How are pre- and prohaptens currently incorporated in our risk assessment methodology (QRA for Dermal Sensitization)?

Anne Marie Api, PhD
Vice President, Human Health Sciences

IDEA Workshop: Pre- and Pro-hapten
October 21, 2015

Initial Step

- Clearly addressing the transformation is an important part of the risk assessment process.
- Our approach is to make the review of the structure the first step in order to determine if abiotic or biotic transformation is likely to occur.
- Materials that are anticipated to undergo abiotic transformation will then be reviewed to determine whether additional preventive measures are needed (e.g. if antioxidants are needed or if hydrolysis is anticipated).

In Vivo Tests (or read across from in vivo tests)

- Relevant biotic transformations will take place in the test species
- Inter-individual variability is taken into account in the identification of the appropriate SAFs
- When animal or human tests are used to establish the NESIL there is no reason to presume that the same metabolic processes will not prevail in consumers as in the test subjects (both qualitatively and quantitatively)

In Silico or *In Vitro* Test Methods

- **A weight of evidence approach will be developed to derive an indication of potency/hazard class which may have to be confirmed using an HRIPT. When testing in humans then,**
  - **Relevant biotic transformations will take place**
  - **Inter-individual variability is taken into account in SAFs**
  - **there is no reason to presume that the same metabolic processes will not prevail in consumers as in the test subjects (both qualitatively and quantitatively)**

In Vitro Skin Sensitization Tests

- In some cases chemicals requiring abiotic activation are detected in the DPRA; however pro-haptens are not readily characterized
- Among other improvements, the Peroxidase Peptide Reactivity Assay (PPRA) builds on the DPRA and incorporates a horseradish peroxidase and hydrogen peroxide system to assess the skin sensitisation potential of pre- and pro-haptens

In Vitro Skin Sensitization Tests

- **Similarly, modifications to the KeratinoSens™ assay have been described that incorporate rat liver S9 fractions to increase the ability to detect pro-haptens within this cell based system**
- **Other test systems proposed focusing on:**
  - **gene expression of a wider set of pathways**
  - **other target genes**
  - **key sensitizer-specific inflammation markers**

In Vitro Skin Sensitization Tests

- **However since these developments are typically newer, the number of chemicals tested is lower as compared to the tests which have already undergone validation.**

Future QRA

- We intend to incorporate the recommendations from the IDEA workshops into the QRA methodology

More Information

Research Institute for Fragrance Materials, Inc.
Tel.: +1-201.689.8089

amapi@rifm.org
RIFM: www.rifm.org