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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Nomination of an *In Vitro* Test Method for the Identification of Contact Allergens: Request for Comments and Data

AGENCY: Division of the National Toxicology Program (DNTP), National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH)

ACTION: Request for Comments and Data

SUMMARY: On behalf of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) requests public comment on an ICCVAM test method nomination for validation studies. The validation studies are proposed to determine the usefulness and limitations of an *in vitro* test method to identify electrophilic substances that have the potential to produce allergic contact dermatitis (ACD). NICEATM also requests data generated using *in vivo* and *in vitro* test methods for assessing ACD hazard potential, including but not limited to guinea pig methods, the murine local lymph node assay, the direct protein reactivity assay, the human cell line activation test, and the KeratinoSens™ assay. Data will be used to develop integrated testing and decision strategies that will also consider incorporation of the nominated test method following adequate validation studies.

DATES: Comments and test method data for assessing ACD hazard potential should be submitted by [insert date 45 days from publication]. Comments and data submitted after this date will be considered in the evaluation where feasible.

FOR FURTHER INFORMATION CONTACT: Dr. William S. Stokes, Director, NICEATM, NIEHS, P.O. Box 12233, Mail Stop: K2-16, Research Triangle Park, NC, 27709, (telephone) 919-541-2384, (fax) 919-541-0947, (email) *niceatm@niehs.nih.gov*. Courier address: NICEATM, NIEHS, Room 2034, 530 Davis Drive, Morrisville, NC 27560.

SUPPLEMENTARY INFORMATION:

Background

The development of alternatives to animal testing for ACD is an ICCVAM priority (ICCVAM, 2008). See *http://iccvam.niehs.nih.gov/methods/immunotox/immunotox.htm* for more information on ICCVAM evaluations of ACD test methods.

Test Method Nomination for Validation Studies

An essential first step in the adverse outcome pathway for skin sensitization is the binding of a potential sensitizer to a dermal protein (Karlberg *et al.*, 2008). Chipinda and co-workers described a rapid screening assay for substances that might react with proteins using the substance nitrobenzenethiol, which contains a reactive thiol group found in proteins, as a probe (Chipinda *et al.,* 2010). Subsequently, a second probe, pyridoxalamine, was added to enable accurate detection of potential sensitizers that react with amine groups found in proteins. Covalent binding of the test substance to the probe is monitored by loss of absorbance or fluorescence. The modified assay identifies electrophilic skin sensitizers, but not prohaptens, which must be metabolized for skin sensitizing activity. The advantages of this assay include (1) the ability to obtain results using low test chemical concentrations, which reduces solubility problems; (2) the ability to run the assay without specialized equipment such as a high performance liquid chromatograph, a flow cytometer, or a mass spectrometer; the assays require

only a simple spectrophotometer and fluorometer; (3) low cost; and (4) rapid results (assay time is less than half a day).

Once validation criteria have been appropriately addressed through validation studies, this method may have the potential to meet regulatory requirements for identifying skin sensitizers in a range of applications as a screening test and as a component of an integrated testing and decision strategy. The test developer from the National Institute of Occupational Safety and Health submitted a nomination requesting that NICEATM and ICCVAM evaluate this method as a screening assay for identification of contact allergens, and proposes collaborations with NICEATM to conduct validation studies and determine the most appropriate decision criteria to maximize the sensitivity and specificity of the *in chemico* assay. The cover letter for the nomination can be viewed on the NICEATM–ICCVAM website (*http://iccvam.niehs.nih.gov/SuppDocs/submission.htm#nomination).*

Draft ICCVAM Priority and Draft Recommended Activities

Based on the information provided by the test method developer and consideration of the ICCVAM prioritization criteria, ICCVAM considers that the nomination is of sufficient interest and applicability to warrant validation studies to characterize its usefulness and limitations for predicting ACD potential of chemicals and products. ICCVAM's draft position is that the nomination should have a high priority for the proposed studies. The ICCVAM preliminary evaluation of the method can be viewed on the NICEATM–ICCVAM website *(http://iccvam.niehs.nih.gov/methods/immunotox/EASA.htm).* ICCVAM proposed contributions to such studies would include review and comments on: (1) the optimization and standardization of the test method protocol, (2) the validation study design, and (3) reference chemical selection

for the validation study. Federal agency programs will consider the nomination priority and recommended activities in determining potential support for validation activities.

As part of the nomination review process, NICEATM invites public comments on the relative draft priority assigned by ICCVAM and the appropriateness of the proposed activities. ICCVAM will finalize its recommendations on the priority and activities for this nomination after considering comments received from the public and the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), which will comment on the ICCVAM draft recommendations at its meeting on September 5–6, 2012. Information about the SACATM meeting is available on the NTP website (*http://ntp.niehs.nih.gov/go/32822*).

Background Information on ICCVAM, NICEATM, and SACATM

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 and promotes the scientific validation and regulatory acceptance of test methods that more accurately assess the safety and hazards of chemicals and products and that reduce, refine (enhance animal well-being and lessen or avoid pain and distress), or replace animal use. The ICCVAM Authorization Act of 2000 (42 U.S.C. 285*l*-3) established ICCVAM as a permanent interagency committee of the NIEHS under NICEATM. NICEATM administers ICCVAM, provides scientific and operational support for ICCVAM-related activities, and conducts independent validation studies to assess the usefulness and limitations of new, revised, and alternative test methods and strategies. NICEATM and ICCVAM welcome the public nomination of new, revised, and alternative test methods and strategies for validation studies and

technical evaluations. Additional information about ICCVAM and NICEATM can be found on the NICEATM-ICCVAM website (*http://iccvam.niehs.nih.gov*).

SACATM was established in response to the ICCVAM Authorization Act [Section 285*l*-3(d)] and is composed of scientists from the public and private sectors. SACATM advises ICCVAM, NICEATM, and the Director of the NIEHS and NTP regarding statutorily mandated duties of ICCVAM and activities of NICEATM. SACATM provides advice on priorities and activities related to the development, validation, scientific review, regulatory acceptance, implementation, and national and international harmonization of new, revised, and alternative toxicological test methods. Additional information about SACATM, including the charter, roster, and records of past meetings, can be found at *http://ntp.niehs.nih.gov/go/167*.

References

Chipinda I, Ajibola RO, Morokinyo MK, Ruwona TB, Simoyi RH, Siegel PD. 2010. Rapid and simple kinetics screening assay for electrophilic dermal sensitizers using nitrobenzenethiol. Chem Res Toxicol 23: 918–925.

ICCVAM. 2008. The NICEATM–ICCVAM Five-Year Plan (2008–2012): A Plan to Advance Alternative Test Methods of High Scientific Quality to Protect and Advance the Health of People, Animals, and the Environment. NIH Publication No. 08-6410. Research Triangle Park, NC: NIEHS. Available: *http://iccvam.niehs.nih.gov/docs/5yearplan.htm.*

Karlberg A-T, Bergström MA, Börje A, Luthman, K, Nilsson JLG. 2008. Allergic Contact Dermatitis—Formation, Structural Requirements, and Reactivity of Skin Sensitizers. Chem Res Toxicol 21: 53–69.

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