Skin sensitisation safety assessment without animal testing: A case study

N. Alépée on behalf of Cosmetics Europe's Skin Tolerance Task Force

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Skin Sensitization Risk Assessment without *in vivo* data

Chemical X is a new cosmetic ingredient.

Challenge: To conduct a risk assessment in the absence of generating new *in vivo* data

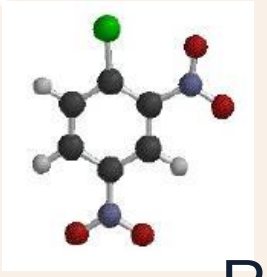
Question: Can Chemical X be used safely* at 0.2 % in a

a) face cream or

b) shower gel?

*Considering only skin sensitization for this case study

Skin Sensitization Risk Assessment

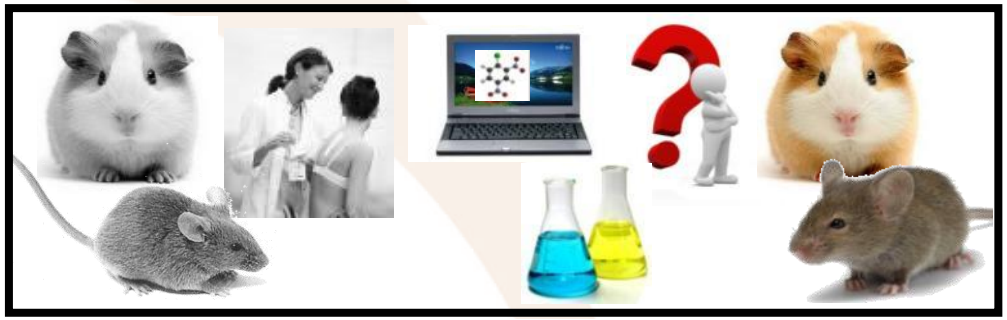


Risk ?

Exposure

X

Hazard



Historical Non-animal *In Vivo*

Risk assessment to **prevent** skin sensitisation in consumers

- What risk does ingredient **X** at conc. **Y** in product **Z** pose to the consumer?

To do so :

- Exposure data – product relevant consumer exposure scenario
- Hazard characterisation data – dose response information

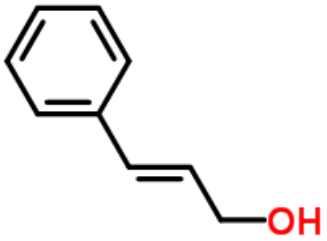
Hazard identification

What information do we have available right now?

- Structural alerts
- *In vitro / in chemico / in silico* data
- Review of analog data / Read-across

Structure

Cinnamyl Alcohol (CAS# 104-54-1)



No alerts for skin sensitization based upon o

- Computational tox. tools (e.g. DEREK)
- Expert chemistry judgement (for alcohols)
- Read-across to similar materials (e.g. benzyl alcohol)

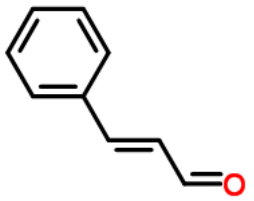
However expert chemistry judgement tells us:

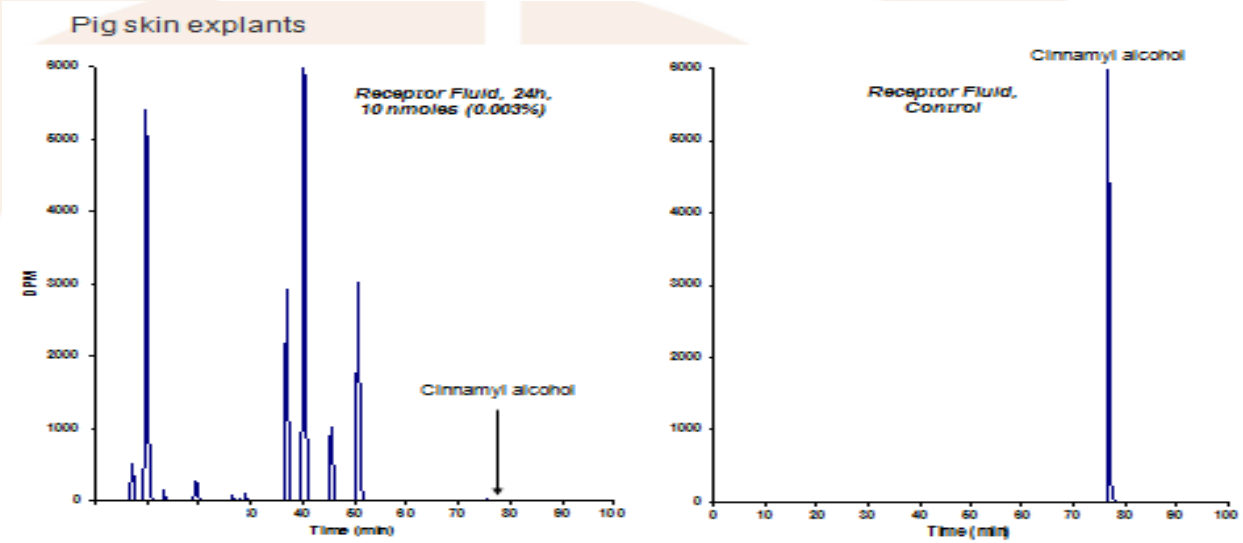
Alcohols can be metabolized / oxidized to aldehydes - known for sensitization potential

How do I address metabolism to a reactive material in my risk assessment with *in vitro / in chemico* tools?

Metabolites?

Possible metabolite: Cinnamic aldehyde





Metabolism study confirmed forming of metabolites

Phys chem / Hazard Data comparison

	MW	Log P	pKa	Solubility (g/l)	Vapour pressure (mm/Hg)
Cinnamyl alcohol	134	1.95	3.98	1.8	0.024
Cinnamic aldehyde	132	2.1		1.4-2.1	0.03

Chemical	LLNA*	Human class*	DPRA	PPRA	KeratinoSens	Sens-IS	h-CLAT	U-SENS
Cinnamyl alcohol	weak	3	positive (low)	Minimal Reactivity	positive	weak	positive	positive
Cinnamic aldehyde	moderate	2	Positive (high)	reactive	positive	strong	positive	positive

Integration of Hazard data

Case Study approach	BASF 2 of 3 (Bauch et al, 2012)	Shiseido (Tsujita-Inoue et al., 2014)	KAO STS (Takenouchi et al 2015)	KAO ITS (Takenouchi et al 2015)	BN ITS3 (Jaworska et al. 2015)	ICCVAM ITS	L'Oreal ITS
Cinnamic alcohol	positive	moderate	weak	weak	pEC3 category.2 (likely translates into weak)	positive	positive
Cinnamic aldehyde	positive	moderate	weak	weak	pEC3 category.3 (likely translates into moderate)	positive	positive

- All data, individual and combined point towards a skin sensitizer
- No clear conclusion on potency

Key questions for risk assessment?

We can conclude

- X is a skin sensitiser
- threshold approaches not appropriate for face cream, maybe shower gel
- need to derive a potency for use in RA

How confident are we in prediction of the potency?

- Is it weak or moderate
- How confident are we that the tools are not underestimating potency?
- What dose per unit area do I assign if I conclude moderate?
  - 100 µg/cm^2 ?
  - Is it appropriate to apply a Quantitative Risk Assessment (QRA) approach with/without additional uncertainty factors ?

Conclusions

Integrated approaches exist to identify sensitisers (Yes / No)

There is still uncertainty as to how accurate the potency predictions are from existing *in vitro/in chemico* tools

There is uncertainty as to how to translate the output of the *in vitro/ in chemico* tools to a metric for use in risk assessment

Additional uncertainty factors might be required if this data were to be used in a standard QRA approach to skin allergy risk assessment

Evaluation of additional case studies will enable us to begin to address these questions