

ICCVAM's Proposed Activities on Alternative Skin Sensitization Test Methods and Testing Strategies

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) is developing a U.S. plan for the evaluation of alternative skin sensitization test methods and testing strategies.

Background: Allergic contact dermatitis (ACD), a skin reaction characterized by localized redness, swelling, blistering, or itching after direct contact with a skin allergen, is an important public health challenge. ACD frequently develops in workers and consumers exposed to skin-sensitizing chemicals and products. Pesticides and other marketed chemicals, including cosmetic ingredients, are routinely tested for skin sensitization hazard so that products can be appropriately labeled for safe use and handling. Fostering the evaluation and promotion of alternative test methods for regulatory use in skin sensitization hazard assessment has been one of ICCVAM's long-standing priorities (see <http://ntp.niehs.nih.gov/go/40445>).

Skin sensitization is a complex process. For substances that initiate the process through covalent binding to skin proteins, the key biological events have been fairly well characterized. These events form the basis for an "adverse outcome pathway" (AOP) for skin sensitization (OECD, 2012). An AOP is a conceptual model that links exposure to a substance to a toxic effect by identifying the sequence of biochemical events required to produce the toxic effect. The AOP for skin sensitization provides a framework for the development of alternative toxicity tests that can assess chemical effects on each biological event in the pathway and thereby provide evidence on whether a substance causes skin sensitization.

ICCVAM is committed toward continued work in this area and believes it has promise for the near-term development of testing strategies that do not require the use of animals. Specific ICCVAM or NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) activities include the following:

- ICCVAM consideration of a nomination from the National Institute of Occupational Safety and Health to assess the electrophilic allergen screening assay, a test method that identifies electrophilic substances that may produce skin sensitization by measuring their tendency to bind to skin proteins, the first key event in the AOP.
- NICEATM collaboration with academic scientists to develop and evaluate chemical structure–activity relationship (SAR) models to predict skin sensitization.
- NICEATM collaboration with industry scientists to develop an open-source Bayesian network as an operational framework for an integrated testing strategy that uses multiple physicochemical, *in silico*, *in chemico*, and *in vitro* inputs to predict skin sensitization properties of test substances.
- NICEATM evaluation of various high-throughput screening assays for skin sensitization in coordination with NIEHS Tox21 activities.

ICCVAM is also aware of significant international efforts to replace the use of animals in skin sensitization testing for hazard and potency assessment by government organizations including the Organisation for Economic Co-operation and Development (OECD) and the European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM), and by the industry organization Cosmetics Europe (formerly COLIPA). Some specific ICCVAM and NICEATM activities in support of international efforts include:

- Providing expertise and advice to EURL ECVAM to support their evaluation of several *in chemico* or *in vitro* methods (the direct peptide reactivity assay, human cell line activation test, KeratinoSensSM, and myeloid U937 skin sensitization test), which cover key events in the AOP for skin sensitization (Adler et al., 2011).
- Participation in the International Cooperation on Alternative Test Methods (ICATM, <http://ntp.niehs.nih.gov/go/40113>), through which ICCVAM and NICEATM help eliminate redundancy in validation studies sponsored by ICATM partners and promote harmonization in the resultant test method recommendations.
- Communication with trade associations and non-government organizations (e.g., Cosmetics Europe) to receive information regularly on efforts toward evaluation of alternative test methods for skin sensitization that cover key events in the AOP and data integration for hazard identification and potency assessment.

ICCVAM's Proposed Plans: ICCVAM's involvement with national and international efforts (see Background above) is consistent with its goal to advance the state of the science for alternative test methods and testing strategies for skin sensitization. ICCVAM is developing a plan of action to augment and support this goal and, as such, is considering the following activities:

- Holding implementation workshops and webinars, and developing guidance documents to promote the use of validated test methods and testing strategies for skin sensitization.
- Participating in OECD skin sensitization activities to ensure that new and relevant test guidelines and guidance meet U.S. regulatory requirements as well as foster cross-fertilization between domestic and international research efforts in skin sensitization testing strategies.
- Participating in validation management groups sponsored by ICATM partner organizations to ensure that the relevant validation studies for skin sensitization test methods and strategies meet U.S. regulatory needs as well as those of the sponsoring country.
- Providing expertise, data, and other resources when feasible to support NICEATM's efforts in the development of an integrated testing strategy for skin sensitizers.
- Evaluating alternative test method and testing strategy submissions for skin sensitization for reliability and relevance for the intended purpose.
- Consulting with organizations that are currently developing alternative test methods and testing strategies for skin sensitization to provide guidance that will increase U.S. regulatory acceptance.
- Encouraging developers of alternative test methods and testing strategies for skin sensitization to discuss their projects with ICCVAM and NICEATM to facilitate refinement of the methods to meet U.S. regulatory needs.
- Communicating information about the availability of funding or other resources to stakeholders that are developing alternative test methods and testing strategies for skin sensitization.
- Conducting, cosponsoring, and/or participating in workshops to review the state of the science and soliciting or providing input for future activities on development and validation of test methods and testing strategies for skin sensitization.