SYSTEMIC TESTING BY THE DERMAL ROUTE CAN BE PRECLUDED BY *IN VITRO* OR *IN SILICO* PERCUTANEOUS ABSORPTION STRATEGIES

Kristie Stoick,[1] Kenneth Nitschke,[2] and Chad Sandusky[1]

[1]Physicians Committee for Responsible Medicine, Washington, DC, USA and [2]Dow Chemical Company, Midland, MI, USA

SUMMARY

New *in silico* and *in vitro* methods for predicting percutaneous absorption make it possible to avoid *in vivo* testing for this endpoint. If there is concern for exposure by the dermal route but chemicals have little or no dermal penetration potential, systemic toxicity tests can also be avoided. In collaboration with Dow Chemical Company, we set out to test the practicality of this concept, using the mixture Commercial Hydroxyethyl Piperazine (CHEP) (1,4-piperazinediethanol, piperazine, hydroxyethylpiperazine, and water), sponsored in the USEPA High Production Volume chemical challenge. Dow had originally proposed a guideline dermal combined reproductive /developmental toxicity test.

Here we present data generated using the QSAR model EPA DERMWIN™. To evaluate the applicability of the model, experimental and modeled absorption data for 10 amines were compared; the ratio of experimental to modeled data was of acceptable concordance and the absorption of CHEP was modeled. The components were predicted to minimally absorb through the skin, with estimated average total absorption at 1.99 mg/kg/day. When considered together with other factors, this estimation supported the conclusion not to conduct a dermal reproductive and developmental toxicity study as originally proposed. This approach can be used to protect public and worker health while avoiding resource- and animal-intensive tests.

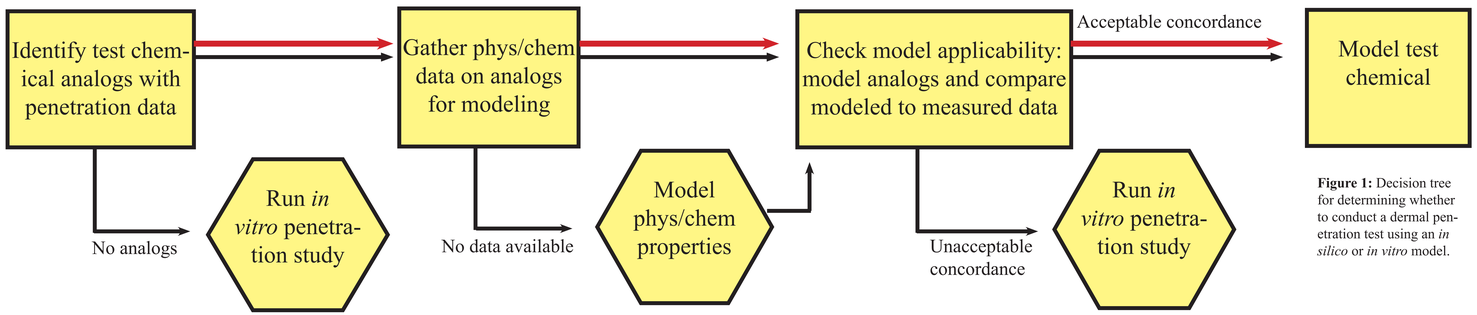
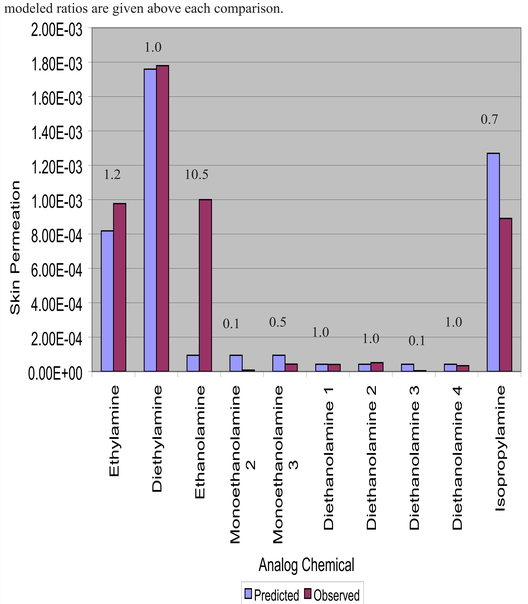


Figure 1: Decision tree for determining whether to conduct a dermal penetration test using an *in silico* or *in vitro* model.

Figure 2: Modeled and measured skin permeation values (cm/hr) for 10 analogous chemicals. Observed/modeled ratios are given above each comparison.



Values from: Patel and Cronin 2001, CEFIC-LRI project number NMALRI-A22UNJM-0007; Brain et al. 2005, Food Chemical Toxicology, 43, 681-690; Sun et al. 1996, Journal of Toxicology: Cutaneous and Ocular Toxicology, 15, 131-146.

METHODS

The experimental process is shown in Figure 1, with our path in red.

A satisfactory concordance (Fig 2) justified modeling the PA of the CHEP components, and this was performed accordingly. The dermal penetration coefficient for each component was then used to calculate the estimated dermal uptake using this equation: dermal uptake (mg) = Kp (cm/hr)*conc (mg/cc)*contact time (hr)*contact area (cm2). Results for each component are shown in Table 1.

*DERMWIN™ was developed by the USEPA and Syracuse Research Corporation and is available publicly as part of the EPISuite suite of programs (http://www.epa.gov/oppt/).

Table 1: Data input and results for DERMWIN™ model. Total body exposure is 1.99 mg/kg/day with a 15 minute contact time.

	Piperazine		Hydroxyethylpiperazine		Dihydroxyethylpiperazine		
INPUT PARAMETER	HAND	WHOLE BODY	HAND	WHOLE BODY	HAND	WHOLE BODY	Unit
Contact surface area	420	16900	420	16900	420	16900	cm^2
Skin permeability coefficient	0.000	0.000	0.000	0.000	0.000	0.000	cm/hr
Contact time	0.25	0.25	0.25	0.25	0.25	0.25	hr
Residue conc. in product	220	220	517	517	275	275	mg/cc
Dermal uptake	1.70E+3	7.00E+4	1.30E+3	5.20E+4	2.10E+2	8.30E+3	ug/event
Contact events per day	1	1	1	1	1	1	#/day
Total uptake	1728	69527	1297	52205	206	8296	ug/day
Mean body weight	65.4	65.4	65.4	65.4	65.4	65.4	kg
Average daily dose	0.03	1.06	0.02	0.8	0	0.13	mg/kg/day

RESULTS/CONCLUSIONS

- Results of the analogous chemical comparisons are shown in Fig. 2. The EPA DERMWIN™ model accurately predicted a chemical's penetration coefficient in humans in 7/10 cases, over-predicted 2/10, and under-predicted 1/10. Observed/modeled ratios ranged from 0.10 to 10.5 (mean 1.71).

- Modeled penetration for the three chemical CHEP components (water was not modeled) is shown in Table 1. Total estimated absorption of CHEP, with a 15 min whole body exposure, would be ~2 mg/kg/day.

- A complete Screening Information Data Set exists for piperazine, the component predicted to have the highest absorbed dose (1.06 mg/kg/day). In addition, CHEP is produced and consumed within a closed system and workers use personal protective equipment.

With the acceptance and continued use of *in vitro* and *in silico* approaches to measure percutaneous absorption, investigators and regulators should consider whether prerequisite PA testing can fit into a weight-of-evidence consideration to avoid dermal systemic testing, including for acute, sensitizing, subchronic, and chronic endpoints when evaluating restricted-use chemicals or in screening-level programs, priority-setting, risk assessment, and other analogous situations.