These formulations were tested on separate days (2 days apart). |
| Domain 4: Test Model | | | | |
| | Metric 12: | Test model (skin) | High | Skin samples were prepared fresh from three Yucatan miniature swine sourced from Sinclair Research Center, Inc. The skin samples were received within 24 hours of harvest and were dermatomed to 320-500 um. Discs with a surface area of 0.64 cm2 were placed into the diffusion cells, and tested on the same day they were received (one concentration). The second concentration was tested on skin that had been stored at 4 degrees C for 2 days prior to use. The authors justified the use of swine skin. The integrity of each sample was tested prior to use, and any samples not meeting the criteria specified by the authors were excluded. |
| | Metric 13: | Number/Replicates per group | Medium | The study included 6 skin replicates per donor (3 swine) totaling 18 replicates per group, which exceeds minimum guideline recommendations. Replicates not meeting skin integrity criteria at the start of the study were excluded (1-2 per experiment). |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The study was conducted under infinite exposure conditions. The target dose was 10 mg of test formulation/cm2, and the measured doses were all 10 mg/cm2. The study did achieve a steady state and the steady state flux and Kp were reported. The study also reported % absorption, which may not be appropriate when using an infinite exposure scenario. However, although the test formulation was applied at >10 mg/cm2, the actual doses of D4 were 6.3 and 10 mg/cm2, which are also higher than typical for a finite-dose scenario. |
| | Metric 15: | Consistency of outcome assessment | Medium | Sufficient information was reported and the same protocol was used across replicates and dose groups. The duration of exposure was the same, and collections were taken at the same time points after the initiation of the study. Although the same protocols were used, the two exposure groups were tested 2-days apart. |
| | Metric 16: | Sampling adequacy and sensitivity | Medium | Sampling details were mostly reported, including handling of samples and any deviations. Each sample was assayed in duplicate. Results were corrected for background radioactivity with the level of detection set at 1x the background value. The number of counts and LOD were not specified. |
| Domain 6: Confounding/Variable Control | | | | |

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**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 17: | Confounding variables in test design and procedures | High | The skin samples used, including the size and number of samples per group were appropriate. Skin integrity was measured using a less desirable method (20-minute tritiated water test). Most results of the skin integrity testing were acceptable. Samples that did not meet the author-reported criteria were excluded. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | High | A separate cited study assessed the solubility of radiolabeled D4 in physiological buffer with 4% BSA. The solubility was determined to be greater than the reported aqueous solubility of the test chemical, and was "more than ten times higher than the expected amount of test article penetrated into the receptor fluid over 24 hr of skin exposure" - when making comparisons with in vitro penetration of neat material through human skin in vitro. |
| Domain 7: Data Presentation and Analysis | | | | |
| | Metric 19: | Data analysis | Low | The methods for calculating the Kp, steady-state flux, and percent absorbed were clearly reported along with statistical methods for comparing absorption between dose levels. Percent absorption estimates were presented across a time series for each compartment of the test system, and Kp/flux measurements were based on the linear/steady-state part of the absorption curve. The CV values for % absorbed were <1 for both the low and high-dose groups. No CV values were provided for the KP and flux values, and these values were reported without measures of variance. |
| | Metric 20: | Data interpretation | Medium | Recovery of the test substance was adequate; 99% and 95.18% for the low and high-dose, respectively. Absorption estimates were calculated from the skin and receptor fluid compartments. It also included recovery from saran wrap that the excised skin was laid on immediately after excision but the calculation did not include tape strips (minus the first two) and ten tape strips were conducted. Information for individual replicates for each compartment analyzed is provided. Kp and flux determinations were based on a steady-state, linear portion of the curve. The majority of the sample volatilized and was collected in the charcoal trap. |
| | Metric 21: | Reporting of data | Medium | Most data were adequately reported and the report included individual replicate data for all compartments and time points. The data tables reporting the steady-state flux and estimated Kp values did not include measures of variance, however, individual cell data were included and could be used to do independent calculations. |

## Overall Quality Determination — Medium

**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Cuticle coat - 95.8% D4; D4-Other (e.g., metabolite, degradant, mixture/product) (Cuticle coat formulation) |
| Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type: | ex vivo pig; Split thickness; 500; Flow-through; Notes: Not Reported |
| Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent): | Semi-occluded (e.g., vapor trap); Skin moisturizer formulation; 95.8 |
| Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin: | 10; 24 hrs; Not Reported |
| Duration of Absorbance Measured; Frequency of Samples: | 24 hrs; 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | At the end of a 24-hr exposure period, skin was blotted using dry swabs, then with cotton applicators moistened with a 1% aqueous soap solution (3-4 times); Yes |
| Total Recovery (percent); Dose Type: | 105.44; Infinite |
| Percent Found in Skin Depot After Washing and Tape Stripping; Comments: | 0.047; Notes: CV = 13% |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments: | 0.047; Notes: CV = 13% |
| Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments: | 0.004; Notes: CV = 25%. Includes receptor fluid, but not rinse. |
| 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): | 0.000000026; Notes: Not Reported; Not Reported; Notes: Not Reported; 0.0246; Notes: Not Reported; Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as [14C] octamethylcyclotetrasiloxane (14C-D4). The position of the radiolabel was not specified. Unlabeled D4 was also used. The CASRN of D4 was provided. The unlabeled D4 was prepared into cuticle coat formulations which were spiked with 14C-D4 to a desired specific activity. The other ingredients in the formulations were not provided. |
| Metric 2: | Test substance source | High | Dow Corning prepared the unlabeled formulations, and HES Chemistry group added the 14C-D4 to the formulations to achieve the target radioactivity concentration. The text also stated that the Dow Corning Life Sciences Innovation Team prepared the radiolabeled test chemical. |

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**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 3: | Test substance purity | High | The purities of unlabeled and radiolabeled D4 were 99.75% and 99.6%, respectively. The radiochemical purities of the formulations was tested using HPLC/RAD the day of dosing and were >99%. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Reference compounds | Low | A concurrent reference compound was not tested along with the test substance. The study text did not specify an established history of test performance in the performing laboratory. |
| | Metric 5: | Assay procedures | Medium | The assay methods and procedures were described and appropriate. The study used a Bronaugh flow-through diffusion cell system under dynamic, semi-occluded conditions. A charcoal basket was placed above the exposure site immediately after the application of the test formulations. The flow rate through the receptor compartment was reported. The receptor fluid was held at 37 ± 1 degree C, and the skin surface temperature was kept at 32 ± 1 degree C. Humidity was not reported. The receptor fluid was the physiological buffer, Hank's Balanced Salt Solution with additions (HEPES, Gentamicin, BSA), which was considered to be appropriate.Receptor fluid samples were collected at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24hrs. The volume collected was not specified. At the end of a 24-hour exposure period, the skin was blotted using dry swabs, then with cotton applicators moistened with a 1% aqueous soap solution (3-4 times). The skin was tape-stripped (10x). The charcoal baskets, holders, swaps, saran wrap, tape strips, flow-through cells, excised skin, and receptor fluid samples were measured for radioactivity using scintillation counting. The number of counts was specified and results were corrected for background radioactivity. |
| | Metric 6: | Standards for tests | Medium | Percent recovery was reported and was within 100 ± 10% of the radioactivity as stated in OECD 428. The skin integrity was tested prior to the application of the test substance using tritiated water. The study reported the following acceptance criteria for the skin integrity test 1) CV between replicates was less than 60% and 2) the average percent dose absorbed for each skin specimen was ≤0.21% which is acceptable. Coefficients of variation were either reported or could be calculated for most datasets. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 7: | Preparation and storage of test substance (chemical) | Medium | The study described the preparation of the test formulations in detail and reported the formulations' storage conditions. Formulations were mixed by vortexing for 15 minutes. The 90% D4 cuticle coat dose formulation had to be mixed by vial inversion and by repeatedly drawing and expelling the formulation with a pipet to obtain sufficienthomogeneity.; the use of a centrifuge was not specified. Solubility in the receptor fluid used was demonstrated in a separate study and was appropriate. |
| | Metric 8: | Consistency of exposure administration | Low | The thickness of the skin samples ranged from 320-500 um, with most samples being >400 um. This is thicker than the recommended range of 200-400 um (OECD 428). |

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**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 9: | Reporting of concentrations | High | Dosing formulations were analyzed for D4 content by gas chromatography with flame ionization. The specific activities and homogeneity were determined using scintillation counting and were reported for each formulation. The target dose was 10 mg/cm2. Actual doses were determined gravimetrically by weighing the dosing pipette pre- and post-dosing and mean average doses were reported. Average doses (mg formulation/cm2 skin were 12.1 and 10.5 mg/cm2 and the doses (mg D4/cm2 skin) were 6.3 and 10.0 mg/cm2 for the low and high dose groups, respectively. |
| | Metric 10: | Exposure frequency | High | The exposure duration was 24 hours, which is consistent with OECD guidelines. |
| | Metric 11: | Number of exposure groups and concentration spacing | Low | Two formulations containing 51.6% or 95.8% D4 were tested. These formulations were tested on separate days (2 days apart). |
| Domain 4: Test Model | | | | |
| | Metric 12: | Test model (skin) | High | Skin samples were prepared fresh from three Yucatan miniature swine sourced from Sinclair Research Center, Inc. The skin samples were received within 24 hours of harvest and were dermatomed to 320-500 um. Discs with a surface area of 0.64 cm2 were placed into the diffusion cells, and tested on the same day they were received (one concentration). The second concentration was tested on skin that had been stored at 4 degrees C for 2 days prior to use. The authors justified the use of swine skin. The integrity of each sample was tested prior to use, and any samples not meeting the criteria specified by the authors were excluded. |
| | Metric 13: | Number/Replicates per group | Medium | The study included 6 skin replicates per donor (3 swine) totaling 18 replicates per group, which exceeds minimum guideline recommendations. Replicates not meeting skin integrity criteria at the start of the study were excluded (1-2 per experiment). |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The study was conducted under infinite exposure conditions. The target dose was 10 mg of test formulation/cm2, and the measured doses were all 10 mg/cm2. The study did achieve a steady state and the steady state flux and Kp were reported. The study also reported % absorption, which may not be appropriate when using an infinite exposure scenario. However, although the test formulation was applied at >10 mg/cm2, the actual doses of D4 were 6.3 and 10 mg/cm2, which are also higher than typical for a finite-dose scenario. |
| | Metric 15: | Consistency of outcome assessment | Medium | Sufficient information was reported and the same protocol was used across replicates and dose groups. The duration of exposure was the same, and collections were taken at the same time points after the initiation of the study. Although the same protocols were used, the two exposure groups were tested 2-days apart. |
| | Metric 16: | Sampling adequacy and sensitivity | Medium | Sampling details were mostly reported, including handling of samples and any deviations. Each sample was assayed in duplicate. Results were corrected for background radioactivity with the level of detection set at 1x the background value. The number of counts and LOD were not specified. |
| Domain 6: Confounding/Variable Control | | | | |

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**Study Citation:** Dow Corning, (2006). In vitro dermal absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) through swine skin when formulated in three personal care applications.

**HERO ID:** 11816665

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 17: | Confounding variables in test design and procedures | High | The skin samples used, including the size and number of samples per group were appropriate. Skin integrity was measured using a less desirable method (20-minute tritiated water test). Most results of the skin integrity testing were acceptable. Samples that did not meet the author-reported criteria were excluded. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | High | A separate cited study assessed the solubility of radiolabeled D4 in physiological buffer with 4% BSA. The solubility was determined to be greater than the reported aqueous solubility of the test chemical, and was "more than ten times higher than the expected amount of test article penetrated into the receptor fluid over 24 hr of skin exposure" - when making comparisons with in vitro penetration of neat material through human skin in vitro. |
| Domain 7: Data Presentation and Analysis | | | | |
| | Metric 19: | Data analysis | Low | The methods for calculating the Kp, steady-state flux, and percent absorbed were clearly reported along with statistical methods for comparing absorption between dose levels. Percent absorption estimates were presented across a time series for each compartment of the test system, and Kp/flux measurements were based on the linear/steady-state part of the absorption curve. The CV values for % absorbed were <1 for both the low and high-dose groups. No CV values were provided for the KP and flux values, and these values were reported without measures of variance. |
| | Metric 20: | Data interpretation | Medium | Recovery of the test substance was adequate; 99% and 95.18% for the low and high-dose, respectively. Absorption estimates were calculated from the skin and receptor fluid compartments. It also included recovery from saran wrap that the excised skin was laid on immediately after excision but the calculation did not include tape strips (minus the first two) and ten tape strips were conducted. Information for individual replicates for each compartment analyzed is provided. Kp and flux determinations were based on a steady-state, linear portion of the curve. The majority of the sample volatilized and was collected in the charcoal trap. |
| | Metric 21: | Reporting of data | Medium | Most data were adequately reported and the report included individual replicate data for all compartments and time points. The data tables reporting the steady-state flux and estimated Kp values did not include measures of variance, however, individual cell data were included and could be used to do independent calculations. |

## Overall Quality Determination — Medium

**Study Citation:** Dow Corning, (1998). Absorption of 14C-octamethylcyclotetrasiloxane using the flow-through diffusion cell system for in vitro dermal absorption in human skin, with cover letter dated 6/29/1998.

**HERO ID:** 5887449

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Neat D4; D4-Parent compound |
| Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type: | ex vivo human; Split thickness; 425.42; Flow-through; Notes: Not Reported |
| Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent): | Semi-occluded (e.g., vapor trap); No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin: | 10.7; 24 hrs; Not Reported |
| Duration of Absorbance Measured; Frequency of Samples: | 24 hrs; Every hour for the first six hours followed by every three hours through the 24-hour exposure period; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | The skin was washed at the end of the 24 hr exposure period. the skin was wiped with a dry swab, then three times with a cotton-tipped applicator moistened with a 1% aqueous solution of hand soap, another dry swab, and 3 ethanol swabs.; Yes |
| Total Recovery (percent); Dose Type: | 91.629; Infinite |
| Percent Found in Skin Depot After Washing and Tape Stripping; Comments: | 0.49; Notes: CV = 4% |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments: | 0.49; Notes: CV = 4% |
| Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments: | 0.01; Notes: SD = 0, no CV |
| Total Percent Absorbed: | 3 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maxium Permeability Coefficient (Kp) (cm/hr); Maxium Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments): | 0.000000062; Notes: Mean of Kp values from experiments 1 and 2 (6.57 and 5.58 x 10^-08). CV not specified; Not Reported; Notes: Not Reported; 0.06; Notes: (5-15 hrs). CV not specified.; Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substances were identified as non-radiolabeled octamethylcyclotetrasiloxane (D4) and radiolabeled [14C]- Ocatmethylcyclotetrasiloxane, CASRN 556-67-2. The location of the radiolabel was not specified. The chemical structure and physical/chemical properties are provided in the published study. The test substances were colorless liquids. |
| Metric 2: | Test substance source | High | The radiolabeled test substance was obtained from Wizard Laboratories, Inc. and the non-labeled test substance was supplied by Dow Corning Corporation. No certificates of analyses or GC or HPLC outputs were included. The study specifies that characterization records are stored in HES archives (DOW Corning). Lot numbers were provided. |

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**Study Citation:** Dow Corning, (1998). Absorption of 14C-octamethylcyclotetrasiloxane using the flow-through diffusion cell system for in vitro dermal absorption in human skin, with cover letter dated 6/29/1998.

**HERO ID:** 5887449

**EVALUATION**

| Domain | | Metric | Rating | Comments |
|---|---|---|---|---|
| | Metric 3: | Test substance purity | High | Purities of the test substances were determined by the Health Environmental Sciences (HES) Testing facility at Dow Corning. The radiochemical purity was determined by HPLC, GM-MS and was 98.71%. The purity of the unlabeled test substance was 99.8%. Specific activity was determined using liquid scintillation analysis. No impurities were specified. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Reference compounds | Low | No appropriate reference compound was used or reported and there is not established history of test performance cited in the report. |
| | Metric 5: | Assay procedures | Low | The methods and procedures are partially described. The study was not conducted according to any guidelines. Details of the flow-through diffusion cell set-up are limited. In two separate experiments, Skin from 6 donors (3 donors/experiment) was mounted in replicate in the flow through chambers. The flow rate was between 1.5 and 2.5 mL/h. The barrier integrity of each sample was tested prior to dosing. The report did not indicate whether the exposures were intended to be finite or infinite. Neat D4 was applied to human skin (6 exposure cells total for both experiments; surface area of 0.64 cm2). The volume applied was not specified. The applied dose ranged from 7.0 to 19.5 mg/cm2 (the target was 8 mg/cm2). For solids, finite exposures are generally 1-5 mg/cm2 (OECD 238), although up to 10 mg/cm2 may be appropriate (OECD 156) and infinite exposures should be >10 mg/cm2 based on OECD 156 guidelines. However, the test substance is a colorless liquid. Kp and flux values were reported suggesting infinite exposure and the authors reported a steady state was reached, but the study also reported % recovery and total absorbed. Specific activity seemed appropriate. The chambers were semi-occluded. Temperature and humidity were not reported. Immediately after dosing charcoal baskets in custom-designed caps were placed above the skin to capture any volatilized material. Receptor fluid samples were collected every hour for the first six hours followed by every three hours through the 24-hour exposure period and analyzed for radioactivity. At the end of the exposure period, the skin was wiped with a dry swab, then three times with a cotton-tipped applicator moistened with a 1% aqueous solution of hand soap, another dry swab, and 3 ethanol swabs. The skin was then tape-stripped 5 times. All of the samples, including the charcoal filter were tested for radioactivity. Radioactivity of the swabs, tape strips, and cell holders was combined and not reported independently. Radioactivity was measured by liquid scintillation analysis. Results were corrected for background radioactivity, and the limit was set at 1x the background values. |

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**Study Citation:** Dow Corning, (1998). Absorption of 14C-octamethylcyclotetrasiloxane using the flow-through diffusion cell system for in vitro dermal absorption in human skin, with cover letter dated 6/29/1998.

**HERO ID:** 5887449

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 6: | Standards for tests | Medium | Criteria used to determine the validity, acceptability, reliability and/or quality of the experiment were mostly reported and were consistent with current guidelines. Skin integrity was measured using tritiated water. The authors specified cutoff levels for the mean percent of tritiated water absorbed was >0 and <0.21% and the CV must be <60%. 2/6 samples (from a single donor) were excluded for not meeting the above criteria. The study reported Kp values of 1.95 ± 0.54 x 10-3 and 1.54 ± 0.29 x 10-3 for the two experiments which are acceptable based on current guidelines. Mean percent recovery was reported (91.63 ± 3.13%). Coefficients of variation were not reported for any endpoints or measurements but can be determined for most of the endpoints based on the data available. Numerical measures of variance were not provided for Kp or flux values, and CVs cannot be determined for those endpoints. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 7: | Preparation and storage of test substance (chemical) | High | Details of the preparation of the test substance were reported. Neat and radiolabeled test substances were mixed to achieve the target-specific activity. Specific activities were measured Storage conditions of the test substances were reported. Issues with the stability of a neat substance are not expected. |
| | Metric 8: | Consistency of exposure administration | Low | Volumes of the test substance applied were not reported. Dosing was inconsistent across replicates. The applied doses were 8.59, 13.75, 19.53, 13.44, 12.66, 13.28, 9.06, 7.66, 7.03, 7.66, 7.81, and 7.97 mg/cm2 in each of the cells listed (six samples in duplicate; average = 10.70 mg/cm2). The doses span what is generally considered finite (<10 mg/cm2) vs. infinite (>10 mg/cm2) exposure scenarios, and therefore could have a significant impact on the study results. Specific activities ranged from 5.39 to 13.75 uCi. It is unclear why there was such a variation in dose. The skin surface area of 0.64 cm2 remained constant. Skin thicknesses ranged from 381- 457 microns; the difference in thickness is considered to be moderate. |
| | Metric 9: | Reporting of concentrations | High | The exposure concentrations of the Neat test substance were clearly reported without ambiguity. Target and actual application doses were reported. The doses applied were determined by weighing the dosing device before and after dosing. |
| | Metric 10: | Exposure frequency | High | The exposure duration (24-hours) was reported and was appropriate for the endpoints evaluated. The authors noted that the dosing period was intended to simulate human use of a personal care product. |
| | Metric 11: | Number of exposure groups and concentration spacing | Low | The study only tested the Neat test substance. Other experiments using antiperspirant formulations containing the test substance were also done, but these are not discussed here. No dilution experiments were conducted. |
| Domain 4: Test Model | | | | |
| | Metric 12: | Test model (skin) | High | The study used human cadaver skin from 5 males (aged 54-74 yrs) and 1 female (49 yrs) obtained within 24 hours of death. The skin was stored at -80 degrees C until use. On day zero of the experiment, the skin samples were thawed and dermatomed. Split thickness was reported as a range (356-457 um). The upper range is above the recommended range of 200-400 um. Skin integrity was assessed at the start of the study using 3H-H2O and the results were reported. |

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**Study Citation:** Dow Corning, (1998). Absorption of 14C-octamethylcyclotetrasiloxane using the flow-through diffusion cell system for in vitro dermal absorption in human skin, with cover letter dated 6/29/1998.

**HERO ID:** 5887449

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 13: | Number/Replicates per group | Medium | Tests were performed on two separate days. On each day two duplicate samples from 3 donors were used, totaling 12 replicates across two days. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Low | This was a non-guideline study. The outcome assessment methods addressed the intended outcomes of interest. Measurement techniques and timing were reported and appropriate. The study determined both Kp and flux, as well as total percent absorbed. The former is an appropriate endpoint for an infinite exposure scenario, and the latter is determined through finite dosing conditions. Dosing volumes were not reported, and it is unclear whether they were consistent with infinite or finite exposures. |
| | 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 were consistent across replicates for each experiment. The protocol was also consistent across experiments. The authors did note that in two cells there was an issue with receptor fluid collection at the 18-hour time point that could have affected the cumulative average of D4. |
| | Metric 16: | Sampling adequacy and sensitivity | High | In total, the study reported adequate sampling for the outcome(s) of interest (n = 12 replicates across two experiments). The number of scintillation counts was not reported, but each sample was counted for 10 minutes. The limit of detection was set at 1x background. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | The study used human cadaver skin from 5 males (aged 54-74 yrs) and 1 female (49 yrs). Skin integrity was assessed using 3H-H2O. Briefly, 3H-H20 was applied to the skin (200uL) for 20 minutes. The 3H-H20 was then removed and receptor fluid was collected for 60 minutes, after which, the test substance was applied. The integrity criteria specified by the authors was a % dose absorbed that was greater than zero and <0.21% and a CV for replicate skin samples of <60%. The author's upper Kp limit for skin permeability was 3 x 10^-3. Only samples that met these criteria were used in the study. There was some variation in skin thickness between samples (381- 457 um). |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | The receptor fluid was Hank's Balanced Salt Solution with 0.6% HEPES, 0.005% Geneticin, and 4% BSA. No solubility testing was conducted. Most of the test substance volatilized, and solubility is not likely to be an issue. |
| Domain 7: Data Presentation and Analysis | | | | |
| | Metric 19: | Data analysis | Low | Means and standard deviations for recoveries in receptor fluid, skin, surface (swabs, tape, cell holders), and the charcoal filter, as well as for % absorbed and % recovery determinations, were reported. The CV for % absorption was <25%.Mathematical calculations used to determine Kp are reported and were appropriate. The Kp was based on the steady-state part of the absorption curve. CV values were not reported for Kp/flux measurements and insufficient data were provided to determine CVs independently. |

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**Study Citation:** Dow Corning, (1998). Absorption of 14C-octamethylcyclotetrasiloxane using the flow-through diffusion cell system for in vitro dermal absorption in human skin, with cover letter dated 6/29/1998.

**HERO ID:** 5887449

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 20: | Data interpretation | Low | Exposure conditions (infinite vs. finite) were not adequately reported to determine if there was proper interpretation of a finite vs. infinite dose. Recovery of the applied test substance was adequate (91.629%) for a volatile test substance. The absorption profile showed that a linear steady state was reached. Absorption vs. time was graphically presented. |
| | Metric 21: | Reporting of data | Medium | Data for most relevant endpoints were reported quantitatively as means ± SD. Individual replicate data were provided. The study did not report tape-stripping measurements individually. |

## Overall Quality Determination Medium

**Study Citation:** Dow Corning, (1998). Absorption of 14C-octamethylcyclotetrasiloxane using the flow-through diffusion cell system for in vitro dermal absorption in human skin, with cover letter dated 6/29/1998.

**HERO ID:** 5887449

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | D4 formulation; D4-Other (e.g., metabolite, degradant, mixture/product) (generic antiperspirant formulation) |
| Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type: | ex vivo human; Split thickness; 402.08; Flow-through; Notes: Not Reported |
| Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent): | Semi-occluded (e.g., vapor trap); D4 was included in an antiperspirant formulation; 62.2 |
| Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin: | 9.5; 24 hrs; Not Reported |
| Duration of Absorbance Measured; Frequency of Samples: | 24 hrs; Every hour for the first six hours followed by every three hours through the 24-hour exposure period; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | The skin was washed at the end of the 24 hr exposure period. the skin was wiped with a dry swab, then three times with a cotton-tipped applicator moistened with a 1% aqueous solution of hand soap, another dry swab, and 3 ethanol swabs.; Yes |
| Total Recovery (percent); Dose Type: | 103.757; Infinite |
| Percent Found in Skin Depot After Washing and Tape Stripping; Comments: | 0.45; Notes: CV = 14% |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments: | 0.45; Notes: CV = 14% |
| Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments: | 0.01; Notes: SD = 0, no CV |
| Total Percent Absorbed: | 4 |
| 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): | 0.000000063; Notes: Mean of Kp values from experiments 1 and 2 (5.51 and 6.98 x 10^-08). CV not specified; Not Reported; Notes: Not Reported; 0.04; Notes: (6-21h). CV not specified.; Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substances were identified as non-radiolabeled octamethylcyclotetrasiloxane (D4) and radiolabeled [14C]- Ocatmethylcyclotetrasiloxane, CASRN 556-67-2. The location of the radiolabel was not specified. The chemical structure and physical/chemical properties are provided in the published study. The test substances were colorless liquids.A formulation containing 62.2% D4 was used for this study. |
| Metric 2: | Test substance source | High | The radiolabeled test substance was obtained from Wizard Laboratories, Inc. and the non-labeled test substance was supplied by Dow Corning Corporation. No certificates of analyses or GC or HPLC outputs were included. The study specifies that characterization records are stored in HES archives (DOW Corning). Lot numbers were provided. |

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**Study Citation:** Dow Corning, (1998). Absorption of 14C-octamethylcyclotetrasiloxane using the flow-through diffusion cell system for in vitro dermal absorption in human skin, with cover letter dated 6/29/1998.

**HERO ID:** 5887449

**EVALUATION**

| Domain | | Metric | Rating | Comments |
|---|---|---|---|---|
| | Metric 3: | Test substance purity | High | Purities of the test substances were determined by the Health Environmental Sciences (HES) Testing facility at Dow Corning. The radiochemical purity was determined by HPLC, GM-MS and was 98.71%. The purity of the unlabeled test substance was 99.8%. Specific activity was determined using liquid scintillation analysis. No impurities were specified. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Reference compounds | Low | No appropriate reference compound was used or reported and there is not established history of test performance cited in the report. |
| | Metric 5: | Assay procedures | Low | The methods and procedures are partially described. The study was not conducted according to any guidelines. Details of the flow-through diffusion cell set-up are limited. In two separate experiments, Skin from 6 donors (3 donors/experiment) was mounted in duplicate in the flow-through chambers (total n =12). The flow rate was between 1.5 and 2.5 mL/h. The barrier integrity of each sample was tested prior to dosing. Samples from two donors were removed during the first experiment. The report did not indicate whether the exposures were intended to be finite or infinite. D4 in an antiperspirant formulation was applied to human skin (6 exposure cells total for both experiments; surface area of 0.64 cm2). The volume applied was not specified. The applied dose ranged from 8.55 to 10.98 mg/cm2 (the target was 8 mg/cm2). For solids, finite exposures are generally 1-5 mg/cm2 (OECD 238), although up to 10 mg/cm2 may be appropriate (OECD 156) and infinite exposures should be >10 mg/cm2 based on OECD 156 guidelines. However, the test substance is a colorless liquid. Kp and flux values were reported suggesting infinite exposure and the authors reported a steady state was reached, but the study also reported % recovery and total absorbed. Specific activity seemed appropriate. The chambers were semi-occluded. Temperature and humidity were not reported. Immediately after dosing charcoal baskets in custom-designed caps were placed above the skin to capture any volatilized material. Receptor fluid samples were collected every hour for the first six hours followed by every three hours through the 24-hour exposure period and analyzed for radioactivity. At the end of the exposure period, the skin was wiped with a dry swab, then three times with a cotton-tipped applicator moistened with a 1% aqueous solution of hand soap, another dry swab, and 3 ethanol swabs. The skin was then tape-stripped 5 times. All of the samples, including the charcoal filter were tested for radioactivity. Radioactivity of the swabs, tape strips, and cell holders was combined and not reported independently. Radioactivity was measured by liquid scintillation analysis. Results were corrected for background radioactivity, and the limit was set at 1x the background values. |

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**Study Citation:** Dow Corning, (1998). Absorption of 14C-octamethylcyclotetrasiloxane using the flow-through diffusion cell system for in vitro dermal absorption in human skin, with cover letter dated 6/29/1998.

**HERO ID:** 5887449

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 6: | Standards for tests | Medium | Criteria used to determine the validity, acceptability, reliability and/or quality of the experiment were mostly reported and were consistent with current guidelines. Skin integrity was measured using tritiated water. The authors specified cutoff levels for the mean percent of tritiated water absorbed was >0 and <0.2221% and the CV must be <60%. 2/6 samples (from a single donor) were excluded for not meeting the above criteria. The study reported Kp values of 1.95 ± 0.54 x 10-3 and 1.54 ± 0.29 x 10-3 for the two experiments which are acceptable based on current guidelines. Mean percent recovery was reported (103.8 76± 1.88%). Coefficients of variation were not reported for any endpoints or measurements but can be determined for most of the endpoints based on the data available. Numerical measures of variance were not provided for Kp or flux values, and CVs cannot be determined for those endpoints. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 7: | Preparation and storage of test substance (chemical) | High | Radiolabeled test substance was mixed with an antiperspirant formulation prepared by Personal Care Science and Technology Group, Dow Corning Corp. The specific activity of the mixture was assessed using liquid scintillation analysis and was 0.5uCi/mg. Homogeneity was evaluated, and acceptable criteria for homogeneity was a CV of <10%. Since the study was conducted on 2 days (6 replicates on day 1, 6 on day 2), two separate dosing solutions were prepared for each day. The % CVs (for homogeneity) were 5.6% and 3.4%, respectively. Stability over time of the formulation was also confirmed. The concentration of D4 in the formulation was 62.2% w/w. |
| | Metric 8: | Consistency of exposure administration | Low | Volumes of the test substance applied were not reported. Dosing was inconsistent across replicates. Average dose was reported to be 9.49 mg D4/cm2. For each replicate, the applied doses were 8.75, 8.94, 10.98, 9.43, 10.40, 8.55, and 8.94 mg/cm2. The doses span what is generally considered finite (<10 mg/cm2) vs. infinite (>10 mg/cm2) exposure scenarios, and therefore could have a significant impact on the study results. The skin surface area of 0.64 cm2 remained constant. Skin thicknesses ranged from 381-432 microns; the difference in thickness is considered to be moderate. |
| | Metric 9: | Reporting of concentrations | High | The exposure concentrations of the formulation and the amount of D4 in the formulation were clearly reported without ambiguity. Target and actual application doses were reported. The doses applied were determined by weighing the dosing device before and after dosing. |
| | Metric 10: | Exposure frequency | High | The exposure duration (24-hours) was reported and was appropriate for the endpoints evaluated. The authors noted that the dosing period was intended to simulate human use of a personal care product. |
| | Metric 11: | Number of exposure groups and concentration spacing | Low | The study tested neat test substance as well as the test substance in an antiperspirant formulation. The purpose of the study was not to identify a dose-response. |
| Domain 4: Test Model | | | | |
| | Metric 12: | Test model (skin) | High | The study used human cadaver skin from 5 males (aged 54-74 yrs) and 1 female (49 yrs) obtained within 24 hours of death. The skin was stored at -80 degrees C until use. On day zero of the experiment, the skin samples were thawed and dermatomed. Split thickness was reported as a range (356-457 um). The upper range is above the recommended range of 200-400 um. Skin integrity was assessed at the start of the study using 3H-H2O and the results were reported. |

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**Study Citation:** Dow Corning, (1998). Absorption of 14C-octamethylcyclotetrasiloxane using the flow-through diffusion cell system for in vitro dermal absorption in human skin, with cover letter dated 6/29/1998.

**HERO ID:** 5887449

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 13: | Number/Replicates per group | Medium | Tests were performed on two separate days. On each day it was intended that there would be two duplicate samples from 3 donors, totaling 12 replicates across two days. There was not enough test formulation on the first day and therefore 2 replicates, from 2 donors (4-total) were used (see HERO 5887282) |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Low | This was a non-guideline study. The outcome assessment methods addressed the intended outcomes of interest. Measurement techniques and timing were reported and appropriate. The study determined both Kp and flux, as well as total percent absorbed. The former is an appropriate endpoint for an infinite exposure scenario, and the latter is determined through finite dosing conditions. Dosing volumes were not reported, and it is unclear whether they were consistent with infinite or finite exposures. |
| | 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 were consistent across replicates for each experiment. The protocol was also consistent across experiments. |
| | Metric 16: | Sampling adequacy and sensitivity | Medium | In total, the study reported adequate sampling for the outcome(s) of interest (n = 8 replicates across two experiments). However, data from two donors were eliminated. Samples from one donor were excluded for failing skin integrity criteria; the second sample was excluded due to an issue with insufficient formulation to complete the test. These omissions are not expected to have a significant impact on the study results. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | The study used human cadaver skin from 5 males (aged 54-74 yrs) and 1 female (49 yrs). Skin integrity was assessed using 3H-H2O. Briefly, 3H-H20 was applied to the skin (200uL) for 20 minutes. The 3H-H20 was then removed and receptor fluid was collected for 60 minutes, after which, the test substance was applied. The integrity criteria specified by the authors was a % dose absorbed that was greater than zero and <0.21 % and a CV for replicate skin samples of <60%. The author's upper Kp limit for skin permeability was 3 x 10^-3. Only samples that met these criteria were used in the study. There was some variation in skin thickness between samples (381-432 um). |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | The receptor fluid was Hank's Balanced Salt Solution with 0.6% HEPES, 0.005% Geneticin, and 4% BSA. No solubility testing was conducted. Most of the test substance volatilized, and solubility is not likely to be an issue. |
| Domain 7: Data Presentation and Analysis | | | | |
| | Metric 19: | Data analysis | Low | Means and standard deviations for recoveries in receptor fluid, skin, surface (swabs, tape, cell holders), and the charcoal filter, as well as for % absorbed and % recovery determinations, were reported. The CV for % absorption was <25%.Mathematical calculations used to determine Kp are reported and were appropriate. The Kp was based on the steady-state part of the absorption curve. CV values were not reported for Kp/flux measurements and insufficient data were provided to determine CVs independently. |

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**Study Citation:** Dow Corning, (1998). Absorption of 14C-octamethylcyclotetrasiloxane using the flow-through diffusion cell system for in vitro dermal absorption in human skin, with cover letter dated 6/29/1998.

**HERO ID:** 5887449

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 20: | Data interpretation | Low | Exposure conditions (infinite vs. finite) were not adequately reported to determine if there was proper interpretation of a finite vs. infinite dose. Recovery of the applied test substance was adequate (103.8%) for a volatile substance. The absorption profile showed that a linear steady state was reached. Absorption vs. time was graphically presented. |
| | Metric 21: | Reporting of data | Medium | Data for most relevant endpoints were reported quantitatively as means ± SD. Individual replicate data were provided. The study did not report tape-stripping measurements individually |

## Overall Quality Determination — Medium

**Study Citation:** GE, (1994). In vitro percutaneous absorption assay of C14-octamethylcyclotetrasiloxane (C14-D4) in rat skin.
**HERO ID:** 5888573

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | D4 -males; D4-Parent compound |
| Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type: | ex vivo rat; Full thickness; Not Reported; Static; Notes: Not Reported |
| Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent): | Semi-occluded (e.g., vapor trap); None described; 100 |
| Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin: | 4.69; 6 hrs; Not Reported |
| Duration of Absorbance Measured; Frequency of Samples: | 6 hrs; 30 minutes, 1, 2, 3, 4, 5, and 6 hours; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | After a 6 hr exposure period, skin was wiped with a dry filter and then by gauze moistened by alcohol. Then an alcohol moistened cotton swab was used to swab the application site.; Yes |
| Total Recovery (percent); Dose Type: | 86.73; Finite |
| Percent Found in Skin Depot After Washing and Tape Stripping; Comments: | 6.03; Notes: CV = 34% |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments: | 6.03; Notes: CV = 34% |
| Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments: | 0.3; Notes: The percent in receptor fluid was 0.205% (CV = 171%), the percent in rinse fluid (rinse of cell and skin vial) was 0.1% (CV = 900%) |
| Total Percent Absorbed: | 6 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maxium Permeability Coefficient (Kp) (cm/hr); Maxium Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments): | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substances were identified as non-radiolabeled octamethylcyclotetrasiloxane (D4) and radiolabeled [14C]- octamethylcyclotetrasiloxane, CASRN 556-67-2. The form and location of the radiolabel was not specified. No chemical structure or physical/chemical details of the test substance were included in the report. |
| Metric 2: | Test substance source | Low | The radiolabeled test substance was obtained from Sigma Chemical Co. The nonlabelled test material was obtained from General Electric. No certificates of analyses or GC or HPLC outputs were included; the test substance was not analytically verified by the performing laboratory. A lot number was provided for the radiolabeled test substance and Sigma can supply certificates of analysis. A lot number for the non-labeled material was not specified, and a website for the supplier could not be located. |

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**Study Citation:** GE, (1994). In vitro percutaneous absorption assay of C14-octamethylcyclotetrasiloxane (C14-D4) in rat skin.
**HERO ID:** 5888573

**EVALUATION**

| Domain | | Metric | Rating | Comments |
|---|---|---|---|---|
| | Metric 3: | Test substance purity | High | The reported radiochemical purity was >98%. The specific activity was reported. The purity of the unlabeled test substance was 99.8%. No impurities were specified. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Reference compounds | Low | The study used a non-standard reference compound as a positive control. Radiolabeled ethanol was applied to skin samples in the same manner as the test substance. No justification for the use of ethanol was provided. |
| | Metric 5: | Assay procedures | Medium | Tests were conducted using a static diffusion cell. A detailed description and image of the diffusion cell was provided. Tests were conducted at 32 degrees C, humidity was not reported. Receptor solutions were continuously mixed at 600 rpm. 15 uL (14.55 mg) of the test solution was applied to each skin sample (area 3.1 cm2) and diffusion cells were covered with a trap basket. Receptor fluid (minimal essential medium [MEM] with 10% BSA and 1% penicillin/streptomycin) was sampled 30 minutes, and 1, 2, 3, 4, 5, and 6 hours after dosing. Equal volumes of receptor medium were added to replace the removed samples. After a 6-hour exposure period, the skin was wiped with a dry filter and then by gauze moistened by alcohol. Then an alcohol moistened cotton swab was used to swab the application site. The skin was then tape-stripped (number of times not specified). Radioactivity was measured using liquid scintillation counting of the receptor fluid samples, gauze, skin wipes, tape strips, charcoal baskets, and remaining skin, as well as in the final receptor solution and a rinse of the apparatus. Tape stripping and wash fractions were combined in the summary table, but individual cell data from each fraction was provided at the end of the study. Details of scintillation counting were inadequately reported. |
| | Metric 6: | Standards for tests | Low | The study authors state that "The integrity of the skin preparations was addressed by concurrently evaluating the penetration of a standard chemical, 1-14C-Ethanol (Sigma Chemical Co.) through a sample of skin." However, the integrity of the skin samples used in the evaluation of the test substance was not assessed. The authors provided no inclusion criteria based on integrity. Mean recovery was reported (86.73 and 76.9% for males and females, respectively). Coefficients of variation were not reported for any endpoints or measurements but can be determined for most of the endpoints based on the data available. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 7: | Preparation and storage of test substance (chemical) | Low | The dosing solution was prepared by mixing the radiolabeled and unlabeled test substance to allow delivery of ~20 uCi in a 15 uL volume. Specific activities of the solutions were reported. No information on the storage of the test chemicals or the timing of the preparation of the test solutions relative to the start of the study was provided. |
| | Metric 8: | Consistency of exposure administration | Low | The test substance volume was reported to be 15 uL. Based on the size of the skin surface the applied mass was 4.69 mg/cm2. This was consistent across samples and is appropriate for a finite exposure scenario. However, the thickness of the skin was not specified, this missing information could have a substantial impact on the study results. |
| | Metric 9: | Reporting of concentrations | Medium | 15uL (14.55 mg) of the test substance was applied to the surface of the skin. The actual volume of test substance applied was verified at dosing by weighing the dosing syringe before and after use. These measurements/sample were not reported. |

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**Study Citation:** GE, (1994). In vitro percutaneous absorption assay of C14-octamethylcyclotetrasiloxane (C14-D4) in rat skin.
**HERO ID:** 5888573

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 10: | Exposure frequency | Low | The exposure duration was 6 hours. The authors did not specify the reasoning for this duration, but 6-hours is not an unreasonable in-use duration. Measurements did not continue past the exposure time. This is not consistent with OECD guidelines that specify continuing collections to 24 hrs. |
| | Metric 11: | Number of exposure groups and concentration spacing | Low | The study only tested undiluted test substance. No justification was provided. |
| Domain 4: Test Model | | | | |
| | Metric 12: | Test model (skin) | Low | Two full-thickness skin samples were obtained from the dorsal surface of 8 young (8-11 weeks old) Sprague Dawley rats (4/sex). The skin was placed in MEM medium until it was placed into diffusion cells. It was not specified how much time elapsed between the collection of the skin samples and the start of the study. Excess fat was removed and skin was cut into disks at least 2.5 cm in diameter. No additional details of skin preparation (e.g., whether it was dermatomed) were provided and the skin thickness was not reported. Once mounted the available skin surface area was 3.1 cm2. No equilibration period was discussed. The integrity of the skin samples used with the test substance was not tested. These missing details are expected to have a significant impact on the interpretation of the study results. |
| | Metric 13: | Number/Replicates per group | Medium | The study included 6 female and 6 male replicates. Data for each sex were reported separately. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | This was a non-guideline study. assessment methods addressed the intended outcomes of interest. 4.69 mg/cm2 of the test substance was loaded onto each skin sample which is appropriate for a finite exposure. Total absorption was reported in a finite study. The authors did not correlate any methods with conditions of use. |
| | 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 were used. The protocol was also consistent across experiments. |
| | Metric 16: | Sampling adequacy and sensitivity | Medium | The number of samples/replicates (12 total) was adequate. The number of scintillation counts/sample was not specified. The signal-to-noise ratio for detection was not indicated; however, it was specified that raw counts were adjusted for quench and background. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Low | Some information was missing to determine whether there were confounding variables in the test design and procedures. Skin thickness was not reported, and skin integrity was not measured. |

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**Study Citation:** GE, (1994). In vitro percutaneous absorption assay of C14-octamethylcyclotetrasiloxane (C14-D4) in rat skin.
**HERO ID:** 5888573

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | The report noted that one male and one female sample showed higher levels of radioactivity in the receptor fluid than the other replicates. This was due to filter paper that had fallen into the receptor fluid allowing the skin to be in direct contact with the medium. It is unclear whether these samples were included in the calculations but the overall % dose absorbed was not appreciably different across replicates, and sufficient data are reported to conduct an independent analysis. The receptor fluid was minimal essential medium [MEM] with 10% BSA and 1% penicillin/streptomycin. Solubility testing was not conducted, but solubility is not likely to be an issue based on the expected low concentrations of the volatile test substance in the receptor fluid. |
| Domain 7: Data Presentation and Analysis | | | | |
| | Metric 19: | Data analysis | Low | Cumulative penetration vs. time was displayed in a figure. The calculations used were clearly described. It is unclear if the absorption estimates accounted for the two outliers noted, but sufficient information is available for independent analysis. CV values were not reported but could be determined using the data provided. More than 50% of the measured endpoints had CV values >50%; however, data are available to allow EPA to calculate an alternate (upper-end) value to account for variability. |
| | Metric 20: | Data interpretation | Medium | The recovery (86.73%) was appropriate for a volatile test substance. Tape strips were not included in the absorption estimate and the number of tape strips was not specified. Tape strip measurements were reported independently to allow for independent analysis. |
| | Metric 21: | Reporting of data | High | Data for all specified outcomes were reported. Individual replicate data were provided along with means ± SD. |

## Overall Quality Determination Low

**Study Citation:** GE, (1994). In vitro percutaneous absorption assay of C14-octamethylcyclotetrasiloxane (C14-D4) in rat skin.
**HERO ID:** 5888573

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | D4 -Females; D4-Parent compound |
| Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type: | ex vivo rat; Full thickness; Not Reported; Static; Notes: Not Reported |
| Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent): | Semi-occluded (e.g., vapor trap); None described; 100 |
| Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin: | 4.69; 6 hrs; Not Reported |
| Duration of Absorbance Measured; Frequency of Samples: | 6 hrs; 30 minutes, 1, 2, 3, 4, 5, and 6 hours; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | After a 6 hr exposure period, skin was wiped with a dry filter and then by gauze moistened by alcohol. Then an alcohol moistened cotton swab was used to swab the application site.; Yes |
| Total Recovery (percent); Dose Type: | 76.9; Finite |
| Percent Found in Skin Depot After Washing and Tape Stripping; Comments: | 10.37; Notes: CV = 3.4% |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments: | 10.37; Notes: CV = 3.4% |
| Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments: | 0.2; Notes: The percent in receptor fluid was 0.03% (CV = 133%), the percent in rinse fluid (rinse of cell and skin vial) was 0.17% (CV = 35%) |
| Total Percent Absorbed: | 11 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maxium Permeability Coefficient (Kp) (cm/hr); Maxium Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments): | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substances were identified as non-radiolabeled octamethylcyclotetrasiloxane (D4) and radiolabeled [14C]- octamethylcyclotetrasiloxane, CASRN 556-67-2. The form and location of the radiolabel was not specified. No chemical structure or physical/chemical details of the test substance were included in the report. |
| Metric 2: | Test substance source | Low | The radiolabeled test substance was obtained from Sigma Chemical Co. The nonlabelled test material was obtained from General Electric. No certificates of analyses or GC or HPLC outputs were included; the test substance was not analytically verified by the performing laboratory. A lot number was provided for the radiolabeled test substance and Sigma can supply certificates of analysis. A lot number for the non-labeled material was not specified, and a website for the supplier could not be located. |
| Metric 3: | Test substance purity | High | The reported radiochemical purity was >98%. The specific activity was reported. The purity of the unlabeled test substance was 99.8%. No impurities were specified. |

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**Study Citation:** GE, (1994). In vitro percutaneous absorption assay of C14-octamethylcyclotetrasiloxane (C14-D4) in rat skin.
**HERO ID:** 5888573

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| Domain 2: Test Design | | | | |
| | Metric 4: | Reference compounds | Low | The study used a non-standard reference compound as a positive control. Radiolabeled ethanol was applied to skin samples in the same manner as the test substance. No justification for the use of ethanol was provided. |
| | Metric 5: | Assay procedures | Medium | Tests were conducted using a static diffusion cell. A detailed description and image of the diffusion cell was provided. Tests were conducted at 32 degrees C, humidity was not reported. Receptor solutions were continuously mixed at 600 rpm. 15 uL (14.55 mg) of the test solution was applied to each skin sample (area 3.1 cm2) and diffusion cells were covered with a trap basket. Receptor fluid (minimal essential medium [MEM] with 10% BSA and 1% penicillin/streptomycin) was sampled 30 minutes, and 1, 2, 3, 4, 5, and 6 hours after dosing. Equal volumes of receptor medium were added to replace the removed samples. After a 6-hour exposure period, the skin was wiped with a dry filter and then by gauze moistened by alcohol. Then an alcohol moistened cotton swab was used to swab the application site. The skin was then tape-stripped (number of times not specified). Radioactivity was measured using liquid scintillation counting of the receptor fluid samples, gauze, skin wipes, tape strips, charcoal baskets, and remaining skin, as well as in the final receptor solution and a rinse of the apparatus. Tape stripping and wash fractions were combined in the summary table, but individual cell data from each fraction was provided at the end of the study. Details of scintillation counting were inadequately reported. |
| | Metric 6: | Standards for tests | Low | The study authors state that "The integrity of the skin preparations was addressed by concurrently evaluating the penetration of a standard chemical, 1-14C-Ethanol (Sigma Chemical Co.) through a sample of skin." However, the integrity of the skin samples used in the evaluation of the test substance was not assessed. The authors provided no inclusion criteria based on integrity. Mean recovery was reported (86.73 and 76.9% for males and females, respectively). Coefficients of variation were not reported for any endpoints or measurements but can be determined for most of the endpoints based on the data available. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 7: | Preparation and storage of test substance (chemical) | Low | The dosing solution was prepared by mixing the radiolabeled and unlabeled test substance to allow delivery of ~20 uCi in a 15 uL volume. Specific activities of the solutions were reported. No information on the storage of the test chemicals or the timing of the preparation of the test solutions relative to the start of the study was provided. |
| | Metric 8: | Consistency of exposure administration | Low | The test substance volume was reported to be 15 uL. Based on the size of the skin surface the applied mass was 4.69 mg/cm2. This was consistent across samples and is appropriate for a finite exposure scenario. However, the thickness of the skin was not specified, this missing information could have a substantial impact on the study results. |
| | Metric 9: | Reporting of concentrations | Medium | 15uL (14.55 mg) of the test substance was applied to the surface of the skin. The actual volume of test substance applied was verified at dosing by weighing the dosing syringe before and after use. These measurements/sample were not reported. |
| | Metric 10: | Exposure frequency | Low | The exposure duration was 6 hours. The authors did not specify the duration but 6-hours is not an unreasonable in-use duration. Measurements did not continue past the exposure time. This is not consistent with OECD guidelines that specify continuing collections to 24 hrs. |

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**Study Citation:** GE, (1994). In vitro percutaneous absorption assay of C14-octamethylcyclotetrasiloxane (C14-D4) in rat skin.
**HERO ID:** 5888573

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 11: | Number of exposure groups and concentration spacing | Low | The study only tested undiluted test substance. No justification was provided. |
| Domain 4: Test Model | | | | |
| | Metric 12: | Test model (skin) | Low | Two full-thickness skin samples were obtained from the dorsal surface of 8 young (8-11 weeks old) Sprague Dawley rats (4/sex). The skin was placed in MEM medium until it was placed into diffusion cells. It was not specified how much time elapsed between the collection of the skin samples and the start of the study. Excess fat was removed and skin was cut into disks at least 2.5 cm in diameter. No additional details of skin preparation (e.g., whether it was dermatomed) were provided and the skin thickness was not reported. Once mounted the available skin surface area was 3.1 cm2. No equilibration period was discussed. The integrity of the skin samples used with the test substance was not tested. These missing details are expected to have a significant impact on the interpretation of the study results. |
| | Metric 13: | Number/Replicates per group | Medium | The study included 6 female and 6 male replicates. Data for each sex were reported separately. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | This was a non-guideline study. assessment methods addressed the intended outcomes of interest. 4.69 mg/cm2 of the test substance was loaded onto each skin sample which is appropriate for a finite exposure. Total absorption was reported in a finite study. The authors did not correlate any methods with conditions of use. |
| | 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 were used. The protocol was also consistent across experiments. |
| | Metric 16: | Sampling adequacy and sensitivity | Medium | The number of samples/replicates (12 total) was adequate. The number of scintillation counts/sample was not specified. The signal-to-noise ratio for detection was not indicated; however, it was specified that raw counts were adjusted for quench and background. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Low | Some information was missing to determine whether there were confounding variables in the test design and procedures. Skin thickness was not reported, and skin integrity was not measured. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | The report noted that one male and one female sample showed higher levels of radioactivity in the receptor fluid than the other replicates. This was due to filter paper that had fallen into the receptor fluid allowing the skin to be in direct contact with the medium. It is unclear whether these samples were included in the calculations but the overall % dose absorbed was not appreciably different across replicates, and sufficient data are reported to conduct an independent analysis. The receptor fluid was minimal essential medium [MEM] with 10% BSA and 1% penicillin/streptomycin. Solubility testing was not conducted, but solubility is not likely to be an issue based on the expected low concentrations of the volatile test substance in the receptor fluid. |
| Domain 7: Data Presentation and Analysis | | | | |

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**Study Citation:** GE, (1994). In vitro percutaneous absorption assay of C14-octamethylcyclotetrasiloxane (C14-D4) in rat skin.
**HERO ID:** 5888573

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 19: | Data analysis | High | Cumulative penetration vs. time was displayed in a figure. The calculations used were clearly described. It is unclear if the absorption estimates accounted for the two outliers noted, but sufficient information is available for independent analysis. CV values were not reported but could be determined using the data provided. More than 50% of the measured endpoints had CV values <25%. however, data are available to allow EPA to calculate an alternate (upper-end) value to account for variability. |
| | Metric 20: | Data interpretation | Medium | The recovery (76.9%) is slightly lower than the guideline recommendations of 100% ± 20% for a volatile test substance. The study authors did not discuss the source of possible losses. However, tape strips were not included in the absorption estimate and the number of tape strips was not specified. Tape strip measurements were reported independently to allow for some independent analysis. |
| | Metric 21: | Reporting of data | High | Data for all specified outcomes were reported. Individual replicate data were provided along with means ± SD. |

## Overall Quality Determination Medium

**Study Citation:** Krenczkowska, D., Mojsiewicz-Pieńkowska, K., Wielgomas, B., Cal, K., Bartoszewski, R., Bartoszewska, S., Jankowski, Z. (2019). The consequences of overcoming the human skin barrier by siloxanes (silicones) Part 1. Penetration and permeation depth study of cyclic methyl siloxanes. Chemosphere 231:607-623.

**HERO ID:** 6833834

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Neat D4; D4-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): | Occluded; No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin: | 149.3; 24 hrs; Not Reported |
| Duration of Absorbance Measured; Frequency of Samples: | 24 hrs; Based on the information provided, no sampling over time was conducted and measurements were only taken at the end of the study.; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | At the end of the exposure period, the skin surface was dried with absorbent paper, then washed with a cotton bud soaked in carbon tetrachloride and blotted dry again.; No |
| Total Recovery (percent); Dose Type: | Not Reported; Infinite |
| Percent Found in Skin Depot After Washing and Tape Stripping; Comments: | Not Reported; Notes: Cumulative doses in skin layers were reported: stratum corneum: 18.3 ug (CV=8.06); epidermis: 4.07 ug (CV= 17.29); dermis: 3.28 ug (CV= 9.85). Data was presented as ug/cm2/24hr. This reviewer multiplied value reported by 0.64 cm2 to obtain ug in each layer. |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments: | Not Reported; Notes: Cumulative doses in skin layers were reported: stratum corneum: 18.3 ug (CV=8.06); epidermis: 4.07 ug (CV= 17.29); dermis: 3.28 ug (CV= 9.85). Data was presented as ug/cm2/24hr. This reviewer multiplied value reported by 0.64 cm2 to obtain ug in each layer. |
| Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments: | Not Reported; Notes: Cumulative dose in fluid acceptor: 1.54 ug (CV= 31.62). This reviewer multiplied value reported by 0.64 cm2 to obtain ug. |
| Total Percent Absorbed: | 0 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maxium Permeability Coefficient (Kp) (cm/hr); Maxium Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments): | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | High | The unlabeled test substance was identified as octamethylcyclotetrasiloxane (D4). No radiolabeled test substance was used. A structure along with physical chemical properties was reported. |
| Metric 2: | Test substance source | High | The test substance was obtained from Sigma-Aldrich, Steinheim, Germany. A lot number was not provided. Certificates of analysis are available on the supplier's website. |

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**Study Citation:** Krenczkowska, D., Mojsiewicz-Pieńkowska, K., Wielgomas, B., Cal, K., Bartoszewski, R., Bartoszewska, S., Jankowski, Z. (2019). The consequences of overcoming the human skin barrier by siloxanes (silicones) Part 1. Penetration and permeation depth study of cyclic methyl siloxanes. Chemosphere 231:607-623.

**HERO ID:** 6833834

**EVALUATION**

| Domain | | Metric | Rating | Comments |
|---|---|---|---|---|
| | Metric 3: | Test substance purity | Medium | The test substance purity was not specified in the study report. Sigma-Aldrich reports purities for this test chemical and the purities are all >98%; however, no catalogue number was provided, so it is unclear which sigma product was used in the study. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Reference compounds | Low | No reference compound was used, and there is no established history of test performance in the performing laboratory. |
| | Metric 5: | Assay procedures | Medium | This study used alternative methods to study the depth of permeation of D4 into human skin. Experiments were conducted in a Franz-type diffusion cell system at 32 degrees C. under occluded conditions for 24 hours. Humidity was not reported. Human cadaver skin samples (presumably full-thickness, but not specified) were mounted onto diffusion cells leaving a surface area of 0.64 cm2. Receptor fluid consisted of an aqueous solution with sodium chloride, 2% Igepal CA 630 (as a surfactant) and 0.005% sodium azide. The fluid was stirred with a magnetic stirrer set at 400 rpm. The skin was equilibrated for 30 minutes prior to use. A 100uL volume (95.6 mg) was applied as an infinite dose onto the skin surface area of 0.64 cm2; equivalent to a loading rate of 149.3 mg/cm2. Water was added to control samples. At the end of the exposure period, the skin surface was dried with absorbent paper, then washed with a cotton bud soaked in carbon tetrachloride and blotted dry again. Skin was tape-stripped to obtain 17 layers of the stratum corneum. A heat-separating technique (in water) was then used to separate the dermis and epidermis. Measurements from each layer (stratum corneum/tape strips), epidermis, and dermis were made using ATR-FTIR spectroscopy. GC-FID chromatography was also conducted on these skin layers, and also the receptor fluid. The limits of quantitation were reported and percent recovery was determined. The epidermis was examined by fluorescent microscopy using fluorescein, sulphorodamine B, and ester hexyl rodamine dyes. These methods differ significantly from a standard dermal absorption study; however, the assay procedures were consistent with the described purposes of the study. |
| | Metric 6: | Standards for tests | Medium | Integrity was assessed using a magnifier and electrical resistance. All measurements were above 2k´Ω/cm2 (mean 52k´Ω/cm2) for surface area of 0.64 cm2 and were considered appropriate for study use. Coefficients of variation were not provided in the study report but could be calculated using the data available. Percent recovery from spiked skin layers and receptor fluid samples was reported (105.50%). The report indicated that validation parameters for the GC-FID method used would be published separately. The ATR-FTIR method was optimized prior to use. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 7: | Preparation and storage of test substance (chemical) | Medium | The test substance was applied neat (no preparation needed). Storage conditions were not reported. No data on stability were provided. |
| | Metric 8: | Consistency of exposure administration | Low | Details of exposure administration were reported. A 100ul volume was applied to all replicates. The skin surface area of 0.64 cm2 was consistent across groups; however, the thickness was not reported. |

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**Study Citation:** Krenczkowska, D., Mojsiewicz-Pieńkowska, K., Wielgomas, B., Cal, K., Bartoszewski, R., Bartoszewska, S., Jankowski, Z. (2019). The consequences of overcoming the human skin barrier by siloxanes (silicones) Part 1. Penetration and permeation depth study of cyclic methyl siloxanes. Chemosphere 231:607-623.

**HERO ID:** 6833834

**EVALUATION**

| Domain | | Metric | Rating | Comments |
|---|---|---|---|---|
| | Metric 9: | Reporting of concentrations | High | The dose of the test substance was reported without ambiguity. A 100uL volume (95.6 mg) was applied as an infinite dose onto the skin surface area of 0.64 cm2; equivalent to a loading rate of 149.3 mg/cm2 |
| | Metric 10: | Exposure frequency | High | The exposure duration was 24 hours, which is consistent with current guidelines, and is an appropriate representation of certain conditions of use. |
| | Metric 11: | Number of exposure groups and concentration spacing | Low | The study only tested the Neat test substance. The study authors noted that this represented the maximum volume that human skin is able to receive. |
| Domain 4: Test Model | | | | |
| | Metric 12: | Test model (skin) | Low | Full-thickness cadaver skin was obtained from the abdomens of 5 females (mean age 40 yrs) and 5 males (mean age 45 years) 24-48 hours after death. Excess fat was trimmed, the skin was washed and stored at -20 degrees C. until use. The thickness was not reported. The skin was defrosted and rehydrated prior to use. Integrity was assessed using a magnifier and electrical resistance. All measurements were above 2k´Ω/cm2 (mean 52k´Ω/cm2) and were considered appropriate for study use. |
| | Metric 13: | Number/Replicates per group | Medium | The study used 5 replicates total (the donor details for each replicate is unclear). The number of replicates is appropriate according to OECD TG 428. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Uninformative | This was a non-guideline study primarily focused on the mechanism of D4 penetration and permeation through the skin. The study only tested the Neat test substance. The study authors noted that this represented the “maximum volume that human skin is able to receive.” However, an undiluted test substance may not represent normal conditions of use. The assessment methods addressed the outcomes of interest specified by the study authors. A 100uL volume (95.6 mg) was applied dose onto the skin surface area of 0.64 cm2; equivalent to a loading rate of 149.3 mg/cm2. This was appropriate for an infinite exposure scenario. The study did not report a Kp value but did report a total cumulative dose over time (based on measurements in each layer of skin (stratum corneum, epidermis, dermis) and in fluid receptor); it was not stated whether a steady state was reached. This study was deemed uninformative because it was not conducted in way that allowed quantification of dermal absorption. The aim of the study was to assess distribution of test substance in the layers of skin. |
| | Metric 15: | Consistency of outcome assessment | High | Details of the outcome assessment protocol were reported and outcomes were assessed consistently across replicates. |
| | Metric 16: | Sampling adequacy and sensitivity | High | The sample size (n =5) was appropriate. OECD guidelines require a minimum of an n=4. The test substance was not radiolabeled. The authors reported the limits of detection for the methods used for quantification. |
| Domain 6: Confounding/Variable Control | | | | |

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**Study Citation:** Krenczkowska, D., Mojsiewicz-Pieńkowska, K., Wielgomas, B., Cal, K., Bartoszewski, R., Bartoszewska, S., Jankowski, Z. (2019). The consequences of overcoming the human skin barrier by siloxanes (silicones) Part 1. Penetration and permeation depth study of cyclic methyl siloxanes. Chemosphere 231:607-623.

**HERO ID:** 6833834

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 17: | Confounding variables in test design and procedures | Low | Insufficient details were provided to adequately assess confounding in the test design and procedures. Skin thickness was not reported. All of the samples passed the criteria for skin integrity, but individual measurements were not provided. Although the methods specified that skin samples were obtained from 5 females and 5 males, other chemicals were tested in the same study, and therefore, the sex of the samples used for the COI is not known. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | Solubility in the receptor fluid was not measured directly, although, the text is suggestive that D4 was soluble. No other confounding variables unrelated to exposure were identified. |
| Domain 7: Data Presentation and Analysis | | | | |
| | Metric 19: | Data analysis | High | The study reported means and relative standard deviations (%). More than half of the RSDs were <25%. The study reported a total cumulative dose for a 24-hour exposure but did not determine Kp/flux values for an infinite exposure scenario |
| | Metric 20: | Data interpretation | Medium | This study deviated from typical dermal absorption studies. The purpose of the study was to determine if and how easily an infinite dose of D4 can penetrate the stratum corneum during a 24-hour exposure and by what mechanism, and to determine the depth of penetration into other layers of the skin. The authors determined the flux through each skin layer and into the receptor fluid and used fluorescence microscopy to observe structural and integrity differences in the stratum corneum of treated samples vs. controls. Based on the context and purposes of the study, the author's interpretation of the data collected was appropriate. |
| | Metric 21: | Reporting of data | Medium | Data were reported for all of the outcomes specified in the methods. Individual data were not provided. |

## Overall Quality Determination — Uninformative

**Study Citation:** Mojsiewicz-Pieńkowska, K., Krenczkowska, D., Bazar, D., Wielgomas, B., Cal, K., Kaliszan, M. (2022). Comparative study of the percutaneous permeation and bioaccumulation of a cyclic siloxane using frozen-thawed and nonfrozen ex vivo human skin. Toxicology In Vitro 82:105379.

**HERO ID:** 11502430

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Nonfrozen skin; D4-Parent compound |
| Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type: | ex vivo human; Full thickness; 1400; Static; Notes: Not Reported |
| Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent): | Occluded; No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin: | 149.3; 24 hrs; Not Reported |
| Duration of Absorbance Measured; Frequency of Samples: | 24 hrs; There was only a single collection at the end of the experiment.; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | At the end of the exposure period, the skin surface was dried with absorbent paper, then washed with a cotton bud soaked in carbon tetrachloride and blotted dry again.; No |
| Total Recovery (percent); Dose Type: | Not Reported; Infinite |
| Percent Found in Skin Depot After Washing and Tape Stripping; Comments: | Not Reported; Notes: The mean amount of D4 in the epidermis was 4.54 ug (CV= 34.8) and the amount in the dermis was 2.11 ug (CV= 21.4). These values were determined by this Reviewer by multiplying the reported amount (7.1 and 3.3 ug/cm2/24 hrs, respectively) by 0.64 cm2 (the surface area of the exposed skin) |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments: | Not Reported; Notes: The mean amount of D4 in the epidermis was 4.54 ug (CV= 34.8) and the amount in the dermis was 2.11 ug (CV= 21.4). These values were determined by this Reviewer by multiplying the reported amount (7.1 and 3.3 ug/cm2/24 hrs, respectively) by 0.64 cm2 (the surface area of the exposed skin) |
| Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments: | Not Reported; Notes: The mean amount of D4 in the receptor fluid was 1.6 ug (CV= 20.5). This was determined by this Reviewer by multiplying the reported amount (2.5 ug/cm2/24 hr) by 0.64 cm2 (the surface area of the exposed skin). |
| Total Percent Absorbed: | 0 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maxium Permeability Coefficient (Kp) (cm/hr); Maxium Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments): | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The unlabeled test substance was identified as octamethylcyclotetrasiloxane (D4). No radiolabeled test substance was used. Physical/chemical properties were reported. No CASRN or structure was provided. |
| Metric 2: | Test substance source | Low | The test substance was sourced from Sigma-Aldrich. No lot, batch, catalogue number, or certificate of analysis was provided. Certificates of analysis can generally be obtained from Sigma-Aldrich if the lot or catalogue number of the exact product is known. The test substance was not analytically verified by the performing laboratory. |

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**Study Citation:** Mojsiewicz-Pieńkowska, K., Krenczkowska, D., Bazar, D., Wielgomas, B., Cal, K., Kaliszan, M. (2022). Comparative study of the percutaneous permeation and bioaccumulation of a cyclic siloxane using frozen-thawed and nonfrozen ex vivo human skin. Toxicology In Vitro 82:105379.

**HERO ID:** 11502430

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 3: | Test substance purity | Low | The test substance purity was not reported; however, Sigma Aldrich typically only sells high grade chemicals. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Reference compounds | Medium | The study did not test reference compounds but the laboratory has demonstrated proficiency in the methods used, and validation of the methods was conducted in HERO 6833834 and 6836150. |
| | Metric 5: | Assay procedures | Medium | This is a non-standard study focused on the evaluation of whether freezing human skin samples influences the integrity and permeation characteristics of D4. Experiments were conducted in sink conditions in a static Franz-type diffusion cell system at 32 degrees C. under occlusion for 24 hours. Occlusion was not specified but is assumed based on the images shown and on previous experiments conducted in the same laboratory using the same study design. Full-thickness human cadaver skin samples (mean thickness 1.40 ± 0.2 mm) were mounted onto diffusion cells leaving a surface area of 0.64 cm2. Eight replicates were included. A 100uL volume (95.6 mg) was applied as an infinite dose onto the skin surface area of 0.64 cm2; equivalent to a loading rate of 149.3 mg/cm2. Receptor fluid consisted of an aqueous solution with sodium chloride, Igepal CA 630 (as a surfactant) and sodium azide. It was not specified whether the receptor fluid was stirred during the experiment. At the end of the exposure period, the skin surface was dried with absorbent paper, then washed with a cotton bud soaked in carbon tetrachloride and blotted dry again. The skin was tape-stripped to obtain 20 layers of the stratum corneum; the first three layers were discarded. A heat-separating technique (in water) was then used to separate the dermis and epidermis. Measurements were made from each layer (stratum corneum, epidermis, and dermis) and the receptor fluid via GC-FID chromatography. The limits of quantitation were not reported, but the sensitivity of the methods used has been described in previous publications by the same laboratory. |
| | Metric 6: | Standards for tests | Medium | Skin integrity was assessed using Electrical Resistance with an author-specified inclusion criteria of 2kΩ/cm2. Separate skin samples from the same donors were examined using fluorescent microscopy to visualize the integrity of the stratum corneum. The study reported CV values for all measured endpoints (see metric 19 for additional details on results). Percent recovery was not reported; however, that was not included as part of the study design. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 7: | Preparation and storage of test substance (chemical) | Medium | The Neat test substance was applied as a single application; no preparation was needed. Storage conditions were not reported for a volatile test substance. |
| | Metric 8: | Consistency of exposure administration | Medium | Exposure administration was consistent across groups with respect to the applied volume, skin surface area and experimental set-up. The study used full-thickness human skin. Skin was obtained from the same anatomical site (abdominal region) and thickness showed a low standard deviation (1.4 ± 0.2 mm). The age of the cadaver ranged from 35-50 years (average age of females was 40 years; average age of males was 45 years). |
| | Metric 9: | Reporting of concentrations | Medium | The test substance doses were reported without ambiguity. A 100uL volume (95.6 mg) was applied as an infinite dose onto the skin surface area of 0.64 cm2; equivalent to a loading rate of 149.3 mg/cm2. Doses of the neat test material were not analytically verified. |

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**Study Citation:** Mojsiewicz-Pieńkowska, K., Krenczkowska, D., Bazar, D., Wielgomas, B., Cal, K., Kaliszan, M. (2022). Comparative study of the percutaneous permeation and bioaccumulation of a cyclic siloxane using frozen-thawed and nonfrozen ex vivo human skin. Toxicology In Vitro 82:105379.

**HERO ID:** 11502430

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 10: | Exposure frequency | High | The 24 hour exposure duration was appropriate for the study type and the outcomes of interest. |
| | Metric 11: | Number of exposure groups and concentration spacing | High | The study only tested Neat (undiluted) test substance which was appropriate given the purposes of the experiment. |
| Domain 4: Test Model | | | | |
| | Metric 12: | Test model (skin) | Low | The study used full-thickness abdominal cadaver skin from 2 males (mean age 45 yrs) and 2 females (mean age 40 yrs), obtained 48 hours after death. Excess fat was removed and skin was washed in 0.9% NaCl and dried and skin from each donor was divided into 4 smaller pieces. The mean thickness was 1.40 $\pm$ 0.2 mm, which is thicker than guideline recommendations of up to 1.0 mm. Half of the samples were left unfrozen, and the other half were frozen at -20 degrees C. for two weeks. The integrity of both samples (nonfrozen and frozen-thawed) was tested prior to exposure using electrical resistance. All of the samples had values above the limit of 2 kilo-ohms/cm2. |
| | Metric 13: | Number/Replicates per group | Medium | A total of 8 replicates were tested (duplicate samples from 4 donors). The number of samples was appropriate based on current OECD guidelines. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Uninformative | This was a non-guideline study. The study only tested the Neat test substance. A 100uL volume (95.6 mg) was applied dose onto the skin surface area of 0.64 cm2; equivalent to a loading rate of 149.3 mg/cm2. This was appropriate for an infinite exposure scenario. The study did not report a Kp/flux value but did report a total cumulative dose over time (based on measurements in each layer of skin (stratum corneum, epidermis, dermis) and in fluid receptor). It was not specified whether the exposure scenario was relevant to the conditions of use, but this was not the purpose of the study. This study was deemed uninformative because it was not conducted in way that allowed quantification of dermal absorption. The aim of the study was to assess distribution of test substance in the layers of skin. |
| | Metric 15: | Consistency of outcome assessment | High | Details regarding the execution of the study protocol for outcome assessment were reported and the outcomes were consistently assessed across replicates. |
| | Metric 16: | Sampling adequacy and sensitivity | High | The study sampled 8 replicates (from 4 donors). Details of the extraction of D4 from tissues and the use of internal standards were provided. GC-FID is sensitive for the outcomes of interest. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | High | Electrical resistance testing resulted in an average of 13.3 kΩ/0.64 cm2 (range 12.2-14.7), or 22.1 $\pm$ 4.1 kΩ/cm2 for non-frozen skin and 14.2.3 kΩ/0.64 cm2 (range 12.2-14.7) or 20.8 $\pm$ 1.01 kΩ/cm2 for frozen skin. Separate samples of skin from the same donors were also examined using fluorescence microscopy to assess the integrity of the stratum corneum. The stratum corneum was intact and showed expected characteristic structures. No differences in integrity were observed between the non-frozen and the frozen skin samples. |

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**Study Citation:** Mojsiewicz-Pieńkowska, K., Krenczkowska, D., Bazar, D., Wielgomas, B., Cal, K., Kaliszan, M. (2022). Comparative study of the percutaneous permeation and bioaccumulation of a cyclic siloxane using frozen-thawed and nonfrozen ex vivo human skin. Toxicology In Vitro 82:105379.

**HERO ID:** 11502430

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | Solubility testing was not conducted in this experiment, but the experiment was run under sink conditions and solubility in the receptor fluid is not expected to have a significant impact on the study results. |
| Domain 7: Data Presentation and Analysis | | | | |
| | Metric 19: | Data analysis | Low | The total amount of D4 diffused into the skin within a 24-hour period was reported. This non-standard study did not measure absorption estimates across a time series. More than half of the CV values were <25% for nonfrozen samples. For frozen samples, half of the CV values were <25% and the other half were between 25% and 50%. 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 | The purpose of this study was to determine whether freezing and thawing human cadaver skin samples compromise its integrity or alters permeation. Data interpretation of the endpoints reported was appropriate. In this study, and others conducted by this laboratory (HEROs 6833834 and 6836150) it is clear the authors conduct these experiments as supplements to the standard dermal absorption studies and to answer specific questions; which for the current study, was to determine whether skin storage conditions affect penetration and permeation of xenobiotics. Therefore, this study did not provide sufficient data to assess standard dermal absorption endpoints. |
| | Metric 21: | Reporting of data | High | Data for all specified outcomes were reported for 8 replicates. CVs were calculated. |

## Overall Quality Determination — Uninformative

**Study Citation:** Mojsiewicz-Pieńkowska, K., Krenczkowska, D., Bazar, D., Wielgomas, B., Cal, K., Kaliszan, M. (2022). Comparative study of the percutaneous permeation and bioaccumulation of a cyclic siloxane using frozen-thawed and nonfrozen ex vivo human skin. Toxicology In Vitro 82:105379.

**HERO ID:** 11502430

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Frozen-thawed skin; D4-Parent compound |
| Skin Material/Species; Skin Preparation; Skin Thickness (um); Diffusion Cell Exposure Setup Type: | ex vivo human; Full thickness; 1400; Static; Notes: Not Reported |
| Occlusion Type; Donor Chamber Vehicle; Concentration of Test Substance in Vehicle (enter as percent): | Occluded; No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Duration of Test Substance on Skin: | 149.3; 24 hrs; Not Reported |
| Duration of Absorbance Measured; Frequency of Samples: | 24 hrs; There was only a single collection at the end of the experiment.; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | At the end of the exposure period, the skin surface was dried with absorbent paper, then washed with a cotton bud soaked in carbon tetrachloride and blotted dry again.; No |
| Total Recovery (percent); Dose Type: | Not Reported; Infinite |
| Percent Found in Skin Depot After Washing and Tape Stripping; Comments: | Not Reported; Notes: The mean amount of D4 in the epidermis was 4.3 ug (CV= 32.7) and the amount in the dermis was 2.5 ug (CV= 27.7). These values were determined by this Reviewer by multiplying the reported amount (6.7 and 3.9 ug/cm2/24 hrs, respectively) by 0.64 cm2 (the surface area of the exposed skin). |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips; Comments: | Not Reported; Notes: The mean amount of D4 in the epidermis was 4.3 ug (CV= 32.7) and the amount in the dermis was 2.5 ug (CV= 27.7). These values were determined by this Reviewer by multiplying the reported amount (6.7 and 3.9 ug/cm2/24 hrs, respectively) by 0.64 cm2 (the surface area of the exposed skin). |
| Percent Found in Receptor Fluid and Receptor Fluid Rinse; Comments: | Not Reported; Notes: The mean amount of D4 in the receptor fluid was 1.7 ug (CV= 32.5). This was determined by this Reviewer by multiplying the reported amount (2.7 ug/cm2/24 hr) by 0.64 cm2 (the surface area of the exposed skin). |
| Total Percent Absorbed: | 0 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maxium Permeability Coefficient (Kp) (cm/hr); Maxium Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments): | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: The study reported the total amount of D4 after diffusion through the skin following a 24-hour exposure of 43.6 ug/cm2/24 hour |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The unlabeled test substance was identified as octamethylcyclotetrasiloxane (D4). No radiolabeled test substance was used. Physical/chemical properties were reported. No CASRN or structure was provided. |
| Metric 2: | Test substance source | Low | The test substance was sourced from Sigma-Aldrich. No lot, batch, catalogue number, or certificate of analysis was provided. Certificates of analysis can generally be obtained from Sigma-Aldrich if the lot or catalogue number of the exact product is known. The test substance was not analytically verified by the performing laboratory. |

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**Study Citation:** Mojsiewicz-Pieńkowska, K., Krenczkowska, D., Bazar, D., Wielgomas, B., Cal, K., Kaliszan, M. (2022). Comparative study of the percutaneous permeation and bioaccumulation of a cyclic siloxane using frozen-thawed and nonfrozen ex vivo human skin. Toxicology In Vitro 82:105379.

**HERO ID:** 11502430

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 3: | Test substance purity | Low | The test substance purity was not reported; however, Sigma Aldrich typically only sells high grade chemicals. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Reference compounds | Medium | The study did not test reference compounds but the laboratory has demonstrated proficiency in the methods used, and validation of the methods was conducted in HERO 6833834 and 6836150. |
| | Metric 5: | Assay procedures | Medium | This is a non-standard study focused on the evaluation of whether freezing human skin samples influences the integrity and permeation characteristics of D4. Experiments were conducted in sink conditions in a static Franz-type diffusion cell system at 32 degrees C. under occlusion for 24 hours. Occlusion was not specified but is assumed based on the images shown and on previous experiments conducted in the same laboratory using the same study design. Full-thickness human cadaver skin samples (mean thickness 1.40 ± 0.2 mm) were mounted onto diffusion cells leaving a surface area of 0.64 cm2. Eight replicates were included. A 100uL volume (95.6 mg) was applied as an infinite dose onto the skin surface area of 0.64 cm2; equivalent to a loading rate of 149.3 mg/cm2. Receptor fluid consisted of an aqueous solution with sodium chloride, Igepal CA 630 (as a surfactant) and sodium azide. It was not specified whether the receptor fluid was stirred during the experiment. At the end of the exposure period, the skin surface was dried with absorbent paper, then washed with a cotton bud soaked in carbon tetrachloride and blotted dry again. The skin was tape-stripped to obtain 20 layers of the stratum corneum; the first three layers were discarded. A heat-separating technique (in water) was then used to separate the dermis and epidermis. Measurements were made from each layer (stratum corneum, epidermis, and dermis) and the receptor fluid via GC-FID chromatography. The limits of quantitation were not reported, but the sensitivity of the methods used has been described in previous publications by the same laboratory. |
| | Metric 6: | Standards for tests | Medium | Skin integrity was assessed using Electrical Resistance with an author-specified inclusion criteria of 2kΩ/cm2. Separate skin samples from the same donors were examined using fluorescent microscopy to visualize the integrity of the stratum corneum. The study reported CV values for all measured endpoints (see metric 19 for additional details on results). Percent recovery was not reported; however, that was not included as part of the study design. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 7: | Preparation and storage of test substance (chemical) | Medium | The Neat test substance was applied as a single application; no preparation was needed. Storage conditions were not reported for a volatile test substance. |
| | Metric 8: | Consistency of exposure administration | Medium | Exposure administration was consistent across groups with respect to the applied volume, skin surface area and experimental set-up. The study used full-thickness human skin. Skin was obtained from the same anatomical site (abdominal region) and thickness showed a low standard deviation (1.4 ± 0.2 mm). The age of the cadaver ranged from 35-50 years (average age of females was 40 years; average age of males was 45 years). |
| | Metric 9: | Reporting of concentrations | Medium | The test substance doses were reported without ambiguity. A 100uL volume (95.6 mg) was applied as an infinite dose onto the skin surface area of 0.64 cm2; equivalent to a loading rate of 149.3 mg/cm2. Doses of the neat test material were not analytically verified. |

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**Study Citation:** Mojsiewicz-Pieńkowska, K., Krenczkowska, D., Bazar, D., Wielgomas, B., Cal, K., Kaliszan, M. (2022). Comparative study of the percutaneous permeation and bioaccumulation of a cyclic siloxane using frozen-thawed and nonfrozen ex vivo human skin. Toxicology In Vitro 82:105379.

**HERO ID:** 11502430

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 10: | Exposure frequency | High | The 24 hour exposure duration was appropriate for the study type and the outcomes of interest. |
| | Metric 11: | Number of exposure groups and concentration spacing | High | The study only tested Neat (undiluted) test substance which was appropriate given the purposes of the experiment. |
| Domain 4: Test Model | | | | |
| | Metric 12: | Test model (skin) | Low | The study used full-thickness abdominal cadaver skin from 2 males (mean age 45 yrs) and 2 females (mean age 40 yrs), obtained 48 hours after death. Excess fat was removed and skin was washed in 0.9% NaCl and dried and skin from each donor was divided into 4 smaller pieces. The mean thickness was 1.40 $\pm$ 0.2 mm, which is thicker than guideline recommendations of up to 1.0 mm. Half of the samples were left unfrozen, and the other half were frozen at -20 degrees C. for two weeks. The integrity of both samples (nonfrozen and frozen-thawed) was tested prior to exposure using electrical resistance. All of the samples had values above the limit of 2 kilo-ohms/cm2. |
| | Metric 13: | Number/Replicates per group | Medium | A total of 8 replicates were tested (duplicate samples from 4 donors). The number of samples was appropriate based on current OECD guidelines. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Uninformative | This was a non-guideline study. The study only tested the Neat test substance. A 100uL volume (95.6 mg) was applied dose onto the skin surface area of 0.64 cm2; equivalent to a loading rate of 149.3 mg/cm2. This was appropriate for an infinite exposure scenario. The study did not report a Kp/flux value but did report a total cumulative dose over time (based on measurements in each layer of skin (stratum corneum, epidermis, dermis) and in fluid receptor). It was not specified whether the exposure scenario was relevant to the conditions of use, but this was not the purpose of the study. This study was deemed uninformative because it was not conducted in way that allowed quantification of dermal absorption. The aim of the study was to assess distribution of test substance in the layers of skin. |
| | Metric 15: | Consistency of outcome assessment | High | Details regarding the execution of the study protocol for outcome assessment were reported and the outcomes were consistently assessed across replicates. |
| | Metric 16: | Sampling adequacy and sensitivity | High | The study sampled 8 replicates (from 4 donors). Details of the extraction of D4 from tissues and the use of internal standards were provided. GC-FID is sensitive for the outcomes of interest. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | High | Electrical resistance testing resulted in an average of 13.3 kΩ/0.64 cm2 (range 12.2-14.7), or 22.1 $\pm$ 4.1 kΩ/cm2 for non-frozen skin and 14.2.3 kΩ/0.64 cm2 (range 12.2-14.7) or 20.8 $\pm$ 1.01 kΩ/cm2 for frozen skin. Separate samples of skin from the same donors were also examined using fluorescence microscopy to assess the integrity of the stratum corneum. The stratum corneum was intact and showed expected characteristic structures. No differences in integrity were observed between the non-frozen and the frozen skin samples. |

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**Study Citation:** Mojsiewicz-Pieńkowska, K., Krenczkowska, D., Bazar, D., Wielgomas, B., Cal, K., Kaliszan, M. (2022). Comparative study of the percutaneous permeation and bioaccumulation of a cyclic siloxane using frozen-thawed and nonfrozen ex vivo human skin. Toxicology In Vitro 82:105379.

**HERO ID:** 11502430

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | Solubility testing was not conducted in this experiment, but the experiment was run under sink conditions and solubility in the receptor fluid is not expected to have a significant impact on the study results. |
| Domain 7: Data Presentation and Analysis | | | | |
| | Metric 19: | Data analysis | Low | The total amount of D4 diffused into the skin within a 24-hour period was reported. This non-standard study did not measure absorption estimates across a time series. More than half of the CV values were <25% for nonfrozen samples. For frozen samples, half of the CV values were <25% and the other half were between 25% and 50%. 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 | The purpose of this study was to determine whether freezing and thawing human cadaver skin samples compromise its integrity or alters permeation. Data interpretation of the endpoints reported was appropriate. In this study, and others conducted by this laboratory (HEROs 6833834 and 6836150) it is clear the authors conduct these experiments as supplements to the standard dermal absorption studies and to answer specific questions; which for the current study, was to determine whether skin storage conditions affect penetration and permeation of xenobiotics. Therefore, this study did not provide sufficient data to assess standard dermal absorption endpoints. |
| | Metric 21: | Reporting of data | High | Data for all specified outcomes were reported for 8 replicates. CVs were calculated. |

## Overall Quality Determination — Uninformative

**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Mass Balance -High dose-6-hr; D4-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Female; Semi-occluded (e.g., gauze) |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 9.78; 24.5 mg/rat |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | 6 hrs; Not Reported; Notes: Not Reported |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | 6 hrs; Animals were sacrificed immediately after the exposure period.; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | The skin was not washed; Yes |
| Total Recovery (percent); Dose Type: | 96.03; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 0.34; Notes: Not Reported |
| Percent Found in Urine ; Comments: | 0; Notes: Not Reported |
| Percent Found in Feces ; Comments: | 0; Notes: Not Reported |
| Percent Found in Blood/Serum ; Comments: | 0; Notes: Not Reported |
| Percent Found in Air ; Comments: | 0.39; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | 0; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | Not Reported; Notes: Not Reported |
| Total Percent Absorbed: | 0 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Carcass =0.05% CV = 40% |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as Octamethylcyclotetrasiloxane (D4) CASRN 556-67-2 and was in liquid form. Unlabeled (244 Fluid) and radiolabeled test substances were used. The position of the radiolabel was not specified. A structure was provided in the published report along with physical/chemical properties. |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 2: | Test substance source | High | The lot numbers were provided. The radiolabeled test substance was supplied by Wizard Laboratories. The un-labeled test substance was supplied by Dow Corning as 244 Fluid. The chemical identities were confirmed by the HES Test Article Characterization Group using GC-MS. |
| | Metric 3: | Test substance purity | High | The mean radiochemical purity was 99.56%. The purity of the unlabeled test substance was 99.62%Radiochemical purities of the dosing solutions were also reported. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Medium | Non-cannulated rats were randomized using a table of random numbers. All animals were within ±20% of the mean body weight of the group. No randomization procedure was used for cannulated animals. |
| | Metric 5: | Standards for Tests | Medium | Percent recovery was reported for all groups. Coefficients of variation were not provided in the study report, but could be calculated using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | High | Preparation and storage details of the purchased test material and all test preparations were reported. Preparation was conducted within 5 days prior to use. Stability was not assessed, but test solutions were analyzed prior to exposure to confirm concentrations. |
| | Metric 7: | Consistency of exposure administration | Medium | Exposures were consistent across groups. The skin area was reported to be 2.5 cm2, although the report also indicated the internal diameter of the skin depot was reported to be 1.8 cm. This area is smaller than expected for a rat; however, the study reports that it was ~10% of the animal's body surface which is consistent with OECD guidelines. The volume of the test substance applied was not specified. The test substance was applied using a syringe, and there was some variation across replicates in the applied dose. |
| | Metric 8: | Reporting of concentrations | High | Concentrations were reported without ambiguity. The specific activity was measured on the day of dosing. The target dose levels were 2, 4.8, and 10 mg/cm2. Individual dosing data were provided. The applied dose was determined gravimetrically. |
| | Metric 9: | Exposure duration | High | Main (mass balance) group animals were exposed for 1, 6, or 24 hours then sacrificed immediately. Wash group animals were exposed for 24 hours, skin was washed, and these animals were kept in metabolism cages for an additional six days. The durations were consistent with current standards for this study type and were meant to mimic possible conditions of use. |
| | Metric 10: | Number of exposure groups and concentration spacing | Medium | The study tested three exposure concentrations distributed at log intervals that cover the range of exposures expected in personal care products. Each concentration was run as a separate experiment with its own control. The authors did not justify using neat vs. dilutions of the test substance. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | High | The study used female CDF (Fisher 344)/CrlBR rats. The source, body weights (122-155g), and age were reported. The study authors justified the strain and sex. |
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | High | Animal husbandry conditions (cage type, temperature, humidity, light cycle, food and water access, air changes per hour) were reported. Animals were housed individually. Conditions were consistent across groups. |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | | Metric | Rating | Comments |
|---|---|---|---|---|
| | Metric 13: | Number of animals per group | Medium | The study used use 4 animals per dose/time point which is consistent with the minimum requirements specified by OECD 427. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The outcome assessment methodology was described in detail and was appropriate for the outcomes of interest. Briefly, in a non-guideline study, neat D4 was applied to the skin of female Fisher 344 rats (n = 12/dose group; 4/dose/time point), under semi-occluded conditions, at 2, 4.8, or 10 mg/cm2 for 1, 6, or 24-hours and then sacrificed. An additional group (n = 4) were exposed to 10 mg/cm2 for 24 hours; the skin was then washed, charcoal baskets were replaced, and animals were returned to metabolism cages for collection of excreta and expired volatiles for an additional 6 days. A subset of rats was cannulated for measuring concentrations in blood during the exposure period. Animals were kept in Roth-style glass metabolism cages. Urine, feces, and air were collected. At the end of exposure (or at 168 hr post-exposure), blood was collected. Skin was washed and tape stripped. Extractions were done from charcoal baskets. Radioactivity was measured from all collections using LSC. The % absorbed dose was calculated from measurements in blood, carcass, excised skin, expired air, urine, feces, and CO2. Portions in the skin washes, stratum corneum (tape stripped), and skin depot were considered to be non-absorbed material. Radioactivity in the charcoal baskets and Teflon tape represented the volatile portion. Measurements in blood in the cannulated rats were expressed as ug D4/g blood and in expired air as ug D4/hr. Detailed methods of sample storage, extractions, and LSC were provided. The authors did not explicitly report whether finite or infinite exposures were used and the volume applied was not specified; based on the endpoints evaluated this was a finite exposure scenario that determined % absorbed. |
| | Metric 15: | Consistency of outcome assessment | High | The outcome assessment protocol was reported and was consistent across groups. |
| | Metric 16: | Sampling adequacy and sensitivity | High | The sample sizes were appropriate. The frequency of collections was reported. Each sample was counted for 10 minutes or at 2 Sigma %value. Corrections for matric background radioactivity were made. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | The same lot numbers of the test chemical were used. Reserve animals were kept to replace any animals that showed signs of skin damage after hair clipping. Animal body weights were all within ±20% of the mean. Measurements in expired air showed some anomalous values. The authors noted that this indicated that several skin depots may have leaked, which resulted in high recoveries of the test material in the expired volatile charcoal traps. Any outliers were removed from the dataset; however smaller leaks may have also occurred potentially confounding results. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | All animals were observed daily for mortality, morbidity, and clinical signs. Gravimetric determinations of dosing showed there were some technical within-group variations in the applied dose (mg/cm2) across replicates which may have contributed to any endpoint variation. |
| Domain 7: Data Presentation and Analysis | | | | |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 19: | Data analysis | High | Statistical methods and calculations were clearly described and appropriate. More than 50% of the endpoint CV values were <25%. Individual data were provided. |
| | Metric 20: | Data interpretation | Medium | The interpretation of results were mostly consistent with current guidelines. Recovery was >90% for all of the groups specified. All of the tape strips (5 strips, that removed all of the stratum coronium) were not included in the absorption estimate. However, all data are available to conduct alternate calculations. |
| | Metric 21: | Reporting of Data | High | Data for all of the outcomes were reported by dose group and time point. Values were presented as mean ± SEM or SD and individual animal data were provided. |

## Overall Quality Determination High

**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Wash group -High dose-24-hr; D4-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Female; Semi-occluded (e.g., gauze) |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 9.78; 24.4 mg/rat |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | 24 hrs; Not Reported; Notes: Not Reported |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | Other; Skin was washed after 24-hours, then animals were kept in metabolism cages for an additional 6 days.; Notes: 168 hours |
| Time Skin was Washed and Method used; Radiolabel Presence: | Skin was washed 3x with a cotton swab soaked with a 1% soap solution, followed by a dry swab, the washed 3x with a cotton swab soaked with 70% ethanol, and one dry swab.; Yes |
| Total Recovery (percent); Dose Type: | 91.69; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 0.08; Notes: Not Reported |
| Percent Found in Urine ; Comments: | 0.08; Notes: Not Reported |
| Percent Found in Feces ; Comments: | 0.02; Notes: Not Reported |
| Percent Found in Blood/Serum ; Comments: | 0; Notes: Not Reported |
| Percent Found in Air ; Comments: | 0.15; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | 0; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | Not Reported; Notes: Not Reported |
| Total Percent Absorbed: | 0 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Carcass =0.02% CV = 0 |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as Octamethylcyclotetrasiloxane (D4) CASRN 556-67-2 and was in liquid form. Unlabeled (244 Fluid) and radiolabeled test substances were used. The position of the radiolabel was not specified. A structure was provided in the published report along with physical/chemical properties. |

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**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 2: | Test substance source | High | The lot numbers were provided. The radiolabeled test substance was supplied by Wizard Laboratories. The un-labeled test substance was supplied by Dow Corning as 244 Fluid. The chemical identities were confirmed by the HES Test Article Characterization Group using GC-MS. |
| | Metric 3: | Test substance purity | High | The mean radiochemical purity was 99.56%. The purity of the unlabeled test substance was 99.62%Radiochemical purities of the dosing solutions were also reported. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Medium | Non-cannulated rats were randomized using a table of random numbers. All animals were within ±20% of the mean body weight of the group. No randomization procedure was used for cannulated animals. |
| | Metric 5: | Standards for Tests | Medium | Percent recovery was reported for all groups. Coefficients of variation were not provided in the study report, but could be calculated using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | High | Preparation and storage details of the purchased test material and all test preparations were reported. Preparation was conducted within 5 days prior to use. Stability was not assessed, but test solutions were analyzed prior to exposure to confirm concentrations. |
| | Metric 7: | Consistency of exposure administration | Medium | Exposures were consistent across groups. The skin area was reported to be 2.5 cm2, although the report also indicated the internal diameter of the skin depot was reported to be 1.8 cm. This area is smaller than expected for a rat; however, the study reports that it was ~10% of the animal's body surface which is consistent with OECD guidelines. The volume of the test substance applied was not specified. The test substance was applied using a syringe, and there was some variation across replicates in the applied dose. |
| | Metric 8: | Reporting of concentrations | High | Concentrations were reported without ambiguity. The specific activity was measured on the day of dosing. The target dose levels were 2, 4.8, and 10 mg/cm2. Individual dosing data were provided. The applied dose was determined gravimetrically. |
| | Metric 9: | Exposure duration | High | Main (mass balance) group animals were exposed for 1, 6, or 24 hours then sacrificed immediately. Wash group animals were exposed for 24 hours, skin was washed, and these animals were kept in metabolism cages for an additional six days. The durations were consistent with current standards for this study type and were meant to mimic possible conditions of use. |
| | Metric 10: | Number of exposure groups and concentration spacing | Medium | The study tested three exposure concentrations distributed at log intervals that cover the range of exposures expected in personal care products. Each concentration was run as a separate experiment with its own control. The authors did not justify using neat vs. dilutions of the test substance. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | High | The study used female CDF (Fisher 344)/CrlBR rats. The source, body weights (122-155g), and age were reported. The study authors justified the strain and sex. |
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | High | Animal husbandry conditions (cage type, temperature, humidity, light cycle, food and water access, air changes per hour) were reported. Animals were housed individually. Conditions were consistent across groups. |

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**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 13: | Number of animals per group | Medium | The study used use 4 animals per dose/time point which is consistent with the minimum requirements specified by OECD 427. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The outcome assessment methodology was described in detail and was appropriate for the outcomes of interest. Briefly, in a non-guideline study, neat D4 was applied to the skin of female Fisher 344 rats (n = 12/dose group; 4/dose/time point), under semi-occluded conditions, at 2, 4.8, or 10 mg/cm2 for 1, 6, or 24-hours and then sacrificed. An additional group (n = 4) were exposed to 10 mg/cm2 for 24 hours; the skin was then washed, charcoal baskets were replaced, and animals were returned to metabolism cages for collection of excreta and expired volatiles for an additional 6 days. A subset of rats was cannulated for measuring concentrations in blood during the exposure period. Animals were kept in Roth-style glass metabolism cages. Urine, feces, and air were collected. At the end of exposure (or at 168 hr post-exposure), blood was collected. Skin was washed and tape stripped. Extractions were done from charcoal baskets. Radioactivity was measured from all collections using LSC. The % absorbed dose was calculated from measurements in blood, carcass, excised skin, expired air, urine, feces, and CO2. Portions in the skin washes, stratum corneum (tape stripped), and skin depot were considered to be non-absorbed material. Radioactivity in the charcoal baskets and Teflon tape represented the volatile portion. Measurements in blood in the cannulated rats were expressed as ug D4/g blood and in expired air as ug D4/hr. Detailed methods of sample storage, extractions, and LSC were provided. The authors did not explicitly report whether finite or infinite exposures were used and the volume applied was not specified; based on the endpoints evaluated this was a finite exposure scenario that determined % absorbed. |
| | Metric 15: | Consistency of outcome assessment | High | The outcome assessment protocol was reported and was consistent across groups. |
| | Metric 16: | Sampling adequacy and sensitivity | High | The sample sizes were appropriate. The frequency of collections was reported. Each sample was counted for 10 minutes or at 2 Sigma %value. Corrections for matric background radioactivity were made. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | The same lot numbers of the test chemical were used. Reserve animals were kept to replace any animals that showed signs of skin damage after hair clipping. Animal body weights were all within ±20% of the mean. Measurements in expired air showed some anomalous values. The authors noted that this indicated that several skin depots may have leaked, which resulted in high recoveries of the test material in the expired volatile charcoal traps. Any outliers were removed from the dataset; however smaller leaks may have also occurred potentially confounding results. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | All animals were observed daily for mortality, morbidity, and clinical signs. Gravimetric determinations of dosing showed there were some technical within-group variations in the applied dose (mg/cm2) across replicates which may have contributed to any endpoint variation. |
| Domain 7: Data Presentation and Analysis | | | | |

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**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 19: | Data analysis | High | Statistical methods and calculations were clearly described and appropriate. More than 50% of the endpoint CV values were <25%. Individual data were provided. |
| | Metric 20: | Data interpretation | Medium | The interpretation of results were mostly consistent with current guidelines. Recovery was >90% for all of the groups specified. All of the tape strips (5 strips, that removed all of the stratum coronium) were not included in the absorption estimate. However, all data are available to conduct alternate calculations. |
| | Metric 21: | Reporting of Data | High | Data for all of the outcomes were reported by dose group and time point. Values were presented as mean ± SEM or SD and individual animal data were provided. |

## Overall Quality Determination High

**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Mass Balance -Mid dose-1-hr; D4-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Female; Semi-occluded (e.g., gauze) |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 4.85; 12.125 mg/rat |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | Other; Not Reported; Notes: 1 hr |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | Other; Animals were sacrificed immediately after the exposure period.; Notes: 1 hr |
| Time Skin was Washed and Method used; Radiolabel Presence: | The skin was not washed; Yes |
| Total Recovery (percent); Dose Type: | 94.77; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 0.52; Notes: Not Reported |
| Percent Found in Urine ; Comments: | 0; Notes: Not Reported |
| Percent Found in Feces ; Comments: | 0; Notes: Not Reported |
| Percent Found in Blood/Serum ; Comments: | 0; Notes: Not Reported |
| Percent Found in Air ; Comments: | 0.27; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | 0; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | Not Reported; Notes: Not Reported |
| Total Percent Absorbed: | 1 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Carcass =0.02% CV = 0 |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as Octamethylcyclotetrasiloxane (D4) CASRN 556-67-2 and was in liquid form. Unlabeled (244 Fluid) and radiolabeled test substances were used. The position of the radiolabel was not specified. A structure was provided in the published report along with physical/chemical properties. |

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**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 2: | Test substance source | High | The lot numbers were provided. The radiolabeled test substance was supplied by Wizard Laboratories. The un-labeled test substance was supplied by Dow Corning as 244 Fluid. The chemical identities were confirmed by the HES Test Article Characterization Group using GC-MS. |
| | Metric 3: | Test substance purity | High | The mean radiochemical purity was 99.56%. The purity of the unlabeled test substance was 99.62%Radiochemical purities of the dosing solutions were also reported. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Medium | Non-cannulated rats were randomized using a table of random numbers. All animals were within ±20% of the mean body weight of the group. No randomization procedure was used for cannulated animals. |
| | Metric 5: | Standards for Tests | Medium | Percent recovery was reported for all groups. Coefficients of variation were not provided in the study report, but could be calculated using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | High | Preparation and storage details of the purchased test material and all test preparations were reported. Preparation was conducted within 5 days prior to use. Stability was not assessed, but test solutions were analyzed prior to exposure to confirm concentrations. |
| | Metric 7: | Consistency of exposure administration | Medium | Exposures were consistent across groups. The skin area was reported to be 2.5 cm2, although the report also indicated the internal diameter of the skin depot was reported to be 1.8 cm. This area is smaller than expected for a rat; however, the study reports that it was ~10% of the animal's body surface which is consistent with OECD guidelines. The volume of the test substance applied was not specified. The test substance was applied using a syringe, and there was some variation across replicates in the applied dose. |
| | Metric 8: | Reporting of concentrations | High | Concentrations were reported without ambiguity. The specific activity was measured on the day of dosing. The target dose levels were 2, 4.8, and 10 mg/cm2. Individual dosing data were provided. The applied dose was determined gravimetrically. |
| | Metric 9: | Exposure duration | High | Main (mass balance) group animals were exposed for 1, 6, or 24 hours then sacrificed immediately. Wash group animals were exposed for 24 hours, skin was washed, and these animals were kept in metabolism cages for an additional six days. The durations were consistent with current standards for this study type and were meant to mimic possible conditions of use. |
| | Metric 10: | Number of exposure groups and concentration spacing | Medium | The study tested three exposure concentrations distributed at log intervals that cover the range of exposures expected in personal care products. Each concentration was run as a separate experiment with its own control. The authors did not justify using neat vs. dilutions of the test substance. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | High | The study used female CDF (Fisher 344)/CrlBR rats. The source, body weights (122-155g), and age were reported. The study authors justified the strain and sex. |
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | High | Animal husbandry conditions (cage type, temperature, humidity, light cycle, food and water access, air changes per hour) were reported. Animals were housed individually. Conditions were consistent across groups. |

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**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 13: | Number of animals per group | Medium | The study used use 4 animals per dose/time point which is consistent with the minimum requirements specified by OECD 427. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The outcome assessment methodology was described in detail and was appropriate for the outcomes of interest. Briefly, in a non-guideline study, neat D4 was applied to the skin of female Fisher 344 rats (n = 12/dose group; 4/dose/time point), under semi-occluded conditions, at 2, 4.8, or 10 mg/cm2 for 1, 6, or 24-hours and then sacrificed. An additional group (n = 4) were exposed to 10 mg/cm2 for 24 hours; the skin was then washed, charcoal baskets were replaced, and animals were returned to metabolism cages for collection of excreta and expired volatiles for an additional 6 days. A subset of rats was cannulated for measuring concentrations in blood during the exposure period. Animals were kept in Roth-style glass metabolism cages. Urine, feces, and air were collected. At the end of exposure (or at 168 hr post-exposure), blood was collected. Skin was washed and tape stripped. Extractions were done from charcoal baskets. Radioactivity was measured from all collections using LSC. The % absorbed dose was calculated from measurements in blood, carcass, excised skin, expired air, urine, feces, and CO2. Portions in the skin washes, stratum corneum (tape stripped), and skin depot were considered to be non-absorbed material. Radioactivity in the charcoal baskets and Teflon tape represented the volatile portion. Measurements in blood in the cannulated rats were expressed as ug D4/g blood and in expired air as ug D4/hr. Detailed methods of sample storage, extractions, and LSC were provided. The authors did not explicitly report whether finite or infinite exposures were used and the volume applied was not specified; based on the endpoints evaluated this was a finite exposure scenario that determined % absorbed. |
| | Metric 15: | Consistency of outcome assessment | High | The outcome assessment protocol was reported and was consistent across groups. |
| | Metric 16: | Sampling adequacy and sensitivity | High | The sample sizes were appropriate. The frequency of collections was reported. Each sample was counted for 10 minutes or at 2 Sigma %value. Corrections for matric background radioactivity were made. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | The same lot numbers of the test chemical were used. Reserve animals were kept to replace any animals that showed signs of skin damage after hair clipping. Animal body weights were all within ±20% of the mean. Measurements in expired air showed some anomalous values. The authors noted that this indicated that several skin depots may have leaked, which resulted in high recoveries of the test material in the expired volatile charcoal traps. Any outliers were removed from the dataset; however smaller leaks may have also occurred potentially confounding results. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | All animals were observed daily for mortality, morbidity, and clinical signs. Gravimetric determinations of dosing showed there were some technical within-group variations in the applied dose (mg/cm2) across replicates which may have contributed to any endpoint variation. |
| Domain 7: Data Presentation and Analysis | | | | |

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**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 19: | Data analysis | High | Statistical methods and calculations were clearly described and appropriate. More than 50% of the endpoint CV values were <25%. Individual data were provided. |
| | Metric 20: | Data interpretation | Medium | The interpretation of results were mostly consistent with current guidelines. Recovery was >90% for all of the groups specified. All of the tape strips (5 strips, that removed all of the stratum coronium) were not included in the absorption estimate. However, all data are available to conduct alternate calculations. |
| | Metric 21: | Reporting of Data | High | Data for all of the outcomes were reported by dose group and time point. Values were presented as mean ± SEM or SD and individual animal data were provided. |

## Overall Quality Determination High

**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Mass Balance -Mid dose-6-hr; D4-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Female; Semi-occluded (e.g., gauze) |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 4.8; 12.05 mg/rat |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | 6 hrs; Not Reported; Notes: Not Reported |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | 6 hrs; Animals were sacrificed immediately after the exposure period.; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | The skin was not washed; Yes |
| Total Recovery (percent); Dose Type: | 98.61; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 0.38; Notes: Not Reported |
| Percent Found in Urine ; Comments: | 0; Notes: Not Reported |
| Percent Found in Feces ; Comments: | 0; Notes: Not Reported |
| Percent Found in Blood/Serum ; Comments: | 0; Notes: Not Reported |
| Percent Found in Air ; Comments: | 0.26; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | 0; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | Not Reported; Notes: Not Reported |
| Total Percent Absorbed: | 0 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Carcass =0.04% CV = 0 |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as Octamethylcyclotetrasiloxane (D4) CASRN 556-67-2 and was in liquid form. Unlabeled (244 Fluid) and radiolabeled test substances were used. The position of the radiolabel was not specified. A structure was provided in the published report along with physical/chemical properties. |

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**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 2: | Test substance source | High | The lot numbers were provided. The radiolabeled test substance was supplied by Wizard Laboratories. The un-labeled test substance was supplied by Dow Corning as 244 Fluid. The chemical identities were confirmed by the HES Test Article Characterization Group using GC-MS. |
| | Metric 3: | Test substance purity | High | The mean radiochemical purity was 99.56%. The purity of the unlabeled test substance was 99.62%Radiochemical purities of the dosing solutions were also reported. |
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| | Metric 4: | Randomized allocation of animals | Medium | Non-cannulated rats were randomized using a table of random numbers. All animals were within ±20% of the mean body weight of the group. No randomization procedure was used for cannulated animals. |
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| | Metric 8: | Reporting of concentrations | High | Concentrations were reported without ambiguity. The specific activity was measured on the day of dosing. The target dose levels were 2, 4.8, and 10 mg/cm2. Individual dosing data were provided. The applied dose was determined gravimetrically. |
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| | Metric 10: | Number of exposure groups and concentration spacing | Medium | The study tested three exposure concentrations distributed at log intervals that cover the range of exposures expected in personal care products. Each concentration was run as a separate experiment with its own control. The authors did not justify using neat vs. dilutions of the test substance. |
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| | Metric 11: | Test animal characteristics | High | The study used female CDF (Fisher 344)/CrlBR rats. The source, body weights (122-155g), and age were reported. The study authors justified the strain and sex. |
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| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 13: | Number of animals per group | Medium | The study used use 4 animals per dose/time point which is consistent with the minimum requirements specified by OECD 427. |
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| | Metric 14: | Outcome assessment methodology | Medium | The outcome assessment methodology was described in detail and was appropriate for the outcomes of interest. Briefly, in a non-guideline study, neat D4 was applied to the skin of female Fisher 344 rats (n = 12/dose group; 4/dose/time point), under semi-occluded conditions, at 2, 4.8, or 10 mg/cm2 for 1, 6, or 24-hours and then sacrificed. An additional group (n = 4) were exposed to 10 mg/cm2 for 24 hours; the skin was then washed, charcoal baskets were replaced, and animals were returned to metabolism cages for collection of excreta and expired volatiles for an additional 6 days. A subset of rats was cannulated for measuring concentrations in blood during the exposure period. Animals were kept in Roth-style glass metabolism cages. Urine, feces, and air were collected. At the end of exposure (or at 168 hr post-exposure), blood was collected. Skin was washed and tape stripped. Extractions were done from charcoal baskets. Radioactivity was measured from all collections using LSC. The % absorbed dose was calculated from measurements in blood, carcass, excised skin, expired air, urine, feces, and CO2. Portions in the skin washes, stratum corneum (tape stripped), and skin depot were considered to be non-absorbed material. Radioactivity in the charcoal baskets and Teflon tape represented the volatile portion. Measurements in blood in the cannulated rats were expressed as ug D4/g blood and in expired air as ug D4/hr. Detailed methods of sample storage, extractions, and LSC were provided. The authors did not explicitly report whether finite or infinite exposures were used and the volume applied was not specified; based on the endpoints evaluated this was a finite exposure scenario that determined % absorbed. |
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| | Metric 16: | Sampling adequacy and sensitivity | High | The sample sizes were appropriate. The frequency of collections was reported. Each sample was counted for 10 minutes or at 2 Sigma %value. Corrections for matric background radioactivity were made. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | The same lot numbers of the test chemical were used. Reserve animals were kept to replace any animals that showed signs of skin damage after hair clipping. Animal body weights were all within ±20% of the mean. Measurements in expired air showed some anomalous values. The authors noted that this indicated that several skin depots may have leaked, which resulted in high recoveries of the test material in the expired volatile charcoal traps. Any outliers were removed from the dataset; however smaller leaks may have also occurred potentially confounding results. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | All animals were observed daily for mortality, morbidity, and clinical signs. Gravimetric determinations of dosing showed there were some technical within-group variations in the applied dose (mg/cm2) across replicates which may have contributed to any endpoint variation. |
| Domain 7: Data Presentation and Analysis | | | | |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 19: | Data analysis | High | Statistical methods and calculations were clearly described and appropriate. More than 50% of the endpoint CV values were <25%. Individual data were provided. |
| | Metric 20: | Data interpretation | Medium | The interpretation of results were mostly consistent with current guidelines. Recovery was >90% for all of the groups specified. All of the tape strips (5 strips, that removed all of the stratum coronium) were not included in the absorption estimate. However, all data are available to conduct alternate calculations. |
| | Metric 21: | Reporting of Data | High | Data for all of the outcomes were reported by dose group and time point. Values were presented as mean ± SEM or SD and individual animal data were provided. |

## Overall Quality Determination High

**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Mass Balance -Mid dose-24-hr; D4-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Female; Semi-occluded (e.g., gauze) |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 4.8; 12.0 mg/rat |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | 24 hrs; Not Reported; Notes: Not Reported |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | 24 hrs; Animals were sacrificed immediately after the exposure period.; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | The skin was not washed; Yes |
| Total Recovery (percent); Dose Type: | 94.57; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 0.23; Notes: Not Reported |
| Percent Found in Urine ; Comments: | 0.04; Notes: Not Reported |
| Percent Found in Feces ; Comments: | 0.01; Notes: Not Reported |
| Percent Found in Blood/Serum ; Comments: | 0; Notes: Not Reported |
| Percent Found in Air ; Comments: | 0.25; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | 0; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | Not Reported; Notes: Not Reported |
| Total Percent Absorbed: | 0 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Carcass =0.04% CV = 0 |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as Octamethylcyclotetrasiloxane (D4) CASRN 556-67-2 and was in liquid form. Unlabeled (244 Fluid) and radiolabeled test substances were used. The position of the radiolabel was not specified. A structure was provided in the published report along with physical/chemical properties. |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 2: | Test substance source | High | The lot numbers were provided. The radiolabeled test substance was supplied by Wizard Laboratories. The un-labeled test substance was supplied by Dow Corning as 244 Fluid. The chemical identities were confirmed by the HES Test Article Characterization Group using GC-MS. |
| | Metric 3: | Test substance purity | High | The mean radiochemical purity was 99.56%. The purity of the unlabeled test substance was 99.62%Radiochemical purities of the dosing solutions were also reported. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Medium | Non-cannulated rats were randomized using a table of random numbers. All animals were within ±20% of the mean body weight of the group. No randomization procedure was used for cannulated animals. |
| | Metric 5: | Standards for Tests | Medium | Percent recovery was reported for all groups. Coefficients of variation were not provided in the study report, but could be calculated using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | High | Preparation and storage details of the purchased test material and all test preparations were reported. Preparation was conducted within 5 days prior to use. Stability was not assessed, but test solutions were analyzed prior to exposure to confirm concentrations. |
| | Metric 7: | Consistency of exposure administration | Medium | Exposures were consistent across groups. The skin area was reported to be 2.5 cm2, although the report also indicated the internal diameter of the skin depot was reported to be 1.8 cm. This area is smaller than expected for a rat; however, the study reports that it was ~10% of the animal's body surface which is consistent with OECD guidelines. The volume of the test substance applied was not specified. The test substance was applied using a syringe, and there was some variation across replicates in the applied dose. |
| | Metric 8: | Reporting of concentrations | High | Concentrations were reported without ambiguity. The specific activity was measured on the day of dosing. The target dose levels were 2, 4.8, and 10 mg/cm2. Individual dosing data were provided. The applied dose was determined gravimetrically. |
| | Metric 9: | Exposure duration | High | Main (mass balance) group animals were exposed for 1, 6, or 24 hours then sacrificed immediately. Wash group animals were exposed for 24 hours, skin was washed, and these animals were kept in metabolism cages for an additional six days. The durations were consistent with current standards for this study type and were meant to mimic possible conditions of use. |
| | Metric 10: | Number of exposure groups and concentration spacing | Medium | The study tested three exposure concentrations distributed at log intervals that cover the range of exposures expected in personal care products. Each concentration was run as a separate experiment with its own control. The authors did not justify using neat vs. dilutions of the test substance. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | High | The study used female CDF (Fisher 344)/CrlBR rats. The source, body weights (122-155g), and age were reported. The study authors justified the strain and sex. |
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | High | Animal husbandry conditions (cage type, temperature, humidity, light cycle, food and water access, air changes per hour) were reported. Animals were housed individually. Conditions were consistent across groups. |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | | Metric | Rating | Comments |
|---|---|---|---|---|
| | Metric 13: | Number of animals per group | Medium | The study used use 4 animals per dose/time point which is consistent with the minimum requirements specified by OECD 427. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The outcome assessment methodology was described in detail and was appropriate for the outcomes of interest. Briefly, in a non-guideline study, neat D4 was applied to the skin of female Fisher 344 rats (n = 12/dose group; 4/dose/time point), under semi-occluded conditions, at 2, 4.8, or 10 mg/cm2 for 1, 6, or 24-hours and then sacrificed. An additional group (n = 4) were exposed to 10 mg/cm2 for 24 hours; the skin was then washed, charcoal baskets were replaced, and animals were returned to metabolism cages for collection of excreta and expired volatiles for an additional 6 days. A subset of rats was cannulated for measuring concentrations in blood during the exposure period. Animals were kept in Roth-style glass metabolism cages. Urine, feces, and air were collected. At the end of exposure (or at 168 hr post-exposure), blood was collected. Skin was washed and tape stripped. Extractions were done from charcoal baskets. Radioactivity was measured from all collections using LSC. The % absorbed dose was calculated from measurements in blood, carcass, excised skin, expired air, urine, feces, and CO2. Portions in the skin washes, stratum corneum (tape stripped), and skin depot were considered to be non-absorbed material. Radioactivity in the charcoal baskets and Teflon tape represented the volatile portion. Measurements in blood in the cannulated rats were expressed as ug D4/g blood and in expired air as ug D4/hr. Detailed methods of sample storage, extractions, and LSC were provided. The authors did not explicitly report whether finite or infinite exposures were used and the volume applied was not specified; based on the endpoints evaluated this was a finite exposure scenario that determined % absorbed. |
| | Metric 15: | Consistency of outcome assessment | High | The outcome assessment protocol was reported and was consistent across groups. |
| | Metric 16: | Sampling adequacy and sensitivity | High | The sample sizes were appropriate. The frequency of collections was reported. Each sample was counted for 10 minutes or at 2 Sigma %value. Corrections for matric background radioactivity were made. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | The same lot numbers of the test chemical were used. Reserve animals were kept to replace any animals that showed signs of skin damage after hair clipping. Animal body weights were all within ±20% of the mean. Measurements in expired air showed some anomalous values. The authors noted that this indicated that several skin depots may have leaked, which resulted in high recoveries of the test material in the expired volatile charcoal traps. Any outliers were removed from the dataset; however smaller leaks may have also occurred potentially confounding results. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | All animals were observed daily for mortality, morbidity, and clinical signs. Gravimetric determinations of dosing showed there were some technical within-group variations in the applied dose (mg/cm2) across replicates which may have contributed to any endpoint variation. |
| Domain 7: Data Presentation and Analysis | | | | |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 19: | Data analysis | High | Statistical methods and calculations were clearly described and appropriate. More than 50% of the endpoint CV values were <25%. Individual data were provided. |
| | Metric 20: | Data interpretation | Medium | The interpretation of results were mostly consistent with current guidelines. Recovery was >90% for all of the groups specified. All of the tape strips (5 strips, that removed all of the stratum coronium) were not included in the absorption estimate. However, all data are available to conduct alternate calculations. |
| | Metric 21: | Reporting of Data | High | Data for all of the outcomes were reported by dose group and time point. Values were presented as mean ± SEM or SD and individual animal data were provided. |

## Overall Quality Determination High

**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Wash group -Mid dose-24-hr; D4-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Female; Semi-occluded (e.g., gauze) |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 4.88; 12.2 mg/rat |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | 24 hrs; Not Reported; Notes: Not Reported |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | Other; Skin was washed after 24-hours, then animals were kept in metabolism cages for an additional 6 days.; Notes: 168 hours |
| Time Skin was Washed and Method used; Radiolabel Presence: | Skin was washed 3x with a cotton swab soaked with a 1% soap solution, followed by a dry swab, the washed 3x with a cotton swab soaked with 70% ethanol, and one dry swab.; Yes |
| Total Recovery (percent); Dose Type: | 96; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 0.09; Notes: Not Reported |
| Percent Found in Urine ; Comments: | 0.07; Notes: Not Reported |
| Percent Found in Feces ; Comments: | 0.01; Notes: Not Reported |
| Percent Found in Blood/Serum ; Comments: | 0; Notes: Not Reported |
| Percent Found in Air ; Comments: | 0.29; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | 0; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | Not Reported; Notes: Not Reported |
| Total Percent Absorbed: | 0 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Carcass =0.02% CV = 0 |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as Octamethylcyclotetrasiloxane (D4) CASRN 556-67-2 and was in liquid form. Unlabeled (244 Fluid) and radiolabeled test substances were used. The position of the radiolabel was not specified. A structure was provided in the published report along with physical/chemical properties. |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 2: | Test substance source | High | The lot numbers were provided. The radiolabeled test substance was supplied by Wizard Laboratories. The un-labeled test substance was supplied by Dow Corning as 244 Fluid. The chemical identities were confirmed by the HES Test Article Characterization Group using GC-MS. |
| | Metric 3: | Test substance purity | High | The mean radiochemical purity was 99.56%. The purity of the unlabeled test substance was 99.62%Radiochemical purities of the dosing solutions were also reported. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Medium | Non-cannulated rats were randomized using a table of random numbers. All animals were within ±20% of the mean body weight of the group. No randomization procedure was used for cannulated animals. |
| | Metric 5: | Standards for Tests | Medium | Percent recovery was reported for all groups. Coefficients of variation were not provided in the study report, but could be calculated using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | High | Preparation and storage details of the purchased test material and all test preparations were reported. Preparation was conducted within 5 days prior to use. Stability was not assessed, but test solutions were analyzed prior to exposure to confirm concentrations. |
| | Metric 7: | Consistency of exposure administration | Medium | Exposures were consistent across groups. The skin area was reported to be 2.5 cm2, although the report also indicated the internal diameter of the skin depot was reported to be 1.8 cm. This area is smaller than expected for a rat; however, the study reports that it was ~10% of the animal's body surface which is consistent with OECD guidelines. The volume of the test substance applied was not specified. The test substance was applied using a syringe, and there was some variation across replicates in the applied dose. |
| | Metric 8: | Reporting of concentrations | High | Concentrations were reported without ambiguity. The specific activity was measured on the day of dosing. The target dose levels were 2, 4.8, and 10 mg/cm2. Individual dosing data were provided. The applied dose was determined gravimetrically. |
| | Metric 9: | Exposure duration | High | Main (mass balance) group animals were exposed for 1, 6, or 24 hours then sacrificed immediately. Wash group animals were exposed for 24 hours, skin was washed, and these animals were kept in metabolism cages for an additional six days. The durations were consistent with current standards for this study type and were meant to mimic possible conditions of use. |
| | Metric 10: | Number of exposure groups and concentration spacing | Medium | The study tested three exposure concentrations distributed at log intervals that cover the range of exposures expected in personal care products. Each concentration was run as a separate experiment with its own control. The authors did not justify using neat vs. dilutions of the test substance. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | High | The study used female CDF (Fisher 344)/CrlBR rats. The source, body weights (122-155g), and age were reported. The study authors justified the strain and sex. |
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | High | Animal husbandry conditions (cage type, temperature, humidity, light cycle, food and water access, air changes per hour) were reported. Animals were housed individually. Conditions were consistent across groups. |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | | Metric | Rating | Comments |
|---|---|---|---|---|
| | Metric 13: | Number of animals per group | Medium | The study used use 4 animals per dose/time point which is consistent with the minimum requirements specified by OECD 427. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The outcome assessment methodology was described in detail and was appropriate for the outcomes of interest. Briefly, in a non-guideline study, neat D4 was applied to the skin of female Fisher 344 rats (n = 12/dose group; 4/dose/time point), under semi-occluded conditions, at 2, 4.8, or 10 mg/cm2 for 1, 6, or 24-hours and then sacrificed. An additional group (n = 4) were exposed to 10 mg/cm2 for 24 hours; the skin was then washed, charcoal baskets were replaced, and animals were returned to metabolism cages for collection of excreta and expired volatiles for an additional 6 days. A subset of rats was cannulated for measuring concentrations in blood during the exposure period. Animals were kept in Roth-style glass metabolism cages. Urine, feces, and air were collected. At the end of exposure (or at 168 hr post-exposure), blood was collected. Skin was washed and tape stripped. Extractions were done from charcoal baskets. Radioactivity was measured from all collections using LSC. The % absorbed dose was calculated from measurements in blood, carcass, excised skin, expired air, urine, feces, and CO2. Portions in the skin washes, stratum corneum (tape stripped), and skin depot were considered to be non-absorbed material. Radioactivity in the charcoal baskets and Teflon tape represented the volatile portion. Measurements in blood in the cannulated rats were expressed as ug D4/g blood and in expired air as ug D4/hr. Detailed methods of sample storage, extractions, and LSC were provided. The authors did not explicitly report whether finite or infinite exposures were used and the volume applied was not specified; based on the endpoints evaluated this was a finite exposure scenario that determined % absorbed. |
| | Metric 15: | Consistency of outcome assessment | High | The outcome assessment protocol was reported and was consistent across groups. |
| | Metric 16: | Sampling adequacy and sensitivity | High | The sample sizes were appropriate. The frequency of collections was reported. Each sample was counted for 10 minutes or at 2 Sigma %value. Corrections for matric background radioactivity were made. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | The same lot numbers of the test chemical were used. Reserve animals were kept to replace any animals that showed signs of skin damage after hair clipping. Animal body weights were all within ±20% of the mean. Measurements in expired air showed some anomalous values. The authors noted that this indicated that several skin depots may have leaked, which resulted in high recoveries of the test material in the expired volatile charcoal traps. Any outliers were removed from the dataset; however smaller leaks may have also occurred potentially confounding results. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | All animals were observed daily for mortality, morbidity, and clinical signs. Gravimetric determinations of dosing showed there were some technical within-group variations in the applied dose (mg/cm2) across replicates which may have contributed to any endpoint variation. |
| Domain 7: Data Presentation and Analysis | | | | |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 19: | Data analysis | High | Statistical methods and calculations were clearly described and appropriate. More than 50% of the endpoint CV values were <25%. Individual data were provided. |
| | Metric 20: | Data interpretation | Medium | The interpretation of results were mostly consistent with current guidelines. Recovery was >90% for all of the groups specified. All of the tape strips (5 strips, that removed all of the stratum coronium) were not included in the absorption estimate. However, all data are available to conduct alternate calculations. |
| | Metric 21: | Reporting of Data | High | Data for all of the outcomes were reported by dose group and time point. Values were presented as mean ± SEM or SD and individual animal data were provided. |

## Overall Quality Determination High

**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Mass Balance -Low dose-1-hr; D4-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Female; Semi-occluded (e.g., gauze) |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 1.88; 4.7 mg/rat |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | Other; Not Reported; Notes: 1 hr |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | Other; Animals were sacrificed immediately after the exposure period.; Notes: 1 hr |
| Time Skin was Washed and Method used; Radiolabel Presence: | The skin was not washed; Yes |
| Total Recovery (percent); Dose Type: | 101.88; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 0.47; Notes: Not Reported |
| Percent Found in Urine ; Comments: | 0; Notes: Not Reported |
| Percent Found in Feces ; Comments: | 0; Notes: Not Reported |
| Percent Found in Blood/Serum ; Comments: | 0; Notes: Not Reported |
| Percent Found in Air ; Comments: | 0.3; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | 0; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | Not Reported; Notes: Not Reported |
| Total Percent Absorbed: | 0 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Carcass =0.02% CV =0 |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as Octamethylcyclotetrasiloxane (D4) CASRN 556-67-2 and was in liquid form. Unlabeled (244 Fluid) and radiolabeled test substances were used. The position of the radiolabel was not specified. A structure was provided in the published report along with physical/chemical properties. |

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**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 2: | Test substance source | High | The lot numbers were provided. The radiolabeled test substance was supplied by Wizard Laboratories. The un-labeled test substance was supplied by Dow Corning as 244 Fluid. The chemical identities were confirmed by the HES Test Article Characterization Group using GC-MS. |
| | Metric 3: | Test substance purity | High | The mean radiochemical purity was 99.56%. The purity of the unlabeled test substance was 99.62%Radiochemical purities of the dosing solutions were also reported. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Medium | Non-cannulated rats were randomized using a table of random numbers. All animals were within ±20% of the mean body weight of the group. No randomization procedure was used for cannulated animals. |
| | Metric 5: | Standards for Tests | Medium | Percent recovery was reported for all groups. Coefficients of variation were not provided in the study report, but could be calculated using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | High | Preparation and storage details of the purchased test material and all test preparations were reported. Preparation was conducted within 5 days prior to use. Stability was not assessed, but test solutions were analyzed prior to exposure to confirm concentrations. |
| | Metric 7: | Consistency of exposure administration | Medium | Exposures were consistent across groups. The skin area was reported to be 2.5 cm2, although the report also indicated the internal diameter of the skin depot was reported to be 1.8 cm. This area is smaller than expected for a rat; however, the study reports that it was ~10% of the animal's body surface which is consistent with OECD guidelines. The volume of the test substance applied was not specified. The test substance was applied using a syringe, and there was some variation across replicates in the applied dose. |
| | Metric 8: | Reporting of concentrations | High | Concentrations were reported without ambiguity. The specific activity was measured on the day of dosing. The target dose levels were 2, 4.8, and 10 mg/cm2. Individual dosing data were provided. The applied dose was determined gravimetrically. |
| | Metric 9: | Exposure duration | High | Main (mass balance) group animals were exposed for 1, 6, or 24 hours then sacrificed immediately. Wash group animals were exposed for 24 hours, skin was washed, and these animals were kept in metabolism cages for an additional six days. The durations were consistent with current standards for this study type and were meant to mimic possible conditions of use. |
| | Metric 10: | Number of exposure groups and concentration spacing | Medium | The study tested three exposure concentrations distributed at log intervals that cover the range of exposures expected in personal care products. Each concentration was run as a separate experiment with its own control. The authors did not justify using neat vs. dilutions of the test substance. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | High | The study used female CDF (Fisher 344)/CrlBR rats. The source, body weights (122-155g), and age were reported. The study authors justified the strain and sex. |
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | High | Animal husbandry conditions (cage type, temperature, humidity, light cycle, food and water access, air changes per hour) were reported. Animals were housed individually. Conditions were consistent across groups. |

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**HERO ID:** 5884197

**EVALUATION**

| Domain | | Metric | Rating | Comments |
|---|---|---|---|---|
| | Metric 13: | Number of animals per group | Medium | The study used use 4 animals per dose/time point which is consistent with the minimum requirements specified by OECD 427. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The outcome assessment methodology was described in detail and was appropriate for the outcomes of interest. Briefly, in a non-guideline study, neat D4 was applied to the skin of female Fisher 344 rats (n = 12/dose group; 4/dose/time point), under semi-occluded conditions, at 2, 4.8, or 10 mg/cm2 for 1, 6, or 24-hours and then sacrificed. An additional group (n = 4) were exposed to 10 mg/cm2 for 24 hours; the skin was then washed, charcoal baskets were replaced, and animals were returned to metabolism cages for collection of excreta and expired volatiles for an additional 6 days. A subset of rats was cannulated for measuring concentrations in blood during the exposure period. Animals were kept in Roth-style glass metabolism cages. Urine, feces, and air were collected. At the end of exposure (or at 168 hr post-exposure), blood was collected. Skin was washed and tape stripped. Extractions were done from charcoal baskets. Radioactivity was measured from all collections using LSC. The % absorbed dose was calculated from measurements in blood, carcass, excised skin, expired air, urine, feces, and CO2. Portions in the skin washes, stratum corneum (tape stripped), and skin depot were considered to be non-absorbed material. Radioactivity in the charcoal baskets and Teflon tape represented the volatile portion. Measurements in blood in the cannulated rats were expressed as ug D4/g blood and in expired air as ug D4/hr. Detailed methods of sample storage, extractions, and LSC were provided. The authors did not explicitly report whether finite or infinite exposures were used and the volume applied was not specified; based on the endpoints evaluated this was a finite exposure scenario that determined % absorbed. |
| | Metric 15: | Consistency of outcome assessment | High | The outcome assessment protocol was reported and was consistent across groups. |
| | Metric 16: | Sampling adequacy and sensitivity | High | The sample sizes were appropriate. The frequency of collections was reported. Each sample was counted for 10 minutes or at 2 Sigma %value. Corrections for matric background radioactivity were made. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | The same lot numbers of the test chemical were used. Reserve animals were kept to replace any animals that showed signs of skin damage after hair clipping. Animal body weights were all within ±20% of the mean. Measurements in expired air showed some anomalous values. The authors noted that this indicated that several skin depots may have leaked, which resulted in high recoveries of the test material in the expired volatile charcoal traps. Any outliers were removed from the dataset; however smaller leaks may have also occurred potentially confounding results. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | All animals were observed daily for mortality, morbidity, and clinical signs. Gravimetric determinations of dosing showed there were some technical within-group variations in the applied dose (mg/cm2) across replicates which may have contributed to any endpoint variation. |
| Domain 7: Data Presentation and Analysis | | | | |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 19: | Data analysis | High | Statistical methods and calculations were clearly described and appropriate. More than 50% of the endpoint CV values were <25%. Individual data were provided. |
| | Metric 20: | Data interpretation | Medium | The interpretation of results were mostly consistent with current guidelines. Recovery was >90% for all of the groups specified. All of the tape strips (5 strips, that removed all of the stratum coronium) were not included in the absorption estimate. However, all data are available to conduct alternate calculations. |
| | Metric 21: | Reporting of Data | High | Data for all of the outcomes were reported by dose group and time point. Values were presented as mean ± SEM or SD and individual animal data were provided. |

## Overall Quality Determination High

**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Mass Balance -low dose-24-hr; D4-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Female; Semi-occluded (e.g., gauze) |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 1.63; 4.05 mg/rat |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | 24 hrs; Not Reported; Notes: Not Reported |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | 24 hrs; Animals were sacrificed immediately after the exposure period.; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | The skin was not washed; Yes |
| Total Recovery (percent); Dose Type: | 96.42; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 0.21; Notes: Not Reported |
| Percent Found in Urine ; Comments: | 0.03; Notes: Not Reported |
| Percent Found in Feces ; Comments: | 0; Notes: Not Reported |
| Percent Found in Blood/Serum ; Comments: | 0; Notes: Not Reported |
| Percent Found in Air ; Comments: | 0.48; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | 0; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | Not Reported; Notes: Not Reported |
| Total Percent Absorbed: | 0 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Carcass =0.02% CV = 0 |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as Octamethylcyclotetrasiloxane (D4) CASRN 556-67-2 and was in liquid form. Unlabeled (244 Fluid) and radiolabeled test substances were used. The position of the radiolabel was not specified. A structure was provided in the published report along with physical/chemical properties. |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 2: | Test substance source | High | The lot numbers were provided. The radiolabeled test substance was supplied by Wizard Laboratories. The un-labeled test substance was supplied by Dow Corning as 244 Fluid. The chemical identities were confirmed by the HES Test Article Characterization Group using GC-MS. |
| | Metric 3: | Test substance purity | High | The mean radiochemical purity was 99.56%. The purity of the unlabeled test substance was 99.62%Radiochemical purities of the dosing solutions were also reported. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Medium | Non-cannulated rats were randomized using a table of random numbers. All animals were within ±20% of the mean body weight of the group. No randomization procedure was used for cannulated animals. |
| | Metric 5: | Standards for Tests | Medium | Percent recovery was reported for all groups. Coefficients of variation were not provided in the study report, but could be calculated using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | High | Preparation and storage details of the purchased test material and all test preparations were reported. Preparation was conducted within 5 days prior to use. Stability was not assessed, but test solutions were analyzed prior to exposure to confirm concentrations. |
| | Metric 7: | Consistency of exposure administration | Medium | Exposures were consistent across groups. The skin area was reported to be 2.5 cm2, although the report also indicated the internal diameter of the skin depot was reported to be 1.8 cm. This area is smaller than expected for a rat; however, the study reports that it was ~10% of the animal's body surface which is consistent with OECD guidelines. The volume of the test substance applied was not specified. The test substance was applied using a syringe, and there was some variation across replicates in the applied dose. |
| | Metric 8: | Reporting of concentrations | High | Concentrations were reported without ambiguity. The specific activity was measured on the day of dosing. The target dose levels were 2, 4.8, and 10 mg/cm2. Individual dosing data were provided. The applied dose was determined gravimetrically. |
| | Metric 9: | Exposure duration | High | Main (mass balance) group animals were exposed for 1, 6, or 24 hours then sacrificed immediately. Wash group animals were exposed for 24 hours, skin was washed, and these animals were kept in metabolism cages for an additional six days. The durations were consistent with current standards for this study type and were meant to mimic possible conditions of use. |
| | Metric 10: | Number of exposure groups and concentration spacing | Medium | The study tested three exposure concentrations distributed at log intervals that cover the range of exposures expected in personal care products. Each concentration was run as a separate experiment with its own control. The authors did not justify using neat vs. dilutions of the test substance. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | High | The study used female CDF (Fisher 344)/CrlBR rats. The source, body weights (122-155g), and age were reported. The study authors justified the strain and sex. |
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | High | Animal husbandry conditions (cage type, temperature, humidity, light cycle, food and water access, air changes per hour) were reported. Animals were housed individually. Conditions were consistent across groups. |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | | Metric | Rating | Comments |
|---|---|---|---|---|
| | Metric 13: | Number of animals per group | Medium | The study used use 4 animals per dose/time point which is consistent with the minimum requirements specified by OECD 427. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The outcome assessment methodology was described in detail and was appropriate for the outcomes of interest. Briefly, in a non-guideline study, neat D4 was applied to the skin of female Fisher 344 rats (n = 12/dose group; 4/dose/time point), under semi-occluded conditions, at 2, 4.8, or 10 mg/cm2 for 1, 6, or 24-hours and then sacrificed. An additional group (n = 4) were exposed to 10 mg/cm2 for 24 hours; the skin was then washed, charcoal baskets were replaced, and animals were returned to metabolism cages for collection of excreta and expired volatiles for an additional 6 days. A subset of rats was cannulated for measuring concentrations in blood during the exposure period. Animals were kept in Roth-style glass metabolism cages. Urine, feces, and air were collected. At the end of exposure (or at 168 hr post-exposure), blood was collected. Skin was washed and tape stripped. Extractions were done from charcoal baskets. Radioactivity was measured from all collections using LSC. The % absorbed dose was calculated from measurements in blood, carcass, excised skin, expired air, urine, feces, and CO2. Portions in the skin washes, stratum corneum (tape stripped), and skin depot were considered to be non-absorbed material. Radioactivity in the charcoal baskets and Teflon tape represented the volatile portion. Measurements in blood in the cannulated rats were expressed as ug D4/g blood and in expired air as ug D4/hr. Detailed methods of sample storage, extractions, and LSC were provided. The authors did not explicitly report whether finite or infinite exposures were used and the volume applied was not specified; based on the endpoints evaluated this was a finite exposure scenario that determined % absorbed. |
| | Metric 15: | Consistency of outcome assessment | High | The outcome assessment protocol was reported and was consistent across groups. |
| | Metric 16: | Sampling adequacy and sensitivity | High | The sample sizes were appropriate. The frequency of collections was reported. Each sample was counted for 10 minutes or at 2 Sigma %value. Corrections for matric background radioactivity were made. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | The same lot numbers of the test chemical were used. Reserve animals were kept to replace any animals that showed signs of skin damage after hair clipping. Animal body weights were all within ±20% of the mean. Measurements in expired air showed some anomalous values. The authors noted that this indicated that several skin depots may have leaked, which resulted in high recoveries of the test material in the expired volatile charcoal traps. Any outliers were removed from the dataset; however smaller leaks may have also occurred potentially confounding results. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | All animals were observed daily for mortality, morbidity, and clinical signs. Gravimetric determinations of dosing showed there were some technical within-group variations in the applied dose (mg/cm2) across replicates which may have contributed to any endpoint variation. |
| Domain 7: Data Presentation and Analysis | | | | |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 19: | Data analysis | High | Statistical methods and calculations were clearly described and appropriate. More than 50% of the endpoint CV values were <25%. Individual data were provided. |
| | Metric 20: | Data interpretation | Medium | The interpretation of results were mostly consistent with current guidelines. Recovery was >90% for all of the groups specified. All of the tape strips (5 strips, that removed all of the stratum coronium) were not included in the absorption estimate. However, all data are available to conduct alternate calculations. |
| | Metric 21: | Reporting of Data | High | Data for all of the outcomes were reported by dose group and time point. Values were presented as mean ± SEM or SD and individual animal data were provided. |

## Overall Quality Determination High

**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Wash group -low dose-24-hr; D4-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Female; Semi-occluded (e.g., gauze) |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 2.1; 5.25 mg/rat |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | 24 hrs; Not Reported; Notes: Not Reported |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | Other; Skin was washed after 24-hours, then animals were kept in metabolism cages for an additional 6 days.; Notes: 168 hours |
| Time Skin was Washed and Method used; Radiolabel Presence: | Skin was washed 3x with a cotton swab soaked with a 1% soap solution, followed by a dry swab, the washed 3x with a cotton swab soaked with 70% ethanol, and one dry swab.; Yes |
| Total Recovery (percent); Dose Type: | 92.99; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 0.09; Notes: Not Reported |
| Percent Found in Urine ; Comments: | 0.06; Notes: Not Reported |
| Percent Found in Feces ; Comments: | 0.01; Notes: Not Reported |
| Percent Found in Blood/Serum ; Comments: | 0; Notes: Not Reported |
| Percent Found in Air ; Comments: | 0.34; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | 0; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | Not Reported; Notes: Not Reported |
| Total Percent Absorbed: | 0 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Carcass =0.01% CV = 0 |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as Octamethylcyclotetrasiloxane (D4) CASRN 556-67-2 and was in liquid form. Unlabeled (244 Fluid) and radiolabeled test substances were used. The position of the radiolabel was not specified. A structure was provided in the published report along with physical/chemical properties. |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 2: | Test substance source | High | The lot numbers were provided. The radiolabeled test substance was supplied by Wizard Laboratories. The un-labeled test substance was supplied by Dow Corning as 244 Fluid. The chemical identities were confirmed by the HES Test Article Characterization Group using GC-MS. |
| | Metric 3: | Test substance purity | High | The mean radiochemical purity was 99.56%. The purity of the unlabeled test substance was 99.62%Radiochemical purities of the dosing solutions were also reported. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Medium | Non-cannulated rats were randomized using a table of random numbers. All animals were within ±20% of the mean body weight of the group. No randomization procedure was used for cannulated animals. |
| | Metric 5: | Standards for Tests | Medium | Percent recovery was reported for all groups. Coefficients of variation were not provided in the study report, but could be calculated using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | High | Preparation and storage details of the purchased test material and all test preparations were reported. Preparation was conducted within 5 days prior to use. Stability was not assessed, but test solutions were analyzed prior to exposure to confirm concentrations. |
| | Metric 7: | Consistency of exposure administration | Medium | Exposures were consistent across groups. The skin area was reported to be 2.5 cm2, although the report also indicated the internal diameter of the skin depot was reported to be 1.8 cm. This area is smaller than expected for a rat; however, the study reports that it was ~10% of the animal's body surface which is consistent with OECD guidelines. The volume of the test substance applied was not specified. The test substance was applied using a syringe, and there was some variation across replicates in the applied dose. |
| | Metric 8: | Reporting of concentrations | High | Concentrations were reported without ambiguity. The specific activity was measured on the day of dosing. The target dose levels were 2, 4.8, and 10 mg/cm2. Individual dosing data were provided. The applied dose was determined gravimetrically. |
| | Metric 9: | Exposure duration | High | Main (mass balance) group animals were exposed for 1, 6, or 24 hours then sacrificed immediately. Wash group animals were exposed for 24 hours, skin was washed, and these animals were kept in metabolism cages for an additional six days. The durations were consistent with current standards for this study type and were meant to mimic possible conditions of use. |
| | Metric 10: | Number of exposure groups and concentration spacing | Medium | The study tested three exposure concentrations distributed at log intervals that cover the range of exposures expected in personal care products. Each concentration was run as a separate experiment with its own control. The authors did not justify using neat vs. dilutions of the test substance. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | High | The study used female CDF (Fisher 344)/CrlBR rats. The source, body weights (122-155g), and age were reported. The study authors justified the strain and sex. |
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | High | Animal husbandry conditions (cage type, temperature, humidity, light cycle, food and water access, air changes per hour) were reported. Animals were housed individually. Conditions were consistent across groups. |

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**EVALUATION**

| Domain | | Metric | Rating | Comments |
|---|---|---|---|---|
| | Metric 13: | Number of animals per group | Medium | The study used use 4 animals per dose/time point which is consistent with the minimum requirements specified by OECD 427. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The outcome assessment methodology was described in detail and was appropriate for the outcomes of interest. Briefly, in a non-guideline study, neat D4 was applied to the skin of female Fisher 344 rats (n = 12/dose group; 4/dose/time point), under semi-occluded conditions, at 2, 4.8, or 10 mg/cm2 for 1, 6, or 24-hours and then sacrificed. An additional group (n = 4) were exposed to 10 mg/cm2 for 24 hours; the skin was then washed, charcoal baskets were replaced, and animals were returned to metabolism cages for collection of excreta and expired volatiles for an additional 6 days. A subset of rats was cannulated for measuring concentrations in blood during the exposure period. Animals were kept in Roth-style glass metabolism cages. Urine, feces, and air were collected. At the end of exposure (or at 168 hr post-exposure), blood was collected. Skin was washed and tape stripped. Extractions were done from charcoal baskets. Radioactivity was measured from all collections using LSC. The % absorbed dose was calculated from measurements in blood, carcass, excised skin, expired air, urine, feces, and CO2. Portions in the skin washes, stratum corneum (tape stripped), and skin depot were considered to be non-absorbed material. Radioactivity in the charcoal baskets and Teflon tape represented the volatile portion. Measurements in blood in the cannulated rats were expressed as ug D4/g blood and in expired air as ug D4/hr. Detailed methods of sample storage, extractions, and LSC were provided. The authors did not explicitly report whether finite or infinite exposures were used and the volume applied was not specified; based on the endpoints evaluated this was a finite exposure scenario that determined % absorbed. |
| | Metric 15: | Consistency of outcome assessment | High | The outcome assessment protocol was reported and was consistent across groups. |
| | Metric 16: | Sampling adequacy and sensitivity | High | The sample sizes were appropriate. The frequency of collections was reported. Each sample was counted for 10 minutes or at 2 Sigma %value. Corrections for matric background radioactivity were made. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | The same lot numbers of the test chemical were used. Reserve animals were kept to replace any animals that showed signs of skin damage after hair clipping. Animal body weights were all within ±20% of the mean. Measurements in expired air showed some anomalous values. The authors noted that this indicated that several skin depots may have leaked, which resulted in high recoveries of the test material in the expired volatile charcoal traps. Any outliers were removed from the dataset; however smaller leaks may have also occurred potentially confounding results. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | All animals were observed daily for mortality, morbidity, and clinical signs. Gravimetric determinations of dosing showed there were some technical within-group variations in the applied dose (mg/cm2) across replicates which may have contributed to any endpoint variation. |
| Domain 7: Data Presentation and Analysis | | | | |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 19: | Data analysis | High | Statistical methods and calculations were clearly described and appropriate. More than 50% of the endpoint CV values were <25%. Individual data were provided. |
| | Metric 20: | Data interpretation | Medium | The interpretation of results were mostly consistent with current guidelines. Recovery was >90% for all of the groups specified. All of the tape strips (5 strips, that removed all of the stratum coronium) were not included in the absorption estimate. However, all data are available to conduct alternate calculations. |
| | Metric 21: | Reporting of Data | High | Data for all of the outcomes were reported by dose group and time point. Values were presented as mean ± SEM or SD and individual animal data were provided. |

## Overall Quality Determination High

**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Mass Balance -High dose-1-hr; D4-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Female; Semi-occluded (e.g., gauze) |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 9.85; 24.6 mg/rat |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | Other; Not Reported; Notes: 1 hr |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | Other; Animals were sacrificed immediately after the exposure period.; Notes: 1 hr |
| Time Skin was Washed and Method used; Radiolabel Presence: | The skin was not washed; Yes |
| Total Recovery (percent); Dose Type: | 76.32; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 0.82; Notes: Not Reported |
| Percent Found in Urine ; Comments: | 0; Notes: Not Reported |
| Percent Found in Feces ; Comments: | 0; Notes: Not Reported |
| Percent Found in Blood/Serum ; Comments: | 0; Notes: Not Reported |
| Percent Found in Air ; Comments: | 0.11; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | 0; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | Not Reported; Notes: Not Reported |
| Total Percent Absorbed: | 1 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Carcass =0.02% CV = 86.6% |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as Octamethylcyclotetrasiloxane (D4) CASRN 556-67-2 and was in liquid form. Unlabeled (244 Fluid) and radiolabeled test substances were used. The position of the radiolabel was not specified. A structure was provided in the published report along with physical/chemical properties. |

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**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 2: | Test substance source | High | The lot numbers were provided. The radiolabeled test substance was supplied by Wizard Laboratories. The un-labeled test substance was supplied by Dow Corning as 244 Fluid. The chemical identities were confirmed by the HES Test Article Characterization Group using GC-MS. |
| | Metric 3: | Test substance purity | High | The mean radiochemical purity was 99.56%. The purity of the unlabeled test substance was 99.62%Radiochemical purities of the dosing solutions were also reported. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Medium | Non-cannulated rats were randomized using a table of random numbers. All animals were within ±20% of the mean body weight of the group. No randomization procedure was used for cannulated animals. |
| | Metric 5: | Standards for Tests | Medium | Percent recovery was reported for all groups. Coefficients of variation were not provided in the study report, but could be calculated using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | High | Preparation and storage details of the purchased test material and all test preparations were reported. Preparation was conducted within 5 days prior to use. Stability was not assessed, but test solutions were analyzed prior to exposure to confirm concentrations. |
| | Metric 7: | Consistency of exposure administration | Medium | Exposures were consistent across groups. The skin area was reported to be 2.5 cm2, although the report also indicated the internal diameter of the skin depot was reported to be 1.8 cm. This area is smaller than expected for a rat; however, the study reports that it was ~10% of the animal's body surface which is consistent with OECD guidelines. The volume of the test substance applied was not specified. The test substance was applied using a syringe, and there was some variation across replicates in the applied dose. |
| | Metric 8: | Reporting of concentrations | High | Concentrations were reported without ambiguity. The specific activity was measured on the day of dosing. The target dose levels were 2, 4.8, and 10 mg/cm2. Individual dosing data were provided. The applied dose was determined gravimetrically. |
| | Metric 9: | Exposure duration | High | Main (mass balance) group animals were exposed for 1, 6, or 24 hours then sacrificed immediately. Wash group animals were exposed for 24 hours, skin was washed, and these animals were kept in metabolism cages for an additional six days. The durations were consistent with current standards for this study type and were meant to mimic possible conditions of use. |
| | Metric 10: | Number of exposure groups and concentration spacing | Medium | The study tested three exposure concentrations distributed at log intervals that cover the range of exposures expected in personal care products. Each concentration was run as a separate experiment with its own control. The authors did not justify using neat vs. dilutions of the test substance. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | High | The study used female CDF (Fisher 344)/CrlBR rats. The source, body weights (122-155g), and age were reported. The study authors justified the strain and sex. |
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | High | Animal husbandry conditions (cage type, temperature, humidity, light cycle, food and water access, air changes per hour) were reported. Animals were housed individually. Conditions were consistent across groups. |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | | Metric | Rating | Comments |
|---|---|---|---|---|
| | Metric 13: | Number of animals per group | Medium | The study used use 4 animals per dose/time point which is consistent with the minimum requirements specified by OECD 427. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The outcome assessment methodology was described in detail and was appropriate for the outcomes of interest. Briefly, in a non-guideline study, neat D4 was applied to the skin of female Fisher 344 rats (n = 12/dose group; 4/dose/time point), under semi-occluded conditions, at 2, 4.8, or 10 mg/cm2 for 1, 6, or 24-hours and then sacrificed. An additional group (n = 4) were exposed to 10 mg/cm2 for 24 hours; the skin was then washed, charcoal baskets were replaced, and animals were returned to metabolism cages for collection of excreta and expired volatiles for an additional 6 days. A subset of rats was cannulated for measuring concentrations in blood during the exposure period. Animals were kept in Roth-style glass metabolism cages. Urine, feces, and air were collected. At the end of exposure (or at 168 hr post-exposure), blood was collected. Skin was washed and tape stripped. Extractions were done from charcoal baskets. Radioactivity was measured from all collections using LSC. The % absorbed dose was calculated from measurements in blood, carcass, excised skin, expired air, urine, feces, and CO2. Portions in the skin washes, stratum corneum (tape stripped), and skin depot were considered to be non-absorbed material. Radioactivity in the charcoal baskets and Teflon tape represented the volatile portion. Measurements in blood in the cannulated rats were expressed as ug D4/g blood and in expired air as ug D4/hr. Detailed methods of sample storage, extractions, and LSC were provided. The authors did not explicitly report whether finite or infinite exposures were used and the volume applied was not specified; based on the endpoints evaluated this was a finite exposure scenario that determined % absorbed. |
| | Metric 15: | Consistency of outcome assessment | High | The outcome assessment protocol was reported and was consistent across groups. |
| | Metric 16: | Sampling adequacy and sensitivity | High | The sample sizes were appropriate. The frequency of collections was reported. Each sample was counted for 10 minutes or at 2 Sigma %value. Corrections for matric background radioactivity were made. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | The same lot numbers of the test chemical were used. Reserve animals were kept to replace any animals that showed signs of skin damage after hair clipping. Animal body weights were all within ±20% of the mean. Measurements in expired air showed some anomalous values. The authors noted that this indicated that several skin depots may have leaked, which resulted in high recoveries of the test material in the expired volatile charcoal traps. Any outliers were removed from the dataset; however smaller leaks may have also occurred potentially confounding results. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | All animals were observed daily for mortality, morbidity, and clinical signs. Gravimetric determinations of dosing showed there were some technical within-group variations in the applied dose (mg/cm2) across replicates which may have contributed to any endpoint variation. |
| Domain 7: Data Presentation and Analysis | | | | |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 19: | Data analysis | High | Statistical methods and calculations were clearly described and appropriate. More than 50% of the endpoint CV values were <25%. Individual data were provided. |
| | Metric 20: | Data interpretation | Medium | The interpretation of results was mostly consistent with current guidelines. Recovery was 76.32%, which is less than the 100 ± 20% specified in OECD 427. The authors speculated that loss occurred when the charcoal basket was removed. All of the tape strips (5 strips, that removed all of the stratum corneum) were not included in the absorption estimate. However, all data are available to conduct alternate calculations. |
| | Metric 21: | Reporting of Data | High | Data for all of the outcomes were reported by dose group and time point. Values were presented as mean ± SEM or SD and individual animal data were provided. |

## Overall Quality Determination — High

**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Mass Balance -High dose-24-hr; D4-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Female; Semi-occluded (e.g., gauze) |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 9.35; 23.4 mg/rat |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | 24 hrs; Not Reported; Notes: Not Reported |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | 24 hrs; Animals were sacrificed immediately after the exposure period.; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | The skin was not washed; Yes |
| Total Recovery (percent); Dose Type: | 93.01; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 0.22; Notes: Not Reported |
| Percent Found in Urine ; Comments: | 0.03; Notes: Not Reported |
| Percent Found in Feces ; Comments: | 0.01; Notes: Not Reported |
| Percent Found in Blood/Serum ; Comments: | 0; Notes: Not Reported |
| Percent Found in Air ; Comments: | 0.29; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | 0; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | Not Reported; Notes: Not Reported |
| Total Percent Absorbed: | 0 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Carcass =0.05% CV = 40% |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as Octamethylcyclotetrasiloxane (D4) CASRN 556-67-2 and was in liquid form. Unlabeled (244 Fluid) and radiolabeled test substances were used. The position of the radiolabel was not specified. A structure was provided in the published report along with physical/chemical properties. |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 2: | Test substance source | High | The lot numbers were provided. The radiolabeled test substance was supplied by Wizard Laboratories. The un-labeled test substance was supplied by Dow Corning as 244 Fluid. The chemical identities were confirmed by the HES Test Article Characterization Group using GC-MS. |
| | Metric 3: | Test substance purity | High | The mean radiochemical purity was 99.56%. The purity of the unlabeled test substance was 99.62%Radiochemical purities of the dosing solutions were also reported. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Medium | Non-cannulated rats were randomized using a table of random numbers. All animals were within ±20% of the mean body weight of the group. No randomization procedure was used for cannulated animals. |
| | Metric 5: | Standards for Tests | Medium | Percent recovery was reported for all groups. Coefficients of variation were not provided in the study report, but could be calculated using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | High | Preparation and storage details of the purchased test material and all test preparations were reported. Preparation was conducted within 5 days prior to use. Stability was not assessed, but test solutions were analyzed prior to exposure to confirm concentrations. |
| | Metric 7: | Consistency of exposure administration | Medium | Exposures were consistent across groups. The skin area was reported to be 2.5 cm2, although the report also indicated the internal diameter of the skin depot was reported to be 1.8 cm. This area is smaller than expected for a rat; however, the study reports that it was ~10% of the animal's body surface which is consistent with OECD guidelines. The volume of the test substance applied was not specified. The test substance was applied using a syringe, and there was some variation across replicates in the applied dose. |
| | Metric 8: | Reporting of concentrations | High | Concentrations were reported without ambiguity. The specific activity was measured on the day of dosing. The target dose levels were 2, 4.8, and 10 mg/cm2. Individual dosing data were provided. The applied dose was determined gravimetrically. |
| | Metric 9: | Exposure duration | High | Main (mass balance) group animals were exposed for 1, 6, or 24 hours then sacrificed immediately. Wash group animals were exposed for 24 hours, skin was washed, and these animals were kept in metabolism cages for an additional six days. The durations were consistent with current standards for this study type and were meant to mimic possible conditions of use. |
| | Metric 10: | Number of exposure groups and concentration spacing | Medium | The study tested three exposure concentrations distributed at log intervals that cover the range of exposures expected in personal care products. Each concentration was run as a separate experiment with its own control. The authors did not justify using neat vs. dilutions of the test substance. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | High | The study used female CDF (Fisher 344)/CrlBR rats. The source, body weights (122-155g), and age were reported. The study authors justified the strain and sex. |
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | High | Animal husbandry conditions (cage type, temperature, humidity, light cycle, food and water access, air changes per hour) were reported. Animals were housed individually. Conditions were consistent across groups. |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 13: | Number of animals per group | Medium | The study used use 4 animals per dose/time point which is consistent with the minimum requirements specified by OECD 427. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The outcome assessment methodology was described in detail and was appropriate for the outcomes of interest. Briefly, in a non-guideline study, neat D4 was applied to the skin of female Fisher 344 rats (n = 12/dose group; 4/dose/time point), under semi-occluded conditions, at 2, 4.8, or 10 mg/cm2 for 1, 6, or 24-hours and then sacrificed. An additional group (n = 4) were exposed to 10 mg/cm2 for 24 hours; the skin was then washed, charcoal baskets were replaced, and animals were returned to metabolism cages for collection of excreta and expired volatiles for an additional 6 days. A subset of rats was cannulated for measuring concentrations in blood during the exposure period. Animals were kept in Roth-style glass metabolism cages. Urine, feces, and air were collected. At the end of exposure (or at 168 hr post-exposure), blood was collected. Skin was washed and tape stripped. Extractions were done from charcoal baskets. Radioactivity was measured from all collections using LSC. The % absorbed dose was calculated from measurements in blood, carcass, excised skin, expired air, urine, feces, and CO2. Portions in the skin washes, stratum corneum (tape stripped), and skin depot were considered to be non-absorbed material. Radioactivity in the charcoal baskets and Teflon tape represented the volatile portion. Measurements in blood in the cannulated rats were expressed as ug D4/g blood and in expired air as ug D4/hr. Detailed methods of sample storage, extractions, and LSC were provided. The authors did not explicitly report whether finite or infinite exposures were used and the volume applied was not specified; based on the endpoints evaluated this was a finite exposure scenario that determined % absorbed. |
| | Metric 15: | Consistency of outcome assessment | High | The outcome assessment protocol was reported and was consistent across groups. |
| | Metric 16: | Sampling adequacy and sensitivity | High | The sample sizes were appropriate. The frequency of collections was reported. Each sample was counted for 10 minutes or at 2 Sigma %value. Corrections for matric background radioactivity were made. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | The same lot numbers of the test chemical were used. Reserve animals were kept to replace any animals that showed signs of skin damage after hair clipping. Animal body weights were all within ±20% of the mean. Measurements in expired air showed some anomalous values. The authors noted that this indicated that several skin depots may have leaked, which resulted in high recoveries of the test material in the expired volatile charcoal traps. Any outliers were removed from the dataset; however smaller leaks may have also occurred potentially confounding results. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | All animals were observed daily for mortality, morbidity, and clinical signs. Gravimetric determinations of dosing showed there were some technical within-group variations in the applied dose (mg/cm2) across replicates which may have contributed to any endpoint variation. |
| Domain 7: Data Presentation and Analysis | | | | |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 19: | Data analysis | Low | Statistical methods and calculations were clearly described and appropriate. Half of the CV values were either >25% but <50%, or were >50%. However, sufficient data are available to conduct an alternative analysis. |
| | Metric 20: | Data interpretation | Medium | The interpretation of results were mostly consistent with current guidelines. Recovery was >90% for all of the groups specified. All of the tape strips (5 strips, that removed all of the stratum coronium) were not included in the absorption estimate. However, all data are available to conduct alternate calculations. |
| | Metric 21: | Reporting of Data | High | Data for all of the outcomes were reported by dose group and time point. Values were presented as mean ± SEM or SD and individual animal data were provided. |

## Overall Quality Determination — High

**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Mass Balance -Low dose-6-hr; D4-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Female; Semi-occluded (e.g., gauze) |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 2.15; 5.38 mg/rat |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | 6 hrs; Not Reported; Notes: Not Reported |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | 6 hrs; Animals were sacrificed immediately after the exposure period.; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | The skin was not washed; Yes |
| Total Recovery (percent); Dose Type: | 92.8; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 0.32; Notes: Not Reported |
| Percent Found in Urine ; Comments: | 0; Notes: Not Reported |
| Percent Found in Feces ; Comments: | 0; Notes: Not Reported |
| Percent Found in Blood/Serum ; Comments: | 0; Notes: Not Reported |
| Percent Found in Air ; Comments: | 0.42; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | 0; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | Not Reported; Notes: Not Reported |
| Total Percent Absorbed: | 0 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Carcass =0.03% CV = 66.7% |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as Octamethylcyclotetrasiloxane (D4) CASRN 556-67-2 and was in liquid form. Unlabeled (244 Fluid) and radiolabeled test substances were used. The position of the radiolabel was not specified. A structure was provided in the published report along with physical/chemical properties. |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 2: | Test substance source | High | The lot numbers were provided. The radiolabeled test substance was supplied by Wizard Laboratories. The un-labeled test substance was supplied by Dow Corning as 244 Fluid. The chemical identities were confirmed by the HES Test Article Characterization Group using GC-MS. |
| | Metric 3: | Test substance purity | High | The mean radiochemical purity was 99.56%. The purity of the unlabeled test substance was 99.62%Radiochemical purities of the dosing solutions were also reported. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Medium | Non-cannulated rats were randomized using a table of random numbers. All animals were within ±20% of the mean body weight of the group. No randomization procedure was used for cannulated animals. |
| | Metric 5: | Standards for Tests | Medium | Percent recovery was reported for all groups. Coefficients of variation were not provided in the study report, but could be calculated using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | High | Preparation and storage details of the purchased test material and all test preparations were reported. Preparation was conducted within 5 days prior to use. Stability was not assessed, but test solutions were analyzed prior to exposure to confirm concentrations. |
| | Metric 7: | Consistency of exposure administration | Medium | Exposures were consistent across groups. The skin area was reported to be 2.5 cm2, although the report also indicated the internal diameter of the skin depot was reported to be 1.8 cm. This area is smaller than expected for a rat; however, the study reports that it was ~10% of the animal's body surface which is consistent with OECD guidelines. The volume of the test substance applied was not specified. The test substance was applied using a syringe, and there was some variation across replicates in the applied dose. |
| | Metric 8: | Reporting of concentrations | High | Concentrations were reported without ambiguity. The specific activity was measured on the day of dosing. The target dose levels were 2, 4.8, and 10 mg/cm2. Individual dosing data were provided. The applied dose was determined gravimetrically. |
| | Metric 9: | Exposure duration | High | Main (mass balance) group animals were exposed for 1, 6, or 24 hours then sacrificed immediately. Wash group animals were exposed for 24 hours, skin was washed, and these animals were kept in metabolism cages for an additional six days. The durations were consistent with current standards for this study type and were meant to mimic possible conditions of use. |
| | Metric 10: | Number of exposure groups and concentration spacing | Medium | The study tested three exposure concentrations distributed at log intervals that cover the range of exposures expected in personal care products. Each concentration was run as a separate experiment with its own control. The authors did not justify using neat vs. dilutions of the test substance. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | High | The study used female CDF (Fisher 344)/CrlBR rats. The source, body weights (122-155g), and age were reported. The study authors justified the strain and sex. |
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | High | Animal husbandry conditions (cage type, temperature, humidity, light cycle, food and water access, air changes per hour) were reported. Animals were housed individually. Conditions were consistent across groups. |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 13: | Number of animals per group | Medium | The study used use 4 animals per dose/time point which is consistent with the minimum requirements specified by OECD 427. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | The outcome assessment methodology was described in detail and was appropriate for the outcomes of interest. Briefly, in a non-guideline study, neat D4 was applied to the skin of female Fisher 344 rats (n = 12/dose group; 4/dose/time point), under semi-occluded conditions, at 2, 4.8, or 10 mg/cm2 for 1, 6, or 24-hours and then sacrificed. An additional group (n = 4) were exposed to 10 mg/cm2 for 24 hours; the skin was then washed, charcoal baskets were replaced, and animals were returned to metabolism cages for collection of excreta and expired volatiles for an additional 6 days. A subset of rats was cannulated for measuring concentrations in blood during the exposure period. Animals were kept in Roth-style glass metabolism cages. Urine, feces, and air were collected. At the end of exposure (or at 168 hr post-exposure), blood was collected. Skin was washed and tape stripped. Extractions were done from charcoal baskets. Radioactivity was measured from all collections using LSC. The % absorbed dose was calculated from measurements in blood, carcass, excised skin, expired air, urine, feces, and CO2. Portions in the skin washes, stratum corneum (tape stripped), and skin depot were considered to be non-absorbed material. Radioactivity in the charcoal baskets and Teflon tape represented the volatile portion. Measurements in blood in the cannulated rats were expressed as ug D4/g blood and in expired air as ug D4/hr. Detailed methods of sample storage, extractions, and LSC were provided. The authors did not explicitly report whether finite or infinite exposures were used and the volume applied was not specified; based on the endpoints evaluated this was a finite exposure scenario that determined % absorbed. |
| | Metric 15: | Consistency of outcome assessment | High | The outcome assessment protocol was reported and was consistent across groups. |
| | Metric 16: | Sampling adequacy and sensitivity | High | The sample sizes were appropriate. The frequency of collections was reported. Each sample was counted for 10 minutes or at 2 Sigma %value. Corrections for matric background radioactivity were made. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | The same lot numbers of the test chemical were used. Reserve animals were kept to replace any animals that showed signs of skin damage after hair clipping. Animal body weights were all within ±20% of the mean. Measurements in expired air showed some anomalous values. The authors noted that this indicated that several skin depots may have leaked, which resulted in high recoveries of the test material in the expired volatile charcoal traps. Any outliers were removed from the dataset; however smaller leaks may have also occurred potentially confounding results. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | All animals were observed daily for mortality, morbidity, and clinical signs. Gravimetric determinations of dosing showed there were some technical within-group variations in the applied dose (mg/cm2) across replicates which may have contributed to any endpoint variation. |
| Domain 7: Data Presentation and Analysis | | | | |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 19: | Data analysis | Low | Statistical methods and calculations were clearly described and appropriate. Half of the CV values were either >25% but <50%, or were >50%. However, sufficient data are available to conduct an alternative analysis. |
| | Metric 20: | Data interpretation | Medium | The interpretation of results were mostly consistent with current guidelines. Recovery was >90% for all of the groups specified. All of the tape strips (5 strips, that removed all of the stratum coronium) were not included in the absorption estimate. However, all data are available to conduct alternate calculations. |
| | Metric 21: | Reporting of Data | High | Data for all of the outcomes were reported by dose group and time point. Values were presented as mean ± SEM or SD and individual animal data were provided. |

## Overall Quality Determination — High

**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | Blood kinetics -High dose-10-hr; D4-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Female; Semi-occluded (e.g., gauze) |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | No vehicle was used; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 8.9; 22.3 mg/rat. |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | Other; Not Reported; Notes: 10 hr |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | Other; Animals were sacrificed immediately after the exposure period.; Notes: 10 hr |
| Time Skin was Washed and Method used; Radiolabel Presence: | The skin was not washed; Yes |
| Total Recovery (percent); Dose Type: | Not Reported; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | Not Reported; Notes: Not Reported |
| Percent Found in Urine ; Comments: | Not Reported; Notes: Not Reported |
| Percent Found in Feces ; Comments: | Not Reported; Notes: Not Reported |
| Percent Found in Blood/Serum ; Comments: | 0; Notes: Not Reported |
| Percent Found in Air ; Comments: | Not Reported; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | 0; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | Not Reported; Notes: Not Reported |
| Total Percent Absorbed: | 0 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as Octamethylcyclotetrasiloxane (D4) CASRN 556-67-2 and was in liquid form. Unlabeled (244 Fluid) and radiolabeled test substances were used. The position of the radiolabel was not specified. A structure was provided in the published report along with physical/chemical properties. |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | | Metric | Rating | Comments |
|---|---|---|---|---|
| | Metric 2: | Test substance source | High | The lot numbers were provided. The radiolabeled test substance was supplied by Wizard Laboratories. The un-labeled test substance was supplied by Dow Corning as 244 Fluid. The chemical identities were confirmed by the HES Test Article Characterization Group using GC-MS. |
| | Metric 3: | Test substance purity | High | The mean radiochemical purity was 99.56%. The purity of the unlabeled test substance was 99.62%Radiochemical purities of the dosing solutions were also reported. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Low | No randomization procedure was used for cannulated animals. |
| | Metric 5: | Standards for Tests | Uninformative | No standards were included for the cannulated rats set aside to determine blood kinetics. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | High | Preparation and storage details of the purchased test material and all test preparations were reported. Preparation was conducted within 5 days prior to use. Stability was not assessed, but test solutions were analyzed prior to exposure to confirm concentrations. |
| | Metric 7: | Consistency of exposure administration | Medium | Exposures were consistent across replicates in this group. The skin area was reported to be 2.5 cm2, although the report also indicated the internal diameter of the skin depot was reported to be 1.8 cm. This area is smaller than expected for a rat; however, the study reports that it was ~10% of the animal's body surface which is consistent with OECD guidelines. The volume of the test substance applied was not specified. The test substance was applied using a syringe, and there was some variation across replicates in the applied dose. |
| | Metric 8: | Reporting of concentrations | High | Concentrations were reported without ambiguity. The specific activity was measured on the day of dosing. The target dose was 10 mg/cm2. Individual dosing data were provided. The applied dose was determined gravimetrically. |
| | Metric 9: | Exposure duration | High | In this kinetic experiment, animals were dosed for 10 hours. This was appropriate for the purposes of this experiment. |
| | Metric 10: | Number of exposure groups and concentration spacing | Medium | Overall, the study tested three exposure concentrations distributed at log intervals that cover the range of exposures expected in personal care products. Each concentration was run as a separate experiment with its own control. This form is for the kinetics experiment, which was run at the high dose only. Since the measurements were below the level of quantitation at all collection points kinetic experiments were not conducted on the lower dose groups. The authors did not justify using neat vs. dilutions of the test substance. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | High | The study used female CDF (Fisher 344)/CrlBR rats. The source, body weights (122-155g), and age were reported. The study authors justified the strain and sex. |
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | High | Animal husbandry conditions (cage type, temperature, humidity, light cycle, food and water access, air changes per hour) were reported. Animals were housed individually. Conditions were consistent across groups. |
| | Metric 13: | Number of animals per group | Medium | The study used use 6 treated animals and 2 controls. The animal number was sufficient for the study type. |

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**Study Citation:** Dow Corning, (2001). In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane in the rat, with cover letter dated 021901.
**HERO ID:** 5884197

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Low | The outcome assessment methodology was described in detail and was appropriate for the outcomes of interest. Briefly, in a non-guideline study, neat D4 was applied to the skin of cannulated female Fisher 344 rats n = 6 treated and n = 2 controls) under semi-occluded conditions 10 mg/cm2 for 10 hours Radioactivity was measured from blood collected at 0.5, 2, 4, and 10 hours. Measurements were expressed as ug D4/g blood. Detailed methods of sample storage, extractions, and LSC were provided. The authors did not explicitly report whether finite or infinite exposures were used and the volume applied was not specified; based on the endpoints evaluated this was a finite exposure scenario that determined % absorbed. This was a side experiment that was part of a complete dermal absorption study. This can be used to supplement the information in the other experiments. |
| | Metric 15: | Consistency of outcome assessment | High | The outcome assessment protocol was reported and was consistent across groups. |
| | Metric 16: | Sampling adequacy and sensitivity | High | The sample sizes were appropriate. The frequency of collections was reported. Each sample was counted for 10 minutes or at 2 Sigma %value. Corrections for matrix background radioactivity were made. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | High | No confounding variables were observed. The same lot numbers of the test chemical were used. Reserve animals were kept to replace any animals that showed signs of skin damage after hair clipping. Animal body weights were all within ±20% of the mean. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | All animals were observed daily for mortality, morbidity, and clinical signs. Gravimetric determinations of dosing showed there were some technical within-group variations in the applied dose (mg/cm2) across replicates which may have contributed to any endpoint variation. |
| Domain 7: Data Presentation and Analysis | | | | |
| | Metric 19: | Data analysis | N/A | No statistical analysis was required. The levels were all below the level of quantitation. It is inappropriate to determine CV values for this endpoint. |
| | Metric 20: | Data interpretation | Uninformative | This was a non-guideline side experiment to look at blood kinetics following D4 exposure. No other endpoints were evaluated for this group of animals and the study is not useful for quantitatively assessing dermal absorption. |
| | Metric 21: | Reporting of Data | High | Data for all of the outcomes were reported by dose group and time point. Values were presented as mean ± SEM or SD and individual animal data were provided. |

## Overall Quality Determination — Uninformative

**Study Citation:** Dow Corning, (1992). A method development study to investigate absorption, distribution and elimination of a [volitile] material with cover letter dated 112392.

**HERO ID:** 5892869

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | 24 hour dermal expsoure; D4-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Male; Occluded |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | Not Reported; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | Not Reported; 100 mg/kg |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | 24 hrs; experiment was not repeated; Notes: Not Reported |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | Other; In expired air, absorption was measured at 12, 24, 32, 48, 56, 72, 80, and 96 hours after dosing. Urine and feces were collected at 24 hour intervals. Tissues/organs and GI tract collected at sacrifice (96 hours following dosing); Notes: 120 |
| Time Skin was Washed and Method used; Radiolabel Presence: | No washing was described; Yes |
| Total Recovery (percent); Dose Type: | 35.1; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | Not Reported; Notes: N/A |
| Percent Found in Urine ; Comments: | 0.7; Notes: N/A |
| Percent Found in Feces ; Comments: | 0.2; Notes: N/A |
| Percent Found in Blood/Serum ; Comments: | Not Reported; Notes: N/A |
| Percent Found in Air ; Comments: | Not Reported; Notes: Data provided are not adequate to determine Kp or Flux. |
| Percent Found in Cage Wash ; Comments: | Not Reported; Notes: Data provided are not adequate to determine Kp or Flux. |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | Not Reported; Notes: N/A |
| Total Percent Absorbed: | 1 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Data provided are not adequate to determine Kp or Flux.; Not Reported; Notes: Data provided are not adequate to determine Kp or Flux.; Not Reported; Notes: Data provided are not adequate to determine Kp or Flux.; Not Reported; Notes: Data provided are not adequate to determine Kp or Flux.; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance is identified definitively by name and CASRN. The test substance is reported to be radiolabeled, but the specific position of the radiolabel was not reported by the study authors. |

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**Study Citation:** Dow Corning, (1992). A method development study to investigate absorption, distribution and elimination of a [volitile] material with cover letter dated 112392.

**HERO ID:** 5892869

**EVALUATION**

| Domain | | Metric | Rating | Comments |
|---|---|---|---|---|
| | Metric 2: | Test substance source | Low | The test substance source is reported as the manufacturer (Dow Corning) which also operates the lab that did the experiments in the reference. The authors provide a reference number for the test substance that seems to be equivalent to a batch/lot number. Certificates of analysis were not provided in the study reports and the chemical identity was not analytically verified. |
| | Metric 3: | Test substance purity | Medium | The test substance is identified as 98% pure, but the authors did not characterize impurities, residual chemicals or solvents. As the chemical meets purity standards, this deficiency is not likely to have a major impact on the results. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Low | The authors did not state how animals were allocated into groups. |
| | Metric 5: | Standards for Tests | Low | Authors did not report on whether the test met pre-existing criteria and few or no QC criteria were reported. Enough information is reported to suggest that there were deviations from OECD criteria, and no washing nor tape stripping was provided. Percent recovery was reported and did not meet the standard criteria of 100 $\pm$ 20%; recovery was 35.1%. Coefficients of variation were not provided in the study report but could be determined using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | Low | Test substance storage conditions were not reported, and due to volatility of D4, there may substantial impacts on the results. Test substance was applied Neat. |
| | Metric 7: | Consistency of exposure administration | Low | Details of exposure administration are not fully reported. The dose is reported as 100 mg/kg to a treatment area of 5.5 cm2. The weight of the rats is not reported and unclear how much variation there was between them. If large differences in weight were seen, test substance applied per cm2 would not be consistent. The volume applied was not reported. The application area should be 5-10% of animal body surface (10 cm2 for rat); the application area was below the recommendation (5.5 cm2). |
| | Metric 8: | Reporting of concentrations | Low | The test substance concentration was reported with minor ambiguity due to using a nominal concentration rather than analytical. The dose is reported as 100 mg/kg to a treatment area of 5.5 cm2. The weight of the rats was not reported, therefore the dose in terms of mg/cm2 cannot be determined. |
| | Metric 9: | Exposure duration | High | The exposure duration was 24 hours and is appropriate to evaluate endpoints of interest. Endpoints were measured at frequent intervals following the end of exposure and allowed the authors to determine detailed kinetics of dermal absorption timing. |
| | Metric 10: | Number of exposure groups and concentration spacing | Low | Only one concentration group was tested, and the authors did not justify this decision. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | Low | The authors only report the test animal species and do not report information on strain, sex, age, or starting body weights. |
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | Low | The animals do not provide sufficient details to evaluate if animal husbandry conditions were appropriate. A note in the "Summary/Recommendations" tab indicates that Roth metabolism cages were used, but no other details regarding housing conditions are reported. |

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**Study Citation:** Dow Corning, (1992). A method development study to investigate absorption, distribution and elimination of a [volitile] material with cover letter dated 112392.
**HERO ID:** 5892869

**EVALUATION**

| Domain | | Metric | Rating | Comments |
|---|---|---|---|---|
| | Metric 13: | Number of animals per group | Medium | The study meets the minimum requirements of 4 animals per group. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Low | The outcome assessment methodology was partially descibed. In a methods development study, rats (n=4, sex/strain not reported) were dermally exposed to 100 mg/kg of 14C radiolabeled D4 on back skin (5.5 cm2) for 24 hours with an occluded glass blister. Animals were placed in metabolic cages and biological compartments were collected including: expired air at 12, 24, 32, 48, 56, 72, 80 and 96 hours, urine and feces every 24 hours (for up to 96 hours post exposure), and in unspecified tissues/organs at sacrifice (at 96 hours post exposure). Radioactivity in collected biological media was measured via a liquid scintillation counter. The outcome of interest was to determine % absorption and total recovery. The authors did not explicitly state whether this study was intended to be finite or infinite exposure, but the methods and outcomes suggest that this was a finite exposure. A few deviations from guidelines were identified, such as lack of tape stripping and a lack of measurements of absorption in blood/serum. The area of skin used in the dermal exposure (5.5 cm2) was less than what is recommended by OECD guidelines (10 cm2). The study did not report if skin was washed after the exposure period. At sacrifice the application area was not analyzed for the amount of test substance in the skin. Details on site preparation were not reported (if fur was clipped). The study did not note clinical signs of the animals after application or if irritation occurred at the site (recommended by OECD guidelines). |
| | Metric 15: | Consistency of outcome assessment | High | The outcome was measured consistently across groups using the same protocol at the same time in different animals. |
| | Metric 16: | Sampling adequacy and sensitivity | Medium | Details regarding sampling were partially reported. Duplicate samples were measured via scintillation. Study indicates that counts were only recorded when samples had stabilized, and all samples were checked for homogeneity. Additionally, the authors used total counts that were at least two times above the background for their calculations. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | The authors did not provide enough information to determine if confounding occurred. Body weights were not provided, and the authors didn't mention if animals with existing abrasions were removed from the study. There is likely no difference in reference number of the test substance between animals as only one reference number was reported. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Low | No attrition or issues with test substance solubility were reported. Solubility was not a factor of concern in this study due to the use of neat test substance. The authors did mention that there were concerns that the test substance escaped/evaporated from the occluded glass blister and wrapping, and the CO2 traps used to measure absorption in expired air weren't changed often enough and may have reached saturation early. Both factors suggest heavy potential confounding. |
| Domain 7: Data Presentation and Analysis | | | | |

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**Study Citation:** Dow Corning, (1992). A method development study to investigate absorption, distribution and elimination of a [volitile] material with cover letter dated 112392.

**HERO ID:** 5892869

**EVALUATION**

| Domain | | Metric | Rating | Comments |
|---|---|---|---|---|
| | Metric 19: | Data analysis | Low | Statistical analysis was not reported. Total recovery in different media was reported; however individual time points for urine and feces were not reported. Data for individual animals are reported. CV values were not reported but can be calculated from the available data. Half of the CV values were >50%. However, sufficient data are available to conduct an alternative analysis |
| | Metric 20: | Data interpretation | Low | The authors do not perform tape stripping and only a few media have absorption characterized, making it very difficult to fully evaluate absorption of the test substance from the available data.Total % recovery is less than 50%, suggesting there is high uncertainty with the results, and the fact that several compartments did not have their absorption measured implied that there is low confidence in the accuracy of the results. The authors, however, were forthcoming about these limitations (as well as confounding from possible evaporation and saturation from CO2 traps) and while this is a significant limitation, the results were not incorrectly interpreted. |
| | Metric 21: | Reporting of Data | Medium | Not all data were reported. Total recovery in different media was reported; however individual time points for urine and feces were not reported. For expired air measurements, only 24, 48, 72, 96 and total were shown. Individual animal data are reported. Total recovery is reported as mean +/-SD with percent recovery calculated by authors. |

## Overall Quality Determination Low

**Study Citation:** GE, (1994). Disposition of C14-octamethylcyclotetrasiloxane (D4) in the rat following cutaneous application.
**HERO ID:** 5888595

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | 6 Hour Exposure (Occluded)- Males; D4-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Male; Occluded |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | N/A; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 5.73; Not Reported |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | 6 hrs; Not Reported; Notes: Not Reported |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | Other; Exposure in different media (but not all media) was measured at 1, 2, 3, 6, 9, 12, 24, 48, 72 and/or 96 hours post exposure.; Notes: 96 hours |
| Time Skin was Washed and Method used; Radiolabel Presence: | At 6 hours, skin was wiped with a dry filter followed by an alcohol moistened gauze (1X). An alcohol moistened cotton swab was used to swab the application site. After the alcohol had dried, skin was stripped with Scotch tape and animals were rewrapped with fresh non-occulsive bandage.; Yes |
| Total Recovery (percent); Dose Type: | 84.05; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 10.7; Notes: CV=31.3. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Percent Found in Urine ; Comments: | 1.53; Notes: CV=31.3. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Percent Found in Feces ; Comments: | 0.34; Notes: CV=31.3. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Percent Found in Blood/Serum ; Comments: | Not Reported; Notes: CV=31.3. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Percent Found in Air ; Comments: | 22; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | Not Reported; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | 1.44; Notes: CV=31.3. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| 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); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |

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**Study Citation:** GE, (1994). Disposition of C14-octamethylcyclotetrasiloxane (D4) in the rat following cutaneous application.
**HERO ID:** 5888595

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 1: | Test substance identity | Medium | The test substance is identified definitively by name. Structure and CASRN were not reported. The test substance is radiolabeled, but the authors did not report the location of the radiolabel on the test substance. |
| | Metric 2: | Test substance source | Low | The radiolabeled test substance was obtained from Sigma Chemical Co., and the non-labeled test substance from General Electric, Waterford, NY. Lot numbers were provided. Certificates of analysis were not provided in the study reports and the chemical identity was not analytically verified by the performing laboratory. |
| | Metric 3: | Test substance purity | Medium | The authors report the purity of both the radiolabeled and non-labeled portions of the test substance as >98%. The authors did not characterize impurities or residual chemicals. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Low | The authors did not describe how animals were allocated into groups, other than stating that color coded tags were assigned to animals following allocation into groups. |
| | Metric 5: | Standards for Tests | Low | Authors did not report on whether the test met pre-existing criteria and few or no QC criteria were reported. Enough information is reported to suggest that there were minor deviations from OECD criteria, particularly regarding tape stripping and washes. Percent recovery was 77.14% for females and 84.05% form males. The study authors did not report whether the test met any pre-established criteria. Coefficients of variation were not provided in the study report but could be determined using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | Low | Test substance storage conditions were not reported, and due to volatility of D4, there may substantial impacts on the results. |
| | Metric 7: | Consistency of exposure administration | Medium | The authors consistently administered the test substance in animals between groups, using the same area of skin, but there was minor variation in volume of the test substance delivered by syringe that is unlikely to have a large impact on the results. The authors also report that animals with pre-existing abrasions were excluded and replaced by a reserve animal of similar body weight. |
| | Metric 8: | Reporting of concentrations | Medium | The test substance concentration was reported with minor ambiguity due to using a nominal concentration rather than analytical. |
| | Metric 9: | Exposure duration | High | The exposure duration was 6 hours and is appropriate to evaluate endpoints of interest. Endpoints were measured at frequent intervals following the end of exposure and allowed the authors to determine detailed dermal absorption timing. |
| | Metric 10: | Number of exposure groups and concentration spacing | Medium | Only one dose group was tested, however the use of one dose was justified by the author's intention to compare the effectiveness of occlusive and non-occlusive materials. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | High | Test animal species, strain, sex, starting age and starting weight were reported and are appropriate to measure endpoints of interest. The source of test animals was reported and is a commercial source with lab-maintained colonies. |
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | Medium | Animal housing conditions such as number of animals per cage and food availability were reported. The animal cage was described as a "Roth-type metabolism cage". Temperature, humidity and light/dark cycle details were not reported. |

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**Study Citation:** GE, (1994). Disposition of C14-octamethylcyclotetrasiloxane (D4) in the rat following cutaneous application.
**HERO ID:** 5888595

| Domain | | Metric | EVALUATION Rating | Comments |
|---|---|---|---|---|
| | Metric 13: | Number of animals per group | Medium | The study had 5 animals/sex/group for occlusive and non-occlusive test groups. This exceeds the minimum guideline requirements of an N =4. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | Details of outcome methodology are reported. Sprague Dawley rats (n=5) had hair clipped from the dorsal surface 24 hours prior to application of test substance. Animals that showed signs of abrasion were not included, but replaced by reserve animals. A Teflon gasket was secured to the skin with Skin Bond (R). 15 ul of test substance was applied to the skin (14.55 mg to a 2.54 cm2 area; 5.73 mg/cm2). This is in agreement with OECD 427 which recommends up to 10 ul/cm2 of liquid be added to the skin in order to mimic potential human exposure. The area was immediately occluded with Saran (R) plastic wrap held into place adhesive tape and an outer layer of Coban (R) elastic wrap. Animals were placed in metabolic cages to collect urine feces and expired air. At 6 hours, skin was wiped with a dry filter followed by an alcohol moistened gauze. An alcohol moistened cotton swab was used to swab application site (all filters, gauze and cotton swab were retained and analyzed for test substance). Skin was tape stripped (number of times was not reported) and animals were rewrapped with fresh non-occlusive bandages. Animals were returned to metabolic cages. After 96 hours, animals were sacrificed. Radioactivity in bandages, wipes, tape, dosing site, feces, urine, Co2 traps, charcoal tube (expired air) and carcass were determined using liquid scintillation counter. The outcome of interest was to determine percent absorption. The authors did not explicitly state whether the intention was to conduct a finite or infinite exposure scenario, but the methods and outcomes suggest this was a finite exposure.The study did not report on signs of toxicity per guidelines or report irritation of skin. Skin was tape stripped after the 6 hours of exposure to remove test substance from the skin. This is a deviation from guidance in which they recommend tape stripping at the time of sacrifice.; however, authors state this was done in order to prevent further exposure. Blood samples were not collected for analysis. |
| | Metric 15: | Consistency of outcome assessment | High | The outcome was measured consistently across groups using the same protocol at the same time in different animals. |
| | Metric 16: | Sampling adequacy and sensitivity | Low | Details regarding sampling were partially reported. The number of evaluations per group (n =5) was appropriate. Study indicates raw counts were adjusted for quench and background. The number of scintillation counts was not specified; raw data were not provided. Timing from the collection of the samples to the reading of them was not provided. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | Starting body weights were reported in a range, but the authors also indicated that animals with abrasions prior to dosing were replaced with animals with similar body weights, implying that starting body weights may have been controlled for, albeit the information provided is not sufficient to fully determine if they were adequately controlled for. There are no differences in batch/lot number between groups. |

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**Study Citation:** GE, (1994). Disposition of C14-octamethylcyclotetrasiloxane (D4) in the rat following cutaneous application.
**HERO ID:** 5888595

| | | EVALUATION | | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | High | No confounding variables, attrition or issues with test substance solubility were reported. The authors also stated that "animals with pre-existing abrasions were excluded to prior to dosing". Solubility was not a factor of concern in this study due to the use of neat test substance. |
| Domain 7: Data Presentation and Analysis | | | | |
| | Metric 19: | Data analysis | Low | Cumulative absorbed dose was reported across timepoints for D4 in urine and expired air.No statistical methods were described. CV values were not reported, but were calculated using the data provided. 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 | The authors did not report enough details on tape stripping (e.g. the number of times the skin was stripped) to determine if the tape stripping values were interpreted correctly. Recovery for males was 84.05% and females was 77.14%. Guidelines recommend recover of +/-20% for volatile substances. Authors attribute this low recover possibly "to the prolonged dosing and dose removal procedures which were carried out in the hood to accommodate the anesthesia." |
| | Metric 21: | Reporting of Data | High | Data were reported consistently across different tissue compartments/bodily fluids, but not every endpoint was measured across all timepoints. Data for all outcomes specified in the methods were reported. Means ± SD were provided |

## Overall Quality Determination Medium

**Study Citation:** GE, (1994). Disposition of C14-octamethylcyclotetrasiloxane (D4) in the rat following cutaneous application.
**HERO ID:** 5888595

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | 6 Hour Exposure (Occluded)- Females; D4-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Female; Occluded |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | N/A; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 5.73; Not Reported |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | 6 hrs; Not Reported; Notes: Not Reported |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | Other; Exposure in different media (but not all media) was measured at 1, 2, 3, 6, 9, 12, 24, 48, 72 and/or 96 hours post exposure.; Notes: 96 hours |
| Time Skin was Washed and Method used; Radiolabel Presence: | At 6 hours, skin was wiped with a dry filter followed by an alcohol moistened gauze (1X). An alcohol moistened cotton swab was used to swab the application site. After the alcohol had dried, skin was stripped with Scotch tape and animals were rewrapped with fresh non-occulsive bandage.; Yes |
| Total Recovery (percent); Dose Type: | 77.14; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 5.3; Notes: CV=42. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Percent Found in Urine ; Comments: | 0.79; Notes: CV=42. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Percent Found in Feces ; Comments: | 0.28; Notes: CV=42. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Percent Found in Blood/Serum ; Comments: | Not Reported; Notes: CV=42. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Percent Found in Air ; Comments: | 21; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | Not Reported; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | 0.98; Notes: CV=42. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Total Percent Absorbed: | 28 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance is identified definitively by name. Structure and CASRN were not reported. The test substance is radiolabeled, but the authors did not report the location of the radiolabel on the test substance. |

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**Study Citation:** GE, (1994). Disposition of C14-octamethylcyclotetrasiloxane (D4) in the rat following cutaneous application.
**HERO ID:** 5888595

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 2: | Test substance source | Low | The radiolabeled test substance was obtained from Sigma Chemical Co., and the non-labeled test substance from General Electric, Waterford, NY. Lot numbers were provided. Certificates of analysis were not provided in the study reports and the chemical identity was not analytically verified by the performing laboratory. |
| | Metric 3: | Test substance purity | Medium | The authors report the purity of both the radiolabeled and non-labeled portions of the test substance as >98%. The authors did not characterize impurities or residual chemicals. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Low | The authors did not describe how animals were allocated into groups, other than stating that color coded tags were assigned to animals following allocation into groups. |
| | Metric 5: | Standards for Tests | Low | Authors did not report on whether the test met pre-existing criteria and few or no QC criteria were reported. Enough information is reported to suggest that there were minor deviations from OECD criteria, particularly regarding tape stripping and washes. Percent recovery was 77.14% for females and 84.05% form males. The study authors did not report whether the test met any pre-established criteria. Coefficients of variation were not provided in the study report but could be determined using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | Low | Test substance storage conditions were not reported, and due to volatility of D4, there may substantial impacts on the results. |
| | Metric 7: | Consistency of exposure administration | Medium | The authors consistently administered the test substance in animals between groups, using the same area of skin, but there was minor variation in volume of the test substance delivered by syringe that is unlikely to have a large impact on the results. The authors also report that animals with pre-existing abrasions were excluded and replaced by a reserve animal of similar body weight. |
| | Metric 8: | Reporting of concentrations | Medium | The test substance concentration was reported with minor ambiguity due to using a nominal concentration rather than analytical. |
| | Metric 9: | Exposure duration | High | The exposure duration was 6 hours and is appropriate to evaluate endpoints of interest. Endpoints were measured at frequent intervals following the end of exposure and allowed the authors to determine detailed dermal absorption timing. |
| | Metric 10: | Number of exposure groups and concentration spacing | Medium | Only one dose group was tested, however the use of one dose was justified by the author's intention to compare the effectiveness of occlusive and non-occlusive materials. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | High | Test animal species, strain, sex, starting age and starting weight were reported and are appropriate to measure endpoints of interest. The source of test animals was reported and is a commercial source with lab-maintained colonies. |
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | Medium | Animal housing conditions such as number of animals per cage and food availability were reported. The animal cage was described as a "Roth-type metabolism cage". Temperature, humidity and light/dark cycle details were not reported. |
| | Metric 13: | Number of animals per group | Medium | The study had 5 animals/sex/group for occlusive and non-occlusive test groups. This exceeds the minimum guideline requirements of an N =4. |

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**Study Citation:** GE, (1994). Disposition of C14-octamethylcyclotetrasiloxane (D4) in the rat following cutaneous application.
**HERO ID:** 5888595

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | Details of outcome methodology are reported. Sprague Dawley rats (n=5) had hair clipped from the dorsal surface 24 hours prior to application of test substance. Animals that showed signs of abrasion were not included, but replaced by reserve animals. A Teflon gasket was secured to the skin with Skin Bond (R). 15 ul of test substance was applied to the skin (14.55 mg to a 2.54 cm2 area; 5.73 mg/cm2). This is in agreement with OECD 427 which recommends up to 10 ul/cm2 of liquid be added to the skin in order to mimic potential human exposure. The area was immediately occluded with Saran (R) plastic wrap held into place adhesive tape and an outer layer of Coban (R) elastic wrap. Animals were placed in metabolic cages to collect urine feces and expired air. At 6 hours, skin was wiped with a dry filter followed by an alcohol moistened gauze. An alcohol moistened cotton swab was used to swab application site (all filters, gauze and cotton swab were retained and analyzed for test substance). Skin was tape stripped (number of times was not reported) and animals were rewrapped with fresh non-occlusive bandages. Animals were returned to metabolic cages. After 96 hours, animals were sacrificed. Radioactivity in bandages, wipes, tape, dosing site, feces, urine, Co2 traps, charcoal tube (expired air) and carcass were determined using liquid scintillation counter. The outcome of interest was to determine percent absorption. The authors did not explicitly state whether the intention was to conduct a finite or infinite exposure scenario, but the methods and outcomes suggest this was a finite exposure.The study did not report on signs of toxicity per guidelines or report irritation of skin. Skin was tape stripped after the 6 hours of exposure to remove test substance from the skin. This is a deviation from guidance in which they recommend tape stripping at the time of sacrifice.; however, authors state this was done in order to prevent further exposure. Blood samples were not collected for analysis. |
| | Metric 15: | Consistency of outcome assessment | High | The outcome was measured consistently across groups using the same protocol at the same time in different animals. |
| | Metric 16: | Sampling adequacy and sensitivity | Low | Details regarding sampling were partially reported. The number of evaluations per group (n =5) was appropriate. Study indicates raw counts were adjusted for quench and background. The number of scintillation counts was not specified; raw data were not provided. Timing from the collection of the samples to the reading of them was not provided. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | Starting body weights were reported in a range, but the authors also indicated that animals with abrasions prior to dosing were replaced with animals with similar body weights, implying that starting body weights may have been controlled for, albeit the information provided is not sufficient to fully determine if they were adequately controlled for. There are no differences in batch/lot number between groups. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | High | No confounding variables, attrition or issues with test substance solubility were reported. The authors also stated that ”animals with pre-existing abrasions were excluded to prior to dosing”. Solubility was not a factor of concern in this study due to the use of neat test substance. |
| Domain 7: Data Presentation and Analysis | | | | |

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**Study Citation:** GE, (1994). Disposition of C14-octamethylcyclotetrasiloxane (D4) in the rat following cutaneous application.
**HERO ID:** 5888595

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 19: | Data analysis | Low | Cumulative absorbed dose was reported across timepoints for D4 in urine and expired air.No statistical methods were described. CV values were not reported, but were calculated using the data provided. 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 | The authors did not report enough details on tape stripping (e.g. the number of times the skin was stripped) to determine if the tape stripping values were interpreted correctly. Recovery for males was 84.05% and females was 77.14%. Guidelines recommend recover of +/-20% for volatile substances. Authors attribute this low recover possibly "to the prolonged dosing and dose removal procedures which were carried out in the hood to accommodate the anesthesia." |
| | Metric 21: | Reporting of Data | High | Data were reported consistently across different tissue compartments/bodily fluids, but not every endpoint was measured across all timepoints. Data for all outcomes specified in the methods were reported. Means ± SD were provided |

## Overall Quality Determination — Medium

**Study Citation:** GE, (1994). Disposition of C14-octamethylcyclotetrasiloxane (D4) in the rat following cutaneous application.
**HERO ID:** 5888595

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | 6 Hour Exposure (non-occluded)- Males; D4-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Male; Unoccluded |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | N/A; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 5.73; Not Reported |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | 6 hrs; Not Reported; Notes: Not Reported |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | Other; Exposure in different media (but not all media) was measured at 1, 2, 3, 6, 9, 12, 24, 48, 72 and/or 96 hours post exposure.; Notes: 96 hours |
| Time Skin was Washed and Method used; Radiolabel Presence: | At 6 hours, skin was wiped with a dry filter followed by an alcohol moistened gauze (1X). An alcohol moistened cotton swab was used to swab the application site. After the alcohol had dried, skin was stripped with Scotch tape and animals were rewrapped with fresh non-occulsive bandage.; Yes |
| Total Recovery (percent); Dose Type: | 102.78; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 6.68; Notes: CV=49.4. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Percent Found in Urine ; Comments: | 0.46; Notes: CV=49.4. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Percent Found in Feces ; Comments: | 0.12; Notes: CV=49.4. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Percent Found in Blood/Serum ; Comments: | Not Reported; Notes: CV=49.4. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Percent Found in Air ; Comments: | 11; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | Not Reported; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | 2.57; Notes: CV=49.4. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Total Percent Absorbed: | 21 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance is identified definitively by name. Structure and CASRN were not reported. The test substance is radiolabeled, but the authors did not report the location of the radiolabel on the test substance. |

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**Study Citation:** GE, (1994). Disposition of C14-octamethylcyclotetrasiloxane (D4) in the rat following cutaneous application.
**HERO ID:** 5888595

| Domain | | Metric | EVALUATION Rating | Comments |
|---|---|---|---|---|
| | Metric 2: | Test substance source | Low | The radiolabeled test substance was obtained from Sigma Chemical Co., and the non-labeled test substance from General Electric, Waterford, NY. Lot numbers were provided. Certificates of analysis were not provided in the study reports and the chemical identity was not analytically verified by the performing laboratory. |
| | Metric 3: | Test substance purity | Medium | The authors report the purity of both the radiolabeled and non-labeled portions of the test substance as >98%. The authors did not characterize impurities or residual chemicals. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Low | The authors did not describe how animals were allocated into groups, other than stating that color coded tags were assigned to animals following allocation into groups. |
| | Metric 5: | Standards for Tests | Low | Authors did not report on whether the test met pre-existing criteria and few or no QC criteria were reported. Enough information is reported to suggest that there were minor deviations from OECD criteria, particularly regarding tape stripping and washes. Percent recovery was reported and did meet the standard criteria of 100 ± 20% The study authors did not report whether the test met any pre-established criteria.Coefficients of variation were not provided in the study report but could be determined using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | Low | Test substance storage conditions were not reported, and due to volatility of D4, there may substantial impacts on the results. |
| | Metric 7: | Consistency of exposure administration | Medium | The authors consistently administered the test substance in animals between groups, using the same area of skin, but there was minor variation in volume of the test substance delivered by syringe that is unlikely to have a large impact on the results. The authors also report that animals with pre-existing abrasions were excluded and replaced by a reserve animal of similar body weight. |
| | Metric 8: | Reporting of concentrations | Medium | The test substance concentration was reported with minor ambiguity due to using a nominal concentration rather than analytical. |
| | Metric 9: | Exposure duration | High | The exposure duration was 6 hours and is appropriate to evaluate endpoints of interest. Endpoints were measured at frequent intervals following the end of exposure and allowed the authors to determine detailed dermal absorption timing. |
| | Metric 10: | Number of exposure groups and concentration spacing | Medium | Only one dose group was tested, however the use of one dose was justified by the author's intention to compare the effectiveness of occlusive and non-occlusive materials. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | High | Test animal species, strain, sex, starting age and starting weight were reported and are appropriate to measure endpoints of interest. The source of test animals was reported and is a commercial source with lab-maintained colonies. |
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | Medium | Animal housing conditions such as number of animals per cage and food availability were reported. The animal cage was described as a "Roth-type metabolism cage". Temperature, humidity and light/dark cycle details were not reported. |
| | Metric 13: | Number of animals per group | Medium | The study had 5 animals/sex/group for occlusive and non-occlusive test groups. This exceeds the minimum guideline requirements of an N =4. |

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**Study Citation:** GE, (1994). Disposition of C14-octamethylcyclotetrasiloxane (D4) in the rat following cutaneous application.
**HERO ID:** 5888595

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | Details of outcome methodology are reported. Sprague Dawley rats (n=5) had hair clipped from the dosal surface 24 hours prior to application of test substance. Animals that showed signs of abrasion were not included, but replaced by reserve animals. A skin depot chamber was secured on the skin with Skin Bond (R). The chamber consisted of a Teflon gasket, an activated charcoal trap, and a plastic cup with a hole to allow for air circulation. 15 ul of test substance was applied to the skin (14.55 mg to a 2.54 cm2 area; 5.73 mg/cm2). The area was immediately occulded with Saran (R) plastic wrap held into place adhesive tape and an outer layer of Coban (R) elastic wrap. Animals were placed in metabolic cages to collect urine feces and expired air. At 6 hours,skin was wiped with a dry filter followed by an alcohol moistened gauze. An achohol moistened cotton swab was used to swab application site (all filters, guaze and cotton swab were retained and analyzed for test substance). Skin was tape stripped and animals were rewrapped with fresh non-occlusive bandages. Animals were returned to metabolic cages. After 96 hours, animals were sacrificed. Radioactivtity in bandages, wipes, tape, dosing site, feces, urine, Co2 traps, charcoal tube (expired air) and carcass were determined using liquid scintillation counter. The outcome of interest was to determine percent absorption. The authors did not explicitly state whether the intention was to conduct a finite or infinite exposure scenario, but the methods and outcomes suggest this was a finite exposure.The study did not report on signs of toxicity per guidelines or report irritation of skin. Skin was tape stripped after the 6 hours of exposure to remove test substance from the skin. This is a deviation from guidance in which they recommend tape stripping at the time of sacrifice. Blood samples were not collected for analysis. |
| | Metric 15: | Consistency of outcome assessment | High | The outcome was measured consistently across groups using the same protocol at the same time in different animals. |
| | Metric 16: | Sampling adequacy and sensitivity | Low | Details regarding sampling were partially reported. The number of evaluations per group (n =5) was appropriate. Study indicates raw counts were adjusted for quench and background. The number of scintillation counts was not specified; raw data were not provided. Timing from the collection of the samples to the reading of them was not provided. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | Starting body weights were reported in a range, but the authors also indicated that animals with abrasions prior to dosing were replaced with animals with similar body weights, implying that starting body weights may have been controlled for, albeit the information provided is not sufficient to fully determine if they were adequately controlled for. There are no differences in batch/lot number between groups. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | High | No confounding variables, attrition or issues with test substance solubility were reported. The authors also stated that ”animals with pre-existing abrasions were excluded to prior to dosing”. Solubility was not a factor of concern in this study due to the use of neat test substance. |
| Domain 7: Data Presentation and Analysis | | | | |

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**Study Citation:** GE, (1994). Disposition of C14-octamethylcyclotetrasiloxane (D4) in the rat following cutaneous application.
**HERO ID:** 5888595

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 19: | Data analysis | Low | Cumulative absorbed dose was reported across timepoints for D4 in urine and expired air.No statistical methods were described. CV values were not reported, but were calculated using the data provided. 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 | The authors did not report enough details on tape stripping (e.g. the number of times the skin was stripped) to determine if the tape stripping values were interpreted correctly. The authors did not report enough details on tape stripping (e.g. the number of times the skin was stripped) to determine if the tape stripping values were interpreted correctly. Total recovery for females was 97.73% and for males was 102.78% |
| | Metric 21: | Reporting of Data | High | Data were reported consistently across different tissue compartments/bodily fluids, but not every endpoint was measured across all timepoints. Data for all outcomes specified in the methods were reported. Means ± SD were provided |

## Overall Quality Determination Medium

**Study Citation:** GE, (1994). Disposition of C14-octamethylcyclotetrasiloxane (D4) in the rat following cutaneous application.
**HERO ID:** 5888595

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | 6 Hour Exposure (non-occluded)- Females; D4-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Female; Unoccluded |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | N/A; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 5.73; Not Reported |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | 6 hrs; Not Reported; Notes: Not Reported |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | Other; Exposure in different media (but not all media) was measured at 1, 2, 3, 6, 9, 12, 24, 48, 72 and/or 96 hours post exposure.; Notes: 96 hours |
| Time Skin was Washed and Method used; Radiolabel Presence: | At 6 hours, skin was wiped with a dry filter followed by an alcohol moistened gauze (1X). An alcohol moistened cotton swab was used to swab the application site. After the alcohol had dried, skin was stripped with Scotch tape and animals were rewrapped with fresh non-occulsive bandage.; Yes |
| Total Recovery (percent); Dose Type: | 97.73; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 5.98; Notes: CV=61.1. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Percent Found in Urine ; Comments: | 0.48; Notes: CV=61.1. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Percent Found in Feces ; Comments: | 0.23; Notes: CV=61.1. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Percent Found in Blood/Serum ; Comments: | Not Reported; Notes: CV=61.1. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Percent Found in Air ; Comments: | 10; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | Not Reported; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | 2.39; Notes: CV=61.1. Animals were first wiped with an alcohol swab, then they were tape stripped a single time at 6 hours and not at the end of the experiment. |
| Total Percent Absorbed: | 18 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Not Reported |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance is identified definitively by name. Structure and CASRN were not reported. The test substance is radiolabeled, but the authors did not report the location of the radiolabel on the test substance. |

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**Study Citation:** GE, (1994). Disposition of C14-octamethylcyclotetrasiloxane (D4) in the rat following cutaneous application.
**HERO ID:** 5888595

| | | EVALUATION | | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 2: | Test substance source | Low | The radiolabeled test substance was obtained from Sigma Chemical Co., and the non-labeled test substance from General Electric, Waterford, NY. Lot numbers were provided. Certificates of analysis were not provided in the study reports and the chemical identity was not analytically verified by the performing laboratory. |
| | Metric 3: | Test substance purity | Medium | The authors report the purity of both the radiolabeled and non-labeled portions of the test substance as >98%. The authors did not characterize impurities or residual chemicals. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Low | The authors did not describe how animals were allocated into groups, other than stating that color coded tags were assigned to animals following allocation into groups. |
| | Metric 5: | Standards for Tests | Low | Authors did not report on whether the test met pre-existing criteria and few or no QC criteria were reported. Enough information is reported to suggest that there were minor deviations from OECD criteria, particularly regarding tape stripping and washes. Percent recovery was reported and did meet the standard criteria of 100 ± 20% The study authors did not report whether the test met any pre-established criteria.Coefficients of variation were not provided in the study report but could be determined using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | Low | Test substance storage conditions were not reported, and due to volatility of D4, there may substantial impacts on the results. |
| | Metric 7: | Consistency of exposure administration | Medium | The authors consistently administered the test substance in animals between groups, using the same area of skin, but there was minor variation in volume of the test substance delivered by syringe that is unlikely to have a large impact on the results. The authors also report that animals with pre-existing abrasions were excluded and replaced by a reserve animal of similar body weight. |
| | Metric 8: | Reporting of concentrations | Medium | The test substance concentration was reported with minor ambiguity due to using a nominal concentration rather than analytical. |
| | Metric 9: | Exposure duration | High | The exposure duration was 6 hours and is appropriate to evaluate endpoints of interest. Endpoints were measured at frequent intervals following the end of exposure and allowed the authors to determine detailed dermal absorption timing. |
| | Metric 10: | Number of exposure groups and concentration spacing | Medium | Only one dose group was tested, however the use of one dose was justified by the author's intention to compare the effectiveness of occlusive and non-occlusive materials. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | High | Test animal species, strain, sex, starting age and starting weight were reported and are appropriate to measure endpoints of interest. The source of test animals was reported and is a commercial source with lab-maintained colonies. |
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | Medium | Animal housing conditions such as number of animals per cage and food availability were reported. The animal cage was described as a "Roth-type metabolism cage". Temperature, humidity and light/dark cycle details were not reported. |
| | Metric 13: | Number of animals per group | Medium | The study had 5 animals/sex/group for occlusive and non-occlusive test groups. This exceeds the minimum guideline requirements of an N =4. |

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**Study Citation:** GE, (1994). Disposition of C14-octamethylcyclotetrasiloxane (D4) in the rat following cutaneous application.
**HERO ID:** 5888595

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | Details of outcome methodology are reported. Sprague Dawley rats (n=5) had hair clipped from the dosal surface 24 hours prior to application of test substance. Animals that showed signs of abrasion were not included, but replaced by reserve animals. A skin depot chamber was secured on the skin with Skin Bond (R). The chamber consisted of a Teflon gasket, an activated charcoal trap, and a plastic cup with a hole to allow for air circulation. 15 ul of test substance was applied to the skin (14.55 mg to a 2.54 cm2 area; 5.73 mg/cm2). The area was immediately occulded with Saran (R) plastic wrap held into place adhesive tape and an outer layer of Coban (R) elastic wrap. Animals were placed in metabolic cages to collect urine feces and expired air. At 6 hours,skin was wiped with a dry filter followed by an alcohol moistened gauze. An achohol moistened cotton swab was used to swab application site (all filters, guaze and cotton swab were retained and analyzed for test substance). Skin was tape stripped and animals were rewrapped with fresh non-occlusive bandages. Animals were returned to metabolic cages. After 96 hours, animals were sacrificed. Radioactivtity in bandages, wipes, tape, dosing site, feces, urine, Co2 traps, charcoal tube (expired air) and carcass were determined using liquid scintillation counter. The outcome of interest was to determine percent absorption. The authors did not explicitly state whether the intention was to conduct a finite or infinite exposure scenario, but the methods and outcomes suggest this was a finite exposure.The study did not report on signs of toxicity per guidelines or report irritation of skin. Skin was tape stripped after the 6 hours of exposure to remove test substance from the skin. This is a deviation from guidance in which they recommend tape stripping at the time of sacrifice. Blood samples were not collected for analysis. |
| | Metric 15: | Consistency of outcome assessment | High | The outcome was measured consistently across groups using the same protocol at the same time in different animals. |
| | Metric 16: | Sampling adequacy and sensitivity | Low | Details regarding sampling were partially reported. The number of evaluations per group (n =5) was appropriate. Study indicates raw counts were adjusted for quench and background. The number of scintillation counts was not specified; raw data were not provided. Timing from the collection of the samples to the reading of them was not provided. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | Medium | Starting body weights were reported in a range, but the authors also indicated that animals with abrasions prior to dosing were replaced with animals with similar body weights, implying that starting body weights may have been controlled for, albeit the information provided is not sufficient to fully determine if they were adequately controlled for. There are no differences in batch/lot number between groups. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | High | No confounding variables, attrition or issues with test substance solubility were reported. The authors also stated that ”animals with pre-existing abrasions were excluded to prior to dosing”. Solubility was not a factor of concern in this study due to the use of neat test substance. |
| Domain 7: Data Presentation and Analysis | | | | |

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**Study Citation:** GE, (1994). Disposition of C14-octamethylcyclotetrasiloxane (D4) in the rat following cutaneous application.
**HERO ID:** 5888595

| | | | EVALUATION | |
|---|---|---|---|---|
| Domain | | Metric | Rating | Comments |
| | Metric 19: | Data analysis | Low | Cumulative absorbed dose was reported across timepoints for D4 in urine and expired air.No statistical methods were described. CV values were not reported, but were calculated using the data provided. 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 | The authors did not report enough details on tape stripping (e.g. the number of times the skin was stripped) to determine if the tape stripping values were interpreted correctly. The authors did not report enough details on tape stripping (e.g. the number of times the skin was stripped) to determine if the tape stripping values were interpreted correctly. Total recovery for females was 97.73% and for males was 102.78% |
| | Metric 21: | Reporting of Data | High | Data were reported consistently across different tissue compartments/bodily fluids, but not every endpoint was measured across all timepoints. Data for all outcomes specified in the methods were reported. Means ± SD were provided |

## Overall Quality Determination Medium

**Study Citation:** University of Rochester Medical Center, (2000). Non-regulated study: Percutaneous absorption studies of octamethylcyclotetrasiloxane (D4) using the human skin/nude mouse model, with cover letter dt'd 021901.

**HERO ID:** 5884202

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | D4- Neat dermal absorption; D4-Parent compound |
| Species; Comments: | Mouse; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Female; Semi-occluded (e.g., gauze) |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | No vehicle was used.; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 15.7; Not Reported |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | 24 hrs; Exposure was not repeated.; Notes: Not Reported |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | Other; The test material was removed after 24-hours, collections of some endpoints were made through 72 hours. Urine, feces, and KOH traps were collected every 24-hours.; Notes: 72 hrs |
| Time Skin was Washed and Method used; Radiolabel Presence: | The skin was not washed.; Yes |
| Total Recovery (percent); Dose Type: | 96.35; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 0.008; Notes: CV = 167% |
| Percent Found in Urine ; Comments: | 0.149; Notes: CV = 167% |
| Percent Found in Feces ; Comments: | 0.39; Notes: CV = 167% |
| Percent Found in Blood/Serum ; Comments: | Not Reported; Notes: CV = 167% |
| Percent Found in Air ; Comments: | 0.053; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | 0.017; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | 0.015; Notes: CV = 167% |
| Total Percent Absorbed: | 0 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Other measurements included the animal skin, carcass, and baseline. |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as Octamethylcyclotetrasiloxane (D4). A structure was provided. Both radiolabeled and unlabeled test substance was used. Some physical/chemical properties were described and the form (a silicone fluid) was reported. The position of the radiolabel was not specified. |

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**Study Citation:** University of Rochester Medical Center, (2000). Non-regulated study: Percutaneous absorption studies of octamethylcyclotetrasiloxane (D4) using the human skin/nude mouse model, with cover letter dt'd 021901.

**HERO ID:** 5884202

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 2: | Test substance source | Low | Two separate lots of radiolabeled test substance were reported, both were prepared by Wizard Laboratories Inc., A single lot was used in the study. The non-labeled test substance was obtained from Dow Corning Corporation. All lot numbers were reported. Certificates of analysis were not provided in the study reports and the chemical identity was not analytically verified by the performing laboratory. |
| | Metric 3: | Test substance purity | High | The purities of the two lots of radiolabeled test substances were 97.3% and 98.9%. The purity of the non-labeled test substance was 99.9%. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Low | The method of animal allocation was not specified. |
| | Metric 5: | Standards for Tests | Medium | The study authors did not report whether the test met any pre-established criteria. The study employed the use of metabolism cages. Validation of the skin depot (e.g., integrity of attachment), and experimental system, included testing for possible saturation of the charcoal basket absorbent was conducted prior to the start of the study. Additionally, preliminary studies with D4 were conducted in order to identify potential problems and to refine techniques. Percent recovery was reported and met the standard criteria of 100 $\pm$ 20% for a volatile test substance. Coefficients of variation were not provided in the study report but could be determined using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | Medium | No preparation of the neat chemical was required. Storage conditions were not reported. |
| | Metric 7: | Consistency of exposure administration | High | All animals were exposed using the same protocol. 10 uL of the neat test substance was applied to human skin grafts transplanted into the same area of mice. The application rate was 15.7 mg/cm2 and the application surface area was 0.66 cm2. |
| | Metric 8: | Reporting of concentrations | Medium | Animals were exposed to the neat test substance. The mass per area (15.7 mg/cm2) was reported. The applications were monitored gravimetrically with an analytical balance. Dosing in mg/kg-day was not specified. Animal body weights at the time of study initiation were not reported, so this calculation could not be made. |
| | Metric 9: | Exposure duration | High | Animals were exposed for 24 hours which is a relevant exposure period according to OECD TG 427. Measurements continued beyond the exposure period to 72 hours. |
| | Metric 10: | Number of exposure groups and concentration spacing | Low | The study only tested the neat test substance. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | Medium | This was a non-traditional study that conducted exposures on human skin grafts translated into mice. Female Balb/C nude mice (n = 7, age not reported) were obtained from NIH Taconic Farm. Starting body weights were reported. Human fetal forearm skin 10-20 mm in diameter, obtained from fetuses ranging in age from 16-22 weeks, was transplanted subcutaneously into the lateral flanks of the nude mice. Three weeks later, the mouse skin and panniculus carnosus overlaying the graft were removed. The animals were then kept for 2-4 months to allow the graft to heal and grow to ~ 25 mm in diameter. |

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**Study Citation:** University of Rochester Medical Center, (2000). Non-regulated study: Percutaneous absorption studies of octamethylcyclotetrasiloxane (D4) using the human skin/nude mouse model, with cover letter dt'd 021901.

**HERO ID:** 5884202

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | High | Animal husbandry conditions (light cycle, temperature, humidity, food and water access, and cage types) were reported and conditions were consistent across animals. |
| | Metric 13: | Number of animals per group | Medium | The study included an N = 7, which exceeds the minimum guideline requirements of an N =4. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Medium | Details of outcome assessment methodology were reported. In brief, skin depots were attached to the human skin grafts in Balb/C mice (N =7). After 15 min, radiolabeled neat D4 (15.7 mg/cm2, 10 uL) was applied to the skin graft (0.66 cm2). Immediately after application, a charcoal basket was put into place and animals were placed into metabolism cages that also contained traps for volatile test substances, and expired CO2 traps. The skin depots and traps were removed after 24 hours. No washing of the skin surface was described. Tape stripping was done in order to cease exposure. Animals remained in the metabolism cages for an additional 48 hours. Urine, feces and KOH traps were collected every 24 hours. The charcoal traps were collected after 72 hours and at the end of the experiment. Animals were euthanized after 72 hours. The human skin graft, mouse skin, carcass, cage wash, charcoal tubes, KOH solutions and bubblers were collected. These collections, and also tape strips, urine and feces were analyzed for radioactivity using liquid scintillation spectrometry. Background corrections for KOH and fecal samples were done. The limits of detection were reported. The outcome of interest was to determine the % total absorbed. Blood samples were not collected. The authors did not explicitly state whether the intention was to conduct a finite or infinite exposure scenario, but the methods and outcomes suggest this was a finite exposure. |
| | Metric 15: | Consistency of outcome assessment | High | The outcome assessment protocol was reported and was carried out consistently across animals. |
| | Metric 16: | Sampling adequacy and sensitivity | Medium | Details regarding sampling were partially reported. The number of evaluations per group (n = 7) was appropriate. The study noted performing KOH background corrections and limits of detection were reported. The number of scintillation counts was not specified. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | High | The authors noted difficulties in analyzing the dispase solutions for trace amounts of D4. They also noted that the recovery of D4 from the tissue preparation and the extraction procedure had not been validated. These were uniform challenges and are not expected to lead to inconsistencies across replicates. Other potentially confounding issues were identified during preliminary studies and were corrected for the main study. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition or health outcomes unrelated to exposure. Solubility was not a factor of concern in this study due to the use of neat test substance. |
| Domain 7: Data Presentation and Analysis | | | | |

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**Study Citation:** University of Rochester Medical Center, (2000). Non-regulated study: Percutaneous absorption studies of octamethylcyclotetrasiloxane (D4) using the human skin/nude mouse model, with cover letter dt'd 021901.

**HERO ID:** 5884202

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 19: | Data analysis | Low | No statistical methods were described. CV values were not reported, but were calculated using the data provided. Less than half of the CV values were >50% (CO2, human skin application site, urine, volatile trap, tape strips, cage rinse, and vaseline); 4 CV values were >25% and <50% (animal skin, feces, percent of dose absorbed, and cage rinse), and the CV values for measurements in the animal carcass, evaporation trap, and percent recovery were <25%. Sufficient data were provided to conduct additional analyses. |
| | Metric 20: | Data interpretation | Medium | The interpretation of the study results was consistent with current guidelines with a few exceptions. The skin of the animals was not washed. Instead, tape stripping was conducted to cease exposure and the radioactivity of the tape likely included unabsorbed test substance that was on the surface of the skin. The absorption estimate included measurements of exhaled CO2, human skin (application site after tape stripping), human skin external graft area, animal skin, carcass, feces and urine (blood was not measured). OECD TG 427 does not include measurements in the skin as an absorbed dose. Skin measurements are considered separately as an absorbable dose. Recovery was 96.350% which is appropriate for a volatile test substance according to current guidelines. There are sufficient data to conduct alternative analysis. |
| | Metric 21: | Reporting of Data | High | Data for all outcomes specified in the methods were reported. Means ± SD were provided and individual animal data were included in the unpublished study report. |

## Overall Quality Determination Medium

**Study Citation:** University of Rochester Medical Center, (2000). Non-regulated study: Percutaneous absorption studies of octamethylcyclotetrasiloxane (D4) using the human skin/nude mouse model, with cover letter dt'd 021901.

**HERO ID:** 5884202

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | D4- Neat skin distribution study; D4-Parent compound |
| Species; Comments: | Mouse; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Female; Semi-occluded (e.g., gauze) |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | No vehicle was used.; 100 |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | 15.7; 10.36 mg |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | 24 hrs; Exposure was not repeated.; Notes: Not Reported |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | 24 hrs; Animals were euthanized 24 hours after dose application.; Notes: Not Reported |
| Time Skin was Washed and Method used; Radiolabel Presence: | The skin was not washed.; Yes |
| Total Recovery (percent); Dose Type: | Not Reported; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 0.00738; Notes: Not Reported |
| Percent Found in Urine ; Comments: | Not Reported; Notes: Not Reported |
| Percent Found in Feces ; Comments: | Not Reported; Notes: Not Reported |
| Percent Found in Blood/Serum ; Comments: | Not Reported; Notes: Not Reported |
| Percent Found in Air ; Comments: | Not Reported; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | Not Reported; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | Not Reported; Notes: Not Reported |
| Total Percent Absorbed: | 0 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: This was a skin distribution study that only measured concentrations in the epidermis, dermis, and adipose layers. |

**EVALUATION**

| Domain | Metric | Rating | Comments |
|---|---|---|---|
| Domain 1: Test Substance | | | |
| Metric 1: | Test substance identity | Medium | The test substance was identified as Octamethylcyclotetrasiloxane (D4). A structure was provided. Both radiolabeled and unlabeled test substance was used. Some physical/chemical properties were described and the form (a silicone fluid) was reported. The position of the radiolabel was not specified. |

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**Study Citation:** University of Rochester Medical Center, (2000). Non-regulated study: Percutaneous absorption studies of octamethylcyclotetrasiloxane (D4) using the human skin/nude mouse model, with cover letter dt'd 021901.

**HERO ID:** 5884202

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 2: | Test substance source | Low | Two separate lots of radiolabeled test substance were reported, both were prepared by Wizard Laboratories Inc., A single lot was used in the study. The non-labeled test substance was obtained from Dow Corning Corporation. All lot numbers were reported. Certificates of analysis were not provided in the study reports and the chemical identity was not analytically verified by the performing laboratory. |
| | Metric 3: | Test substance purity | High | The purities of the two lots of radiolabeled test substances were 97.3% and 98.9%. The purity of the non-labeled test substance was 99.9%. |
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Low | The method of animal allocation was not specified. |
| | Metric 5: | Standards for Tests | Medium | The study authors did not report whether the test met any pre-established criteria. The study employed the use of metabolism cages. Validation of the skin depot (e.g., integrity of attachment), and experimental system, including testing for possible saturation of the charcoal basket absorbent, was conducted prior to the start of the study. Additionally, preliminary studies with D4 were conducted to identify potential problems and to refine techniques. Percent recovery was not reported; however, this was a skin distribution study and recovery was not part of the study design. Coefficients of variation were not provided in the study report but could be determined using the data provided. |
| Domain 3: Exposure Characterization | | | | |
| | Metric 6: | Preparation and storage of test substance (chemical) | Medium | No preparation of the neat chemical was required. Storage conditions were not reported. |
| | Metric 7: | Consistency of exposure administration | High | All animals were exposed using the same protocol. 10 uL of the neat test substance was applied to human skin grafts transplanted into the same area of mice. The application rate was 15.7 mg/cm2 and the application surface area was 0.66 cm2. |
| | Metric 8: | Reporting of concentrations | Medium | Animals were exposed to the neat test substance. The mass per area (15.7 mg/cm2) and area of the application site (0.66 cm2) was reported. The applications were monitored gravimetrically with an analytical balance. Dosing in mg/kg-day was not specified. Animal body weights at the time of study initiation were not reported, so this calculation could not be made. |
| | Metric 9: | Exposure duration | High | Animals were exposed for 24 hours which is a relevant exposure period according to OECD TG 427. |
| | Metric 10: | Number of exposure groups and concentration spacing | Low | The study only tested the neat test substance. |
| Domain 4: Test Model | | | | |
| | Metric 11: | Test animal characteristics | Medium | This was a non-traditional study that conducted exposures on human skin grafts translated into mice. Female Balb/C nude mice (n = 4, age not reported) were obtained from NIH Taconic Farm. Starting body weights were reported. Human fetal forearm skin 10-20 mm in diameter, obtained from fetuses ranging in age from 16-22 weeks, was transplanted subcutaneously into the lateral flanks of the nude mice. Three weeks later, the mouse skin and panniculus carnosus overlaying the graft were removed. The animals were then kept for 2-4 months to allow the graft to heal and grow to ~ 25 mm in diameter. |

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**HERO ID:** 5884202

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 12: | Adequacy and consistency of animal husbandry conditions | High | Animal husbandry conditions (light cycle, temperature, humidity, food and water access, and cage types) were reported and conditions were consistent across animals. |
| | Metric 13: | Number of animals per group | Medium | The study included an N = 4, which meets the minimum guideline requirements of an N = 4. |
| Domain 5: Outcome Assessment | | | | |
| | Metric 14: | Outcome assessment methodology | Low | This is a non-guideline skin distribution study. Briefly, skin depots were attached to the human skin grafts (N =4). Non-labeled neat D4 (15.7 mg/cm2, 10 uL) was applied to a skin area of 0.66 cm2. After application, a charcoal basket was put into place and animals were placed into metabolism cages that also contained traps for volatile test substances. 24-hours after application, animals were euthanized. The skin depot was removed and the human tissue, charcoal basket, and volatile substance traps were collected. No tape stripping was done. The graft site was separated from the rest of the animal. Adipose tissue was cut away, and the epidermis and dermis were separated after soaking in RPMI media and dispase for 24-hrs. The tissue samples, dispase solutions, charcoal baskets, and volatile substance traps were analyzed (SOP XLIII). D4 analysis was done using GC/MS. The limit of detection was reported (2 ng/mL). D4 levels in the epidermis, dermis, and adipose tissue were reported which was consistent with the goals of the experiment.The authors did not explicitly state whether the intention was to conduct a finite or infinite exposure scenario, but the methods and outcomes suggest this was a finite exposure. |
| | Metric 15: | Consistency of outcome assessment | High | The outcome assessment protocol was reported and was carried out consistently across animals. |
| | Metric 16: | Sampling adequacy and sensitivity | Medium | Details regarding sampling were partially reported. The number of evaluations per group (n = 4) was appropriate. GC/MC is generally considered to be a sensitive method, although no sensitivity analysis was described. |
| Domain 6: Confounding/Variable Control | | | | |
| | Metric 17: | Confounding variables in test design and procedures | High | The authors noted that the recovery of D4 from the tissue preparation and the extraction procedure had not been validated. Other potentially confounding issues were identified during preliminary studies and were corrected for the main study. |
| | Metric 18: | Confounding variables in outcomes unrelated to exposure | Medium | There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition or health outcomes unrelated to exposure. Solubility was not a factor of concern in this study due to the use of neat test substance. |
| Domain 7: Data Presentation and Analysis | | | | |
| | Metric 19: | Data analysis | Low | The endpoints were appropriate for the study type; noting that this is not a standard dermal absorption study. No statistical methods were described. CV values were not reported, but were calculated using the data provided. CV values for all of the samples were >50%. Sufficient information is provided to conduct alternative analysis. |
| | Metric 20: | Data interpretation | Medium | Interpretation of the study results is appropriate. The results show distribution of radioactivity in various skin layers at a set point in time (24-hours). |

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**Study Citation:** University of Rochester Medical Center, (2000). Non-regulated study: Percutaneous absorption studies of octamethylcyclotetrasiloxane (D4) using the human skin/nude mouse model, with cover letter dt'd 021901.

**HERO ID:** 5884202

**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| | Metric 21: | Reporting of Data | High | Data for all outcomes specified in the methods were reported. Means ± SD were provided and individual animal data were included in the unpublished study report. |

## Overall Quality Determination Medium