The Colipa Research and Method Development Program for Identifying and Characterizing Skin Sensitizers without Animal Testing

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Summary

At present, animal test methods are required to characterize the potential for new chemicals to induce skin allergy. There are currently several large research programs that aim to deliver new non-animal test methods for skin sensitization. Colipa participates intensively in this international research effort through continuous funding of research to explore the processes governing the induction of skin sensitization and the development of new methods incorporating this acquired knowledge. Our ongoing research portfolio continues to provide new insights into the biological processes driving skin sensitization, with the goal of defining a toolbox of non-animal test methods capable of characterizing skin sensitizer potency without the need for new animal test data.

Keywords: skin sensitization, in vitro test, risk assessment

Allergic contact dermatitis (ACD) is the clinical condition resulting from skin sensitization, which is a delayed-type hypersensitivity reaction induced by small reactive chemicals (hapten). To ensure that ingredients in cosmetic products do not induce skin sensitization (and hence do not cause ACD in consumers), a risk assessment is performed to evaluate the risk to humans and to substantiate the safety decision. To make a safety decision the risk assessor uses information on the concentration of the ingredient in the product and how the product is used by consumers, as well as available hazard characterization data (Loretz et al., 2005, 2006). At present, if significant skin exposure to a new ingredient is predicted, animal test data (e.g. mouse local lymph node assay (LLNA) data) may need to be generated to characterize the skin sensitization potential/potency of the ingredient and thereby inform the risk assessment decision. Given the increasing public and political concerns surrounding the generation of data on cosmetic ingredients in animals, the development of non-animal (in vitro, in chemico, and in silico) test methods and non-animal risk assessment approaches for skin sensitization remains a high priority for the cosmetic industry.

Non-animal test methods for skin sensitization need to cover the complex interactions of a chemical with the different compartments of the immune system. The chemical must penetrate the skin and react with endogenous proteins. Some chemicals, termed prohaptenes, require activation through skin metabolism in order to become haptenes capable of binding to skin proteins. Haptenated carrier-proteins are internalized and processed by immature dendritic cells (DCs) that become activated. The activated DCs start to migrate from the epidermis into the draining lymph node, complete maturation, and present fragments of the haptenated carrier-proteins to T-cells, resulting in an antigen-specific immune response (Enk and Katz, 1992; Cumberbatch et al., 1992).

There are several large programs of ongoing research that aim to deliver new non-animal test methods for skin sensitization. Colipa, the European cosmetics industry trade association, participates intensively in this international research effort through continuous funding of research to explore the toxicity pathways governing the induction of skin sensitization, the development of new methods incorporating the acquired knowledge, and as a member of the Sensitiv consortium (Aeby et al., 2010; Maxwell et al., 2011).

Our ongoing research portfolio (direct funding of eight research and method-development projects and participation in Colipa-affiliated projects) continues to provide new insights into the biological processes driving skin sensitization. Three in vitro test methods for the detection of potential sensitzers, i.e., the Direct Peptide Reactivity Assay (DPRA) (Gerberick et al., 2007), the human Cell Line Activation Test (h-CLAT) (Ashikaga et al., 2007), and the h-ClAt (Ashikaga et al., 2007), are currently being explored.
et al., 2010; Sakaguchi et al., 2010), and the Myeloid U937 Skin Sensitization Test (MUSST) (Ade et al., 2006) are now being pre-validated by the European Centre for the Validation of Alternative Methods (ECVAM). In parallel, a focused evaluation of other available non-animal test methods is being conducted in collaboration with each method developer (see Fig. 1).

A large number of non-animal test methods for skin sensitization are currently in late stage method development or under evaluation (termed “non-animal toolbox”); however, the majority of these non-animal toolbox test methods have only been shown to be successful in predicting sensitizer potential (Adler et al., 2011). Given that sensitizer potency information is required to inform risk assessment decision making, there is an ongoing effort within the field to develop testing strategy approaches capable of integrating “non-animal toolbox” datasets to predict sensitizer potency information. At present, several groups have demonstrated progress in improving sensitizer potential predictions through data integration, but the ability to reliably predict sensitizer potency information and the ability to apply non-animal exposure (i.e. skin bioavailability, metabolism) information to risk assessment decision-making remain key gaps.

The knowledge gained by this global research effort, and the synergies that should appear, will allow the development of novel non-animal test methods for the identification and characterization of skin sensitizing chemicals. Moreover, the overall strategic goal of this program is to develop a toolbox of in silico/in vitro predictive assays that could be used in concert and allow skin sensitization risk assessment decisions to be made without the need for new animal test data.

References


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