Safety & Environmental Assurance Centre

Refinement of Physiologically-Based Kinetic (PBK) Models of Skin Absorption using Surrogate Partition Coefficient Data.

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Introduction

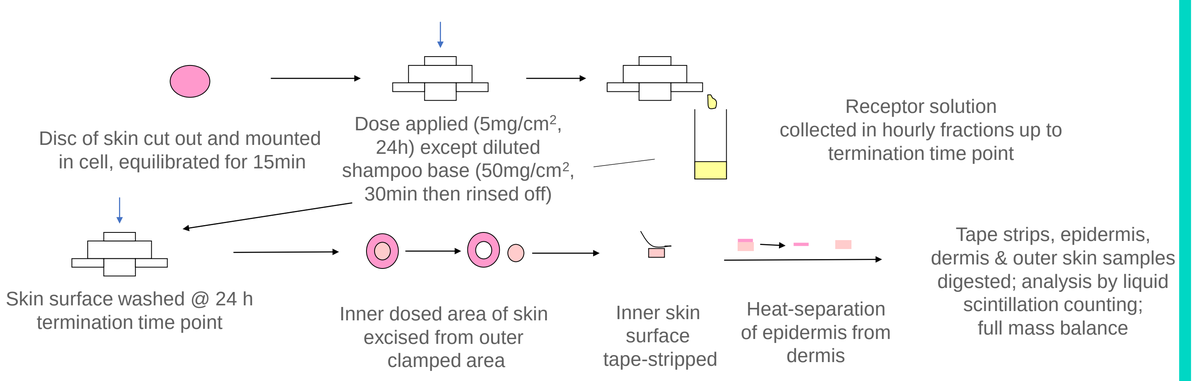
Assessment of systemic exposure to topically applied personal care product ingredients relies on accurate determination of the extent of ingredient absorption into the skin. Ex vivo skin absorption studies designed to mimic the in-use situation (e.g. OECD 428[1], SCCS Notes of Guidance[2]) , provide a reliable estimate of skin absorption. The first step of skin absorption is partitioning of the ingredient out of the vehicle applied and into the stratum corneum and the ease with which this happens is dependent on the physical/chemical properties of both the ingredient and the vehicle. A cosmetic ingredient may be used in a wide range of product types and running an ex vivo skin absorption experiment for every type of vehicle is not practical.

Physiologically-based kinetic modelling (PBK) tools such as the Simulations Plus Inc Transdermal Compartmental Absorption and Transit (TCAT™) module can be used to predict the uptake of a chemical by the skin. The method uses a default vehicle/water partition coefficient; the aim of this work was to refine the TCAT™ module modelling by measuring partition coefficients using the non-biological membrane polydimethylsiloxane (PDMS) to calculate specific vehicle/water partition coefficients for three chemicals in a range of formulations.

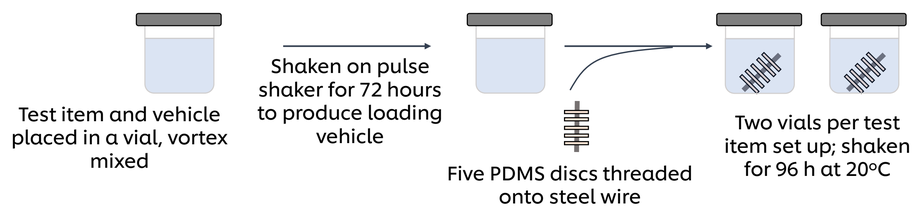
Test Items & Formulations

[1-Methyl-^{14}C]caffeine, [3-^{14}C]Coumarin, 4-Hexyl[U-^{14}C]resorcinol carrier diluted and prepared in each vehicle (Water; 10% v/v Ethanol (aq); 25% v/v Ethanol (aq); 80% v/v Ethanol (aq); Ethanol; Olive Oil; Shampoo base; Vaseline Intensive Care Lotion) at a final concentration of 0.5% (w/w). For the skin absorption study, the shampoo test preparations were diluted ten-fold with water prior to application to the skin. PDMS sheets (1 mm thickness) were obtained from Goodfellow, Cambridge.

Data Generation – Skin Absorption



Data Generation – Partition Coefficient



At t = 96 h:

- Each wire plus discs removed from vehicle/formulation, dipped in ultrapure water, discs removed from wire, wiped with lint-free cloth, weighed and immersed in scintillation cocktail for 24 hours.
- 5 Aliquots of loading solution from each vial taken
- All samples analysed by liquid scintillation counting

$$Partition\ coefficient = \frac{Concentration\ of\ test\ item\ in\ PDMS\ disc}{Concentration\ of\ test\ item\ in\ the\ vehicle}$$

PBK parameters/methods

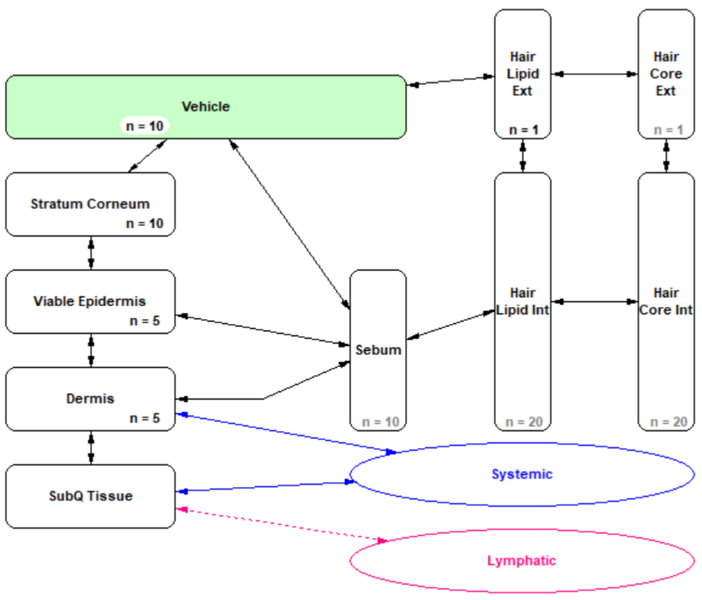
PBK modelling and simulations for dermal absorption were conducted using GastroPlus 9.8 (Simulation Plus, Lancaster, CA, USA) TCATTM module (see schematic below). Human-In Vitro Abdomen was chosen as the dermal physiology.

Inputs:

- Formulation - vehicle/water partitioning, diffusivity, solubility, evaporation;
- Interaction with Skin - partitioning and diffusivity in SC, VE and D;
- Dosing - ex vivo skin penetration scenario.

Vehicle-water partition coefficient parameterised as the default value (1 in TCAT) or derived from PDMS data for comparison, where:

$$PC_{vehicle:\ water} = PC_{vehicle:\ PDMS} / PC_{water:\ PDMS}$$



Schematic diagram of the TCAT module in GastroPlus showing how the different compartments are connected to one another and the rest of the body

Results

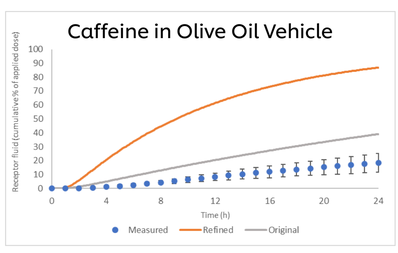
Table 1. PDMS/Vehicle and Vehicle/Water partition coefficients

Test Item	Solvent	PDMS/Solvent partition ratio	VH/Water Partition coefficient
Coumarin	Water	1.9	1
Coumarin	10% Ethanol	1.6	1.20
Coumarin	25% Ethanol	0.7	2.68
Coumarin	80% Ethanol	0.1	35.1
Coumarin	Ethanol	0.1	21.3
Coumarin	Olive Oil	0.2	11.3
Coumarin	10% shampoo	1.9	0.98
Coumarin	Body Lotion	1.0	1.92
Caffeine	Water	0.08	1
Caffeine	10% Ethanol	0.06	1.27
Caffeine	25% Ethanol	0.03	2.44
Caffeine	80% Ethanol	0.01	8.55
Caffeine	Ethanol	0.06	1.19
Caffeine	Olive Oil	0.37	0.20
Caffeine	10% shampoo	0.09	0.85
Caffeine	Body Lotion	0.04	1.94
4HR	Water	3.33	1
4HR	10% Ethanol	2.67	1.25
4HR	25% Ethanol	0.29	11.7
4HR	80% Ethanol	0.01	539
4HR	Ethanol	0.02	144
4HR	Olive Oil	0.02	183
4HR	10% shampoo	0.09	39.2
4HR	Body Lotion	0.02	136

Table 2. Qualitative assessment of success of using VH/Water PC to refine PBK predictions

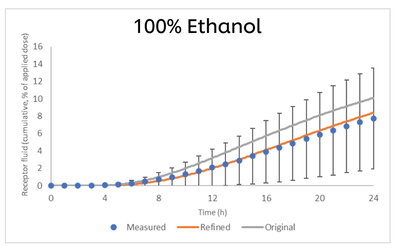
	Accuracy of PBK prediction					
	Coumarin		Caffeine		4-Hexylresorcinol	
	Original	Refined	Original	Refined	Original	Refined
Ethanol	-	++	+	+	++	+++
80% Ethanol	-	+	-	++	+	++
25% Ethanol	++	++	-	+	+	+
10% Ethanol	+	+	-	-	+	+
Olive Oil	-	+++	+	-	-	++
Shampoo	+	+	-	-	-	+++
Body Lotion	++	+++	-	-	-	+++

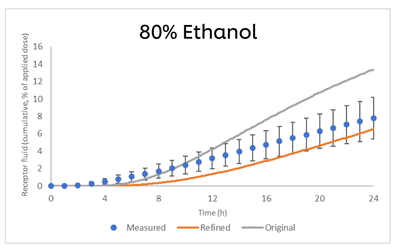
+++ prediction accurate; ++ prediction fair; + similar shape of curve; - prediction poor

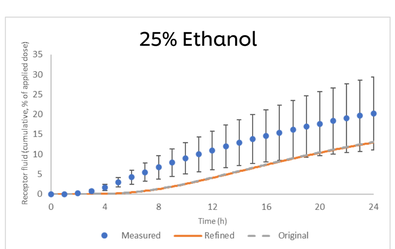


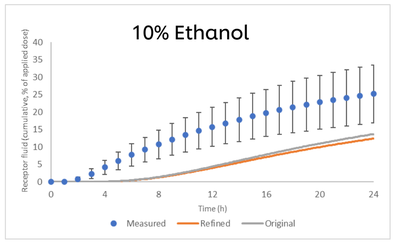
Results – 4-Hexylresorcinol in each vehicle

Ethanol-Water Vehicle

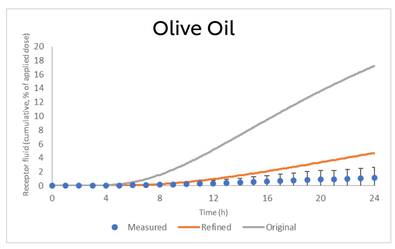


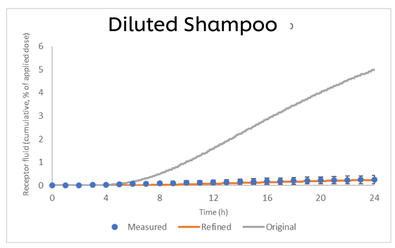


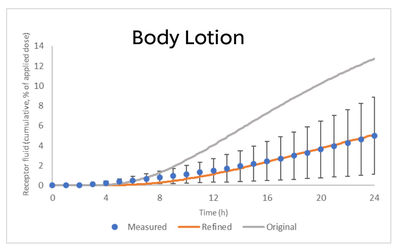




Other Vehicles







Left) Time course data for Ethanol-Water vehicle. Water/Ethanol ratio increasing from top to bottom
Right) Time course results for other Vehicles.

Key: measured = results of the skin absorption study; original = PBK uses the TCAT default of 1; refined = PBK uses VH/water partition coefficient derived from PDMS study data

Physical/chemical parameters

Test Item	MW (g/mol)	Log P	Sw (mg/L)
Caffeine	194.19	-0.07	21600[a]
Coumarin	146.14	1.39	1900[b]
4-Hexylresorcinol	194.27	3.45	500[c]

Data from US National Library of Medicine ChemIDPlus;
Log P and water solubility are experimental values.
[a] Measured at 25°C; [b] Measured at 20°C; [c] Measured at 18°C

Results and Conclusions

The vehicle water partition coefficient calculated from the PDMS data ranged from 0.08 (caffeine – water) to 539 (4-hexylresorcinol – 80% ethanol). Using the calculated vehicle/water partition coefficients in general improved predictions for coumarin and 4-HR, but had little effect on those for caffeine, with one instance where the prediction became less accurate (caffeine – olive oil). Early findings indicate the method is more effective for hydrophobic test items compared to hydrophilic ones.

Preliminary results suggest that the method offers a promising new approach to parameterisation of PBPK models for skin absorption studies for hydrophobic chemicals.

1. OECD (2004). Test Guideline 428: Skin absorption: In Vitro Method. OECD, Paris.
2. SCCS (Scientific Committee on Consumer Safety), SCCS/1358/10, Basic criteria for the in vitro assessment of dermal absorption of cosmetic ingredients, 22 June 2010

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