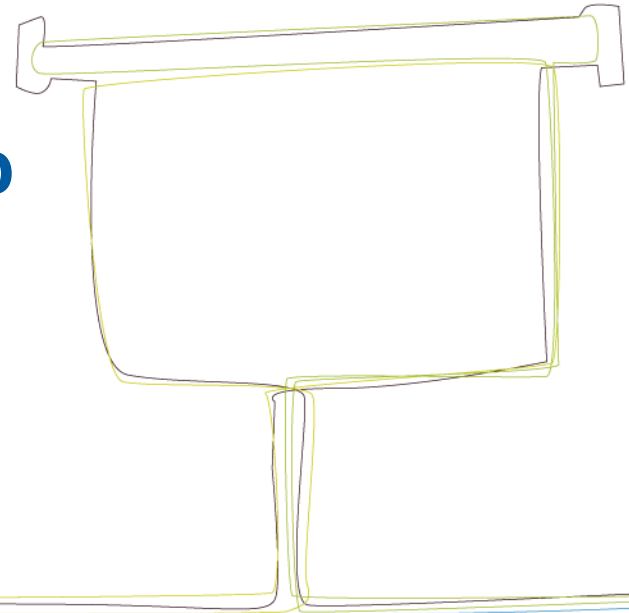




# Initial summary of the 'Expert' Pre- and prohaptens workshop

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# Overview



- Focus of attention has been on a very limited range of fragrances where there is the most knowledge. Difficult for the Rapporteur to identify how representative these are of fragrances as a whole.
- Estimates of the percentage of fragrances that mediate their allergenic effects through abiotic (pre) and/or biotic transformations is uncertain- in the minority?
- A number of well known 'facts' now need to be re-examined ie what fragrances are we certain act as pre and pro haptens
- Heavy reliance on LLNA. Need to also consider what to do about pre- and pro haptens when animal testing isn't allowed.

# QUESTIONS



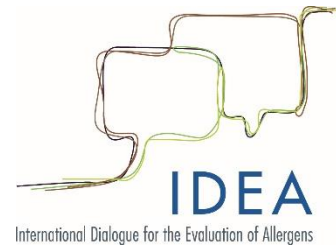
- i) What do we know?
- ii) What do we not know?
- iii) What are the priorities for action and why?

# AREAS COVERED AT THE WORKSHOP



- Uptake/adsorption.
- Abiotic transformation (activation and detoxification).
- Biotic transformation (activation and detoxification).
- Influence of transporter proteins, local non-specific binding / reservoirs.
- Impact of ingredient modifiers (inducers, inhibitors, etc.).
- Receptor proteins resulting an immune response.
- Cross reactivity.

# Absorption/uptake Predictive models



## Known:

- a) Good models exist. Ex vivo skin from human /pig OK but rat (and presumably mice?) NOT e.g. because more rapid penetration
- b) Viability not very critical but must be intact and contaminant free

## Uncertain:

Variation in skin due to disease limited

## Priorities: ???

# Abiotic transformation (prehaptens)

## Know:

- a) More important than biotic
- b) Oxidative mechanisms most common

## Unknown /challenges

- a) Limited understanding of processes involved
- b) Chemical measurement of reactive products remains very challenging

## Priority

A more predictive model

# Biotransformation (prohaptens)



## Known:

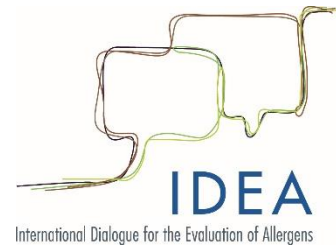
- a) Many of the DM enzymes quite well categorised and location in different cell types
- b) A number of useful models
- c) Good background of studies of formation of reactive metabolites from non-fragrance chemicals

## Uncertain:

- a) Characterisation of the properties required of an ultimate hapten and balance of activation and deactivation
- b) Sensitive viability criteria for an *in-vitro* prep

## Priorities: ??

# Transporters/binding/ reservoirs



## Known:

A number of transporter proteins identified in skin

## Uncertain:

- a) Limited understanding of their contribution to triggering an immune response
- b) Poor understanding of potential reservoir effects

## Priorities:

Better understanding of the relationship between uptake rate/extent, elimination and formation of reactive intermediates



# Impact of other ingredients

## Known:

- a) Other ingredients can modify uptake.
- b) There is a potential for ingredients to induce or inhibit metabolism

## Uncertain:

Knowledge of the importance of such ingredients other than on uptake is unclear

## Priorities: ??

# Receptor proteins and immune response



## Known:

- a) Reasonably good understanding of the mode of action resulting in an immune response
- b) Cross reactivity limited to very closely related fragrances

## Uncertain:

- a) Gap in understanding of the relationship between induction and elicitation
- b) Why ultimate haptens don't inevitably cause mutations (also electrophiles)

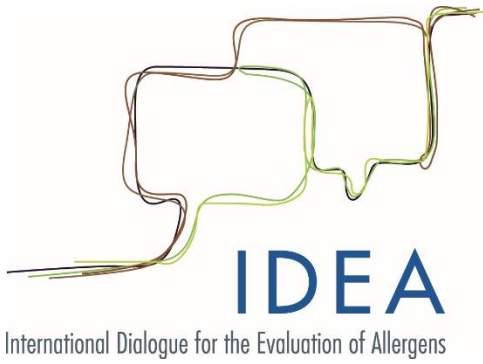
## Priorities: ??

# Overall conclusions

- \* Very useful workshop focussed on current science
- \* Progress has been made since the last workshop and some additional topics introduced (eg QSAR)
- Many outstanding issues

## Questions:

- i) How confident are we that we will pick up pre- and pro-haptens using QRA 2.
- ii) Do we need to make a major review of priorities for further work?



Thank you for  
your attention

