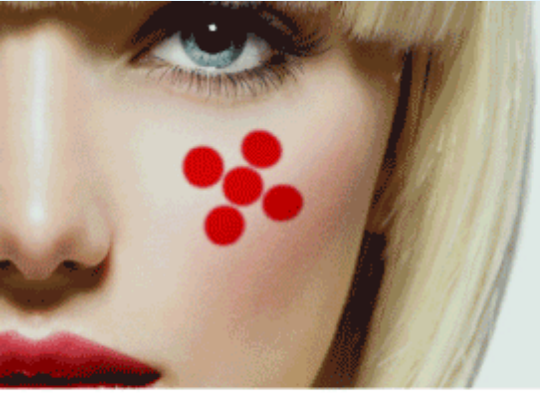

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Occupational and Environmental Exposure of the Skin to Chemicals
19 to 21 September 2016

Skin Absorption of Four Formulated Organophosphorus Pesticides at Application and Full Strength

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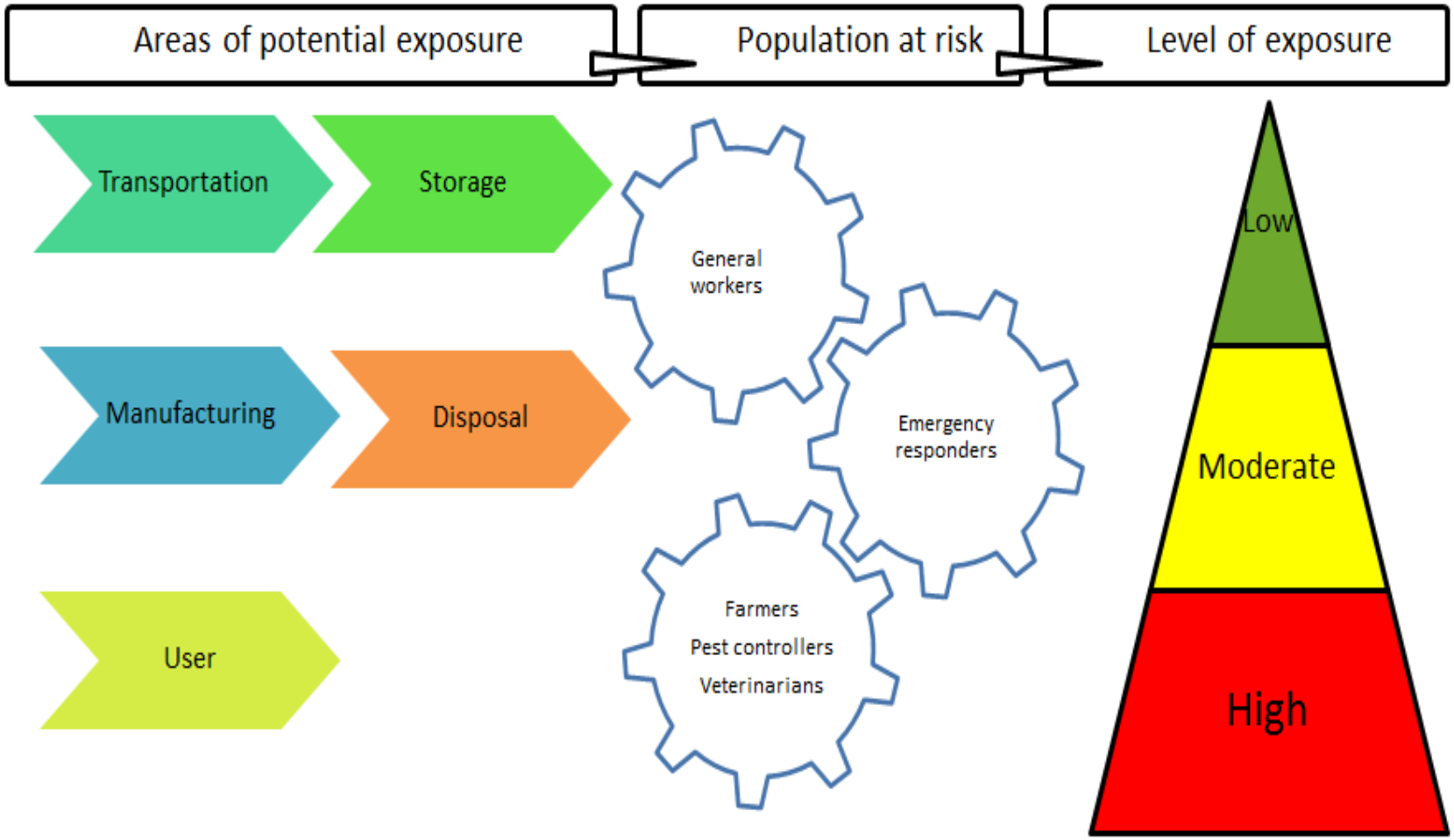
Overview

- OPs as a dermal hazard
- Rationale for research
- Experimental design
- Findings
- Interpretation
- Implications

OP Exposure Opportunities



Rationale

- The widespread use of organophosphorus pesticides (OPs) in developing countries is associated with significant morbidity and mortality.
- Dermal exposure studies of commercially available products can inform risk assessments and decisions regarding skin protection.
- However, there appear to be no skin absorption studies of a series of formulated products with differing physicochemical properties.

Experimental Design

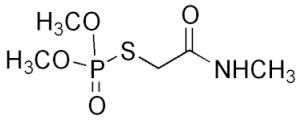
- Four OPs registered for use in Australia (omethoate, mevinphos, dichlorvos and diazinon) with differing octanol-water partition coefficients (log K_{ow} : – 0.7 to 3.8) were investigated using human skin *in vitro* for up to 8 hours at room temperature in an infinite dose protocol.
- Tests were conducted at the full strength formulation (relevant for transport and mixing activities) and application strength (relevant for spraying).

Compound	MW	Log K_{ow} (exp)	Solubility mg/L[a]	Calc Mol volume*	Calc molecular polar surface area[b]
Omethoate	213.2	-0.74	readily soluble	174.95	64.65
Mevinphos	224.1	0.13	600,000	189.565	71.1
Dichlorvos	221.0	1.9	8,000	155.546	44.8
Diazinon	304.3	3.81	40	273.146	53.5

[a]HSDB Hazardous Substances Data Bank, National Library of Medicine

*in cubic Angstroms

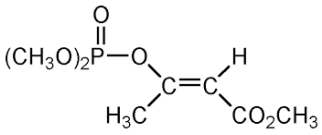
[b] Angstrom squared (from Molinspiration.com)



Omethoate

814g/L

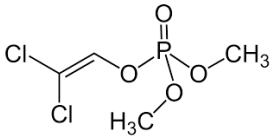
0.6 g/L



Mevinphos

1.1kg/L

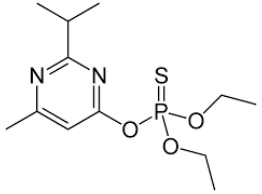
0.7 g/L



Dichlorvos

1.4 kg/L

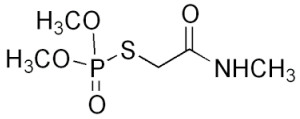
6 g/L



Diazinon

804 g/L

0.5 g/L



Omethoate

814g/L

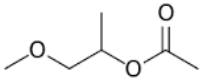
0.6 g/L

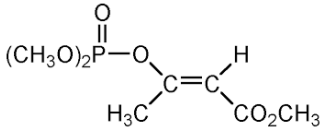
Folimat 800

Contains 400 g/L

PGMEA,

(1-methoxy-2-acetoxypropane)





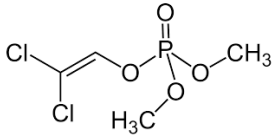
Mevinphos

1.1kg/L

0.7 g/L

Phosdrin

Essentially pure



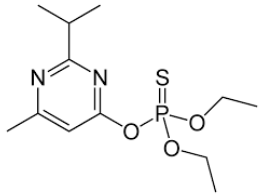
Dichlorvos

1.4 kg/L

6 g/L

DDVP Technical Grade

Essentially pure (98%)



Diazinon

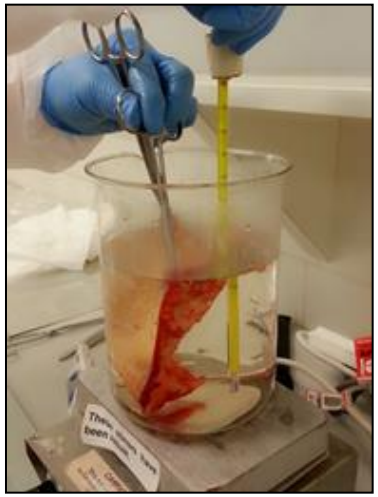
804 g/L

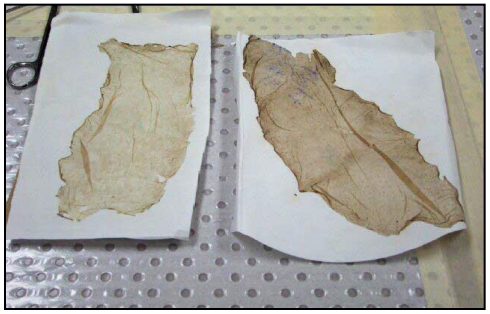
0.5 g/L

Barmac Diazinon

20% hydrocarbon solvents

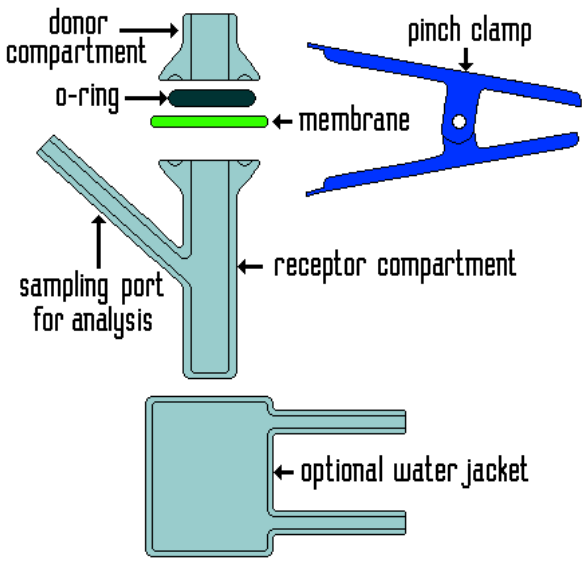
Heat-separated epidermis from human donors



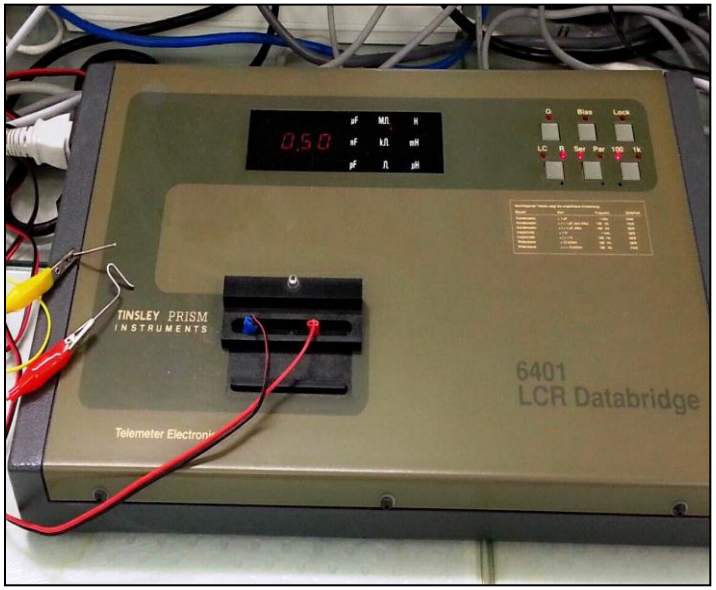


Human skin donors were three females, Caucasian, and aged from 35 to 58 with no obvious signs of skin damage or scarring/tattooing.

Skin penetration testing - Static Franz cell



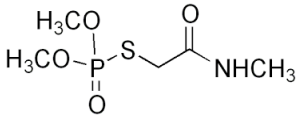
Skin Barrier Integrity Testing - Electrical Impedance

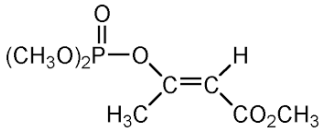


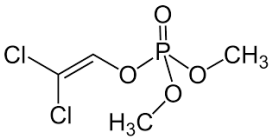
Tinsley LCR Databridge 6401 was used to evaluate skin barrier integrity in vivo

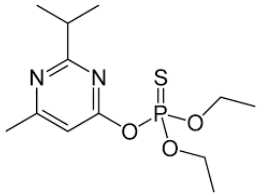
Summary of HPLC-UV conditions for the tested OPs

	Omethoate	Mevinphos	Dichlorvos	Diazinon
Mobile phase	Aqueous methanol 30:70 v/v	Aqueous acetonitrile 40:60 v/v	Aqueous acetonitrile 40:60 v/v	Aqueous acetonitrile 70:30 v/v
Flowrate (mL/min)	0.5	0.8	1.4	1.0
Retention time (min)	5.4	4.2	5.1	6.2
Wavelength (nm)	220	210	220	250







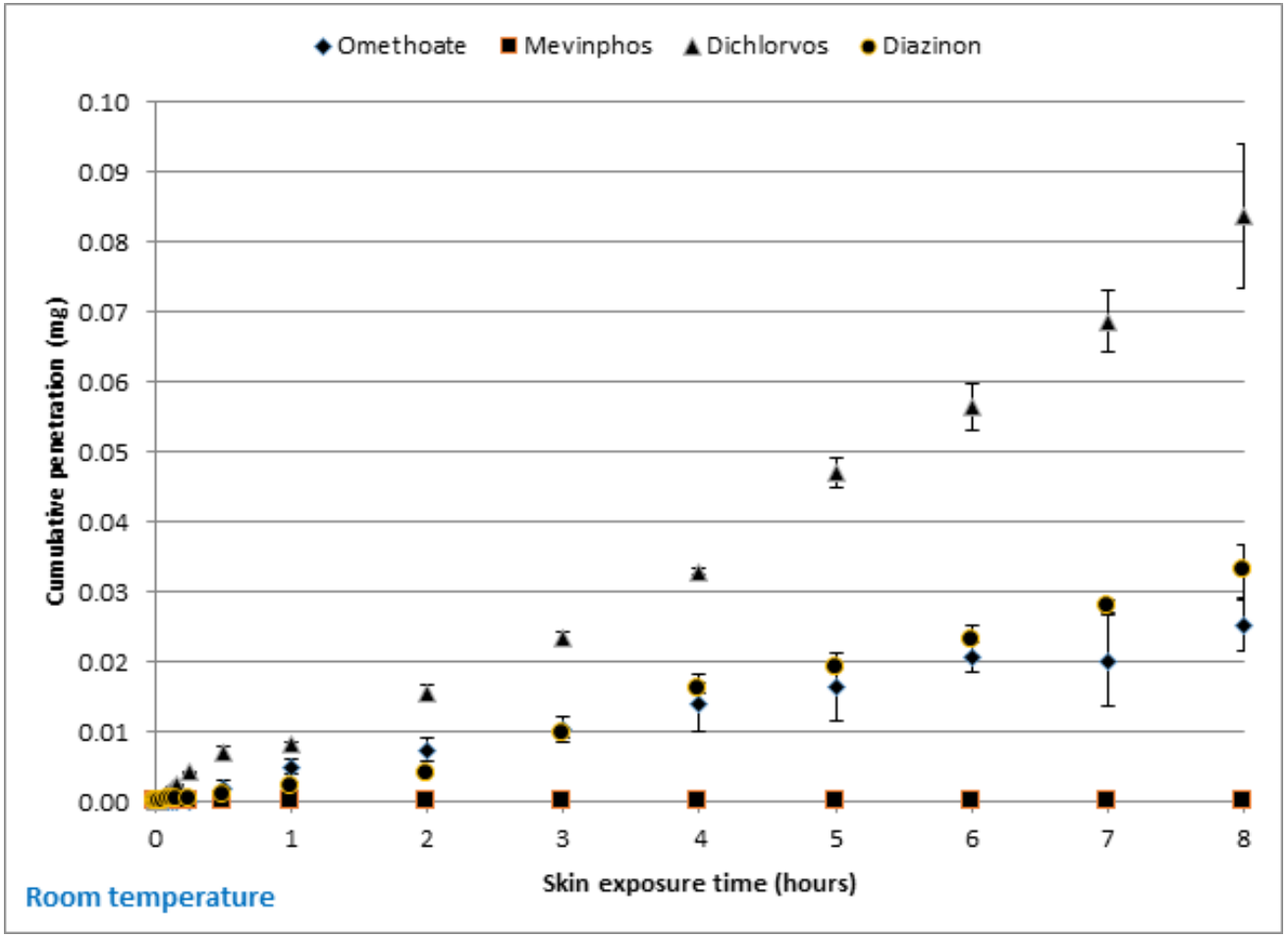


Limit of quantification typically 0.01µg/ml

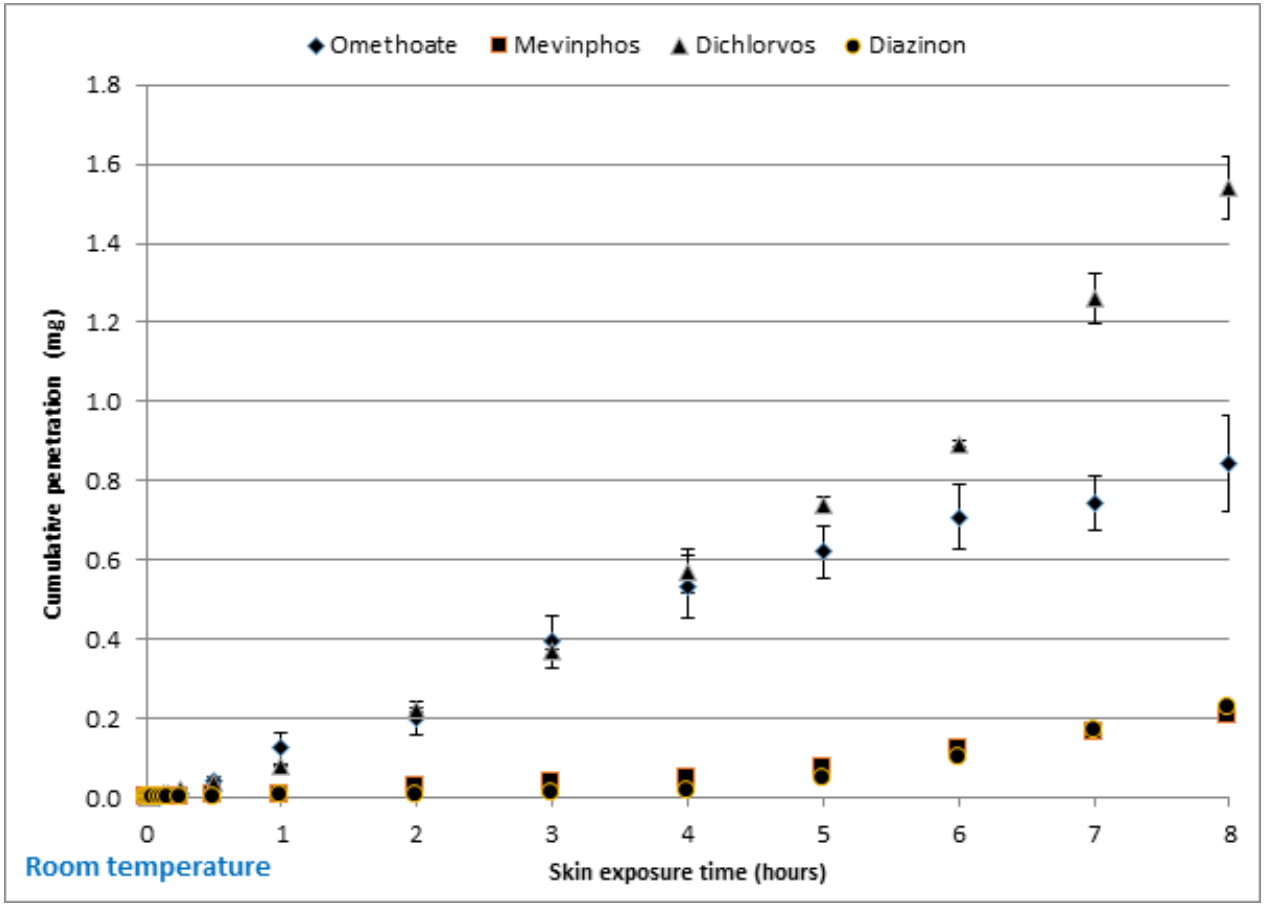
Main Findings

- Penetration rates varied with OP, with dichlorvos penetrating rapidly and to a greater extent than the others.
- For all OPs, higher concentration resulted in a faster penetration rate and increased cumulative penetration.
- At application strength the order for cumulative penetration was dichlorvos, diazinon, omethoate and mevinphos.
- For the concentrates, the order was dichlorvos, omethoate, diazinon and mevinphos.

Time profile of penetration – application strength



Time profile of penetration – concentrate



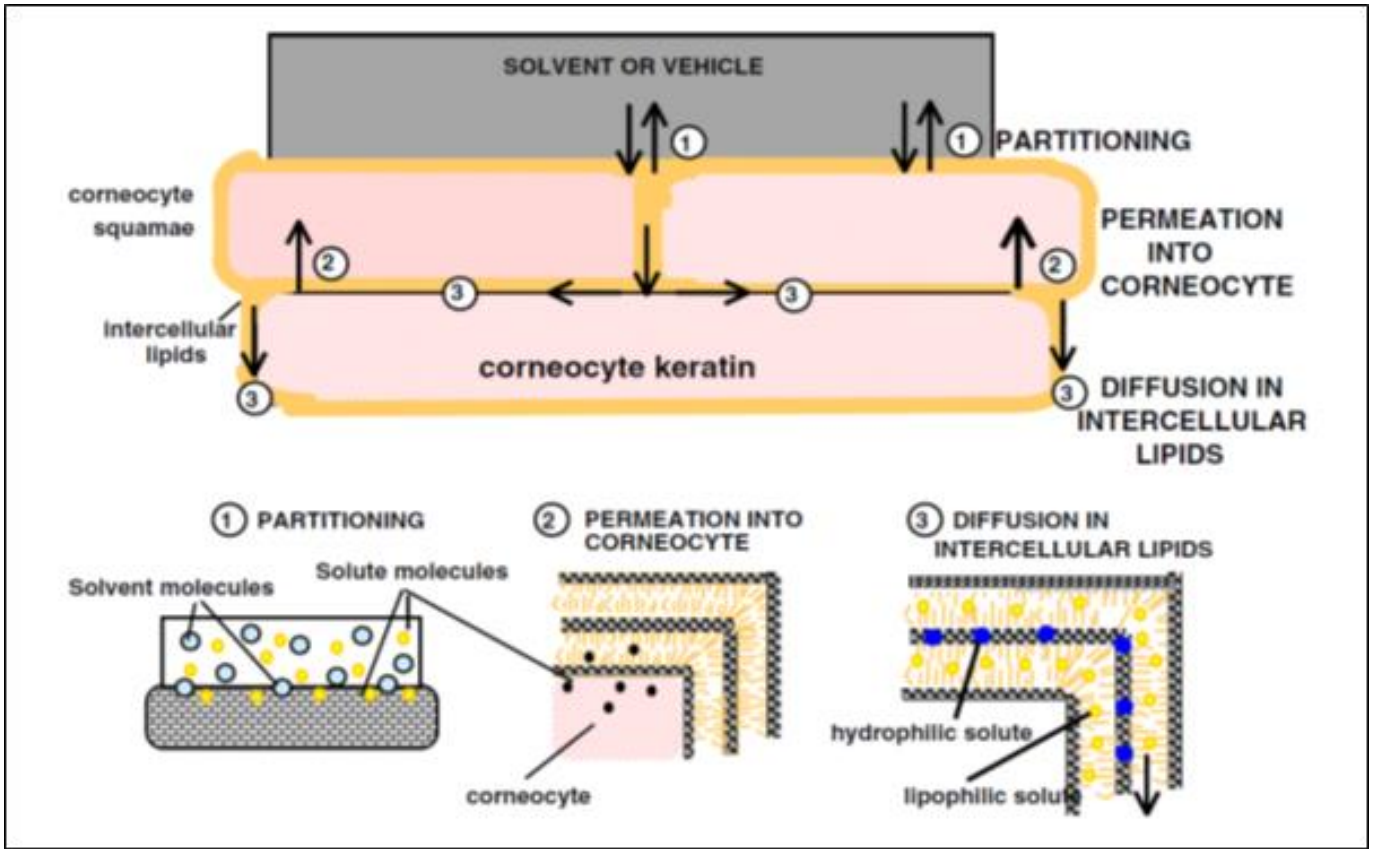
Skin penetration results

		Omethoate (log K_{ow} = -0.74)	Mevinphos (log K_{ow} = 0.13)	Dichlorvos (log K_{ow} = 1.9)	Diazinon (log K_{ow} = 3.81)
Application strength	Breakthrough time (mins)	15	10	0.5	1
	Average maximum flux (µg/cm^2/min)	0.2	0.003	0.6	0.2
	Average cumulative penetration (mg)	0.025	0.00025	0.084	0.033
Concentrate	Breakthrough time (mins)	6	2	0.5	0.5
	Average maximum flux (µg/cm^2/min)	4.9	7.0	9.8	1.7
	Average cumulative penetration (mg)	0.84	0.21	1.54	0.23

Room temperature 23C

Interpretation

- Comparing individual OPs at specific conditions did not demonstrate consistent penetration trends with $\log K_{ow}$, except for breakthrough times.
- Apart from the proportional effect of dilution, the findings for the concentrates may be explained by the presence of co-solvents, altering pesticide partitioning in the stratum corneum.
- In the case of dichlorvos, penetration kinetics and equilibria may be enhanced due to small molecular size and moderate lipophilicity.



Intercellular and transcellular routes of chemical penetration through the 'brick and mortar' structure of the upper skin Source: Anissimov et al. (2013)

Estimated Time to Exceed Acceptable Daily Intake

	Omethoate	Mevinphos	Dichlorvos	Diazinon
Application Strength	10-15 min	3-4 hrs	0.5 min	1-2 min
Concentrate	4-6 min	4-6 min	< 0.5 min	< 0.5 min

Extrapolated: Hands only, 800 cm^2

Implications

- Cherrie, Semple and Brouwer (2004) showed that in general, uptake of undiluted chemicals will be faster than in dilute form, due to the large concentration difference between the skin layer and the blood supply.
- However, there may not be a proportional relationship between applied concentration and skin penetration due to complex solute/solvent interactions, i.e. partitioning and diffusion processes, and the influence of co-solvents.

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Thank you

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