Development of QRA II

Jim Bridges

Starting point for the review

- How has the science advanced since QRA I?
- Is the QRA simply one aspect of general toxicology eg in terms of safety factors or must it be addressed differently?
- How do we define the population are we trying to protect, everyone?
- Can each unanticipated increase in allergy caused by an individual fragrance be assigned to failure of:

  - *the methodology itself?*

  - *its application?*

  - *use of its outcome?*

What are we trying to achieve in the short term (June/ July2014)?

A practical methodology that can be widely used that is:

- Effective in terms of improved consumer protection
- A significant improvement on existing methodology
- Based on current scientific and clinical knowledge both on fragrances and other dermal allergens
- Acceptable to regulatory authorities

issues that need to be considered

- Is the **hazard end point** for the QRA:

-*Threshold for induction?*

-*Threshold for sensitisation even in the absence of allergy?*

-*The threshold for allergy?*

- What is the range (in dose per unit area terms) of relevant **inter-individual variability** in the population group of concern in response to fragrance exposure. And are the reasons for this variability understood and quantifiable?

- What is the **range of exposure** of the population group of concern to a particular fragrance (and related chemicals?) and how should this information be used in the QRA?

Main differences between QRA I and QRA II?

- Use of Creme model on actual exposure to replace conservative assumptions on exposure.

- Use of current scientific and clinical knowledge for the selection of appropriate SAF's

- Other?

Consideration of exposure

Scope: simple external exposure or including physicochemical factors (eg stability, matrix, chemical build up in skin due to use frequency) that influence skin penetration

Guideline requirement: how to use aggregate exposure data.

Feedback loop: how to use data from clinical experience, substantial increases in use, other product exposure.

Consideration of safety (uncertainty) factors

- **Application:** based on scientific /clinical data, unambiguous, simple to apply and transparent. Separate consideration of fragrance QRA and individual product QRA?
- **How many?**: As few as possible or specific factors for each known variable
- **Assigned values**: Conservative and potential to reduce or minimal and potential to increase.
- **Comparisons: Should** the SAF selection take account of those used in other domains for dermal allergens

Issues not specifically addressed so far include:

- Whether additional SAF's are needed to allow for:

  - pre and pro hapten conversion to haptens

  - reduction in methods available to identify the allergic potential of new fragrances.

* Utilisation of data bases eg on non fragrance allergens / relevant on-going activities on non-fragrances and non animal tests in WoE

- Evidence to support the effectiveness of QRA II
- Cumulative exposure of MoA related chemicals

What do we need for the next workshop?

A working draft of the proposed QRA II for finalisation which:

-is adapted from QRA I

-is supported by suitable case histories

-is in a format likely to be acceptable to the JRC and SCCS

-highlights important gaps/areas where decisions are still required

Further steps

Develop an action plan to:

- Implement of QRAII widely
- Gather data to assess the effectiveness of QRA II.
- Further progress of the QRA II model to narrow uncertainties
- Adapt the QRA for new fragrances in the absence of opportunities to use animal test.