IDEA
International Dialogue for the Evaluation of Allergens

PRE AND PRO-HAPTENS: INITIAL CONCLUSIONS AND WHAT NEXT?

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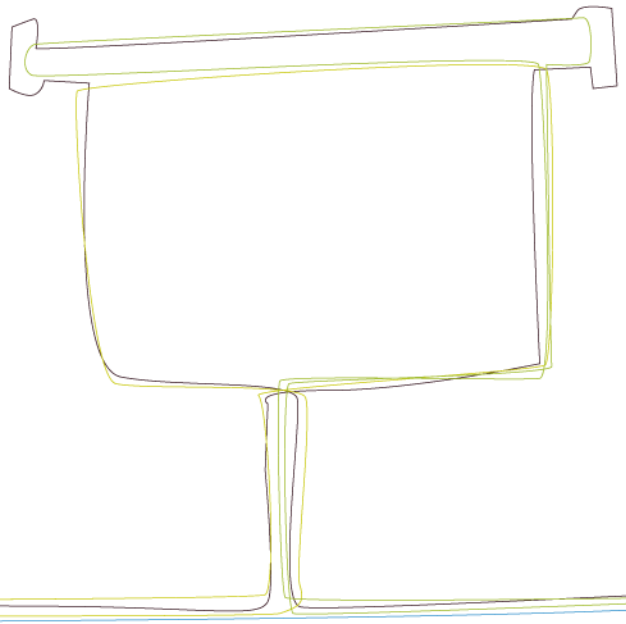

MY TAKE HOME MESSAGES FROM THE WORKSHOP

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- Haptens, pro haptens pre haptens should only be treated as separate entities if there is evidence to justify this. The fact that a chemical has been shown to be a pre hapten doesn't exclude the likelihood that its not a prohapten*.
- Cross reactivity is uncommon. Predictive tools based on SAR aspects need to include 3D considerations.
- The discussions have been focussed on specific aspects of a few well studied fragrances. How do the conclusions relate to the wider world of fragrances.

*NB *What are the criteria, for each fragrance of interest, to show that it is not metabolised in the skin to the final active form(s)?*

IMPORTANT INFORMATION GAPS AND QUESTIONS ?

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Do we have sufficient understanding of:

- the ability of chemicals to reach and be retained at the sites for biotic and abiotic transformation?
- the nature and relative quantities of each reactive product generated
- for the chemical/products generated, the processes for transfer to and reaction with target proteins, (e.g. 3D structure, potential for inactivation in the skin) ?

NB do we have sufficient knowledge of the ‘drug ‘ metabolism in human skin and the inter-individual variability

MISSING FROM THE DISCUSSIONS: ARE THEY UNIMPORTANT FROM AN RA PERSPECTIVE?

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- The metabolising activity in the skin other than hydroperoxide generation and hydrolysis (challenge of ultimate metabolite characterisation and analysis).
- The impact of skin enzyme inducers, very mild stress/lipid peroxidation and stimulation of reactive oxygen defence mechanisms.

NB In the wider world of research on active metabolite formation reduction and various types of conjugation are also important

PRIORITIES FOR THE DEVELOPMENT OF THE QRA?

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i) Incorporation of pre and prohaptens in QRA 2 and non-animal QRA3?

ii) Facilitate patient studies since progress depends on comparison of RA findings with high quality clinical studies (centre selection, ROAT, patient selection-key factors)

iii) Extend the aggregate exposure model to incorporate other important sources of individual fragrance exposure.

AREAS OF APPLICATION OF PRE- AND PRO- HAPTEN KNOWLEDGE*

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1. Revision of QRA 2 to incorporate the strategy for addressing prehaptens (assumed that prohaptens are largely addressed in the LLNA and HRIPT?)
2. Identify the strategy to be adopted when testing using LLNA and HRIPT are no longer permitted (for prehaptens the strategy could be based on 1. but allowance for prohaptens will be crucial)
3. Better understanding of mode of action (to improve confidence in the RA. Initial focus on identifying the ultimate reactive metabolite).

* Parallel activities for IDEA?

REVISION OF QRA 2: A TIERED APPROACH?

Tier 1. Exposure of the product to worst case conditions for the generation of reactive species

Simply oxidation and hydrolysis?

Tier 2. If positive in tier 1 then identify conditions to minimise the generation of the reactive species.

Tier 3. If important characterise the prehapten.

NB May be raised as a topic by JRC/SCCS

2. NON-ANIMAL TESTING STRATEGY: A TIERED APPROACH ?

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Tier 1. SAR considerations. Predictive tool for reactive product formation.

Needs a validated and publically accessible data based. False negatives not acceptable.

Tier 2. A panel of in vitro tests to identify whether likely to have sensitisation potential.

Development of some tests well advanced but unreliable indicators of potency for man

Tier 3. ???

NB May be raised as a topic by JRC/SCCS

THE GROUND STATE OF THE BIOLOGICAL SCIENCES IS UNCERTAINTY AND WISDOM* IS DEFINED BY HOW WE COPE WITH IT

Adapted from A Gawande

*Good scientific practice?

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Thank you for your attention