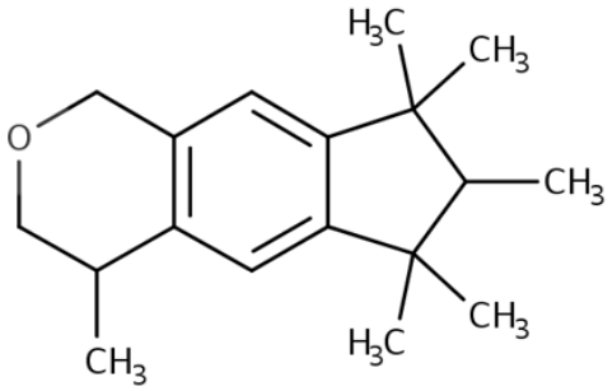
United States
Environmental Protection Agency

March 2026
Office of Chemical Safety and
Pollution Prevention

Draft Data Quality Evaluation Information for Dermal Absorption for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[γ]-2-benzopyran (HHCB)

Systematic Review Support Document for the Draft Risk Evaluation

CASRN 1222-05-5



March 2026

This supplemental file contains information regarding the data evaluation results for data sources that met the PECO screening criteria for the *Draft Risk Evaluation for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[γ]-2-benzopyran (HHCB)* 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 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[γ]-2-benzopyran (HHCB)*.

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: An-eX, (2001). In-vitro human skin penetration of radiolabelled fragrance material HHCB (redacted).
Chemical: HHCB
Exposure Type: Parent compound
HERO ID: 13006533
Unique ID: Main study; 6% Volpo N20 in PBS

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	The test substance was identified as unlabeled HHCB (1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[G]-2-benzopyran and isomers) and radiolabeled HHCB [UL-phenyl-14C)]. There is no indication if the radiolabel is in a metabolically stable position. A CAS No. was not provided.
	Metric 2:	Test substance source	High	The test substances were supplied by the Sponsor (Research Institute for Fragrance Materials). A certificate of analysis for the radiolabeled test substance was provided by Wizard Laboratories Inc. It is unclear if the sponsor manufactured the unlabeled test substance or obtained it from a commercial company. Lot numbers were reported for the unlabelled and radiolabeled material.
	Metric 3:	Test substance purity	High	The purity for unlabeled test substance was 98.5% and the radiolabeled test material had a radiochemical purity of 99.3%.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Medium	There was no reference compound identified. The experiments were conducted by An-eX analytical services ltd. According to their website, this company performs in vitro skin penetration evaluations for customers and, therefore, is technically proficient in running these types of studies.
	Metric 5:	Assay procedures	Medium	Human epidermal skin was mounted into static diffusion cells. The source and preparation of the skin were described. The apparatus (horizontal Franz-type diffusion cells) was clearly described and included a drawing. Epidermal membranes were floated onto water and taken up onto a 25mm diameter filter paper support and then mounted onto the diffusion cells. The diagram shows the filter paper support between the membrane and the receptor fluid. The skin surface area was maintained at 32 $\pm$ 1 degree C throughout the experiment. Humidity was not described. Skin integrity was assessed prior to dosing with tritiated water. The receptor fluid used was phosphate-buffered saline containing 6% Volpo N20; pH was 7.4 +/-0.1. Magnetic stir bars were used to stir the receptor fluid chambers continuously. Solubility of the test substance in the receptor fluid was previously assessed as >2000ug/ml and therefore not rate-limiting. The receptor volume was reported in Appendix 2. The skin surface area was about 1 cm2 (exact area reported in Appendix 2). The donor cell was not occluded. The volume applied and dose of HHCB were reported for each cell in Appendix 2. Receptor fluid (200 μL) was collected at 1, 2, 6, 12, and 24 hours. The study does not report if the volume was added back. After the 24-hour exposure test substance was removed by gently wiping a dry cotton bud on the skin. The epidermal membrane was tape stripped 10 times with adhesive tape. Radioactivity in the surface wipes, donor chamber, tape strips, skin, filter paper and receptor fluid was assessed by scintillation counting. Quantification was sensitive, but the LOD was not reported. The number of scintillation counts was not specified

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Unique ID: Main study; 6% Volpo N20 in PBS

Domain	Metric		Rating	Comments
	Metric 6:	Standards for tests	Medium	The integrity of the membrane was determined by measuring permeation of tritiated water. No cell had a water permeability >2.1 x 10-3 cm/hr. Recovery of test material was 92.1%. CVs could be calculated for all compartments evaluated.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of test substance was partially reported. The non-radiolabeled test substance was prepared as a 1% (w/v) solution in ethanol (246.52 mg into 25 ml) and spiked with radiolabeled test substance (3.31 mg). The final concentration was 0.999% HHCB (w/v). Details of mixing were not specified, but homogeneity and the specific activity were assessed by scintillation counting. Solubility in the receptor fluid was confirmed prior to the start of the study. No information is provided as to how far in advance the test solution was made or storage. Given the vehicle was ethanol, potential volatilization of the test solution may have occurred without proper storage.
	Metric 8:	Consistency of exposure administration	Medium	The area of the exposed skin and applied volume were reported for each individual cell. Variations were small with CVs <7%.
	Metric 9:	Reporting of concentrations	Medium	The target dose of 200 ug/cm2 was reported. Authors calculated dose based on measured volume applied and measured area of cell. The concentration of test solution was not analytically verified. The donor cell was not occluded, since the vehicle was ethanol, evaporation of the vehicle may have occurred thereby increasing the concentration of the test solution.
	Metric 10:	Exposure frequency	High	Exposure duration was reported and appropriate for determining absorption. The test substance was in contact with the skin for 24 hours. Samples of receptor fluid were collected for a total of 24 hours.
	Metric 11:	Number of exposure groups and concentration spacing	Low	Only one dose was studied (target dose of 20 ul/cm2 of a 1% solution in ethanol) applied dose ~200 ug/cm2. No justification was provided why this dose was chosen.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The samples were from three female donors (2 Caucasian and one Asian); the age of 2 donors was reported. Two samples were from abdominal surgery, and one from breast surgery. Skin was stored at -20oC and thawed before processing. The epidermis was gently removed from the dermis after immersing the skin sections in water at 60 degrees C for 50 seconds. Split thickness samples are preferred, although the use of an epidermal layer is acceptable. The thickness of membranes was not reported. Skin integrity results were reported.
	Metric 13:	Number/Replicates per group	Low	The number of donors was slightly lower than recommended. Guidelines recommend 8 replicates/dose from at least 4 donors (2 replicates/donor). This study examined 4 replicates from 3 donors for a total of 12 replicates/dose.
Domain 5: Outcome Assessment				

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Chemical: HHCB
Exposure Type: Parent compound
HERO ID: 13006533
Unique ID: Main study; 6% Volpo N20 in PBS

Domain	Metric		Rating	Comments
	Metric 14:	Outcome assessment methodology	Medium	The outcome assessment methodology addressed the intended outcome(s) of interest and was sensitive for the outcome(s) of interest. The selected formulation in ethanol was deemed to be the most appropriate, considering the highest concentration of HHCB is found in ethanolic products. Approximately 20ul/cm2 of test solution was applied to the skin. This volume is slightly more than the recommended amount of 10ul/cm2 for finite dosing and unlikely to substantially impact results. This corresponds to ~200 ug/cm2. Absorption was measured over 24 hours. The amount of test substance in the skin, donor cell, tape strips, surface wipes, receptor fluid, and filter paper were reported. The total absorbed dose was calculated from levels in the epidermis, remaining stratum corneum after tape stripping, the filter paper, and the receptor fluid. The 10 tape strips were not included in the calculation. The text noted this was per SCCNFP guidelines. Data on tape strips are available for alternate absorption calculations.
	Metric 15:	Consistency of outcome assessment	High	The outcome assessment protocols were reported and were consistent across groups.
	Metric 16:	Sampling adequacy and sensitivity	Medium	Samples were collected 5 times over 24-hour period (at 1, 2, 6, 12, and 24 hours). OECD Guidelines recommends 6-12 sampling points over 24 hours. Cumulative permeation into the receptor fluid is graphically shown. Samples were counted for radioactivity using a Wallac 1409 liquid scintillation counter. The study did not report the number of scintillation counts/sample or the LOD. Two undosed negative control cells were included; no radioactivity was detected.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Skin samples were obtained from 3 donors. Two samples were abdominal skin, and one was breast. The age of one donor was unknown; the two others were close in age (28 and 35 years old). One woman was Asian and the other 2 were Caucasian. These differences in donor skin may confound results. The skin thickness was not measured; variation in thickness may result in inconsistencies between samples. Skin integrity (measure by titrated water) was acceptable for all samples.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Absorption estimates were based on appropriate measurements. Percent absorption estimates were presented for each compartment of the test system, The CV for total absorbed dose was 40%. CVs for each compartment can be calculated with the provided data and were $> 25\%$ and $< 50\%$ for more than half the samples however data are available for EPA to calculate an alternate (upper end) value to account for variability in the results.

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HERO ID: 13006533
Unique ID: Main study; 6% Volpo N20 in PBS

Domain	Metric		Rating	Comments
	Metric 20:	Data interpretation	Medium	Total recovery was 92.1%. The amount of test substance in tape strips was reported as strip 1, 2-3, 4-6, and 7-10. The amount of test substance in the skin after tape stripping was also reported. Donor cells were unoccluded. Given the volatility of the vehicle, a carbon trap would be useful to determine how much test sample evaporated. Data from a satellite experiment performed by this lab suggest possibly 2.4% of the test substance may have evaporated; however, the test conditions for this satellite experiment were not the same as this experiment (used PTFE surface membrane instead of skin).
	Metric 21:	Reporting of data	High	Data were adequately reported as means ± SD and as individual cells. Concentrations in receptor fluids over time were also graphically displayed.

Overall Quality Determination Medium

Study Citation: An-eX, (2001). In-vitro human skin penetration of radiolabelled fragrance material HHCB (redacted).
Chemical: HHCB
Exposure Type: Parent compound
HERO ID: 13006533
Unique ID: Receptor fluid study; 50/50 ethanol/water

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	The test substance was identified as unlabeled HHCB (1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[G]-2-benzopyran and isomers) and radiolabeled HHCB [UL-phenyl-14C)]. There is no indication whether the radiolabel is in a metabolically stable position. A CAS No was not provided.
	Metric 2:	Test substance source	High	The test substances were supplied by the Sponsor (Research Institute for Fragrance Materials). A certificate of analysis for the radiolabeled test substance was provided from Wizard Laboratories Inc. It is unclear if the sponsor manufactured the unlabeled test substance or obtained it from a commercial company. Lot numbers were reported for the unlabelled and radiolabeled material.
	Metric 3:	Test substance purity	High	The purity for unlabeled test substance was 98.5% and the radiolabeled test material had a radiochemical purity of 99.3%.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Medium	There was no reference compound identified. The experiments were conducted by An-eX analytical services ltd. According to their website, this company performs in vitro skin penetration evaluations for customers and therefore is technically proficient in running these types of studies.
	Metric 5:	Assay procedures	Medium	Human epidermal skin was mounted into static diffusion cells. The source and preparation of the skin were described. The apparatus (horizontal Franz-type diffusion cells) was clearly described and included a drawing. Epidermal membranes were floated onto water and taken up onto a 25mm diameter filter paper support and then mounted onto the diffusion cells. The diagram shows the filter paper support between the membrane and the receptor fluid. The skin surface area was maintained at 32 $\pm$ 1 degree C throughout the experiment. Humidity was not described. Skin integrity was assessed prior to dosing with tritiated water. The receptor fluid used was 50/50 ethanol/water. Magnetic stir bars were used to stir the receptor fluid chambers continuously. Solubility of the test substance in the receptor fluid was assessed as ~1581ug/ml and therefore not rate-limiting. The receptor volume was reported in Appendix 4. The skin surface area was about 1 cm2 (exact area reported in Appendix 2). The donor cell was not occluded. The volume applied and dose of HHCB were reported for each cell in Appendix 2. Receptor fluid (200 ul) was collected at 1, 2, 6, 12, and 24 hours. The study does not report whether the volume was added back. After the 24-hour exposure, the test substance was removed by gently wiping a dry cotton bud on the skin. The epidermal membrane was tape stripped 10 times with adhesive tape. Radioactivity in the surface wipes, donor chamber, tape strips, skin, filter paper and receptor fluid was assessed by scintillation counting. Quantification was sensitive and the LOD was not reported. The number of scintillation counts was not specified.
	Metric 6:	Standards for tests	Medium	The integrity of the membrane was determined by measuring permeation of tritiated water. No cell had a water permeability >1.77 x 10-3 cm/hr. Recovery of test material was 95.1%. CVs could be calculated for all compartments evaluated.

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Chemical: HHCB
Exposure Type: Parent compound
HERO ID: 13006533
Unique ID: Receptor fluid study; 50/50 ethanol/water

Domain	Metric		Rating	Comments
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of test substance was partially reported. The non-radiolabeled test substance was prepared as a 1% (w/v) solution in ethanol (246.52 mg into 25 ml) and spiked with radiolabeled test substance (3.31 mg). The final concentration was 0.999% HHCB (w/v). Details of mixing were not specified, but homogeneity and the specific activity were assessed by scintillation counting. Solubility in the receptor fluid was confirmed prior to the start of the study. No information is provided as to how far in advance the test solution was made or storage. Given the vehicle was ethanol, potential volatilization of the test solution may have occurred without proper storage.
	Metric 8:	Consistency of exposure administration	Medium	The area of the exposed skin and applied volume were reported for each individual cell. Variations were small with CVs <9%.
	Metric 9:	Reporting of concentrations	Medium	The target dose of 200 ug/cm2 was reported. The authors calculated the dose based on the measured volume applied and the measured area of the cell. The concentration of the test solution was not analytically verified. The donor cell was not occluded; however, the lack of occlusion is representative of the expected conditions of use.
	Metric 10:	Exposure frequency	High	Exposure duration was reported and appropriate for determining absorption. The test substance was in contact with the skin for 24 hours. Samples of receptor fluid were collected for a total of 24 hours.
	Metric 11:	Number of exposure groups and concentration spacing	Low	Only one dose was studied (target dose of 20 ul/cm2 of a 1% solution in ethanol) applied dose ~200 ug/cm2. No justification was provided why this dose was chosen.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	Skin samples were obtained from 3 donors. Two samples were breast skin, and one was abdominal. The ages of the donors were 63, 34, and 24 years of age. Skin was stored at -20oC and thawed before processing. The epidermis was gently removed from the dermis after immersing the skin sections in water at 60 degrees C for 50 seconds. Split thickness samples are preferred, although the use of an epidermal layer is acceptable. The thickness of membranes was not reported. Skin integrity results were reported.9
	Metric 13:	Number/Replicates per group	Low	The number of donors was slightly lower than recommended. Guidelines recommend 8 replicates/dose from at least 4 donors (2 replicates/donor). This study examined 3 donors; one donor was repeated twice and the other two were ran once, for a total of 4 replicates/dose.
Domain 5: Outcome Assessment				

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Chemical: HHCB
Exposure Type: Parent compound
HERO ID: 13006533
Unique ID: Receptor fluid study; 50/50 ethanol/water

Domain	Metric		Rating	Comments
	Metric 14:	Outcome assessment methodology	Medium	The outcome assessment methodology addressed the intended outcome(s) of interest and was sensitive for the outcome(s) of interest. The selected formulation in ethanol was deemed to be the most appropriate, considering the highest concentration of HHCB is found in ethanolic products. Approximately 20ul/cm2 of test solution was applied to the skin. This volume is slightly more than the recommended amount of 10ul/cm2 for finite dosing and unlikely to substantially impact results. This corresponds to ~200 ug/cm2. Absorption was measured over 24 hours. The amount of test substance in the skin, donor cell, tape strips, surface wipes, receptor fluid, and filter paper were reported. The total absorbed dose was calculated from levels in the epidermis, remaining stratum corneum after tape stripping, the filter paper, and the receptor fluid. The 10 tape strips were not included in the calculation. The text noted this was per SCCNFP guidelines. Data on tape strips are available for alternate absorption calculations.
	Metric 15:	Consistency of outcome assessment	High	The outcome assessment protocols were reported and were consistent across groups.
	Metric 16:	Sampling adequacy and sensitivity	Medium	Samples were collected 5 times over 24-hour period (at 1, 2, 6, 12, and 24 hours). OECD Guidelines recommends 6-12 sampling points over 24 hours. Cumulative permeation into the receptor fluid is graphically shown. Samples were counted for radioactivity using a Wallac 1409 liquid scintillation counter. The study did not report the number of scintillation counts/sample or the LOD. Two undosed negative control cells were included; no radioactivity was detected.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Skin samples were obtained from 3 donors. Two samples were breast skin and one was abdominal. The ages of the donors were 63, 34, and 24 years of age. The skin thickness was not measured; variation in thickness may result in inconsistencies between samples. Skin integrity (measure by titrated water) was acceptable for all samples.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Absorption estimates were based on appropriate measurements. Percent absorption estimates were presented for each compartment of the test system, The CV for total absorbed dose was 41%. CVs for each compartment can be calculated with the provided data and were $>$ 25% and $<$ 50% for more than half the samples however data are available for EPA to calculate an alternate (upper end) value to account for variability in the results.
	Metric 20:	Data interpretation	Medium	Total recovery was adequate 100 +/-10%. The amount of test substance in tape strips was reported as strip 1, 2-3, 4-6, and 7-10. The amount of test substance in the skin after tape stripping was also reported. Donor cells were unoccluded. Given the volatility of the vehicle, a carbon trap would be useful to determine how much test sample evaporated. Data from a satellite experiment performed by this lab suggest possibly 3.5% of the test substance may have evaporated; however, the test conditions for this satellite experiment were not the same as this experiment (used PTFE surface membrane instead of skin).

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Chemical: HHCB
Exposure Type: Parent compound
HERO ID: 13006533
Unique ID: Receptor fluid study; 50/50 ethanol/water

Domain	Metric	Rating	Comments
	Metric 21: Reporting of data	High	Data were adequately reported as means ± SD and as individual cells. Concentrations in receptor fluids over time were also graphically displayed.

Overall Quality Determination Medium

Study Citation: An-eX, (2001). In-vitro human skin penetration of radiolabelled fragrance material HHCB (redacted).
Chemical: HHCB
Exposure Type: Parent compound
HERO ID: 13006533
Unique ID: Receptor fluid study; 4% BSA in PBS

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	The test substance was identified as unlabeled HHCB (1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[G]-2-benzopyran and isomers) and radiolabeled HHCB [UL-phenyl-14C)]. There is no indication if the radiolabel is in a metabolically stable position. A CAS No was not provided.
	Metric 2:	Test substance source	High	The test substances were supplied by the Sponsor (Research Institute for Fragrance Materials). A certificate of analysis for the radiolabeled test substance was provided by Wizard Laboratories Inc. It is unclear if the sponsor manufactured the unlabeled test substance or obtained it from a commercial company. Lot numbers were reported for the unlabelled and radiolabeled material.
	Metric 3:	Test substance purity	High	The purity for unlabeled test substance was 98.5% and the radiolabeled test material had a radiochemical purity of 99.3%.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Medium	There was no reference compound identified. The experiments were conducted by An-eX analytical services ltd. According to their website, this company performs in vitro skin penetration evaluations for customers and therefore is technically proficient in running these types of studies.
	Metric 5:	Assay procedures	Medium	Human epidermal skin was mounted into static diffusion cells. The source and preparation of the skin were described. The apparatus (horizontal Franz-type diffusion cells) was clearly described and included a drawing. Epidermal membranes were floated onto water and taken up onto a 25mm diameter filter paper support and then mounted onto the diffusion cells. The diagram shows the filter paper support between the membrane and the receptor fluid. The skin surface area was maintained at 32 $\pm$ 1 degree C throughout the experiment. Humidity was not described. Skin integrity was assessed prior to dosing with tritiated water. The receptor fluid used was 4% bovine serum albumin, fraction V in PBS. Magnetic stir bars were used to stir the receptor fluid chambers continuously. Solubility of the test substance in the receptor fluid was assessed to be ~527 ug/ml therefore not rate-limiting. The receptor volume was reported in Appendix 4. The skin surface area was about 1 cm2 (exact area reported in Appendix 2). The donor cell was not occluded. The volume applied and dose of HHCB were reported for each cell in Appendix 2. The donor cell was not occluded. The volume applied and dose of HHCB were reported for each cell in Appendix 2. Receptor fluid (200 ul) was collected at 1, 2, 6, 12, and 24 hours. The study does not report if the volume was added back. After the 24 hour exposure test substance was removed by gently wiping a dry cotton bud on the skin. The epidermal membrane was tape stripped 10 times with adhesive tape. Radioactivity in the surface wipes, donor chamber, tape strips, skin, filter paper and receptor fluid was assessed by scintillation counting. Quantification was sensitive and the LOD was not reported. The number of scintillation counts was not specified.
	Metric 6:	Standards for tests	Medium	The integrity of the membrane was determined by measuring permeation of tritiated water. No cell had a water permeability >2.45 x 10-3 cm/hr. Recovery of test material was 94.2%. CVs could be calculated for all compartments evaluated.

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	Metric 8:	Consistency of exposure administration	Medium	The area of the exposed skin and applied volume were reported for each individual cell. Variations were small with CVs <9%.
	Metric 9:	Reporting of concentrations	Low	The target dose of 200 ug/cm2 was reported. Authors calculated dose based on measured volume applied and measured area of cell. The concentration of test solution was not analytically verified. The donor cell was not occluded, since the vehicle was ethanol, evaporation of the vehicle may have occurred thereby increasing the concentration of the test solution.
	Metric 10:	Exposure frequency	High	Exposure duration was reported and appropriate for determining absorption. The test substance was in contact with the skin for 24 hours. Samples of receptor fluid were collected for a total of 24 hours.
	Metric 11:	Number of exposure groups and concentration spacing	Low	Only one dose was studied (target dose of 20 ul/cm2 of a 1% solution in ethanol) applied dose ~200 ug/cm2. No justification was provided why this dose was chosen.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	Skin samples were obtained from 3 donors. Two samples were breast skin, and one was abdominal. The ages of the donors were 63, 34, and 20 years of age. Skin was stored at -20oC and thawed before processing. The epidermis was gently removed from the dermis after immersing the skin sections in water at 60 degrees C for 50 seconds. Split thickness samples are preferred, although the use of an epidermal layer is acceptable. The thickness of membranes was not reported. Skin integrity results were reported.
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	Metric 14:	Outcome assessment methodology	Medium	The outcome assessment methodology addressed the intended outcome(s) of interest and was sensitive for the outcome(s) of interest. The selected formulation in ethanol was deemed to be the most appropriate, considering the highest concentration of HHCB is found in ethanolic products. Approximately 20ul/cm2 of test solution was applied to the skin. This volume is slightly more than the recommended amount of 10ul/cm2 for finite dosing and unlikely to substantially impact results. This corresponds to ~200 ug/cm2. Absorption was measured over 24 hours. The amount of test substance in the skin, donor cell, tape strips, surface wipes, receptor fluid, and filter paper were reported. The total absorbed dose was calculated from levels in the epidermis, remaining stratum corneum after tape stripping, the filter paper, and the receptor fluid. The 10 tape strips were not included in the calculation. The text noted this was per SCCNFP guidelines. Data on tape strips are available for alternate absorption calculations.
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Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Skin samples were obtained from 3 donors. Two samples were breast skin, and one was abdominal. The ages of the donors were 63, 34, and 20 years of age. The skin thickness was not measured; variation in thickness may result in inconsistencies between samples. Skin integrity (measure by titrated water) was acceptable for all samples.High levels of HHCB were seen in the filter paper supports impacting the amount of HHCB that entered the receptor fluid. Study authors state “it is possible that BSA may have bound to the filter paper and localized much of the permeated HHBC on the filter paper, thus potentially reducing the measured receptor phase values”. The filter paper supports contained 0.195% of the applied dose and the receptor fluid contained 0.2% of the applied dose.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Absorption estimates were based on appropriate measurements. Percent absorption estimates were presented for each compartment of the test system, The CV for total absorbed dose was 49%. CVs for each compartment can be calculated with the provided data and were $>$ 25% and $<$ 50% for more than half the samples however data are available for EPA to calculate an alternate (upper end) value to account for variability in the results.

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Study Citation: An-eX, (2001). In-vitro human skin penetration of radiolabelled fragrance material HHCB (redacted).
Chemical: HHCB
Exposure Type: Parent compound
HERO ID: 13006533
Unique ID: Receptor fluid study; 4% BSA in PBS

Domain	Metric		Rating	Comments
	Metric 20:	Data interpretation	Medium	Total recovery was adequate 100 +/-10%. The amount of test substance in tape strips was reported as strip 1, 2-3, 4-6, and 7-10. The amount of test substance in the skin after tape stripping was also reported. Donor cells were unoccluded. Given the volatility of the vehicle, a carbon trap would be useful to determine how much test sample evaporated. Data from a satellite experiment performed by this lab suggest possibly 3.5% of the test substance may have evaporated; however, the test conditions for this satellite experiment were not the same as this experiment (used PTFE surface membrane instead of skin).
	Metric 21:	Reporting of data	High	Data were adequately reported as means ± SD and as individual cells. Concentrations in receptor fluids over time were also graphically displayed.

Overall Quality Determination Medium

Study Citation: An-eX, (2001). In-vitro human skin penetration of radiolabelled fragrance material HHCB (redacted).
Chemical: HHCB
Exposure Type: Parent compound
HERO ID: 13006533
Unique ID: Receptor fluid study; 6% Volpo N20 in PBS

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	The test substance was identified as unlabeled HHCB (1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[G]-2-benzopyran and isomers) and radiolabeled HHCB [UL-phenyl-14C)]. There is no indication if the radiolabel is in a metabolically stable position. A CAS No was not provided.
	Metric 2:	Test substance source	High	The test substances were supplied by the Sponsor (Research Institute for Fragrance Materials). A certificate of analysis for the radiolabeled test substance was provided from Wizard Laboratories Inc. It is unclear if the sponsor manufactured the unlabeled test substance or obtained it from a commercial company. Lot numbers were reported for the unlabelled and radiolabeled material.
	Metric 3:	Test substance purity	High	The purity for unlabeled test substance was 98.5% and the radiolabeled test material had a radiochemical purity of 99.3%.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Medium	There was no reference compound identified. The experiments were conducted by An-eX analytical services ltd. According to their website, this company performs in vitro skin penetration evaluations for customers and therefore is technically proficient in running these types of studies.
	Metric 5:	Assay procedures	Medium	Human epidermal skin was mounted into static diffusion cells. The source and preparation of the skin were described. The apparatus (horizontal Franz-type diffusion cells) was clearly described and included a drawing. Epidermal membranes were floated onto water and taken up onto a 25mm diameter filter paper support and then mounted onto the diffusion cells. The diagram shows the filter paper support between the membrane and the receptor fluid. The skin surface area was maintained at 32 $\pm$ 1 degree C throughout the experiment. Humidity was not described. Skin integrity was assessed prior to dosing with tritiated water. The receptor fluid used was 6% Volpo N20 in PBS. Magnetic stir bars were used to stir the receptor fluid chambers continuously. Solubility of the test substance in the receptor fluid was assessed as >2000ug/ml and therefore not rate-limiting. The receptor volume was reported in Appendix 4. The skin surface area was about 1 cm2 (exact area reported in Appendix 2). The donor cell was not occluded. The volume applied and dose of HHCB were reported for each cell in Appendix 2. The donor cell was not occluded. The volume applied and dose of HHCB were reported for each cell in Appendix 2. Receptor fluid (200 ul) was collected at 1, 2, 6, 12, and 24 hours. The study does not report if the volume was added back. After the 24 hour exposure test substance was removed by gently wiping a dry cotton bud on the skin. The epidermal membrane was tape stripped 10 times with adhesive tape. Radioactivity in the surface wipes, donor chamber, tape strips, skin, filter paper and receptor fluid was assessed by scintillation counting. Quantification was sensitive and the LOD was not reported. The number of scintillation counts was not specified.
	Metric 6:	Standards for tests	Medium	The integrity of the membrane was determined by measuring permeation of tritiated water. No cell had a water permeability >2.05 x 10-3 cm/hr. Recovery of test material was 92.8%. CVs could be calculated for all compartments evaluated.

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Study Citation: An-eX, (2001). In-vitro human skin penetration of radiolabelled fragrance material HHCB (redacted).
Chemical: HHCB
Exposure Type: Parent compound
HERO ID: 13006533
Unique ID: Receptor fluid study; 6% Volpo N20 in PBS

Domain	Metric		Rating	Comments
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of test substance was partially reported. The non-radiolabeled test substance was prepared as a 1% (w/v) solution in ethanol (246.52 mg into 25 ml) and spiked with radiolabeled test substance (3.31 mg). The final concentration was 0.999% HHCB (w/v). Details of mixing were not specified, but homogeneity and the specific activity were assessed by scintillation counting. Solubility in the receptor fluid was confirmed prior to the start of the study. No information is provided as to how far in advance the test solution was made or storage. Given the vehicle was ethanol, potential volatilization of the test solution may have occurred without proper storage.
	Metric 8:	Consistency of exposure administration	Medium	The area of the exposed skin and applied volume were reported for each individual cell. Variations were small with CVs <9%.
	Metric 9:	Reporting of concentrations	Medium	The target dose of 200 ug/cm2 was reported. The authors calculated the dose based on the measured volume applied and the measured area of the cell. The concentration of the test solution was not analytically verified. The donor cell was not occluded; however, the lack of occlusion is representative of the expected conditions of use.
	Metric 10:	Exposure frequency	High	Exposure duration was reported and appropriate for determining absorption. The test substance was in contact with the skin for 24 hours. Samples of receptor fluid were collected for a total of 24 hours.
	Metric 11:	Number of exposure groups and concentration spacing	Low	Only one dose was studied (target dose of 20 ul/cm2 of a 1% solution in ethanol) applied dose ~200 ug/cm2. No justification was provided why this dose was chosen.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	Skin samples were obtained from 4 donors. Three samples were breast skin, and one was abdominal. The ages of the donors were 63, 34, 24, and 20 years of age. Skin was stored at -20oC and thawed before processing. The epidermis was gently removed from the dermis after immersing the skin sections in water at 60 degrees C for 50 seconds. Split thickness samples are preferred, although the use of an epidermal layer is acceptable. The thickness of membranes was not reported. Skin integrity results were reported.
	Metric 13:	Number/Replicates per group	Low	The number of donors was slightly lower than recommended. Guidelines recommend 8 replicates/dose from at least 4 donors (2 replicates/donor). This study examined 4 donors; each donor skin was only examined once for a total of 4 replicates/dose.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	The outcome assessment methodology addressed the intended outcome(s) of interest and was sensitive for the outcome(s) of interest. The selected formulation in ethanol was deemed to be the most appropriate considering the highest concentration of HHCB is found in ethanolic products. Approximately 20ul/cm2 of test solution was applied to the skin. This volume is slightly more than the recommended amount of 10ul/cm2 for finite dosing and unlikely to substantially impact results. Absorption was measured over 24 hours. The amount of test substance in the skin, donor cell, tape strips, surface wipes, receptor fluid, and filter paper were reported. Percent absorbed was properly calculated.
	Metric 15:	Consistency of outcome assessment	High	The outcome assessment protocols were reported and were consistent across groups.

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Study Citation: An-eX, (2001). In-vitro human skin penetration of radiolabelled fragrance material HHCB (redacted).
Chemical: HHCB
Exposure Type: Parent compound
HERO ID: 13006533
Unique ID: Receptor fluid study; 6% Volpo N20 in PBS

Domain	Metric		Rating	Comments
	Metric 16:	Sampling adequacy and sensitivity	Medium	Samples were collected 5 times over 24-hour period (at 1, 2, 6, 12, and 24 hours). OECD Guidelines recommends 6-12 sampling points over 24 hours. Cumulative permeation into the receptor fluid is graphically shown. Samples were counted for radioactivity using a Wallac 1409 liquid scintillation counter. The study did not report the number of scintillation counts/sample or the LOD. Two undosed negative control cells were included; no radioactivity was detected.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Skin samples were obtained from 4 donor. Three samples were breast skin, and one was abdominal. The ages of the donors were 63, 34, 24, and 20 years of age. The skin thickness was not measured; variation in thickness may result in inconsistencies between samples. Skin integrity (measure by titrated water) was acceptable for all samples.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Absorption estimates were based on appropriate measurements. Percent absorption estimates were presented for each compartment of the test system, The CV for total absorbed dose was 36%. CVs for each compartment can be calculated with the provided data and were $>$ 25% and $<$ 50% for more than half the samples however data are available for EPA to calculate an alternate (upper end) value to account for variability in the results.
	Metric 20:	Data interpretation	Medium	Total recovery was adequate 100 +/-10%. The amount of test substance in tape strips was reported as strip 1, 2-3, 4-6, and 7-10. The amount of test substance in the skin after tape stripping was also reported. Donor cells were unoccluded. Given the volatility of the vehicle, a carbon trap would be useful to determine how much test sample evaporated. Data from a satellite experiment performed by this lab suggest possibly 3.5% of the test substance may have evaporated; however, the test conditions for this satellite experiment were not the same as this experiment (used PTFE surface membrane instead of skin).
	Metric 21:	Reporting of data	High	Data were adequately reported as means $\pm$ SD and as individual cells. Concentrations in receptor fluids over time were also graphically displayed.

Overall Quality Determination — Medium

Study Citation:	Zhang, X., Yu, Y., Gu, Y., Li, X., Zhang, X., Yu, Y. (2017). In vitro determination of transdermal permeation of synthetic musks and estimated dermal uptake through usage of personal care products. Chemosphere 173:417-424.
Chemical:	HHCB
Exposure Type:	Parent compound
HERO ID:	3603871
Unique ID:	HHCB

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Low	The authors did not identify the CASRN or report exact chemical structure or identify isomers; they did, however, identify the compound as galaxolide (abbreviated as HHCB). The test substance was not radiolabeled.
	Metric 2:	Test substance source	Low	The authors analyzed for HHCB when conducting the dermal absorption experiments. There was no information on chemical source.
	Metric 3:	Test substance purity	Low	Purity and grade were not reported.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	The authors did not mention whether they used a reference compound.
	Metric 5:	Assay procedures	Low	The amount used was 1x10-4 mg (100 ng) as the base amount for determining permeation across different exposure times. Levels ranging from 50 - 1,000 ng (5x10-5 to 1x10-3 mg) were used to test the influence of exposure concentration on absorption rates when applied to the skin for 24 hrs. It is assumed (although not clear) from the reference that this was for a diffusion cell area of 2.26 cm2. If so, the amount applied per cm2 varied from 2.21x10-5 to 4.4x10-4 mg/cm2. These are much lower than typical values (1-5 mg/cm2) suggested by OECD TG 428. The study reported that concentrations of HHCB in various personal care products range from 3.98 to 6 x 10^-4 mg/g product). There is no information on whether the amount applied was diluted or if applied neat. EPA assumes that it was applied neat in the absence of information to suggest otherwise. The test substance was apparently not radiolabeled. Receptor fluid was not the recommended physiological solution but was water - HHCB is at least slightly soluble in water (1.75 mg/L). Sponges (not well described) were used to capture the volatilized HHCB, but it is not clear whether they would capture all of the volatilized chemical. The authors do not state whether it is a static or flow-through system (assumed to be static because stir bars are used in the receptor fluid). The description of tape stripping was confusing - in one place it appeared that 10 strips were taken, and in another it mentioned 20 strips. It is unclear how the tape strips were grouped into the six different groups that were mentioned. The dermatomed skin thickness was about 1 mm (higher than suggested but still acceptable).
	Metric 6:	Standards for tests	Uninformative	The authors did not identify standards and inadequate data were provided to asses the validity and reliability of the study. A mass recovery of >85 % was reported for musks in general, but no specific value was provided for the test substance and the data were not shown; skin integrity was not assessed. Some data including transdermal permeation over time was shown in a figure with means ± SD; however, this is not enough to consider the study reliable.
Domain 3: Exposure Characterization				

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Chemical: HHCB
Exposure Type: Parent compound
HERO ID: 3603871
Unique ID: HHCB

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Low	No information was provided on preparation and storage of the test substance.
	Metric 8:	Consistency of exposure administration	Low	Although the Franz cell was identified as being 2.26 cm2, it was not entirely clear that it was the skin surface area. Information on volume was not available and mass amounts were only mentioned in the results.
	Metric 9:	Reporting of concentrations	Medium	The amounts were noted only in the results section.
	Metric 10:	Exposure frequency	Low	A good range of exposure durations was used (4 to 24 hours) but no post-washing (post-exposure) samples were taken.
	Metric 11:	Number of exposure groups and concentration spacing	Low	The main analysis appears to be using 100 ng (4-5 samples). A range was also used (5 to 1000 ng) but exact levels were only provided in a graph. The authors did not state whether the test substances were applied as neat applications or whether there was a solvent used. The amounts were very low compared with suggested "typical" values in OECD TG 428. For comparison, from analytical measurements of HHCB in dust and personal care products, the estimated total daily dermal intake and uptake is 5.08 x 10^4 and 5.79 x 10^3 ng/kg bw/day.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	The source of the porcine skin, storage temperature, and dermatoming procedure were provided, but information on batch/lot was not provided, and skin thickness (1 mm) was not typical.
	Metric 13:	Number/Replicates per group	Medium	The main analysis using 100 ng used 4 to 5 samples; however, the investigation of different exposures (5 to 1000 ng) did not appear to use more than a single sample per exposure.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	Outcome assessment methodology was not well described.
	Metric 15:	Consistency of outcome assessment	Low	Consistency in outcome assessment methods was not described; the tape stripping discussion was confusing.
	Metric 16:	Sampling adequacy and sensitivity	Medium	For the main analysis, it appears that the number of replicates was the same as the number of samples taken (4-5). However, other details were lacking, and it is not clear whether 4 or 5 samples were taken for HHCB. Penetration distribution analysis was from 7-8 samples, and the relationship between mean permeation and exposure amount was from 4 samples.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Low	There was no information on skin integrity and if authors even assessed the integrity of the samples.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	There is no information on confounding factors. Based on amount of HHCB applied to skin, solubility is not likely to be an issue even though solubility is slight (1.75 mg/L).

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Chemical: HHCB
Exposure Type: Parent compound
HERO ID: 3603871
Unique ID: HHCB

Domain	Metric	Rating	Comments
Domain 7: Data Presentation and Analysis			
	Metric 19: Data analysis	Low	There is no information on whether outliers were excluded. The only endpoint showing means with standard deviations was permeation over time.
	Metric 20: Data interpretation	Low	The authors say that they excluded the levels in the stratum corneum by excluding tape strips from groups I and II. However, the description of tape stripping is confusing (groups I and II appear to include more than two tape strips, although this is still unclear). Although the authors note that recovery was greater than 85%, there is no quantitative information available to understand the amount in each compartment or whether the results were normalized for recovery. The study did report that tape strips I and II contained 17.7% and 8.0% of the test substance, and these layers accounted for 70% of the compound that was detected in the skin. The study text indicated recovery of 0.3% in receptor fluids. Together, these only account for a small percentage of the applied dose, suggesting the majority of the test substance was recovered in remaining compartments (sponges and skin washes), but this is unclear. The limitations in reporting preclude the ability to confidently interpret the study results.
	Metric 21: Reporting of data	Low	Significant information was not provided. Information was provided only in graphical form for some outcomes.

Overall Quality Determination — Uninformative

Study Citation: Ford, R. A., Hawkins, D. R., Schwarzenbach, R., Api, A. M. (1999). The systemic exposure to the polycyclic musks, AHTN and HHCB, under conditions of use as fragrance ingredients: Evidence of lack of complete absorption from a skin reservoir. Toxicology Letters 111(1-2):133-142.
Chemical: HHCB
Exposure Type: Parent compound
HERO ID: 5428448
Unique ID: HHCB in rats

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	The test substance was identified by name 1,3,4,6,7,8-hexahydro- 4,6,6,7,8,8 - hexamethylcyclopenta - γ - 2 -benzopyran (HHCB). No CASRN or structure were provided, and this chemical is a mixture of various enantiomers/isomers. The authors stated that the chemical was labeled on the aromatic ring.
	Metric 2:	Test substance source	Low	The sources of labeled and unlabeled test substance were identified, but the authors did not provide batch numbers and did not state whether they analyzed the chemical after receipt from the companies.
	Metric 3:	Test substance purity	High	The purity was stated and acceptable (99% for the radiolabeled substance; 98% for the unlabeled substance). Impurities were not identified.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Low	The study did not report how animals were assigned to groups.
	Metric 5:	Standards for Tests	Low	The authors reported recovery of radioactivity higher than 90% (and they indirectly refer to the standard by noting that this was a good recovery). They also state that radioactivity less than 2x higher than background was considered to be below the limit of accurate determination. However, there is no information on variability among samples or a discussion of acceptability as it relates to variability across samples.
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	Low	The authors state information on the preparation of the test substance for application to skin. However, there was no information on storage.
	Metric 7:	Consistency of exposure administration	Medium	The authors state that HHCB was dissolved in 70% ethanol at a nominal dose of 0.1 mg/cm2 over 9 cm2 in a volume of 200 ul and sampled all animals at the same timepoints after dosing. No information was provided on any deviations. Based on the description of methods, EPA expects any deviations to be small.
	Metric 8:	Reporting of concentrations	Medium	The authors reported point estimates for the doses and reported both weight and volume. The authors did not describe any analytical verification of the test substance.
	Metric 9:	Exposure duration	High	The authors exposed the animal skin (under occlusion) to the test substance for 6 hours and then cleaned the skin with cotton swabs with 70% ethanol, and a fresh cover was applied. This duration is consistent with OECD 427 guidelines.
	Metric 10:	Number of exposure groups and concentration spacing	Low	Only one dose group was used (4.5 mg/kg HHCB in 70% ethanol). The authors noted that HHCB is normally found in alcohol based fragrances, justifying the vehicle. However, they also state that the percentage of HHCB in the products is generally 2.4% or less.
Domain 4: Test Model				

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Study Citation: Ford, R. A., Hawkins, D. R., Schwarzenbach, R., Api, A. M. (1999). The systemic exposure to the polycyclic musks, AHTN and HHCB, under conditions of use as fragrance ingredients: Evidence of lack of complete absorption from a skin reservoir. Toxicology Letters 111(1-2):133-142.
Chemical: HHCB
Exposure Type: Parent compound
HERO ID: 5428448
Unique ID: HHCB in rats

Domain	Metric		Rating	Comments
	Metric 11:	Test animal characteristics	Medium	The authors report using male Lister-Hooded (pigmented) rats but did not report age or weight at the start of the study.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	Low	No information was provided on animal husbandry.
	Metric 13:	Number of animals per group	Low	Only two animals per timepoint were sacrificed.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	The amount of test substance for finite doing by weight was lower than the 'typical' application (0.1 mg/cm2). The authors used 200 ul of the solvent - if this was for the full surface area, the amount per cm2 was approximately 22.2 ul/cm2; the values match a finite dose more than an infinite dose even though the authors used occlusion for the test. The excreta (feces, urine, exhaled air) and tissues were appropriately measured at appropriate timepoints.
	Metric 15:	Consistency of outcome assessment	High	The authors note that sacrifices occurred at 0.1, 1, 3, 6, 12, 24, 48, 72. and 120 h after dosing.
	Metric 16:	Sampling adequacy and sensitivity	Medium	Sampling times were adequate (see metric 15) but it is not clear how radioactivity that is less than 2x background levels were reported (e.g., as the value or as zero).
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Information is limited, but there is no info to suggest that there were differences among study groups re: test substance batches etc.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	There was no information to support or dismiss the suggestion that there were differences among groups in animal attrition, health outcomes unrelated to exposure, or solubility that could influence the outcome assessment.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Uninformative	No details regarding statistical analysis were provided (e.g., whether outliers were excluded). Only 2 samples were taken at each timepoint so it is assumed no outliers were excluded because data were described as mean values. Coefficients of variance were not reported and could not be calculated since the authors did not provide SD.
	Metric 20:	Data interpretation	Low	There is significant uncertainty in characterizing whether the study represents a finite or infinite dose. The study authors noted there was a significant amount of test material detected in the fresh dressing applied, indicating that some of the test substance remaining in the skin reservoir following the wash was lost by reverse diffusion or desquamation (the ratio of systemic absorption to reverse absorption was 2:1). Therefore, an assumption that all material in the skin would ultimately be absorbed by be an exaggeration of bioavailability. Overall, recovery was generally within 10% of 100%.
	Metric 21:	Reporting of Data	High	Data were reported for individual tissues/excreta and for all individual timepoints evaluated.

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Study Citation:	Ford, R. A., Hawkins, D. R., Schwarzenbach, R., Api, A. M. (1999). The systemic exposure to the polycyclic musks, AHTN and HHCB, under conditions of use as fragrance ingredients: Evidence of lack of complete absorption from a skin reservoir. Toxicology Letters 111(1-2):133-142.
Chemical:	HHCB
Exposure Type:	Parent compound
HERO ID:	5428448
Unique ID:	HHCB in rats

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