June 06, 2025

Docket: EPA-HQ-OPPT-2018-0426.

The following document associated with the 1,1-Dichloroethane (CASRN 75-34-3) Test Order for *in vitro* Dermal Absorption data is included in this PDF in support of the Risk Evaluation for 1,1-Dichloroethane:

1. 1,1-Dichloroethane Dermal Absorption Study Analysis

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Following is an EPA analysis of the Vinyl Institute submission for the 1,1-dichloroethane *in vitro* dermal absorption final study report and supplements the *Risk Evaluation for 1,1-Dichloroethane – Supplemental Information: in vitro Dermal Absorption Study Calculation Sheet* (U.S. EPA, 2025).

A Test Order for an *in vitro* dermal absorption study was issued and conducted for 1,1-dichloroethane and data received (Labcorp Early Development, 2024). The Test Order instructed to follow guideline OECD 428 (2004) and referenced OECD GD28 (2004) and OECD GD156 (2022), The EU EFSA dermal guidance compliance was not required. The guideline study utilized human skin which is typically obtained from cosmetic surgery. The testing was composed of skin from 92 percent female and 8 percent male samples, which does not represent the workforce nor general population demographics. It is unknown whether the test samples represented minorities, people with skin diseases or other susceptibilities identified in the 1,1-dichloroethane risk evaluation. The dermal absorption of 0.3 percent is used to estimate dermal exposure and is derived from this Test Order study data as described in the following paragraphs with standard OECD analysis approaches applied to account for data uncertainty and susceptible groups.

The main substances for worker exposures are neat 1,1-dichloroethane and 50 percent 1,1-dichloroethane in 1,2-dichloroethane as the vehicle, with raw dermal absorption values ranging from 0.08 to 0.21 percent and 0.04 to 0.27 percent, respectively. The raw mean absorption values were 0.13 percent and 0.12 percent, respectively. These two substances as worker conditions of use (COU) had mass balance recoveries of 54 to 58 percent, which is below the OECD threshold of 80 percent for volatile substances. The data supports that there was simultaneous dermal absorption and evaporation of the 1,1-dichloroethane since there was a strong signal in both the receptor chamber and the vapor trap. We do not know to where the missing mass partitioned. To be human health protective, EPA did not assume that the missing mass is not absorbable, nor was it assumed that all of the missing mass simply evaporated. Instead it was assumed that part of the missing mass is potentially absorbable. If the 1,1-dichloroethane merely evaporated, then it should have been quantified in the vapor trap – which the study did not report.

Section 108 in the recent OECD Guidance Document 156 (OECD GD156, 2022) recommends several approaches to correct the data for missing mass, rather than declaring the study as unacceptable:

1) "One approach would be to normalise the measured dermal absorption value [for losses]. This approach assumes that losses occurred in all matrices equally."
2) "A second approach would be to include all the unrecovered material in the amount that is potentially absorbed."
3) "A third approach would be to exclude the replicates with low recoveries and only the replicates with high recovery should be used to derive the absorption. However, as exclusion reduces the overall number of replicates, a balance must be found between uncertainty resulting from low recoveries vs. uncertainty from a lower number of acceptable replicates."

Approach 1 was chosen by EPA as the most relevant means of data normalization for missing mass. This approach is a data-derived method where only a portion of the missing mass is potentially absorbed and the corrected absorption is calculated from the known magnitude of absorption and the known ratio of mass recovered. The equation for Mass Corrected Percent Absorption is presented in Equation 1, where the % absorption for the missing mass is equal to the measured % absorption of the known mass.

Equation 1

$$Mass\ Corrected\ Percent\ Absorption = \%\ Absorption \div (\%\ Mass\ Balance \div 100)$$

The highest dermal absorption value reported in the study was 0.27 percent at 50 percent 1,1-dichloroethane in 1,2-dichloroethane as the vehicle with a mass balance corrected value of 0.59 percent absorption. This replicate also had one of the lowest mass recoveries of 46 percent, thus the guideline study indicates that there is simultaneously dermal absorption and evaporation processes occurring. Thus, this data would underestimate the dermal absorption for 'under the glove' scenarios where evaporation is reduced and absorption is increased. The mean absorption for neat and 50 percent 1,1-dichloroethane ranged from 0.12 percent to 0.22 percent for the raw and mass corrected values, respectively.

For the main worker COUs of neat and 50 percent 1,1-dichloroethane, all of the replicate recoveries were below the 80 percent OECD threshold and exclusion of replicates as outlined in Approach 3 would have made little difference in the overall results, and the reduced data confidence due to decreased numbers of replicates also did not warrant selecting Approach 3. Approach 2 is a very conservative path for risk assessment as it would imply over 40 percent dermal absorption. Given this level of potential absorption deviating significantly from the test data, EPA did not choose Approach 2 and as described above, instead chose Approach 1, normalizing the data.

The dermal absorption data coefficient of variation (%CV) was 38 to 200 percent and the %CV for the dermal permeability Kp values were 31 to 82 percent (see Table 1). All of the results had high variability that exceeds OECD recommendations for an upper limit of 25 percent. For addressing high data variability OECD GD156 states in Section 110: "…if variation between replicates for an in vivo study is not considered adequate (e.g. the standard deviation is equal to or greater than 25% of the mean), then a value other than the mean or possibly rejecting the study entirely may be considered." And in section 111 the Guidelines state, "The use of the upper confidence limit (95% confidence interval) addresses uncertainty about mean absorption due to sampling variability. This approach is reasonably conservative and could reduce the need to repeat studies."

In general, EPA exposure assessments regularly report the 95th percentile exposures to be human health protective and specifically to include subpopulations that are potentially highly exposed or more susceptible to the hazards of 1,1-dichloroethane (PESS). In the case of 1,1-dichloroethane, workers have been identified as a population more likely than other subpopulations to be highly exposed, given the potential for exposures to neat 1,1-dichloroethane in the workplace. The 95 percent UCL is simply the raw mean value + Excel T Test Confidence Interval (named CONFIDENCE.T in Excel). The inputs to this Excel function are alpha=0.05, standard deviation and N number of replicates. The raw data was corrected according to OECD GD156 guidance for high data variability. For a worker COU, the mass balance corrected mean absorption for neat 1,1-dichloroethane was 0.22 percent and the 95 percent upper confidence limit was 0.31 percent dermal absorption, or similar to the mean dermal absorption reported for the close analog 1,2-dichloroethane at 0.21 percent absorption. The highest mass-balance corrected absorption based on a 95 percent UCL value was 0.39 percent absorption for 50 percent 1,1-dichloroethane in the 1,2-dichloroethane vehicle. In the case of the 1,1-dichloroethane OECD 428 study cohorts at various experimental conditions where the mass recovery was over 80 percent, the 95 percent UCL absorption values ranged from 0.03 to 0.12 percent. However, OECD 428 states: "The test substance preparation (e.g., neat, diluted or formulated material containing the test substance which is applied to the skin) should be the same (or a realistic surrogate) as that to which humans or other potential target species may be exposed." Thus, the absorption data in the isopropylmyristate (IPM) vehicle and absorptions of 1,1-dichloroethane at concentrations of 1 percent and 10 percent are not

relevant to TSCA uses in the risk evaluation. By Fick's Law, higher chemical concentrations tend to increase dermal permeability, which is reflected by the higher dermal absorption values for neat 1,1-dichloroethane and 50 percent 1,1-dichloroethane in 1,2-dichloroethane conditions of use data. Therefore, only the dermal absorption values for the neat 1,1-dichloroethane and 50 percent 1,1-dichloroethane in 1,2-dichloroethane TSCA conditions of use absorption values should be used for risk calculations. Overall, an intermediate dermal absorption value of 0.3 percent was selected for the risk evaluation. The mean K_p value and the 95 percent upper confidence limit for neat 1,1-dichloroethane were 0.00229 and 0.00371 cm/hour, respectively.

EPA also compared the 1,1-dichloroethane dermal absorption estimate of 0.3 percent with that of its isomer, 1,2-dichloroethane. 1,2-dichloroethane has an identical molecular weight and a very similar log Kow value as 1,1-dichloroethane, key parameters for EPA dermal modeling. The reported *in vitro* mean K_p value for the analog 1,2-dichloroethane was similar to 1,1-dichloroethane at 0.00109 cm/hour for the neat chemical (Schenk et al., 2018) and the estimated fraction absorbed was also similar at 0.6 percent using default settings for the American Industrial Hygiene Association (AIHA) skin permeation model, IHSkinPerm (https://www.aiha.org/public-resources/consumer-resources/apps-and-tools-resource-center/aiha-risk-assessment-tools/ihskinperm).

Table 1. 1,1-Dichloroethane Percent Dermal Absorption Results

Sample	Low Value	High Value	Mean Value	% CV	% Mass Balance
1% 1,1-Dichloroethane in IPM Vehicle	ND	0.101	0.02	200.0	88.87
10% 1,1-Dichloroethane in IPM Vehicle	ND	0.015	<0.01	100.0	87.68
50% 1,1-Dichloroethane in IPM Vehicle	0.003	0.09	0.06	66.7	87.66
1% 1,1-Dichloroethane in 1,2-ichloroethane Vehicle	ND	0.135	0.05	120.0	55.42
10%1,1-Dichloroethane in 1,2-ichloroethane Vehicle	ND	0.045	0.02	100.0	92.76
50% 1,1-Dichloroethane in 1,2-ichloroethane Vehicle	0.044	0.267	0.12	75.0	54.36
Neat, 100% 1,1-Dichloroethane	0.080	0.212	0.13	38.5	58.42

ND: Not Detected
Red text indicates values outside the recommended range.

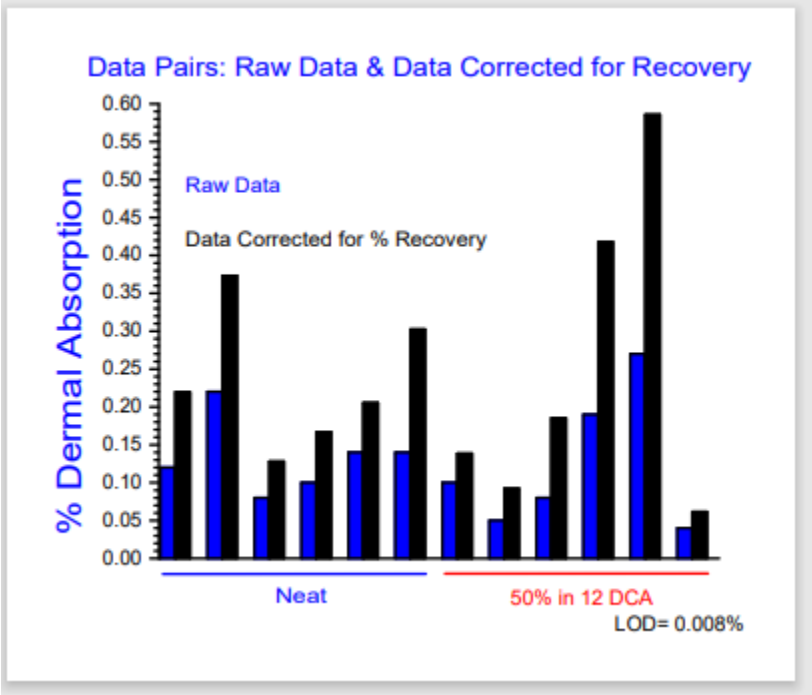

Figure 1. 1,1-Dichloroethane Dermal Absorption Data: Raw Data and Data Corrected for Recovery

REFERENCES

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