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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Request for Information on Alternative Skin Sensitization Test Methods and Testing Strategies and for Comment on ICCVAM's Proposed Activities

SUMMARY: 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. The National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) requests information that ICCVAM might use to develop this plan and comments on proposed ICCVAM activities.

DATES: Information should be submitted by December 9, 2013.

ADDRESSES: Responses submitted by email to niceatm@niehs.nih.gov are preferred.

NICEATM, National Institute of Environmental Health Sciences, P.O. Box 12233, Mail

Stop: K2-16, Research Triangle Park, NC 27709. Website:

<http://ntp.niehs.nih.gov/go/niceatm>.

FOR FURTHER INFORMATION CONTACT: Dr. Warren S. Casey, Acting Director, NICEATM; email: warren.casey@nih.gov; telephone: (919) 316-4729.

SUPPLEMENTARY INFORMATION:

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 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 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 guidances meet U.S. regulatory requirements as well as foster cross-fertilization between domestic and international research efforts in skin sensitization.
- 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.

Request for Comments: ICCVAM invites its stakeholders to consider the proposed activities identified above and provide comment on the following:

- The role that ICCVAM should play in the development and evaluation of alternative skin sensitization test methods and testing strategies.
- The potential contributions that regulated industries, nongovernment organizations, or other interested parties might make toward these efforts.

Request for Information: As noted above, ICCVAM is developing plans to augment and support activities that will advance the state of the science for alternative skin sensitization test methods and testing strategies. As part of this process, ICCVAM is interested in receiving information on the state of the science regarding alternative test methods and testing strategies for skin sensitization and about activities of which ICCVAM may not be aware.

Input Received: Information and comments in response to this notice can be submitted by email (niceatm@niehs.nih.gov). Persons should include their name, affiliation (if applicable), mailing address, telephone, email, and sponsoring organization (if any) with their communications. The deadline for receipt of the requested information is December 9, 2013. Responses to this notice will be posted on the NTP website (<http://ntp.niehs.nih.gov/go/40498>) and persons submitting them will be identified by name and affiliation or sponsoring organization, if applicable. During development of its plan for advancing alternative skin sensitization test methods and testing strategies,

ICCVAM will carefully consider the information and comments received in response to this notice and will also consult with ICATM partners and the OECD.

Responses to this request are voluntary. No proprietary, classified, confidential, or sensitive information should be included in responses. This request for input is for planning purposes only and is not a solicitation for applications or an obligation on the part of the U.S. Government to provide support for any ideas identified in response to the request. Please note that the U.S. Government will not pay for the preparation of any information submitted or for its use of that information.

Background Information on ICCVAM and NICEATM: ICCVAM is an interagency committee composed of representatives from 15 Federal regulatory and research agencies that require, use, generate, or disseminate toxicological and safety testing information. ICCVAM conducts technical evaluations of new, revised, and alternative safety testing methods and integrated testing strategies with regulatory applicability. ICCVAM also works to promote the scientific validation and regulatory acceptance of testing methods that more accurately assess the safety and hazards of chemicals and products and that replace, reduce, or refine (enhance animal well-being and lessen or avoid pain and distress) animal use. NICEATM provides scientific and operational support for ICCVAM and conducts independent validation studies and other activities to assess the usefulness and limitations of new, revised, and alternative test methods and strategies. ICCVAM and NICEATM welcome the public nomination of new, revised, and alternative test methods and strategies for validation studies and technical evaluations. Additional information about NICEATM and ICCVAM can be found on the NTP website at <http://ntp.niehs.nih.gov/go/niceatm> and <http://ntp.niehs.nih.gov/go/iccvam>.

The ICCVAM Authorization Act of 2000 (42 U.S.C. 285l–3) provides the authority for ICCVAM and NICEATM involvement in activities relevant to the development of alternative test methods. The ICCVAM Authorization Act established ICCVAM as a permanent interagency committee of the NIEHS under NICEATM. As stated in the ICCVAM Authorization Act, ICCVAM acts to ensure that new and revised test methods are validated to meet the needs of Federal agencies, increase the efficiency and effectiveness and Federal agency test method review, and optimize utilization of scientific expertise outside the Federal Government.

References

Adler S, Basketter D, Creton S, et al. 2011. Alternative (non-animal) methods for cosmetics testing: current status and future prospects-2010. Arch Toxicol 85: 367-485.

OECD. 2012. OECD Series on Testing and Assessment No. 168. The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins. Part 1: Scientific Assessment. Paris:OECD Publishing. Available: <http://www.oecd.org/env/ehs/testing/seriesontestingandassessmentpublicationsbynumber.htm>

Dated:

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John R. Bucher,

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