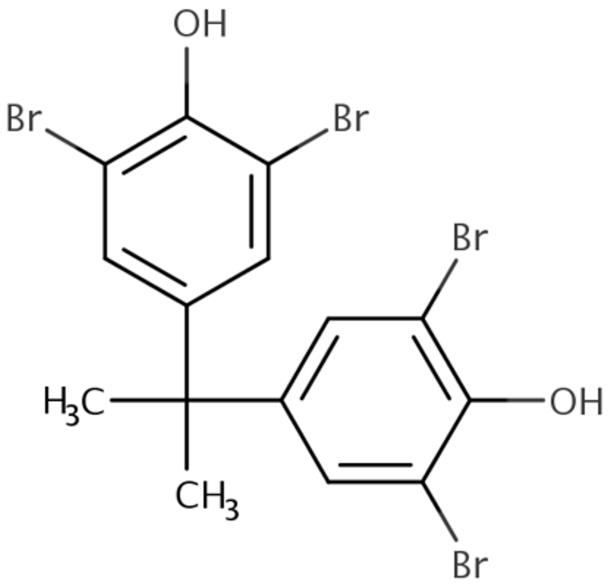
United States
Environmental Protection Agency

May 2026
Office of Chemical Safety and
Pollution Prevention

Draft Data Quality Evaluation Information for Dermal Absorption for 4,4-(1-Methylethylidene)bis[2,6-dibromophenol] (TBBPA)

Systematic Review Support Document for the Draft Risk Evaluation

CASRN: 79-94-7



May 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 4,4'-(1-Methylethylidene)bis[2, 6-dibromophenol] (TBBPA)* and were used to characterize dermal absorption. EPA conducted data quality evaluation based on author-reported descriptions and results; additional analyses (*e.g.*, statistical analyses performed during data integration into the risk evaluation) potentially conducted by EPA are not contained in this supplemental file. Key parameters and corresponding data for each condition were not extracted from the reference. EPA used the TSCA systematic review process described in the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (also referred to as the '2021 Draft Systematic Review Protocol'). Any updated steps in the systematic review process since the publication of the 2021 Draft Systematic Review Protocol are described in the *Draft Systematic Review Protocol for 4,4'-(1-Methylethylidene)bis[2, 6-dibromophenol] (TBBPA)*.

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

Table of Contents

HERO ID	Reference	Page
In vitro		
3022878	Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.	**4**
12340684	Charles River Laboratories, (2024). The in vitro percutaneous absorption of radiolabelled TBBPA in eleven dosing scenarios through human split-thickness skin.	**24**
7415560	Inveresk Research International, (2005). The in vitro percutaneous adsorption of radiolabelled tetrabromobisphenol-A (TBBPA) through human skin.	**36**
3162048	Knudsen, G. A., Hughes, M. F., Mcintosh, K. L., Sanders, J. M., Birnbaum, L. S. (2015). Estimation of tetrabromobisphenol A (TBBPA) percutaneous uptake in humans using the parallelogram method. Toxicology and Applied Pharmacology 289(2):323-329.	**39**
In vivo - Animal		
5490805	Yu, Y., Li, L., Li, H., Yu, X., Zhang, Y., Wang, Q., Zhou, Z., Gao, D., Ye, H., Lin, B., Ma, R. (2017). In vivo assessment of dermal adhesion, penetration, and bioavailability of tetrabromobisphenol A. Environmental Pollution 228:305-310.	**45**
5636895	Yu, Y., Xiang, M., Gao, D., Ye, H., Wang, Q., Zhang, Y., Li, L., Li, H. (2018). Assimilation, distribution and toxicity of tetrabromobisphenol A to female Wistar rats through subchronic dermal exposure. International Biodeterioration & Biodegradation 128:171-176.	**48**
3364227	Yu, Y., Xiang, M., Gao, D., Ye, H.,ao, Wang, Q., Zhang, Y., Li, L., Li, H.,ui (2016). Absorption and excretion of Tetrabromobisphenol A in male Wistar rats following subchronic dermal exposure. Chemosphere 146:189-194.	**51**

Study Citation:	Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical:	TBBPA
Exposure Type:	Parent compound
HERO ID:	3022878
Unique ID:	Kp calculation- 500 ng/cm2

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Low	The test substance name was given as "Tetrabromobisphenol-A" but there was no CASRN provided in the study. The current website of the supplier lists TBBPA as 3,3',5,5'-Tetrabromobisphenol-A and does provide a CASRN of 79-94-7, but it is unclear if this is the same product purchased at the time of the study. A radiolabeled compound was not used for the experiment, but a radiolabeled standard was used and mixed with the unlabeled compound when analyzing the chemical after the experiment was over. Based on potential variability in chemical structure, EPA is rating this metric as low.
	Metric 2:	Test substance source	Low	The source of the test chemical was identified (Wellington Laboratories Inc, Canada). No information on the batch/lot number was provided, and the performing laboratory did not analytically verify the test substance. The supplier's website does provide certificates of analysis upon request.
	Metric 3:	Test substance purity	Medium	Purity was not reported.; however, the supplier website indicates that all products are sold with >98% purity.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Medium	Although the authors were not entirely clear regarding whether reference compounds were used for all experiments (EPISKIN, EpiDerm and human ex vivo skin), they state that reference compounds are used - negative (decabromodiphenyl ethane) and positive (Triton-X-100) controls. Although there are differences in the log Kow's between ref. compound and test substance - Triton-X-100 is 7.95 (https://foodb.ca/compounds/FDB017723) vs. 4.75 for TBBPA (scope document), absorption responses of the reference compounds were appropriate (0% for decabromodiphenyl ethane and 97 +/-4% for Triton-X-100).

Continued on next page . . .

. . . continued from previous page

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Kp calculation- 500 ng/cm2

Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Low	A Franz diffusion was used. No information was provided on whether the cell provided a good seal around the skin sample. A static method with magnetic stirring was used, although it is not clear whether stirring was constant. DMEM culture medium was used as receptor fluid with 5% bovine serum albumin added for maximum solubility of TBBPA. Temperature of the receptor fluid was maintained at 32 deg. C. No information on humidity was provided. A volume of 100 μL was used; the surface area of skin wasn't provided, but could be calculated from other information (1 cm2). Skin surface washing used 1:1 hexane: ethyl acetate. The authors didn't mention whether the chambers were occluded, although the figure suggests the experiment was unoccluded. This leads to questions about whether volatilization of the vehicle was controlled. Significant volatilzation of acetone may have occurred, effectively increasing the concentration of TBBPA in the donor chamber. Doses used were 500 and 1000 ng/cm2 but the authors justify this amount as based on real-world exposure to dust. They also note that the levels "were chosen to ensure that the concentrations in the receptor fluid during the experiment did not exceed 10% of the saturation solubility." Overall, lack of control for volatilization, lack of other information and use of the stated solvent rather than an aqueous soap for skin washing led to a rating of low for this metric.
	Metric 6:	Standards for tests	Low	Criteria for obtained skin samples were reported (no stretchmarks, scars or hair); however, criteria for skin integrity were not reported. The study does report that integrity was tested using trans-epidermal electrical resistance and methylene blue; however, acceptable criteria are not reported. Percent recovery was >85%, which is acceptable for unlabeled compounds. Coefficients of variation were not reported, but could be calculated using the reported data for each compartment.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	No information on storage and stability was provided. Although TBBPA isn't expected to hydrolyze and volatility is low, it can degrade with a range of half-lives as short as 17 minutes. No information was provided to suggest control of possible photodegradation.
	Metric 8:	Consistency of exposure administration	Medium	The same volume (100 ul) and skin surface areas were used for both concentrations, but no information was provided about the volumes used for the positive and negative controls. Full thickness skin of 500 +/- 80 um was used. Skin surface area was not reported but can be calculated based on reported information (calculated by reviewer to be 1 cm2; based on application of 100 ul of 5 ng/ul solution to obtain a dose of 500 ng/cm2)
	Metric 9:	Reporting of concentrations	Medium	Nominal concentrations (point estimates) were reported.
	Metric 10:	Exposure frequency	High	Skin samples were exposed to TBBPA for 24 hrs; washing occurred at the end of this period, and sampling occurred at several timepoints within the 24-hour period. This is acceptable according to OECD TG 428.

Continued on next page . . .

. . . continued from previous page

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Kp calculation- 500 ng/cm2

Domain	Metric		Rating	Comments
	Metric 11:	Number of exposure groups and concentration spacing	High	Only 2 doses were tested (500 and 1000 ng/cm2); three doses are preferred; however, OECD 428 TG states that "normally more than one concentration of the test substance is used in typical formulations, spanning the realistic range of potential human exposures." The authors justified the two concentrations based on expected exposures to TBBPA via indoor dust. They also note that levels "were chosen to ensure that the concentrations in the receptor fluid during the experiment did not exceed 10% of the saturation solubility."
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	The authors used fresh excised human breast skin from 3 donors. Full-thickness skin was used, but it was 500 μm (acceptable because it was $<$ 1 mm). Full-thickness skin may be used if it is not excessive. The lot/batch of skin was not reported. Skin integrity was evaluated via standard trans-epidermal electrical resistance and methylene blue; however, results from these tests were not reported. The authors report that one skin patch failed the membrane integrity test, but do not report what acceptable values were.
	Metric 13:	Number/Replicates per group	Medium	OECD TG 428 says: "Acceptable data from a minimum of four replicates per test preparation are required," but doesn't identify the number of donors needed. This study used samples from 3 donors, and all tests were performed in triplicate. The authors reported that "one excised human skin patch failed the membrane integrity test." It is unclear if this means one replicate failed or if all skin samples from one donor failed integrity. Regardless, a minimum of 2 donors tested in triplicate meets guideline requirements.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The test substance was prepared in acetone at concentrations of 5 ng/μL or 10 ng/μL. Based on the information provided, the application rate was 100 μL of test solution/cm2, which is appropriate for an infinite dose scenario of a liquid. A steady state was reached. The authors calculated Kp from an infinite dose scenario. Measurements were taken from receptor fluid, receptor rinse, skin (depot), skin wash, and donor rinse. The frequency of collection from the receptor fluid (0.25, 0.5, 0.75, 1, 2, 4, 6, 10, 12, 18, 20 and 24 h) was appropriate
	Metric 15:	Consistency of outcome assessment	Medium	The same receptor fluid and sampling times were used across replicates. The extraction methods were described, and consistent methods were applied to the samples. Although negative controls are not specified in OECD TG (428, 156, 28). The supplemental material indicates a "field" blank, comprising skin tissue exposed to solvent only, was performed with each sample batch (n = 9). Further details regarding the treatment of this sample are not provided, so consistency is unclear.
	Metric 16:	Sampling adequacy and sensitivity	High	The sampling intervals were adequate to allow a graphical representation of the results. At least 5 data points in the linear range were obtained. LC-MS/MS is sensitive for the measurement of non-radiolabeled substances. It was reported that background detection was low; no compounds were detected above the LOD in field blank samples. An LOD of 42 pg/cm2, based on a 10:1 signal-to-noise ratio, was reported. Good recovery indicates adequacy of the extraction methods.

Continued on next page . . .

. . . continued from previous page

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Kp calculation- 500 ng/cm2

Domain	Metric		Rating	Comments
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Low	Tissue lots/batches were not reported, although skin samples came from the same company from females of similar age (36, 33, and 37). One skin sample failed integrity tests, although the criteria for acceptance were not reported, and quantitative results of the integrity test were not provided. Any inclusion/exclusion of outliers was not described.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	Solubility in the receptor fluid was not reported but concentrations were not expected to lead to solubility concerns.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Details of Kp determination were provided, and the Kp was determined based on a linear/steady-state portion of the absorption curve containing at least 5 data points. The coefficients of variation for the steady state Kp and flux were not reported with CV and could not be determined (Data enabling an independent statistical analysis or to calculate an upper end value for Kp were not provided). The study did provide mean and SD for percent of exposure dose in the receptor fluid at 24 hours; variation between samples was low (5.37% +/- 0.65%).
	Metric 20:	Data interpretation	Low	It appears the authors used an infinite dose to calculate the permeation coefficient. Recovery was sufficient for an unlabeled test substance (85.65% for TBBPA for ex vivo skin).
	Metric 21:	Reporting of data	Uninformative	The study reports flux, permeation coefficient and lag time in Table 2, but does not report whether this data is for the 1000 ng/cm2 dose or the 500 ng/cm2 dose group. Since it cannot be discerned which dose this data pertains to, the study was deemed uninformative. The study does not report the cumulative absorption over time for the 500 ng/cm2 dose group.

Overall Quality Determination Uninformative

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Kp calculation- 1000 ng/cm2

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Low	The test substance name was given as "Tetrabromobisphenol-A" but there was no CASRN provided in the study. The current website of the supplier lists TBBPA as 3,3',5,5'-Tetrabromobisphenol-A and does provide a CASRN of 79-94-7, but it is unclear if this is the same product purchased at the time of the study. A radiolabeled compound was not used for the experiment, but a radiolabeled standard was used and mixed with the unlabeled compound when analyzing the chemical after the experiment was over. Based on potential variability in chemical structure, EPA is rating this metric as low.
	Metric 2:	Test substance source	Low	The source of the test chemical was identified (Wellington Laboratories Inc, Canada). No information on the batch/lot number was provided, and the performing laboratory did not analytically verify the test substance. The supplier's website does provide certificates of analysis upon request
	Metric 3:	Test substance purity	Medium	Purity was not reported.; however, the supplier website indicates that all products sold have a purity of >98%.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Medium	Although the authors were not entirely clear regarding whether reference compound were used for all experiments (EPISKIN, EpiDerm and human ex vivo skin), they state that reference compounds are used - negative (decabromodiphenyl ethane) and positive (Triton-X-100) controls. Although there are differences in the log Kow's between ref. compound and test substance - Triton-X-100 is 7.95 (https://foodb.ca/compounds/FDB017723) vs. 4.75 for TBBPA (scope document), absorption responses of the reference compounds were appropriate (0% for decabromodiphenyl ethane and 97 +/-4% for Triton-X-100).
	Metric 5:	Assay procedures	Low	A Franz diffusion was used. No information was provided on whether the cell provided a good seal around the skin sample. A static method with magnetic stirring was used, although it is not clear whether stirring was constant. DMEM culture medium was used as receptor fluid with 5% bovine serum albumin added for maximum solubility of TBBPA. The temperature of the receptor fluid was maintained at 32 °C. No information on humidity was provided. A volume of 100 μL was used; the surface area of skin wasn't provided, but could be calculated from other information (1 cm2). Skin surface washing used 1:1 hexane: ethyl acetate. The authors didn't mention whether the chambers were occluded, although the figure suggests the experiment was unoccluded. This leads to questions about whether volatilization of the vehicle was controlled. Significant volatilzation of acetone may have occurred, effectively increasing the concentration of TBBPA in the donor chamber. Doses used were 500 and 1000 ng/cm2, but the authors justify this amount as based on real world exposure to dust. They also note that the levels "were chosen to ensure that the concentrations in the receptor fluid during the experiment did not exceed 10% of the saturation solubility." Overall, lack of control for volatilization, lack of other information and use of the stated solvent rather than an aqueous soap for skin washing led to a rating of low for this metric.

Continued on next page . . .

. . . continued from previous page

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Kp calculation- 1000 ng/cm2

Domain	Metric		Rating	Comments
	Metric 6:	Standards for tests	Low	Criteria for obtained skin samples were reported (no stretchmarks, scars or hair); however, criteria for skin integrity were not reported. The study does report that integrity was tested using trans-epidermal electrical resistance and methylene blue; however, acceptable criteria are not reported. Percent recovery was >85%, which is acceptable for unlabeled compounds. Coefficients of variation were not reported, but could be calculated using the reported data for each compartment.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	No information on storage and stability was provided. Although TBBPA isn't expected to hydrolyze and volatility is low, it can degrade with a range of half-lives as short as 17 minutes. No information was provided to suggest control of possible photodegradation.
	Metric 8:	Consistency of exposure administration	Medium	The same volume (100 ul) and skin surface areas were used for both concentrations, but no information was provided about the volumes used for the positive and negative controls. Full-thickness skin of 500 +/- 80 μm was used. Skin surface area was not reported, but can be calculated based on reported information (calculated by reviewer to be 1 cm2; based on application of 100 μL of 5 ng/μL solution to obtain a dose of 500 ng/cm2)
	Metric 9:	Reporting of concentrations	Medium	Nominal concentrations (point estimates) were reported.
	Metric 10:	Exposure frequency	High	Skin samples were exposed to TBBPA for 24 hrs; washing occurred at the end of this period, and sampling occurred at several timepoints within the 24-hour period. This is acceptable according to OECD TG 428.
	Metric 11:	Number of exposure groups and concentration spacing	High	Only 2 doses were tested (500 and 1000 ng/cm2); three doses are preferred; however, OECD 428 TG states that "normally more than one concentration of the test substance is used in typical formulations, spanning the realistic range of potential human exposures." The authors justified the two concentrations based on expected exposures to TBBPA via indoor dust. They also note that levels "were chosen to ensure that the concentrations in the receptor fluid during the experiment did not exceed 10% of the saturation solubility."
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	The authors used fresh excised human breast skin from 3 donors. Full-thickness skin was used, but it was 500 μm (acceptable because it was < 1 mm). Full-thickness skin may be used if it is not excessive. The lot/batch of skin was not reported. Skin integrity was evaluated via standard trans-epidermal electrical resistance and methylene blue; however, results from these tests were not reported. The authors report that one skin patch failed the membrane integrity test, but do not report what acceptable values were.
	Metric 13:	Number/Replicates per group	Medium	OECD TG 428 says: "Acceptable data from a minimum of four replicates per test preparation are required," but doesn't identify the number of donors needed. This study used samples from 3 donors, and all tests were performed in triplicate. The authors reported that "one excised human skin patch failed the membrane integrity test." It is assumed this was one replicate, and the remaining number of samples meets guideline requirements.

Continued on next page . . .

. . . continued from previous page

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Kp calculation- 1000 ng/cm2

Domain	Metric		Rating	Comments
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The test substance was prepared in acetone at concentrations of 5 ng/μL or 10 ng/μL. Based on the information provided, the application rate was 100 μL of test solution/cm2, which is appropriate for an infinite dose scenario of a liquid. A steady state was reached. The authors calculated Kp from an infinite dose scenario. Measurements were taken from receptor fluid, receptor rinse, skin (depot), skin wash, and donor rinse. The frequency of collection from the receptor fluid (0.25, 0.5, 0.75, 1, 2, 4, 6, 10, 12, 18, 20 and 24 h) was appropriate
	Metric 15:	Consistency of outcome assessment	Medium	The same receptor fluid and sampling times were used across replicates. The extraction methods were described, and consistent methods were applied to the samples. Although negative controls are not specified in OECD TG (428, 156, 28). The supplemental material indicates a "field" blank, comprising skin tissue exposed to solvent only, was performed with each sample batch (n = 9). Further details regarding the treatment of this sample are not provided, so consistency is unclear.
	Metric 16:	Sampling adequacy and sensitivity	High	The sampling intervals were adequate to allow a graphical representation of the results. At least 5 data points in the linear range were obtained. LC-MS/MS is sensitive for the measurement of non-radiolabeled substances. It was reported that background detection was low; no compounds were detected above the LOD in field blank samples. An LOD of 42 pg/cm2, based on a 10:1 signal-to-noise ratio, was reported. Good recovery indicates adequacy of the extraction methods.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Low	Tissue lots/batches were not reported, although skin samples came from the same company from females of similar age (36, 33, and 37). One skin sample failed integrity tests, although the criteria for acceptance were not reported, and quantitative results of the integrity test were not provided. Any inclusion/exclusion of outliers was not described.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	Solubility in the receptor fluid was not reported, but concentrations were not expected to lead to solubility concerns.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Details of Kp determination were provided, and the Kp was determined based on a linear/steady-state portion of the absorption curve containing at least 5 data points. The concentrations of the test substance in the receptor fluid were presented across time for some but not all time points. The coefficients of variation for the steady state Kp and flux were not reported with CV and could not be determined (Data enabling an independent statistical analysis or to calculate an upper end value for Kp were not provided). The study did provide mean and SD for percent of exposure dose in the receptor fluid at 24 hours; variation between samples was low (5.26% +/- 0.64%).
	Metric 20:	Data interpretation	Low	It appears the authors used an infinite dose to calculate the permeation coefficient. Recovery was sufficient for an unlabeled test substance (85.65% for TBBPA for ex vivo skin).

Continued on next page . . .

...continued from previous page

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Kp calculation- 1000 ng/cm2

Domain	Metric	Rating	Comments
	Metric 21: Reporting of data	Uninformative	The study reports the amount of test substance in the receptor fluid for the 1000 ng/cm2 group at 1, 6-, 12-, 18-, and 24-hour timepoints in bar graph form (but not for the other timepoints). Individual cell data were not reported. The study reports flux, permeation coefficient and lag time in Table 2, but does not report whether this data is for the 1000 ng/cm2 dose or the 500 ng/cm2 dose group. Since it cannot be discerned which dose this data pertains to, the study was deemed uninformative.

Overall Quality Determination Uninformative

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Cumulative permeation- acetone

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Low	The test substance name was given as "Tetrabromobisphenol-A" but there was no CASRN provided in the study. The current website of the supplier lists TBBPA as 3,3',5,5'-Tetrabromobisphenol-A and does provide a CASRN of 79-94-7, but it is unclear if this is the same product purchased at the time of the study. A radiolabeled compound was not used for the experiment, but a radiolabeled standard was used and mixed with the unlabeled compound when analyzing the chemical after the experiment was over. Based on potential variability in chemical structure, EPA is rating this metric as low.
	Metric 2:	Test substance source	Low	The source of the test chemical was identified (Wellington Laboratories Inc., Canada). No information on the batch/lot number was provided, and the performing laboratory did not analytically verify the test substance. The supplier's website does provide certificates of analysis upon request.
	Metric 3:	Test substance purity	Medium	Purity was not reported; however, the supplier website indicates that all products are sold with a purity of >98%.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Medium	Although the authors were not entirely clear regarding whether reference compounds were used for all experiments (EPISKIN, EpiDerm and human ex vivo skin), they state that reference compounds are used - negative (decabromodiphenyl ethane) and positive (Triton-X-100) controls. Although there are differences in the log Kow's between ref. compound and test substance - Triton-X-100 is 7.95 (https://foodb.ca/compounds/FDB017723) vs. 4.75 for TBBPA (scope document), absorption responses of the reference compounds were appropriate (0% for decabromodiphenyl ethane and 97 +/-4% for Triton-X-100).
	Metric 5:	Assay procedures	Low	A Franz diffusion was used. No information was provided on whether the cell provided a good seal around the skin sample. A static method with magnetic stirring was used, although it is not clear whether stirring was constant. DMEM culture medium was used as receptor fluid with 5% bovine serum albumin added for maximum solubility of TBBPA. The temperature of the receptor fluid was maintained at 32 °C. No information on humidity was provided. A volume of 100 μL was used; the surface area of skin wasn't provided, but could be calculated from other information (1 cm2). Skin surface washing used 1:1 hexane: ethyl acetate. The authors didn't mention whether the chambers were occluded, although the figure suggests the experiment was unoccluded. This leads to questions about whether volatilization of the vehicle was controlled. Significant volatilzation of acetone may have occurred, effectively increasing the concentration of TBBPA in the donor chamber. A dose of 500 ng/cm2 was used. The authors justify this amount as based on real-world exposure to dust. They also note that the levels "were chosen to ensure that the concentrations in the receptor fluid during the experiment did not exceed 10% of the saturation solubility." Overall, lack of control for volatilization, lack of other information and use of the stated solvent rather than an aqueous soap for skin washing led to a rating of low for this metric.

Continued on next page . . .

. . . continued from previous page

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Cumulative permeation- acetone

Domain	Metric		Rating	Comments
	Metric 6:	Standards for tests	Low	Criteria for obtained skin samples were reported (no stretchmarks, scars or hair); however, criteria for skin integrity were not reported. The study does report that integrity was tested using trans-epidermal electrical resistance and methylene blue; however, acceptable criteria are not reported. Coefficients of variation were not reported and could not be calculated; the study authors did not report variance. Percent recovery was acceptable for an unlabeled test substance.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	No information on storage and stability was provided. Although TBBPA isn't expected to hydrolyze and volatility is low, it can degrade with a range of half-lives as short as 17 minutes. No information was provided to suggest control of possible photodegradation.
	Metric 8:	Consistency of exposure administration	Medium	The same volume (100 μL) and skin surface areas were used for both concentrations, but no information was provided about the volumes used for the positive and negative controls. Full-thickness skin of 500 +/- 80 μm was used. Skin surface area was not reported, but can be calculated based on reported information (calculated by reviewer to be 1 cm2; based on application of 100 μL of 5 ng/μL solution to obtain a dose of 500 ng/cm2)
	Metric 9:	Reporting of concentrations	Medium	Nominal concentrations (point estimates) were reported.
	Metric 10:	Exposure frequency	High	Skin samples were exposed to TBBPA for 24 hrs; washing occurred at the end of this period, and sampling occurred at several timepoints within the 24-hour period. This is acceptable according to OECD TG 428.
	Metric 11:	Number of exposure groups and concentration spacing	High	Only 1 dose was tested (500 ng/cm2); three doses are preferred; however, OECD 428 TG states that "normally more than one concentration of the test substance is used in typical formulations, spanning the realistic range of potential human exposures." The authors justified the concentrations based on expected exposures to TBBPA via indoor dust. They also note that levels "were chosen to ensure that the concentrations in the receptor fluid during the experiment did not exceed 10% of the saturation solubility." The purpose of this study was to compare permeation of the test chemical in 3 different vehicles; therefore, one dose was sufficient.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	The authors used fresh excised human breast skin from 3 donors. Full-thickness skin was used, but it was 500 μm (acceptable because it was $<$ 1 mm). Full-thickness skin may be used if it is not excessive. The lot/batch of skin was not reported. Skin integrity was evaluated via standard trans-epidermal electrical resistance and methylene blue; however, results from these tests were not reported. The authors report that one skin patch failed the membrane integrity test, but do not report what acceptable values were.

Continued on next page . . .

. . . continued from previous page

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Cumulative permeation- acetone

Domain	Metric		Rating	Comments
	Metric 13:	Number/Replicates per group	Medium	OECD TG 428 says: "Acceptable data from a minimum of four replicates per test preparation are required," but doesn't identify the number of donors needed. This study used samples from 3 donors, and all tests were performed in triplicate. The authors reported that "one excised human skin patch failed the membrane integrity test." It is assumed this was one replicate, and the remaining number of samples meets guideline requirements.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The test substance was prepared in acetone at concentrations of 5 ng/μL. Based on the information provided, the application rate was 100 μL of test solution/cm², which is appropriate for an infinite dose scenario of a liquid. Measurements were taken from receptor fluid, receptor rinse, skin (depot), skin wash, and donor rinse. The frequency of collection from the receptor fluid (0.25, 0.5, 0.75, 1, 2, 4, 6, 10, 12, 18, 20 and 24 h) was appropriate
	Metric 15:	Consistency of outcome assessment	Medium	The same receptor fluid and sampling times were used across replicates. The extraction methods were described, and consistent methods were applied to samples. Although negative controls are not specified in OECD TG (428, 156, 28). The supplemental material indicates a "field" blank, comprising skin tissue exposed to solvent only, was performed with each sample batch (n = 9). Further details regarding the treatment of this sample are not provided, so consistency is unclear.
	Metric 16:	Sampling adequacy and sensitivity	High	The sampling intervals were adequate to allow a graphical representation of the results. LC-MS/MS is sensitive for measurement of non-radiolabeled substances. It was reported that background detection was low; no compounds were detected above the LOD in field blank samples. An LOD of 42 pg/cm2, based on a 10:1 signal to noise ratio, was reported.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Low	Tissue lots/batches were not reported, although skin samples came from the same company from females of similar age (36, 33, and 37). One skin sample failed integrity tests, although the criteria for acceptance were not reported, and quantitative results of the integrity test were not provided. Any inclusion/exclusion of outliers was not described.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	Solubility in the receptor fluid was not reported, but concentrations were not expected to lead to solubility concerns.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Uninformative	No statistical methods or calculations were performed on the data collected. The purpose of these experiments was to compare the permeation of the test substance in 3 different vehicles, not to calculate Kp. The study shows permeation into the receptor fluid at all time points (without variability) but did not report information that would allow for independent calculation of Kp.
	Metric 20:	Data interpretation	Uninformative	It appears the authors used an infinite dose. Interpretation of results was not consistent with standards and guidelines. Kp was not calculated.

Continued on next page . . .

. . . continued from previous page

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Cumulative permeation- acetone

Domain	Metric		Rating	Comments
	Metric 21:	Reporting of data	Low	Cumulative permeation into the receptor fluid was shown graphically for all time points; however, variability and n/group were not shown.

Overall Quality Determination — Uninformative

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Cumulative permeation- 30% acetone in water

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Low	The test substance name was given as "Tetrabromobisphenol-A" but there was no CASRN provided in the study. The current website of the supplier lists TBBPA as 3,3',5,5'-Tetrabromobisphenol-A and does provide a CASRN of 79-94-7, but it is unclear if this is the same product purchased at the time of the study. A radiolabeled compound was not used for the experiment, but a radiolabeled standard was used and mixed with the unlabeled compound when analyzing the chemical after the experiment was over. Based on potential variability in chemical structure, EPA is rating this metric as low.
	Metric 2:	Test substance source	Low	The source of the test chemical was identified (Wellington Laboratories Inc., Canada). No information on the batch/lot number was provided, and the performing laboratory did not analytically verify the test substance. The supplier's website does provide certificates of analysis upon request.
	Metric 3:	Test substance purity	Medium	Purity was not reported.; however, the supplier website indicates that all products are sold with >98% purity.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Medium	Although the authors were not entirely clear regarding whether reference compounds were used for all experiments (EPISKIN, EpiDerm and human ex vivo skin), they state that reference compounds are used - negative (decabromodiphenyl ethane) and positive (Triton-X-100) controls. Although there are differences in the log Kow's between ref. compound and test substance - Triton-X-100 is 7.95 (https://foodb.ca/compounds/FDB017723) vs. 4.75 for TBBPA (scope document), absorption responses of the reference compounds were appropriate (0% for decabromodiphenyl ethane and 97 +/-4% for Triton-X-100).
	Metric 5:	Assay procedures	Low	A Franz diffusion was used. No information was provided on whether the cell provided a good seal around the skin sample. A static method with magnetic stirring was used, although it is not clear whether stirring was constant. DMEM culture medium was used as receptor fluid with 5% bovine serum albumin added for maximum solubility of TBBPA. The temperature of the receptor fluid was maintained at 32 °C. No information on humidity was provided. A volume of 100 μL was used; the surface area of skin wasn't provided, but could be calculated from other information (1 cm2). Skin surface washing used 1:1 hexane: ethyl acetate. The authors didn't mention whether the chambers were occluded, although the figure suggests the experiment was unoccluded. This leads to questions about whether volatilization of the vehicle was controlled. Significant volatilzation of acetone may have occurred, effectively increasing the concentration of TBBPA in the donor chamber. A dose of 500 ng/cm2 was used. The authors justify this amount as based on real-world exposure to dust. They also note that the levels "were chosen to ensure that the concentrations in the receptor fluid during the experiment did not exceed 10% of the saturation solubility." Overall, lack of control for volatilization, lack of other information and use of the stated solvent rather than an aqueous soap for skin washing led to a rating of low for this metric.

Continued on next page . . .

. . . continued from previous page

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Cumulative permeation- 30% acetone in water

Domain	Metric		Rating	Comments
	Metric 6:	Standards for tests	Low	Criteria for obtained skin samples were reported (no stretchmarks, scars or hair); however, criteria for skin integrity were not reported. The study does report that integrity was tested using trans-epidermal electrical resistance and methylene blue; however, acceptable criteria are not reported. Coefficients of variation were not reported and could not be calculated; the study authors did not report variance. Percent recovery was acceptable for an unlabeled test substance.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	No information on storage and stability was provided. Although TBBPA isn't expected to hydrolyze and volatility is low, it can degrade with a range of half-lives as short as 17 minutes. No information was provided to suggest control of possible photodegradation.
	Metric 8:	Consistency of exposure administration	Medium	The same volume (100 μL) and skin surface areas were used for both concentrations, but no information was provided about the volumes used for the positive and negative controls. Full-thickness skin of 500 +/- 80 μm was used. Skin surface area was not reported but can be calculated based on reported information (calculated by reviewer to be 1 cm2; based on application of 100 μL of 5 ng/μL solution to obtain a dose of 500 ng/cm2)
	Metric 9:	Reporting of concentrations	Medium	Nominal concentrations (point estimates) were reported.
	Metric 10:	Exposure frequency	High	Skin samples were exposed to TBBPA for 24 hrs; washing occurred at the end of this period, and sampling occurred at several timepoints within the 24-hour period. This is acceptable according to OECD TG 428.
	Metric 11:	Number of exposure groups and concentration spacing	High	Only 1 dose was tested (500 ng/cm2); three doses are preferred; however, OECD 428 TG states that "normally more than one concentration of the test substance is used in typical formulations, spanning the realistic range of potential human exposures." The authors justified the concentrations based on expected exposures to TBBPA via indoor dust. They also note that levels "were chosen to ensure that the concentrations in the receptor fluid during the experiment did not exceed 10% of the saturation solubility." The purpose of this study was to compare permeation of the test chemical in 3 different vehicles; therefore, one dose was sufficient.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	The authors used fresh excised human breast skin from 3 donors. Full-thickness skin was used, but it was 500 μm (acceptable because it was $<$ 1 mm). Full-thickness skin may be used if it is not excessive. The lot/batch of skin was not reported. Skin integrity was evaluated via standard trans-epidermal electrical resistance and methylene blue; however, results from these tests were not reported. The authors report that one skin patch failed the membrane integrity test, but do not report what acceptable values were.

Continued on next page . . .

. . . continued from previous page

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Cumulative permeation- 30% acetone in water

Domain	Metric		Rating	Comments
	Metric 13:	Number/Replicates per group	Medium	OECD TG 428 says: "Acceptable data from a minimum of four replicates per test preparation are required,", but doesn't identify the number of donors needed. This study used samples from 3 donors, and all tests were performed in triplicate. The authors reported that "one excised human skin patch failed the membrane integrity test." It is assumed this was one replicate and the remaining number of samples meets guideline requirements.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The test substance was prepared in acetone at concentrations of 5 ng/μL. Based on the information provided, the application rate was 100 μL of test solution/cm2, which is appropriate for an infinite dose scenario of a liquid. Measurements were taken from receptor fluid, receptor rinse, skin (depot), skin wash, and donor rinse. The frequency of collection from the receptor fluid (0.25, 0.5, 0.75, 1, 2, 4, 6, 10, 12, 18, 20 and 24 h) was appropriate
	Metric 15:	Consistency of outcome assessment	Medium	The same receptor fluid and sampling times were used across replicates. The extraction methods were described, and consistent methods were applied to the samples. Although negative controls are not specified in OECD TG (428, 156, 28). The supplemental material indicates a "field" blank, comprising skin tissue exposed to solvent only, was performed with each sample batch (n = 9). Further details regarding the treatment of this sample are not provided, so consistency is unclear.
	Metric 16:	Sampling adequacy and sensitivity	High	The sampling intervals were adequate to allow a graphical representation of the results. LC-MS/MS is sensitive for the measurement of non-radiolabeled substances. It was reported that background detection was low; no compounds were detected above the LOD in field blank samples. An LOD of 42 pg/cm2, based on a 10:1 signal-to-noise ratio, was reported.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Low	Tissue lots/batches were not reported, although skin samples came from the same company from females of similar age (36, 33, and 37). One skin sample failed integrity tests, although the criteria for acceptance were not reported, and quantitative results of the integrity test were not provided. Any inclusion/exclusion of outliers was not described.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	Solubility in the receptor fluid was not reported but concentrations were not expected to lead to solubility concerns.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Uninformative	No statistical methods or calculations were performed on the data collected. The purpose of these experiments was to compare the permeation of the test substance in 3 different vehicles, not to calculate Kp. The study shows permeation into the receptor fluid at all time points (without variability) but did not report information that would allow for independent calculation of Kp.
	Metric 20:	Data interpretation	Uninformative	It appears the authors used an infinite dose. Interpretation of results was not consistent with standards and guidelines. Kp was not calculated.

Continued on next page . . .

...continued from previous page

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Cumulative permeation- 30% acetone in water

Domain	Metric	Rating	Comments
	Metric 21: Reporting of data	Low	Cumulative permeation into the receptor fluid was shown graphically for all time points; however, variability and n/group were not shown.

Overall Quality Determination — Uninformative

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Cumulative permeation- 20% Tween 80 in water

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Low	The test substance name was given as "Tetrabromobisphenol-A" but there was no CASRN provided in the study. The current website of the supplier lists TBBPA as 3,3',5,5'-Tetrabromobisphenol-A and does provide a CASRN of 79-94-7, but it is unclear if this is the same product purchased at the time of the study. A radiolabeled compound was not used for the experiment, but a radiolabeled standard was used and mixed with the unlabeled compound when analyzing the chemical after the experiment was over. Based on potential variability in chemical structure, EPA is rating this metric as low.
	Metric 2:	Test substance source	Low	The source of the test chemical was identified (Wellington Laboratories Inc, Canada). No information on the batch/lot number was provided, and the performing laboratory did not analytically verify the test substance. The supplier's website does provide certificates of analysis upon request.
	Metric 3:	Test substance purity	Medium	Purity was not reported.; however, the supplier website indicates that all products are sold with >98% purity.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Medium	Although the authors were not entirely clear regarding whether reference compounds were used for all experiments (EPISKIN, EpiDerm and human ex vivo skin), they state that reference compounds are used - negative (decabromodiphenyl ethane) and positive (Triton-X-100) controls. Although there are differences in the log Kow's between ref. compound and test substance - Triton-X-100 is 7.95 (https://foodb.ca/compounds/FDB017723) vs. 4.75 for TBBPA (scope document), absorption responses of the reference compounds were appropriate (0% for decabromodiphenyl ethane and 97 +/-4% for Triton-X-100).
	Metric 5:	Assay procedures	Medium	A Franz diffusion was used. No information was provided on whether the cell provided a good seal around the skin sample. A static method with magnetic stirring was used, although it is not clear whether stirring was constant. DMEM culture medium was used as receptor fluid with 5% bovine serum albumin added for maximum solubility of TBBPA. The temperature of the receptor fluid was maintained at 32 °C. No information on humidity was provided. A volume of 100 μL was used; the surface area of skin wasn't provided, but could be calculated from other information (1 cm2). Skin surface washing used 1:1 hexane: ethyl acetate. The authors didn't mention whether the chambers were occluded, although the figure suggests the experiment was unoccluded. A dose of 500 ng/cm2 was used. The authors justify this amount as based on real-world exposure to dust. They also note that the levels "were chosen to ensure that the concentrations in the receptor fluid during the experiment did not exceed 10% of the saturation solubility." Overall, lack of information and use of the stated solvent rather than an aqueous soap for skin washing led to a rating of medium for this metric.

Continued on next page . . .

. . . continued from previous page

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Cumulative permeation- 20% Tween 80 in water

Domain	Metric		Rating	Comments
	Metric 6:	Standards for tests	Low	Criteria for obtained skin samples were reported (no stretchmarks, scars or hair); however, criteria for skin integrity were not reported. The study does report that integrity was tested using trans-epidermal electrical resistance and methylene blue; however, acceptable criteria are not reported. Coefficients of variation were not reported and could not be calculated; the study authors did not report variance. Recovery was appropriate for an unlabeled test substance.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	No information on storage and stability was provided. Although TBBPA isn't expected to hydrolyze and volatility is low, it can degrade with a range of half-lives as short as 17 minutes. No information was provided to suggest control of possible photodegradation.
	Metric 8:	Consistency of exposure administration	Medium	The same volume (100 μL) and skin surface areas were used for both concentrations, but no information was provided about the volumes used for the positive and negative controls. Full-thickness skin of 500 +/- 80 μm was used. Skin surface area was not reported but can be calculated based on reported information (calculated by reviewer to be 1 cm2; based on application of 100 μL of 5 ng/μL solution to obtain a dose of 500 ng/cm2)
	Metric 9:	Reporting of concentrations	Medium	Nominal concentrations (point estimates) were reported.
	Metric 10:	Exposure frequency	High	Skin samples were exposed to TBBPA for 24 hrs; washing occurred at the end of this period, and sampling occurred at several timepoints within the 24-hour period. This is acceptable according to OECD TG 428.
	Metric 11:	Number of exposure groups and concentration spacing	High	Only 1 dose was tested (500 ng/cm2); three doses are preferred; however, OECD 428 TG states that "normally more than one concentration of the test substance is used in typical formulations, spanning the realistic range of potential human exposures." The authors justified the concentrations based on expected exposures to TBBPA via indoor dust. They also note that levels "were chosen to ensure that the concentrations in the receptor fluid during the experiment did not exceed 10% of the saturation solubility." The purpose of this study was to compare permeation of the test chemical in 3 different vehicles; therefore, one dose was sufficient.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	The authors used fresh excised human breast skin from 3 donors. Full-thickness skin was used, but it was 500 μm (acceptable because it was $<$ 1 mm). Full-thickness skin may be used if it is not excessive. The lot/batch of skin was not reported. Skin integrity was evaluated via standard trans-epidermal electrical resistance and methylene blue; however, results from these tests were not reported. The authors report that one skin patch failed the membrane integrity test, but do not report what acceptable values were.

Continued on next page . . .

. . . continued from previous page

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Cumulative permeation- 20% Tween 80 in water

Domain	Metric		Rating	Comments
	Metric 13:	Number/Replicates per group	Medium	OECD TG 428 says: "Acceptable data from a minimum of four replicates per test preparation are required,", but doesn't identify the number of donors needed. This study used samples from 3 donors, and all tests were performed in triplicate. The authors reported that "one excised human skin patch failed the membrane integrity test." It is assumed this was one replicate, and the remaining number of samples meets guideline requirements.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The test substance was prepared in acetone at concentrations of 5 ng/μL. Based on the information provided, the application rate was 100 μL of test solution/cm2, which is appropriate for an infinite dose scenario of a liquid. Measurements were taken from receptor fluid, receptor rinse, skin (depot), skin wash, and donor rinse. The frequency of collection from the receptor fluid (0.25, 0.5, 0.75, 1, 2, 4, 6, 10, 12, 18, 20 and 24 h), was appropriate
	Metric 15:	Consistency of outcome assessment	Medium	The same receptor fluid and sampling times were used across replicates. The extraction methods were described, and consistent methods were applied to the samples. Although negative controls are not specified in OECD TG (428, 156, 28). The supplemental material indicates a "field" blank, comprising skin tissue exposed to solvent only, was performed with each sample batch (n = 9). Further details regarding the treatment of this sample are not provided, so consistency is unclear.
	Metric 16:	Sampling adequacy and sensitivity	High	The sampling intervals were adequate to allow a graphical representation of the results. LC-MS/MS is sensitive for the measurement of non-radiolabeled substances. It was reported that background detection was low; no compounds were detected above the LOD in field blank samples. An LOD of 42 pg/cm2, based on a 10:1 signal-to-noise ratio, was reported.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Low	Tissue lots/batches were not reported, although skin samples came from the same company from females of similar age (36, 33, and 37). One skin sample failed integrity tests, although the criteria for acceptance were not reported, and quantitative results of the integrity test were not provided. Any inclusion/exclusion of outliers was not described.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	Solubility in the receptor fluid was not reported, but concentrations were not expected to lead to solubility concerns.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Uninformative	No statistical methods or calculations were performed on the data collected. The purpose of these experiments was to compare the permeation of the test substance in 3 different vehicles, not to calculate Kp. The study shows permeation into the receptor fluid at all time points (without variability) but did not report information that would allow for independent calculation of Kp.
	Metric 20:	Data interpretation	Uninformative	It appears the authors used an infinite dose. Interpretation of results was not consistent with standards and guidelines. Kp was not calculated.

Continued on next page . . .

. . . continued from previous page

Study Citation: Abdallah, M. A., Pawar, G., Harrad, S. (2015). Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environment International 84:64-70.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3022878
Unique ID: Cumulative permeation- 20% Tween 80 in water

Domain	Metric	Rating	Comments
	Metric 21: Reporting of data	Low	Cumulative permeation into the receptor fluid was shown graphically for all time points; however, variability and n/group were not shown.

Overall Quality Determination Uninformative

Study Citation:	Charles River Laboratories, (2024). The in vitro percutaneous absorption of radiolabelled TBBPA in eleven dosing scenarios through human split-thickness skin.
Chemical:	TBBPA
Exposure Type:	Parent compound
HERO ID:	12340684
Unique ID:	Finite- Neat: 5 mg/cm2; 1 mg/cm2

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The chemical was definitively identified and included the CASRN. Both radiolabeled and non-radiolabeled TBBPA were included. The structure was reported for the radiolabeled substance noting the location of the radiolabel within the structure. The particle size of the unlabeled substance was determined.
	Metric 2:	Test substance source	High	The test substance was verified analytically, and the batch number and supplier were provided. The certificates of analysis were provided in the study Appendices.
	Metric 3:	Test substance purity	Medium	The purity of the unlabeled test substance was >99%; the radiopurity of the radiolabeled test substance reported as 97.9% from the manufacture and was confirmed to be 98.8% via HPLC. Impurities were not identified
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	The lab provided acceptable historical results for testosterone and caffeine. “Charles River undertakes routine internal studies with reference chemicals to demonstrate the performance and reliability of the test system (Page, L (2024). The In Vitro Percutaneous Absorption of [14C]-Testosterone Through Human Split-Thickness Skin: Comparison of Receptor Fluids. Charles River Study No. 00999472).”
	Metric 5:	Assay procedures	High	The lab described methods: test preparations/dilutions including volumes applied; physiological compatibility of receptor fluid; tape stripping materials and procedures; static diffusion set up and preparation; skin washing; timing of sampling, etc. The lab assessed solubility in acetone, receptor fluid, and vehicles and conducted particle size analysis of the unlabeled test substance. The methods were justified where necessary
	Metric 6:	Standards for tests	Medium	The lab used the electrical resistance method to assess skin integrity at the beginning of the study and cited a standard of acceptability (10.9 kOhms or greater). The lab also provided the results of skin integrity using the trans-epidermal water loss (TEWL) method but did not provide a standard for acceptability for the TEWL results. The lab discussed the need for recovery to be 100+/-10%. The lab did not discuss the need to keep variability among samples low (e.g., coefficient of variations lower than 25%).
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	High	Detailed information was provided on expected stability, the stock solution, procedures related to mixing of the test preparations, and storage conditions (in freezer at -20C). TBBPA can photodegrade with a range of half-lives as short as 17 minutes; however, stability tests confirmed that the test item was stable over the dosing period.
	Metric 8:	Consistency of exposure administration	Medium	The lab used several experiments with different dilutions (and the neat substance) that included finite and infinite doses. The exposures were consistent across similar types of doses.
	Metric 9:	Reporting of concentrations	High	The exposures were reported without ambiguity.

Continued on next page . . .

. . . continued from previous page

Study Citation: Charles River Laboratories, (2024). The in vitro percutaneous absorption of radiolabelled TBBPA in eleven dosing scenarios through human split-thickness skin.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 12340684
Unique ID: Finite- Neat: 5 mg/cm2; 1 mg/cm2

Domain	Metric		Rating	Comments
	Metric 10:	Exposure frequency	High	The exposure duration was reported and appropriate. The finite doses were stopped at 8 hours and samples taken through 24 hours.
	Metric 11:	Number of exposure groups and concentration spacing	High	For the finite dose groups, neat scenarios and three dilutions were used.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	Details were provided on source and storage of skin samples, sex and age of donors, method of dermatoming and the resulting split thickness (from 300 to 400 um).
	Metric 13:	Number/Replicates per group	Medium	Each experimental condition used 8 samples (and 4 donors).
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The selected formulations were reasonable for the uses of TBBPA. In addition, the amounts loaded per cm2 were appropriate for finite dosing scenarios.
	Metric 15:	Consistency of outcome assessment	High	The outcomes were assessed consistently across similar dosing conditions.
	Metric 16:	Sampling adequacy and sensitivity	High	The number of timepoints for sampling was adequate. The lab increased the number of minutes for sampling to 60 min if radioactivity was low. They also had a 30 dpm limit of reliable measurement.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	All study groups were of the same size. Skin tissues were of adequate thickness (ranging from 300 to 400 um). The lab used an acceptable method of skin integrity testing (electrical resistance) and samples were replaced if they did not meet the standard (10.9 kOhm) that was stated. Although handling of skin tissues was similar, they came from two different sources.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	The study report included both individual results and the mean values for separate measurements (skin wash, combined tape strip data, exposed skin, receptor fluid, receptor chamber wash, etc.); for individual time points in the receptor fluid; and for the two separate skin washes. The variation among samples was often large (CV% $>$ 25); however sufficient data are provided for EPA to calculate an alternate (upper-end) value to account for variability in the results.
	Metric 20:	Data interpretation	High	Mass balance was good (95.81 and 97.75%). Appropriate values were provided to allow calculation of dermal absorption and individual replicates and sample results were provided for EPA to calculate values as well.
	Metric 21:	Reporting of data	High	Data were reported for all outcomes (means and standard deviations) and in detail along with individual replicates.

Continued on next page . . .

. . . continued from previous page

Study Citation:	Charles River Laboratories, (2024). The in vitro percutaneous absorption of radiolabelled TBBPA in eleven dosing scenarios through human split-thickness skin.
Chemical:	TBBPA
Exposure Type:	Parent compound
HERO ID:	12340684
Unique ID:	Finite- Neat: 5 mg/cm2; 1 mg/cm2

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

Study Citation: Charles River Laboratories, (2024). The in vitro percutaneous absorption of radiolabelled TBBPA in eleven dosing scenarios through human split-thickness skin.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 12340684
Unique ID: Finite- 50% in IPM, 10% in IPM, 1% in IPM

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The chemical was definitively identified and included the CASRN. Both radiolabeled and non-radiolabeled TBBPA were included. The structure was reported for the radio-labeled substance noting the location of the radiolabel within the structure. The particle size of the unlabeled substance was determined.
	Metric 2:	Test substance source	High	The test substance was verified analytically, and the batch number and supplier were provided. The certificates of analysis were provided in the study Appendices.
	Metric 3:	Test substance purity	Medium	The purity of the unlabeled test substance was >99%; the radiopurity of the radiolabeled test substance reported as 97.9% from the manufacture and was confirmed to be 98.8% via HPLC. Impurities were not identified
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	The lab provided acceptable historical results for testosterone and caffeine. “Charles River undertakes routine internal studies with reference chemicals to demonstrate the performance and reliability of the test system (Page, L (2024). The In Vitro Percuta-neous Absorption of [14C]-Testosterone Through Human Split-Thickness Skin: Com-parison of Receptor Fluids. Charles River Study No. 00999472).”
	Metric 5:	Assay procedures	High	The lab described methods: test preparations/dilutions including volumes applied; phys-iological compatibility of receptor fluid; tape stripping materials and procedures; static diffusion set up and preparation; skin washing; timing of sampling, etc. The lab assessed solubility in acetone, receptor fluid, and vehicles and conducted particle size analysis of the unlabeled test substance. The methods were justified where necessary
	Metric 6:	Standards for tests	Medium	The lab used the electrical resistance method to assess skin integrity at the beginning of the study and cited a standard of acceptability (10.9 kOhms or greater). The lab also provided the results of skin integrity using the trans-epidermal water loss (TEWL) method but did not provide a standard for acceptability for the TEWL results. The lab discussed the need for recovery to be 100+/-10%. The lab did not discuss the need to keep variability among samples low (e.g., coefficient of variations lower than 25%).
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test sub-stance (chemical)	High	Detailed information was provided on expected stability, the stock solution, procedures related to mixing of the test preparations, and storage conditions (in freezer at -20C). TBBPA can photodegrade with a range of half-lives as short as 17 minutes; however, stability tests confirmed that the test item was stable over the dosing period.
	Metric 8:	Consistency of exposure administration	Medium	The lab used several experiments with different dilutions (and the neat substance) that included finite and infinite doses. The exposures were consistent across similar types of doses.
	Metric 9:	Reporting of concentrations	High	The exposures were reported without ambiguity.
	Metric 10:	Exposure frequency	High	The exposure duration was reported and appropriate. The finite doses were stopped at 8 hours and samples taken through 24 hours.

Continued on next page . . .

. . . continued from previous page

Study Citation: Charles River Laboratories, (2024). The in vitro percutaneous absorption of radiolabelled TBBPA in eleven dosing scenarios through human split-thickness skin.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 12340684
Unique ID: Finite- 50% in IPM, 10% in IPM, 1% in IPM

Domain	Metric		Rating	Comments
	Metric 11:	Number of exposure groups and concentration spacing	High	For the finite dose groups, neat scenarios and three dilutions were used.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	Details were provided on source and storage of skin samples, sex and age of donors, method of dermatoming and the resulting split thickness (from 300 to 400 um).
	Metric 13:	Number/Replicates per group	Medium	Each experimental condition used 8 samples (and 4 donors).
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The selected formulations were reasonable for the uses of TBBPA. In addition, the amounts loaded per cm2 were appropriate for finite dosing scenarios.
	Metric 15:	Consistency of outcome assessment	High	The outcomes were assessed consistently across similar dosing conditions.
	Metric 16:	Sampling adequacy and sensitivity	High	The number of timepoints for sampling was adequate. The lab increased the number of minutes for sampling to 60 min if radioactivity was low. They also had a 30 dpm limit of reliable measurement.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	All study groups were of the same size. Skin tissues were of adequate thickness (ranging from 300 to 400 um). The lab used an acceptable method of skin integrity testing (electrical resistance) and samples were replaced if they did not meet the standard (10.9 kOhm) that was stated. Although handling of skin tissues was similar, they came from two different sources.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	Solubility was measured and acceptable. Some cloudiness was observed for the highest dilutions (50%) after overnight stirring of preparations. However, before the experiment was run, the test article recovery was good in the test preparations (104.48 to 106.03%) and variability was low among preparations (CVs of 1.25 to 2.71%) so there was consistency across preparations. The test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	The study report included both individual results and the mean values for separate measurements (skin wash, combined tape strip data, exposed skin, receptor fluid, receptor chamber wash, etc.); for individual time points in the receptor fluid; and for the two separate skin washes. The variation among samples was often large (CV% $>$ 25); however sufficient data are provided for EPA to calculate an alternate (upper-end) value to account for variability in the results.
	Metric 20:	Data interpretation	High	Mass balance was good (98.19−98.94%). Appropriate values were provided to allow calculation of dermal absorption and individual replicates and sample results were provided for EPA to calculate values as well.

Continued on next page . . .

. . . continued from previous page

Study Citation:	Charles River Laboratories, (2024). The in vitro percutaneous absorption of radiolabelled TBBPA in eleven dosing scenarios through human split-thickness skin.
Chemical:	TBBPA
Exposure Type:	Parent compound
HERO ID:	12340684
Unique ID:	Finite- 50% in IPM, 10% in IPM, 1% in IPM

Domain	Metric	Rating	Comments
	Metric 21: Reporting of data	High	Data were reported for all outcomes (means and standard deviations) and in detail along with individual replicates.

Overall Quality Determination High

Study Citation:	Charles River Laboratories, (2024). The in vitro percutaneous absorption of radiolabelled TBBPA in eleven dosing scenarios through human split-thickness skin.
Chemical:	TBBPA
Exposure Type:	Parent compound
HERO ID:	12340684
Unique ID:	Finite- 50% in Receptor fluid, 10% in Receptor fluid; 1% in Receptor fluid

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The chemical was definitively identified and included the CASRN. Both radiolabeled and non-radiolabeled TBBPA were included. The structure was reported for the radio-labeled substance noting the location of the radiolabel within the structure. The particle size of the unlabeled substance was determined.
	Metric 2:	Test substance source	High	The test substance was verified analytically, and the batch number and supplier were provided. The certificates of analysis were provided in the study Appendices.
	Metric 3:	Test substance purity	Medium	The purity of the unlabeled test substance was >99%; the radiopurity of the radiolabeled test substance reported as 97.9% from the manufacture and was confirmed to be 98.8% via HPLC. Impurities were not identified
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	The lab provided acceptable historical results for testosterone and caffeine. “Charles River undertakes routine internal studies with reference chemicals to demonstrate the performance and reliability of the test system (Page, L (2024). The In Vitro Percuta-neous Absorption of [14C]-Testosterone Through Human Split-Thickness Skin: Com-parison of Receptor Fluids. Charles River Study No. 00999472).”
	Metric 5:	Assay procedures	High	The lab described methods: test preparations/dilutions including volumes applied; phys-iological compatibility of receptor fluid; tape stripping materials and procedures; static diffusion set up and preparation; skin washing; timing of sampling, etc. The lab assessed solubility in acetone, receptor fluid, and vehicles and conducted particle size analysis of the unlabeled test substance. The methods were justified where necessary
	Metric 6:	Standards for tests	Medium	The lab used the electrical resistance method to assess skin integrity at the beginning of the study and cited a standard of acceptability (10.9 kOhms or greater). The lab also provided the results of skin integrity using the trans-epidermal water loss (TEWL) method but did not provide a standard for acceptability for the TEWL results. The lab discussed the need for recovery to be 100+/-10%. The lab did not discuss the need to keep variability among samples low (e.g., coefficient of variations lower than 25%).
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test sub-stance (chemical)	High	Detailed information was provided on expected stability, the stock solution, procedures related to mixing of the test preparations, and storage conditions (in freezer at -20C). TBBPA can photodegrade with a range of half-lives as short as 17 minutes; however, stability tests confirmed that the test item was stable over the dosing period.
	Metric 8:	Consistency of exposure administration	Medium	The lab used several experiments with different dilutions (and the neat substance) that included finite and infinite doses. The exposures were consistent across similar types of doses.
	Metric 9:	Reporting of concentrations	High	The exposures were reported without ambiguity.
	Metric 10:	Exposure frequency	High	The exposure duration was reported and appropriate. The finite doses were stopped at 8 hours and samples taken through 24 hours.

Continued on next page . . .

. . . continued from previous page

Study Citation: Charles River Laboratories, (2024). The in vitro percutaneous absorption of radiolabelled TBBPA in eleven dosing scenarios through human split-thickness skin.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 12340684
Unique ID: Finite- 50% in Receptor fluid, 10% in Receptor fluid; 1% in Receptor fluid

Domain	Metric		Rating	Comments
	Metric 11:	Number of exposure groups and concentration spacing	High	For the finite dose groups, neat scenarios and three dilutions were used.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	Details were provided on source and storage of skin samples, sex and age of donors, method of dermatoming and the resulting split thickness (from 300 to 400 um).
	Metric 13:	Number/Replicates per group	Medium	Each experimental condition used 8 samples (and 4 donors).
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The selected formulations were reasonable for the uses of TBBPA. In addition, the amounts loaded per cm2 were appropriate for finite dosing scenarios.
	Metric 15:	Consistency of outcome assessment	High	The outcomes were assessed consistently across similar dosing conditions.
	Metric 16:	Sampling adequacy and sensitivity	High	The number of timepoints for sampling was adequate. The lab increased the number of minutes for sampling to 60 min if radioactivity was low. They also had a 30 dpm limit of reliable measurement.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	All study groups were of the same size. Skin tissues were of adequate thickness (ranging from 300 to 400 um). The lab used an acceptable method of skin integrity testing (electrical resistance) and samples were replaced if they did not meet the standard (10.9 kOhm) that was stated. Although handling of skin tissues was similar, they came from two different sources.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	Solubility was measured and acceptable. Some cloudiness was observed for the highest dilutions (50%) after overnight stirring of preparations. However, before the experiment was run, the test article recovery was good in the test preparations (106.52 to 110.12%) and variability was low among preparations (CVs of 0.46 to 2.14%) so there was consistency across preparations. The test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	The study report included both individual results and the mean values for separate measurements (skin wash, combined tape strip data, exposed skin, receptor fluid, receptor chamber wash, etc.); for individual time points in the receptor fluid; and for the two separate skin washes. The variation among samples was often large (CV% $>$ 25); however sufficient data are provided for EPA to calculate an alternate (upper-end) value to account for variability in the results.
	Metric 20:	Data interpretation	High	Mass balance was good (96.25−103.37%). Appropriate values were provided to allow calculation of dermal absorption and individual replicates and sample results were provided for EPA to calculate values as well.

Continued on next page . . .

...continued from previous page

Study Citation:	Charles River Laboratories, (2024). The in vitro percutaneous absorption of radiolabelled TBBPA in eleven dosing scenarios through human split-thickness skin.
Chemical:	TBBPA
Exposure Type:	Parent compound
HERO ID:	12340684
Unique ID:	Finite- 50% in Receptor fluid, 10% in Receptor fluid; 1% in Receptor fluid

Domain	Metric	Rating	Comments
	Metric 21: Reporting of data	High	Data were reported for all outcomes (means and standard deviations) and in detail along with individual replicates.

Overall Quality Determination High

Study Citation: Charles River Laboratories, (2024). The in vitro percutaneous absorption of radiolabelled TBBPA in eleven dosing scenarios through human split-thickness skin.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 12340684
Unique ID: Infinite- 50% in IPM, 10% in IPM, 1% in IPM

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The chemical was definitively identified and included the CASRN. Both radiolabeled and non-radiolabeled TBBPA were included. The structure was reported for the radiolabeled substance noting the location of the radiolabel within the structure. The particle size of the unlabeled substance was determined.
	Metric 2:	Test substance source	High	The test substance was verified analytically, and the batch number and supplier were provided. The certificates of analysis were provided in the study Appendices.
	Metric 3:	Test substance purity	Medium	The purity of the unlabeled test substance was >99%; the radiopurity of the radiolabeled test substance reported as 97.9% from the manufacture and was confirmed to be 98.8% via HPLC. Impurities were not identified
Domain 2: Test Design				
	Metric 4:	Reference compounds	High	The lab provided acceptable historical results for testosterone and caffeine. "Charles River undertakes routine internal studies with reference chemicals to demonstrate the performance and reliability of the test system (Page, L (2024). The In Vitro Percutaneous Absorption of [14C]-Testosterone Through Human Split-Thickness Skin: Comparison of Receptor Fluids. Charles River Study No. 00999472)."
	Metric 5:	Assay procedures	High	The lab described methods: test preparations/dilutions including volumes applied; physiological compatibility of receptor fluid; static diffusion set up and preparation; timing of sampling, etc. The lab assessed solubility in acetone, receptor fluid, and vehicles and conducted particle size analysis of the unlabeled test substance. The methods were justified where necessary.
	Metric 6:	Standards for tests	Medium	The lab used the electrical resistance method to assess skin integrity at the beginning of the study and cited a standard of acceptability (10.9 kOhms or greater). The lab also provided the results of skin integrity using the trans-epidermal water loss (TEWL) method but did not provide a standard for acceptability for the TEWL results. The lab discussed the need for recovery to be 100+/-10%. The lab did not discuss the need to keep variability among samples low (e.g., coefficient of variations lower than 25%).
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	High	Detailed information was provided on expected stability, the stock solution, procedures related to mixing of the test preparations, and storage conditions (in freezer at -20C). TBBPA can photodegrade with a range of half-lives as short as 17 minutes; however, stability tests confirmed that the test item was stable over the dosing period.
	Metric 8:	Consistency of exposure administration	Medium	The lab used several experiments with different dilutions (and the neat substance) that included finite and infinite doses. The exposures were consistent across similar types of doses.
	Metric 9:	Reporting of concentrations	High	The exposures were reported without ambiguity.
	Metric 10:	Exposure frequency	High	The exposure duration was reported and appropriate. The infinite doses were stopped at 24 hours and samples taken through 24 hours

Continued on next page . . .

. . . continued from previous page

Study Citation: Charles River Laboratories, (2024). The in vitro percutaneous absorption of radiolabelled TBBPA in eleven dosing scenarios through human split-thickness skin.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 12340684
Unique ID: Infinite- 50% in IPM, 10% in IPM, 1% in IPM

Domain	Metric		Rating	Comments
	Metric 11:	Number of exposure groups and concentration spacing	High	The study also used three dilutions for the infinite scenarios. Because none of the uses are for vehicles that do not react immediately, the lab used only isopropyl myristate as a vehicle, which is acceptable.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	Details were provided on source and storage of skin samples, sex and age of donors, method of dermatoming and the resulting split thickness (from 300 to 400 um).
	Metric 13:	Number/Replicates per group	Medium	Each experimental condition used 8 samples (and 4 donors).
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The selected formulations were reasonable for the uses of TBBPA. In addition, the amounts loaded per cm2 were appropriate for infinite dosing scenarios.
	Metric 15:	Consistency of outcome assessment	High	The outcomes were assessed consistently across similar dosing conditions.
	Metric 16:	Sampling adequacy and sensitivity	High	The number of timepoints for sampling was adequate. The lab increased the number of minutes for sampling to 60 min if radioactivity was low. They also had a 30 dpm limit of reliable measurement.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	All study groups were of the same size. Skin tissues were of adequate thickness (ranging from 300 to 400 um). The lab used an acceptable method of skin integrity testing (electrical resistance) and samples were replaced if they did not meet the standard (10.9 kOhm) that was stated. Although handling of skin tissues was similar, they came from two different sources.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	Solubility was measured and acceptable. Some cloudiness was observed for the highest dilutions (50%) after overnight stirring of preparations. However, before the experiment was run, the test article recovery was good in the test preparations (97.98 to 101.39%) and variability was low among preparations (CVs of 0.54 to 4.5%) so there was consistency across preparations. The test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	The study report included both individual results and the mean values for cumulative absorption. The variation among samples was often large (CV% $>$ 25); however sufficient data are provided for EPA to calculate an alternate (upper-end) value to account for variability in the results.
	Metric 20:	Data interpretation	High	The Kp and linear phase of absorption were derived from an appropriate exposure condition (infinite dose). Recovery was not reported but this determination is not relevant for infinite dose applications.
	Metric 21:	Reporting of data	High	Data were reported for all outcomes (means and standard deviations) and in detail along with individual replicates.

Continued on next page . . .

...continued from previous page

Study Citation:	Charles River Laboratories, (2024). The in vitro percutaneous absorption of radiolabelled TBBPA in eleven dosing scenarios through human split-thickness skin.
Chemical:	TBBPA
Exposure Type:	Parent compound
HERO ID:	12340684
Unique ID:	Infinite- 50% in IPM, 10% in IPM, 1% in IPM

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

Study Citation: Inveresk Research International, (2005). The in vitro percutaneous adsorption of radiolabelled tetrabromobisphenol-A (TBBPA) through human skin.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 7415560
Unique ID: TBBPA

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Radiolabeled compound was used. The test substance name and CASRN was provided. The location of the radiolabel was reported and in a position that is considered metabolically stable.
	Metric 2:	Test substance source	High	The source and batches were identified for the radiolabeled substance; source was identified for the unlabeled substance.
	Metric 3:	Test substance purity	High	Purity (> 99%) was reported for labelled and unlabeled substance and impurities identified for the unlabeled substance.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No reference compounds were mentioned and it is not known whether the laboratory has historical control reference compound data.
	Metric 5:	Assay procedures	High	The authors use a flow-through diffusion cell with 1.5 ml/hr flow rate. No information was provided on whether the cell provided a good seal around the skin sample. The skin source and preparation were described. The receptor fluid was 1:1 ethanol to water and the authors said TBBPA was soluble in the fluid. Human skin was obtained from patients (25-57 years old) from the breast or upper arm. The skin temperature was maintained at 32 °C. The surface area of skin was 0.64 cm2 and application was about 1.9 mg/cm2. The volume was stated as well (6.4 uL). No information on humidity was provided. The tape stripping method was described. The diffusion cell was open to the atmosphere (unoccluded). Samples were analyzed using a liquid scintillation counter with automatic quench correction by external standard. Samples were counted for 5 minutes (titrated water was counted for 1 minute). A reliability limit of 30 d.p.m above background was instituted.
	Metric 6:	Standards for tests	Medium	Skin integrity was determined using titrated water. Skin samples exhibiting a Kp >2.5e-3 cm/hr were excluded; this is in agreement with current guidance and acceptable. Data are shown in Appendix 7. Percent recovery was within 10% or 100%. Sufficient data were provided to determine the coefficients of variation (see metric 19 for more details).
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Preparation and storage of the test substance were described. Both the radiolabeled and non-radiolabeled test substance were stored in the dark. Although TBBPA isn't expected to hydrolyze and volatility is low, it can degrade with a range of half lives as short at 17 minutes. No information was provided to suggest control of possible photodegradation during preparation.
	Metric 8:	Consistency of exposure administration	Medium	The test substance was administered consistently across groups. A volume of 6.4uL (2 mg/cm2) of the [14C]-TBBPA in acetone solution was consistently applied to each skin replicate. The acetone was then allowed to evaporate. The skin thicknesses ranged from 390 to 400 microns, which was acceptable. The skin surface area (0.64 cm2) was consistent across groups.

Continued on next page . . .

. . . continued from previous page

Study Citation: Inveresk Research International, (2005). The in vitro percutaneous adsorption of radiolabelled tetrabromobisphenol-A (TBBPA) through human skin.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 7415560
Unique ID: TBBPA

Domain	Metric		Rating	Comments
	Metric 9:	Reporting of concentrations	High	Nominal and analytical concentrations (point estimates) were reported.
	Metric 10:	Exposure frequency	High	Skin samples were exposed to TBBPA for 8 hrs and assessed at a final post-exposure time of 24 hrs. Samples were taken hourly until 8 hrs and every 2 hrs from 8 to 24 hrs.
	Metric 11:	Number of exposure groups and concentration spacing	Low	Only one concentration was used even though OECD TG 428 suggests 2 or more. The study text indicated that "The draft EU risk assessment report assumes a worst workplace dermal exposure of ca 1.9 mg/cm^2, this dose will be applied using an acetone vehicle."
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	Skin was obtained from the breast (6 samples) or upper arm (one sample) of females aged 25-57. Skin was stored at -20 degrees C. Prior to use, the skin samples were thawed and dermatomed using a Zimmer electric dermatome. Split thickness skin was used (390 to 400 um). The authors used a tritiated water transmembrane method to evaluate skin integrity.
	Metric 13:	Number/Replicates per group	Medium	OECD TG 156 recommends 8 replicates total from at least 4 donors = 2 replicates/donor. The authors used results using 8 replicates from 6 donors.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	The test substance evaluated was essentially 100% (neat) after evaporation of acetone (a relevant concentration for workers) and an 8-hour dosing period was used (matching worker exposures). The applied dose was reported to be 2.00322 mg/cm2; which is agreement with OECD guidelines of 1-5 mg/cm2 of skin for solids in a finite exposure scenario. The receptor fluid was collected hourly from 0-8 hours and then every 2 hours from 8-24 hours post dose. After 8 hours of exposure, the skin was washed with 50 uL of soap concentrate using a Q-tip and rinsed with 500 uL of water (wash repeated 3 more times). Measurement techniques were appropriate and percent absorption was calculated in a finite exposure scenario.
	Metric 15:	Consistency of outcome assessment	High	Methods that are described appear to be consistent across replicates (in skin preparation, cell diffusion set up, amount of test substance, volume applied, surface area of skin, timepoints evaluated).
	Metric 16:	Sampling adequacy and sensitivity	High	Sampling of receptor fluid was done throughout the experiment and the number of replicates was adequate (8 replicates for 6 donors). Radioactivity of the test substance preparation and quantity applied to the skin surface was verified with 7 replicates of scintillation counting; washing methods and other measurements were analyzed using duplicate aliquots for scintillation counting. Large volumes were taken for scintillation counting for some measurements. Blank samples were subtracted from sample counts. A limit of reliable measurement of 30 d.p.m. above background was instituted by this laboratory. Individual scintillation counts were not shown. A graphical representation of absorption over time is shown.
Domain 6: Confounding/Variable Control				

Continued on next page . . .

. . . continued from previous page

Study Citation: Inveresk Research International, (2005). The in vitro percutaneous adsorption of radiolabelled tetrabromobisphenol-A (TBBPA) through human skin.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 7415560
Unique ID: TBBPA

Domain	Metric		Rating	Comments
	Metric 17:	Confounding variables in test design and procedures	Medium	Tissue lots/batches of skin were not reported (although they appear to have come from the same hospital). One outlier was identified and excluded but it is not entirely clear why this would have been excluded (a priori criteria not stated). Skin integrity was checked and only acceptable replicates were used.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	Solubility in the receptor fluid was not reported for individual replicates but the authors note that TBBPA was soluble (generally) in the chosen receptor fluid (1:1 ethanol:water).
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Statistical methods were minimally described. Absorption into receptor fluid was shown on a graph for each sampling time point and for individual replicates. Additional information was provided for each replicate for the 24 hr timepoint. Percent absorption was appropriately calculated. The CVs for the total absorbed dose was 66%. Sufficient data are provided for EPA to calculate an alternate (upper-end) value to account for variability in the results.
	Metric 20:	Data interpretation	Medium	Recovery was sufficient and high (103.86%). Data are presented for the outlier so the absorption can be calculated with this value as needed. Absorption didn't include the amount remaining in skin and the authors didn't report the top 2 tape strips separately (they combined first 5 tape strips). However, the total amount remaining in skin could be calculated from the available data. Percent absorption was appropriately calculated (finite dose used and steady state wasn't reached).
	Metric 21:	Reporting of data	Medium	The absorption (penetration) profile with time was reported but data were for interim sampling times were reported only graphically. The authors do present the total amounts of TBBPA recovered for each step of the process in a table.

Overall Quality Determination Medium

Study Citation:	Knudsen, G. A., Hughes, M. F., Mcintosh, K. L., Sanders, J. M., Birnbaum, L. S. (2015). Estimation of tetrabromobisphenol A (TBBPA) percutaneous uptake in humans using the parallelogram method. Toxicology and Applied Pharmacology 289(2):323-329.
Chemical:	TBBPA
Exposure Type:	Parent compound
HERO ID:	3162048
Unique ID:	Human cadaver skin (in vitro)

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Radiolabeled compound was used. The test substance name and structure was provided. The location of the radiolabel was reported and in a metabolically stable position.
	Metric 2:	Test substance source	High	The source and batch number information was provided.
	Metric 3:	Test substance purity	High	Both radiolabel and chemical purity were stated and good (> 98%).
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No reference compounds were mentioned and it is not known whether the laboratory has historical control reference compound data.
	Metric 5:	Assay procedures	Medium	The authors used a flow-through diffusion system that pumped receptor fluid at a rate of 1.8 mL/hr. The receptor fluid used had been demonstrated to maintain the viability of skin for 24 hrs. The diffusion cell was heated with 35 °C water (OECD TG recommends maintaining the temperature at 32 °C). No information on humidity was provided. The authors reported using a volume of 10 μL of acetone. Surface area of skin was appropriate (0.64 cm2, within the range of 0.3 to 5 cm2 as typical surface areas identified in OECD TG 28). Skin surface washing used an appropriate method - Joy liquid (1:1 with water). The authors didn't mention whether the chambers were occluded. This leads to questions about whether volatilization of the vehicle was controlled. Significant volatilization of acetone could have occurred. According to OECD TG 428, the target amount identified to apply to the skin is 1-5 mg/cm2; the authors used 100 nmol/cm2. The molecular weight of TBBPA is 543.9 g/mol; therefore, the amount added to the skin was 54.39 μg/cm2 or 0.05439 mg/cm2. This is below the recommended test amount. The authors didn't explicitly say why they used this amount of TBBPA; however, it was noted that a previous study commissioned for REACH "concluded that less than 2% of a 2 mg/cm2 dose of TBBPA was bioavailable." 2% of 2 mg/cm2 is 0.04 mg/cm2.
	Metric 6:	Standards for tests	Medium	The integrity of human skin was measured using tritiated water. The authors report the mean percentage of dose [3H]-H2O in the receptor fluid was less than 0.05% (indicating intact barrier); individual cell data not provided. It is not reported whether any cells did not meet the criteria. Recovery was 98.6%. Coefficient of variation could be calculated with available data.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	No information on storage and stability was provided. Although TBBPA isn't expected to hydrolyze and volatility is low, there is a possibility that it can degrade via photodegradation quickly and should be stored in the dark.
	Metric 8:	Consistency of exposure administration	Medium	The same volume, skin surface areas, and amount of TBBPA were used for both human and rat skin experiments. Skin thickness was reported as 294 +/-57 um; individual cells were not reported.
	Metric 9:	Reporting of concentrations	Medium	Nominal concentrations (point estimates) were reported.

Continued on next page . . .

. . . continued from previous page

Study Citation: Knudsen, G. A., Hughes, M. F., Mcintosh, K. L., Sanders, J. M., Birnbaum, L. S. (2015). Estimation of tetrabromobisphenol A (TBBPA) percutaneous uptake in humans using the parallelogram method. Toxicology and Applied Pharmacology 289(2):323-329.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3162048
Unique ID: Human cadaver skin (in vitro)

Domain	Metric		Rating	Comments
	Metric 10:	Exposure frequency	High	Skin samples were exposed to TBBPA for 24 hrs; washing occurred at the end of this period, and sampling occurred at 6, 12, 18 and 24 hrs. This is acceptable according to OECD TG 428.
	Metric 11:	Number of exposure groups and concentration spacing	Low	Only one exposure concentration was reported; no references were provided to indicate whether it represents realistic exposures. However, the authors state that they "applied the principles of the parallelogram approach to the dermal exposure estimates to estimate a likely level following in vivo human systemic exposures to a relevant dose of dermally applied TBBPA," indicating an intent to use relevant exposure levels.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	Dorsal/scapular skin was excised $\leq$12 hours post-mortem. Skin was stored at -80 degrees C until use. Skin came from 3 donors (1 male and 2 female), ages 71-77 years. Skin was thawed on the day of the experiment and dermatomed using Padgett dermatome. The thickness was measured to be 294 +/- 57 μm. The source was identified, but not the lot or batch. The integrity of human skin was measured using tritiated water. The authors report that the mean percentage of dose [3H]-H2O in the receptor fluid was less than 0.05% (indicating an intact barrier); individual cell data were not provided.
	Metric 13:	Number/Replicates per group	Low	Human skin was obtained from 3 donors and tests were performed in quadruplicate for a total of 12 data points. OECD 156 recommends using 8 replicates from at least 4 donors. Since only 3 donors were studied, this metric was downgraded.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	Authors appropriately calculated percent absorption (because their experiment reflected the use of a finite dose); however, dosing was below the recommended range for finite dosing. Receptor fluid fractions were collected every 6 hrs until 24 hrs post-dosing; this frequency allowed for the data to be reported graphically. Skin was washed six times with a 1:1 mixture of Joy liquid soap: water, and wash fractions were pooled. Skin washes, chamber washes, weigh boats, receptor fluid collections, 10 tape strips (collected individually), and skin were analyzed for radioactivity by scintillation counting. The techniques and timing of measurements were appropriate and sensitive to the outcomes of interest.
	Metric 15:	Consistency of outcome assessment	High	Details of the 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.
	Metric 16:	Sampling adequacy and sensitivity	Medium	Sampling of the receptor fluid throughout the 24-hr period appeared to be adequate (6, 12, 18, and 24 h). The extraction method was described, and a consistent method was applied to the samples. Radioactivity was determined using scintillation counting with details provided; however, the sensitivity and limit of detection were not reported.
Domain 6: Confounding/Variable Control				

Continued on next page . . .

. . . continued from previous page

Study Citation: Knudsen, G. A., Hughes, M. F., Mcintosh, K. L., Sanders, J. M., Birnbaum, L. S. (2015). Estimation of tetrabromobisphenol A (TBBPA) percutaneous uptake in humans using the parallelogram method. Toxicology and Applied Pharmacology 289(2):323-329.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3162048
Unique ID: Human cadaver skin (in vitro)

Domain	Metric		Rating	Comments
	Metric 17:	Confounding variables in test design and procedures	Low	Tissue batches/lots were not reported (although they came from the same source). The integrity of human skin was demonstrated using the transepidermal tritiated water loss method (as 0.05%); however, the inclusion/exclusion of outliers was not described. The integrity of Individual cells is not reported.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	Solubility in the receptor fluid was not reported, but the use of 10% fetal bovine solution is expected to help with solubility, and a flow-through method was used, so the fluid was replenished with 0% test substance (rate was 1.8 mL/hr).
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Cumulative dose in the receptor fluid is shown graphically for each time point. The CVs were 30% for the percentage in receptor fluid, 53% for the percentage in skin (indicated in the study as absorbed), and 3% for unabsorbed (washed and tape stripping). Data enabling an independent statistical analysis or to calculate an upper end value for the fraction absorbed were not provided.
	Metric 20:	Data interpretation	Low	Recovery was good (99%) and the integrity of the skin was demonstrated for human skin. The authors considered the unabsorbed % to be washes and 10 tape strippings (this is greater than the recommendation of the first 2 strippings). They did not report data for each tape strip; therefore, recalculations can not be done.
	Metric 21:	Reporting of data	Low	The profile of penetration into the receptor fluid over time was reported graphically (with standard deviations), but only the final time point was reported numerically in a table. Values of the amounts in skin (identified as absorbed), receptor fluid (identified as penetrated) and washings/tape strips (unabsorbed) were reported. Tape strip values were not reported separately, and the total amount (or individual strip amount) that was removed was not reported. Tape stripping information was combined with washings, and thus, absorption couldn't be recalculated. Individual replicate information was also not reported (e.g., to understand the large CV for the fraction in human skin).

Overall Quality Determination Medium

Study Citation: Knudsen, G. A., Hughes, M. F., Mcintosh, K. L., Sanders, J. M., Birnbaum, L. S. (2015). Estimation of tetrabromobisphenol A (TBBPA) percutaneous uptake in humans using the parallelogram method. Toxicology and Applied Pharmacology 289(2):323-329.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3162048
Unique ID: Rat skin (ex vivo)

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	A radiolabeled compound was used. The test substance name and structure were provided. The location of the radiolabel was reported to be in a metabolically stable position.
	Metric 2:	Test substance source	High	The source and batch number information was provided.
	Metric 3:	Test substance purity	High	Radiolabel and chemical purity were stated and good (> 98%).
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No reference compounds were mentioned, and it is not known whether the laboratory has historical control reference compound data.
	Metric 5:	Assay procedures	Medium	The authors used a flow-through diffusion system that pumped receptor fluid at a rate of 1.8 mL/hr. The receptor fluid used had been demonstrated to maintain the viability of skin for 24 hrs. The diffusion cell was heated with 35 °C water (OECD TG recommends maintaining the temperature at 32 °C). No information on humidity was provided. The authors reported using a volume of 10 μL of acetone. Surface area of skin was appropriate (0.64 cm2, within the range of 0.3 to 5 cm2 as typical surface areas identified in OECD TG 28). Skin surface washing used an appropriate method - Joy liquid (1:1 with water). The authors didn't mention whether the chambers were occluded. This leads to questions about whether volatilization of the vehicle was controlled. Significant volatilization of acetone could have occurred. According to OECD TG 428, the target amount identified to apply to the skin is 1-5 mg/cm2; the authors used 100 nmol/cm2. The molecular weight of TBBPA is 543.9 g/mol; therefore, the amount added to the skin was 54.39 μg/cm2 or 0.05439 mg/cm2. This is below the recommended test amount. The authors didn't explicitly say why they used this amount of TBBPA; however, it was noted that a previous study commissioned for REACH "concluded that less than 2% of a 2 mg/cm2 dose of TBBPA was bioavailable." 2% of 2 mg/cm2 is 0.04 mg/cm2.
	Metric 6:	Standards for tests	Low	The integrity of rat skin was not measured. Recovery was 98.8%; the coefficient of variation could be calculated with available data. The authors don't discuss criteria and standards, but provide enough detail in the results to compare with established standards.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	No information on storage and stability was provided. Although TBBPA isn't expected to hydrolyze and volatility is low, there is a possibility that it can degrade via photodegradation quickly and should be stored in the dark.
	Metric 8:	Consistency of exposure administration	Medium	The same volume, skin surface areas and amount of TBBPA were used for both human and rat skin experiments. Skin thickness was reported as 244 +/-25 um; individual cells were not reported.
	Metric 9:	Reporting of concentrations	Medium	Nominal concentrations (point estimates) were reported.
	Metric 10:	Exposure frequency	High	Skin samples were exposed to TBBPA for 24 hrs; washing occurred at the end of this period, and sampling occurred at 6, 12, 18 and 24 hrs. This is acceptable according to OECD TG 428.

Continued on next page . . .

. . . continued from previous page

Study Citation: Knudsen, G. A., Hughes, M. F., Mcintosh, K. L., Sanders, J. M., Birnbaum, L. S. (2015). Estimation of tetrabromobisphenol A (TBBPA) percutaneous uptake in humans using the parallelogram method. Toxicology and Applied Pharmacology 289(2):323-329.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3162048
Unique ID: Rat skin (ex vivo)

Domain	Metric		Rating	Comments
	Metric 11:	Number of exposure groups and concentration spacing	Low	Only one exposure concentration was reported; no information was given on whether it represents realistic exposures. However, the authors state that they "applied the principles of the parallelogram approach to the dermal exposure estimates to estimate a likely level following in vivo human systemic exposures to a relevant dose of dermally applied TBBPA," indicating an intent to use relevant exposure levels.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	Skin from female Wistar Han rats was obtained. Dorsal skin was clipped the day prior to harvest. Skin was excised on the day of shipment and stored at -80 degrees C until use. Skin was thawed on the day of the experiment and dermatomed using Padgett dermatome. The thickness was measured to be 244 +/- 25um. The source was identified. Integrity was not reported because it was not tested prior to use. This study was already downgraded for not testing skin integrity (see Metric 6).
	Metric 13:	Number/Replicates per group	Medium	Rat skin was obtained from 4 donors, and tests were performed in triplicate for a total of 12 data points. OECD 156 recommends using 8 replicates from at least 4 donors.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	Authors appropriately calculated percent absorption (because their experiment reflected the use of a finite dose); however, dosing was below the recommended range for finite dosing. Receptor fluid fractions were collected every 6 hrs until 24 hrs post-dosing; this frequency allowed for the data to be reported graphically. Skin was washed six times with a 1:1 mixture of Joy liquid soap: water, and wash fractions were pooled. Skin washes, chamber washes, weigh boats, receptor fluid collections, 10 tape strips (collected individually), and skin were analyzed for radioactivity by scintillation counting. The techniques and timing of measurements were appropriate and sensitive to the outcomes of interest.
	Metric 15:	Consistency of outcome assessment	High	Details of the 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.
	Metric 16:	Sampling adequacy and sensitivity	Medium	Sampling of the receptor fluid throughout the 24-hr period appeared to be adequate (6, 12, 18, and 24 h). The extraction method was described, and a consistent method was applied to the samples. Radioactivity was determined using scintillation counting with details provided; however, the sensitivity and the limit of detection were not reported.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Low	Tissues batches/lots were not reported (although they came from the same source). Integrity of rat skin was not determined. Inclusion/exclusion of outliers was not described.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	Solubility in the receptor fluid was not reported, but use of 10% fetal bovine solution is expected to help with solubility, and a flow-through method was used, so the fluid was replenished with 0% test substance (rate was 1.8 mL/hr).

Continued on next page . . .

. . . continued from previous page

Study Citation: Knudsen, G. A., Hughes, M. F., Mcintosh, K. L., Sanders, J. M., Birnbaum, L. S. (2015). Estimation of tetrabromobisphenol A (TBBPA) percutaneous uptake in humans using the parallelogram method. Toxicology and Applied Pharmacology 289(2):323-329.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3162048
Unique ID: Rat skin (ex vivo)

Domain	Metric		Rating	Comments
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	High	Statistical methods were clearly described. Cumulative dose in the receptor fluid is shown graphically for each time point. The CVs were 20% for the percentage in receptor fluid, 8% for the percentage in skin, and 3% for unabsorbed (washed and tape stripping). Data enabling an independent statistical analysis were not provided. It is unclear if outliers were accounted for in the analysis.
	Metric 20:	Data interpretation	Low	Recovery was good (98.8%). The authors considered the unabsorbed % to be washes and 10 tape strippings (this is greater than the recommendation of the first 2 strippings). They did not report data for each tape strip; therefore, recalculations cannot be done.
	Metric 21:	Reporting of data	Low	The profile of penetration into the receptor fluid over time was reported graphically (with standard deviations), but only the final time point was reported numerically in a table. Values of the amounts in skin (identified as absorbed), receptor fluid (identified as penetrated) and washings/tape strips (unabsorbed) were reported. Tape strip values were not reported separately, and the total amount (or individual strip amount) that was removed was not reported. Tape stripping information was combined with washings, and thus, absorption couldn't be recalculated. Individual replicate information was also not reported.

Overall Quality Determination Medium

Study Citation: Yu, Y., Li, L., Li, H., Yu, X., Zhang, Y., Wang, Q., Zhou, Z., Gao, D., Ye, H., Lin, B., Ma, R. (2017). In vivo assessment of dermal adhesion, penetration, and bioavailability of tetrabromobisphenol A. Environmental Pollution 228:305-310.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 5490805
Unique ID: Kp

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Low	The test material was identified by name as tetrabromobisphenol A. No CASRN or structure were provided. Based on potential variability in chemical structure, the rating of this metric is low. The test substance was not radiolabeled.
	Metric 2:	Test substance source	Low	The source of the test substance was not reported, nor was the test substance analytically verified by the performing laboratory.
	Metric 3:	Test substance purity	Low	The purity was not reported.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Low	The study does not report how animals were allocated to study groups.
	Metric 5:	Standards for Tests	Low	The study authors did not report whether the test met any pre-established criteria. The study did not measure recovery or report CV values. CVs could be calculated for the unabsorbed amount in washes and tape stripping, and for the percentage of dose in urine, feces and serum (data presented as means +/-SD).
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	Low	Preparation details were reported. The test substance was sieved using a stainless-steel sieve 13.2 cm in diameter. The particles ranged in diameter between 0.1 and 100 um. The test substance was then slightly moistened with normal saline and then applied to the skin. Storage details were not provided; although TBBPA isn't expected to hydrolyze and volatility is low, it can degrade with a range of half-lives as short as 17 minutes. No information was provided to suggest control of possible photodegradation
	Metric 7:	Consistency of exposure administration	High	Details of exposure administration are reported. Moistened test material was applied to a "6x6 cm2 area" on the back; this is presumed to be a 36 cm2 area, and an area of at least 10 cm2 is recommended. The exposure doses ranged from 5.97 to 173.25 mg/animal (males) and 4.59 to 141.91 mg/animal (females). Skin was clipped prior to application. The authors refer to an early study of theirs for preparation and treatments (HERO 3364227), which states skin was clipped 24 hours prior to application. The test substance was sieved using a stainless-steel sieve 13.2 cm in diameter to ensure the particle size of the applied test substance was between 0.1 and 100 μm. Patches remained in place for 6 hrs/day. There is no information provided suggesting major inconsistencies between groups.
	Metric 8:	Reporting of concentrations	Medium	Nominal doses were reported. No analytical measurements were made.
	Metric 9:	Exposure duration	High	The exposure duration was appropriate. The test substance was applied to the skin for 6 hours. The skin was then swabbed 10 times using cotton soaked with a moderate amount of methanol (to maximize recovery). The animals were then placed in metabolic cages where urine and feces were collected for 18 hours.

Continued on next page . . .

. . . continued from previous page

Study Citation: Yu, Y., Li, L., Li, H., Yu, X., Zhang, Y., Wang, Q., Zhou, Z., Gao, D., Ye, H., Lin, B., Ma, R. (2017). In vivo assessment of dermal adhesion, penetration, and bioavailability of tetrabromobisphenol A. Environmental Pollution 228:305-310.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 5490805
Unique ID: Kp

Domain	Metric		Rating	Comments
	Metric 10:	Number of exposure groups and concentration spacing	Low	The study applied 20, 60, 200, or 600 mg/kg/day. Doses and duration of exposure were determined from related literature (IPCS, 1995; EU Risk Assessment Report, 2006). The study also reported a "exposure doses" as mg/animal and an "applied dose" in mg (Table 1) It is unclear why the applied dose (mg) would be different than the mg/animal dose, and in the study text "applied dose" is in mg/animal and matches what is specified as the applied dose (mg) in the table. The "exposure doses" in Table 1 are not further mentioned in any study text.
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	High	The study used male and female Wistar rats obtained from the Academy of Military Medical Science. Age and initial weight were reported.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	High	Husbandry conditions (temperature, humidity, light-dark cycle, diet, water availability) were reported and appropriate.
	Metric 13:	Number of animals per group	Medium	The number of animals/group was appropriate (n=6/sex).
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	The study applied 4.29 to 116.89 mg to a 36 cm2 area of skin for 6 hours. This equates to doses ranging from 0.12 to 3.25 mg/cm2. The authors calculated Kp; the dose applied is below the recommended 10 mg/cm2 (infinite dose) for determining Kp. If the dose is non-depletable over the duration of the 6 hours, it can be used to determine Kp. The authors report and unabsorbed amount of test substance for each dose (amount in washes and tape stripping [number of tape strips not reported]); therefore, the doses appear to be non-depleting. It is unclear if the sites were occluded, which is required for infinite exposures. The sites were covered with medical gauze and tape. After 6 hours of exposure, the skin was swabbed 10 times with cotton-soaked methanol; guidelines recommend using soap and water to wash off the test substance, as it is most applicable to a real-world situation. Skin was tape stripped, but the method of tape stripping was not reported. The amount of test substance in the urine, feces and serum was reported. The skin was not examined for irritation. The amount of test substance in the skin (application site) or in the carcass was not determined. No cage washes were described.
	Metric 15:	Consistency of outcome assessment	High	Outcomes were assessed consistently across study groups.
	Metric 16:	Sampling adequacy and sensitivity	Medium	Samples were analyzed via HPLC-MS/MS mass spectrometer, which is sensitive for measuring the unlabeled test substance. The detection limit for TBBPA was 0.01 ng/g fat, 0.03 ng/mL, and 0.02 ng/g dw in the serum, urine, and feces, respectively. Urine and feces were collected for 18 hours post-exposure; the amount of test substance was determined only in the final collected amount (not at different time points). Serum concentrations were determined at sacrifice (18 hours post-exposure).
Domain 6: Confounding/Variable Control				

Continued on next page . . .

. . . continued from previous page

Study Citation: Yu, Y., Li, L., Li, H., Yu, X., Zhang, Y., Wang, Q., Zhou, Z., Gao, D., Ye, H., Lin, B., Ma, R. (2017). In vivo assessment of dermal adhesion, penetration, and bioavailability of tetrabromobisphenol A. Environmental Pollution 228:305-310.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 5490805
Unique ID: Kp

Domain	Metric		Rating	Comments
	Metric 17:	Confounding variables in test design and procedures	Medium	Initial starting weights were 180+/- 20 grams. The test substance lot/batch number was not reported. Skin irritation or damage was not assessed. There is no indication that there were differences in the area of skin exposed. Although not all information is reported, there is no indication that differences existed among the study groups.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	All animals are accounted for in the results, implying no animals died. The test substance was applied essentially neat (moistened with saline); therefore, solubility issues do not apply. It is unclear if there was any damaged tissue.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Formulas used to calculate Kp were shown. Kp was calculated using the dermal partition coefficient and steady-state flux represented the fraction of TBBPA not bound to albumin. If Kp is measured as a partition coefficient using only the amount applied to the skin and amount in blood, there could be significant inaccuracies in the parameter estimation. Thickness of skin was reported to be 1.657 mm based on "Wang 2013. Transdermal Permeation Behavior Study of Calciportriol Ointment. Master's thesis of Julin University" This reference was unavailable for review. CVs were not reported but could be calculated for the percentage of dose in urine, feces, serum and unabsorbed. For CVs >50%, data was available for EPA to calculate an alternate value to account for variability in results.
	Metric 20:	Data interpretation	Low	It appears the amount of test substance applied was non-depleting as test substance was detected in the wash and tape strips, indicating the exposure scenario was appropriate for Kp determination. Calculations reported in the study were confusing or not well explained. The study reported an "adhesion rate" as a percentage, which is an unexpected unit for something described as a rate. To calculate adhesion coefficients, the study used the "exposure dose", which is not further mentioned or explained in the text, rather than the "applied dose."
	Metric 21:	Reporting of Data	Uninformative	The study reports data for percentage of the applied dose excreted in the urine, feces and serum, and for the amount of unabsorbed dose (washes and tape stripping) with means and SD. The authors report a Kp for TTBPA, but do not report which dose group was used for the calculation.

Overall Quality Determination — Uninformative

Study Citation: Yu, Y., Xiang, M., Gao, D., Ye, H., Wang, Q., Zhang, Y., Li, L., Li, H. (2018). Assimilation, distribution and toxicity of tetrabromobisphenol A to female Wistar rats through subchronic dermal exposure. International Biodeterioration & Biodegradation 128:171-176.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 5636895
Unique ID: 90-day exposure

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Low	The test material was identified by name as tetrabromobisphenol A (TBBPA). No CASRN or structure were provided. Based on the potential variability in chemical structure, this metric is rated low.
	Metric 2:	Test substance source	Low	The source of the test substance (Tokyo Chemical Industry, Shanghai, China) was reported. A batch/lot number was not provided. The chemical identity was not verified by the performing laboratory and the website of the source was not found.
	Metric 3:	Test substance purity	High	The purity was reported to be >98%.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Medium	Animals were randomly assigned to groups; the method was not reported.
	Metric 5:	Standards for Tests	Low	No criteria were stated in the study. The study did not measure recovery or report CV values. Concentrations of test substance in the urine and feces over the course of the study were reported graphically with SD; CVs could be calculated for these values. CVs could also be calculated for the amount of test substance in the serum, urine and feces on day 90.
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	Low	Details of test substance preparation were adequate. The test substance was ground to a median diameter of 30 μm for better homogenization and absorption, then was "slightly moistened with physiological saline and applied". Storage details were not provided; although TBBPA isn't expected to hydrolyze and volatility is low, it can degrade with a range of half-lives as short as 17 minutes. No information was provided to suggest control of possible photodegradation.
	Metric 7:	Consistency of exposure administration	High	Based on the information provided, exposures were consistent across groups. Moistened test material was applied to a "6x6 cm2 area" on the back of the animals. This is presumed to be a 36 cm2 area, which is ~10% of the surface area of animals with the reported body weight. Skin was clipped 24 hours prior to application and clipped when required throughout the study (90 days). The test substance remained on the skin for 6 hrs/day. A vehicle control group received treatment in the same manner with normal saline only. Another control group was only shaved.
	Metric 8:	Reporting of concentrations	Medium	Nominal doses were reported. No analytical measurements were made.
	Metric 9:	Exposure duration	Uninformative	Animals were exposed for 6 hours/day for 90 days. Feces and urine were collected at 0 and 24 hours, and then every 10 days during the 90-day experiment. The 90-day exposure was not typical for dermal absorption studies.
	Metric 10:	Number of exposure groups and concentration spacing	High	The study applied 0, 20, 60, 100, or 600 mg/kg/day. Doses were selected based on experiment animal strains, the half lethal dose (LD50) of TBBPA, duration of exposure and related literature (IPCS, 1995; EU Risk Assessment Report, 2006).

Continued on next page . . .

. . . continued from previous page

Study Citation: Yu, Y., Xiang, M., Gao, D., Ye, H., Wang, Q., Zhang, Y., Li, L., Li, H. (2018). Assimilation, distribution and toxicity of tetrabromobisphenol A to female Wistar rats through subchronic dermal exposure. International Biodeterioration & Biodegradation 128:171-176.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 5636895
Unique ID: 90-day exposure

Domain	Metric		Rating	Comments
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	High	The study used female Wistar rats obtained from Academy of Military Medical Science. Age and initial weight were reported.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	High	Husbandry conditions (temperature, humidity, light-dark cycle, diet, water availability) were reported and appropriate.
	Metric 13:	Number of animals per group	Medium	The number of animals/group was appropriate (n=6).
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Uninformative	Outcome assessment was not appropriate. Urine and feces were collected at 0 and 24 hours and then every 10 days for the 90-day exposure; blood was collected at the time of sacrifice (after 90 days of exposure). Metric guidelines state "if experiments continue beyond 1 day, measurements should be made daily in order to evaluate all excreta and tissues". Skin or carcass was not evaluated. Skin was not examined for signs of irritation or damage. The body weights of the animals were not reported; therefore, the dose in mg/cm2 could not be determined, except for day 90, where the dose is reported as mg/animal. For day 90, the study reports percentage of the test substance in the urine, blood and feces based on the 90-day dose. This is not appropriate since animals were receiving daily applications, and the test substance likely accumulated in the body.
	Metric 15:	Consistency of outcome assessment	High	Outcomes were assessed consistently across study groups.
	Metric 16:	Sampling adequacy and sensitivity	Uninformative	Samples were analyzed via HPLC-MS/MS mass spectrometer. The sampling interval for urine and feces (0 and 24 hours and then every 10 days) was not appropriate to determine absorption.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Initial starting weights were 180+/- 20 grams. The test substance lot/batch number was not reported. Skin irritation or damage was not reported. There is no indication that there were differences in the area of skin exposed. Although not all information is reported, there is no indication that differences existed among the study groups.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	Clinical observations were made daily; however, the study did not report these findings (positive or negative). All animals are accounted for in the results, implying no animals died. The test substance was applied essentially neat (moistened with saline); therefore, solubility issues do not apply. It is unclear if there was any damaged tissue.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Uninformative	The study reported concentration of test substance in the urine and feces over the 90-day exposure graphically and amount in the blood, urine and feces at the end of the experiment (Table 2). The study reports amount of test substance in the blood, urine and feces at 90-days and converts it to a percentage of dose based on what was applied to the animal on day 90. This is not appropriate as the test substance may have accumulated in the body over the 90 days. CVs were not reported but could be calculated for these data.

Continued on next page . . .

...continued from previous page

Study Citation: Yu, Y., Xiang, M., Gao, D., Ye, H., Wang, Q., Zhang, Y., Li, L., Li, H. (2018). Assimilation, distribution and toxicity of tetrabromobisphenol A to female Wistar rats through subchronic dermal exposure. International Biodeterioration & Biodegradation 128:171-176.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 5636895
Unique ID: 90-day exposure

Domain	Metric		Rating	Comments
	Metric 20:	Data interpretation	Uninformative	The study design did not align with standard OECD guidelines for determining dermal absorption. Due to the differences (90-day exposure; urine and feces collected every 10 days) dermal absorption cannot be accurately determined. The study did not report the amount of test substance in the skin. The study did not report % recovery.
	Metric 21:	Reporting of Data	High	Data were presented for the outcomes assessed (graphically or in a table). Means were reported with measures of variance.

Overall Quality Determination Uninformative

Study Citation: Yu, Y., Xiang, M., Gao, D., Ye, H.,ao, Wang, Q., Zhang, Y., Li, L., Li, H.,ui (2016). Absorption and excretion of Tetrabromobisphenol A in male Wistar rats following subchronic dermal exposure. Chemosphere 146:189-194.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3364227
Unique ID: TBBPA

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Low	The test material was identified by name as tetrabromobisphenol A. No CASRN or structure were provided. Based on potential variability in chemical structure, the rating or this metric is low.
	Metric 2:	Test substance source	Low	The source of the test substance was not reported nor was the test substance analytically verified by the performing laboratory.
	Metric 3:	Test substance purity	Low	The purity was not reported.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Medium	Animals were randomly assigned to groups; method not reported.
	Metric 5:	Standards for Tests	Low	No criteria were stated in the study. The study did not measure recovery. CV can be calculated using reported data for day 90; for other days, data would need to be extracted from graphs.
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	Low	Details of test substance preparation are limited. Test substance was "slightly moistened with physiological saline and applied". Storage details were not provided; although TBBPA isn't expected to hydrolyze and volatility is low, it can degrade with a range of half-lives as short as 17 minutes. No information was provided to suggest control of possible photodegradation.
	Metric 7:	Consistency of exposure administration	High	Details of exposure administration are reported. Moistened test material was applied to a "6x6 cm2 area" on the back; this is presumed to be a 36 cm2 area, and an area of at least 10 cm2 is recommended. The doses applied ranged from 20-600 mg/kg/day. Skin was clipped 24 hours prior to application and clipped when required throughout the study (90 days). Patches remained in place for 6 hrs/day. The study included a vehicle (saline) control group that was treated in the same manner as the test groups. A sham control (animals shaved, but otherwise not exposed) group was also included. There is no information provided suggesting major inconsistencies between groups.
	Metric 8:	Reporting of concentrations	Medium	Nominal doses were reported. No analytical measurements were made.
	Metric 9:	Exposure duration	Uninformative	Animals were exposed for 6 hours/day for 90 days. Feces and urine were collected at 0 and 24 hours, and then every 10 days during the 90-day experiment. Blood was collected at the end of the 90-day exposure. A 90-day exposure is not typical for dermal absorption studies. Metric guidelines state, "if experiments continue beyond 1 day, measurements should be made daily."
	Metric 10:	Number of exposure groups and concentration spacing	High	The study applied 0, 20, 60, 100, or 600 mg/kg/day. Doses were selected based on experiment animal strains, the half lethal dose (LD50) of TBBPA, duration of exposure and related literature (IPCS, 1995; EU Risk Assessment Report, 2006).

Continued on next page . . .

. . . continued from previous page

Study Citation: Yu, Y., Xiang, M., Gao, D., Ye, H.,ao, Wang, Q., Zhang, Y., Li, L., Li, H.,ui (2016). Absorption and excretion of Tetrabromobisphenol A in male Wistar rats following subchronic dermal exposure. Chemosphere 146:189-194.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3364227
Unique ID: TBBPA

Domain	Metric		Rating	Comments
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	High	The study used male Wistar rats obtained from Academy of Military Medical Science. Age and initial weight were reported.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	High	Husbandry conditions (temperature, humidity, light-dark cycle, diet, water availability) were reported and appropriate.
	Metric 13:	Number of animals per group	Medium	The number of animals/group was appropriate (n=6).
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Uninformative	Outcome assessment was not appropriate. Urine and feces were collected at 0 and 24 hours and then every 10 days for the 90-day exposure; blood was collected at the time of sacrifice (after 90 days of exposure). Skin or carcass was not evaluated. Skin was not examined for signs of irritation or damage. The body weights of the animals were not reported; therefore, the dose in mg/cm2 could not be determined, except for day 90 where the dose is reported as mg/animal. For day 90, the study reports the percentage of the test substance in the urine, blood and feces based on the 90-day dose. This is not appropriate since animals were receiving daily applications and the test substance likely accumulated in the body. Also, if irritation or damage occurred at the application site, absorption may have been affected.
	Metric 15:	Consistency of outcome assessment	High	Outcomes were assessed consistently across study groups.
	Metric 16:	Sampling adequacy and sensitivity	Uninformative	Samples were analyzed via HPLC-MS/MS mass spectrometer. The sampling interval for urine and feces (0, 24 hours and then every 10 days) was not appropriate to determine absorption.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Initial starting weights were 180+/- 20 grams. The test substance lot/batch number was not reported. Skin irritation or damage was not assessed. There is no indication that there were differences in the area of skin exposed. Although not all information is reported, there is no indication that differences existed among the study groups.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	Clinical observations were made daily; however, the study did not report these findings. All animals are accounted for in the results, implying no animals died. The test substance was applied essentially neat (moistened with saline); therefore, solubility issues do not apply. It is unclear if there was any damaged tissue.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Uninformative	The study reported the concentration of the test substance in the urine and feces over the 90-day exposure graphically and the amount in the blood, urine and feces at the end of the experiment (Table 2). The study reports the amount of test substance in the blood, urine and feces at 90 days and converts it to a percentage of dose based on what was applied to the animal on day 90. This is not appropriate as the test substance may have accumulated in the body over the 90 days.

Continued on next page . . .

. . . continued from previous page

Study Citation: Yu, Y., Xiang, M., Gao, D., Ye, H.,ao, Wang, Q., Zhang, Y., Li, L., Li, H.,ui (2016). Absorption and excretion of Tetrabromobisphenol A in male Wistar rats following subchronic dermal exposure. Chemosphere 146:189-194.
Chemical: TBBPA
Exposure Type: Parent compound
HERO ID: 3364227
Unique ID: TBBPA

Domain	Metric		Rating	Comments
	Metric 20:	Data interpretation	Uninformative	The study design did not align with standard OECD guidelines for determining dermal absorption. Due to the differences (90-day exposure; urine and feces collected every 10 days) dermal absorption cannot be accurately determined. The study did not report % recovery.
	Metric 21:	Reporting of Data	Medium	Data were presented for most of the outcomes assessed (graphically or in a table). Means were reported with measures of variance for the 90-day data; other data points could be extracted from graphically presented data. Clinical signs were not reported.

Overall Quality Determination Uninformative