ICCVAM Roadmap for Skin Sensitization Testing

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CPSC

SACATM Meeting, September 27, 2016

Research Triangle Park, NC

Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture
Department of Defense • Department of Energy • Department of the Interior • Department of Transportation
Environmental Protection Agency • Food and Drug Administration • National Institute for Occupational Safety and Health
National Institutes of Health • National Cancer Institute • National Institute of Environmental Health Sciences
National Library of Medicine • Occupational Safety and Health Administration

ICCVAM Skin Sensitization Working Group (SSWG)

- 9 Agencies/Centers
- 24 Researchers and Regulators
- Includes representative from EURL-ECVAM

ATSDR, CPSC, EPA-OPP, EPA-OPPT, FDA-CFSAN, FDA-CDER, FDA-CDRH, FDA-NCTR, NIEHS-NTP
EURL-ECVAM

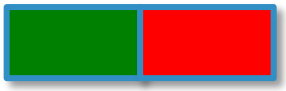
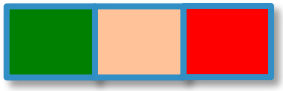
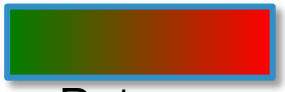
U.S. Statutes and Regulations

US Statute/Regulations	Agency
Federal Hazardous Substances Act (FHSA) (1964): 16 CFR 1500.3: **Consumer Products**	CPSC
Labeling of Hazardous Art Materials Act (LHAMA) (1988): 16 CFR 1500.14: **Art Materials**	CPSC
Federal Insecticide, Fungicide, and Rodenticide Act (U.S.C. Title 7, Chapter 6): 40 CFR 156, 40 CFR 158.500, 40 CFR 158.2230: **Antimicrobials**	EPA
Federal Insecticide, Fungicide, and Rodenticide Act (U.S.C. Title 7, Chapter 6): 40 CFR 156, 40 CFR 158.500, 40 CFR 158.2230: **Pesticides**	EPA
Toxic Substances Control Act (TSCA; 1976): 40 CFR 700-799: **Industrial Chemicals**	EPA
Federal Food, Drug, and Cosmetic Act (1938): **Cosmetics**	FDA
Federal Food, Drug, and Cosmetic Act (1938): **Pharmaceuticals**	FDA
Occupational Safety and Health Act (1970): 29 CFR 1910.1200: **Workplace Chemicals**	OSHA

Challenges

- Animal methods currently provide the reference data for evaluating alternatives
  - Results are variable
  - Many testing strategies outperform the LLNA in predicting human outcomes
- Data requirements vary across U.S. and global regulatory authorities and are often ambiguous
- Limited coverage of chemical space
- Overcoming regulatory and institutional inertia
  - Education and training

Validating Alternative Methods

		Reference Animal Method	Classification Criteria
EPA	Pesticides	 LLNA	NS S  Hazard
United States Consumer Product Safety Commission	Household Products	 LLNA	NS S SS  Potency
FDA	Dermatological Products	 GPMT	 Potency

Accuracy of Animal Test Methods Compared to Human Data

LLNA

Hazard	Potency
~75%	~60%

GPMT / Buehler

Hazard	Potency
~72%	~60%

ICCVAM. 1999. NIH Publication No. 99-4494
ICCVAM. 2010. NIH Publication No. 11-7709
Urbisch et al. 2015. Reg Tox Pharm 71:337-351.
Kleinstreuer et al. 2016 in preparation

Reproducibility of LLNA Data

Toxicology in Vitro 34 (2016) 220–228

Contents lists available at ScienceDirect

Toxicology in Vitro

journal homepage: www.elsevier.com/locate/toxinvit

Analysis of the Local Lymph Node Assay (LLNA) variability for assessing the prediction of skin sensitisation potential and potency of chemicals with non-animal approaches

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How concordant are LLNA outcomes?

- ~78% for hazard
- ~62% for GHS potency classification

Key Strategic Activities

- Design and evaluate integrated approaches for testing and assessment of data using validated alternative methods (DPRA, KeratinoSens, h-CLAT, others ongoing), including the use of additional in silico tools (e.g., QSAR)
- Validate NIOSH Electrophilic Allergen Screening Assay (EASA), a lower cost alternative to DPRA
- Increase the number of chemicals tested in vitro to expand chemical space and facilitate acceptance by US agencies
- Start working <u>now</u> on international harmonization

Models to Predict Hazard (Pos/Neg)

- Support vector machine had the best performance
- For LLNA, best 7 models had accuracy of 89-96%
- For Human, best 6 models had accuracy of 92%

Research article

Journal of Applied Toxicology

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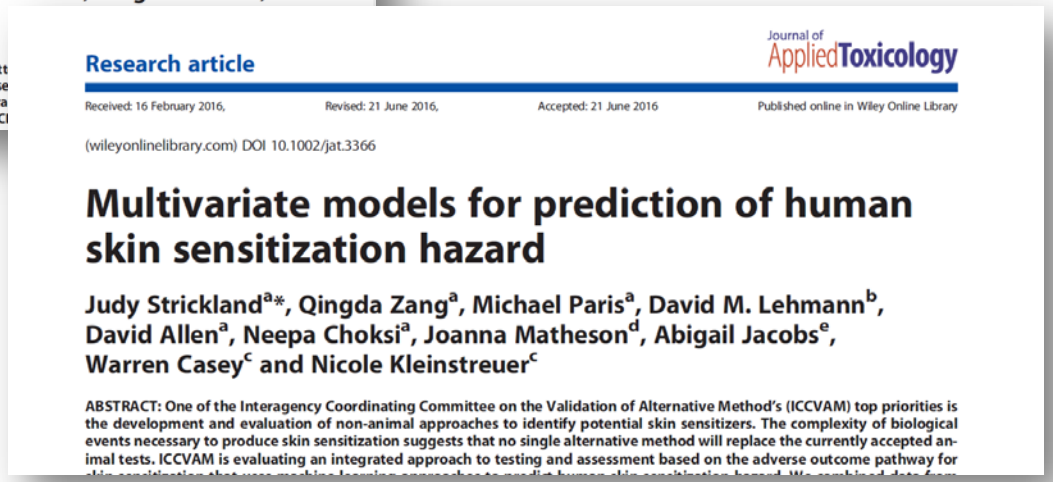
(wileyonlinelibrary.com) DOI 10.1002/jat.3281

Integrated decision strategies for skin sensitization hazard

Judy Strickland[a], Qingda Zang[a], Nicole Kleinstreuer[a], Michael Paris[a], David M. Lehmann[b], Neepa Choksi[a], Joanna Matheson[c], Abigail Jacobs[d], Anna Lowit[e], David Allen[a] and Warren Casey[f]*

ABSTRACT: One of the top priorities of the Interagency Coordinating Committ
(ICCVAM) is the identification and evaluation of non-animal alternatives for skin se
is a complex process, the key biological events of the process have been well chara
proposed by the Organisation for Economic Co-operation and Development (OEC



Research article

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Multivariate models for prediction of human skin sensitization hazard

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ABSTRACT: One of the Interagency Coordinating Committee on the Validation of Alternative Method's (ICCVAM) top priorities is the development and evaluation of non-animal approaches to identify potential skin sensitizers. The complexity of biological events necessary to produce skin sensitization suggests that no single alternative method will replace the currently accepted animal tests. ICCVAM is evaluating an integrated approach to testing and assessment based on the adverse outcome pathway for

Models to Predict Skin Sensitization Potency

- Models for predicting strong (GHS 1A), weak (GHS 1B), and nonsensitizers
- Accuracy for predicting LLNA = 90%
- Accuracy for predicting Human = 81%

  (LLNA = 69% for human data using same chemicals)
- Analysis completed, manuscript under internal review

Expanding Coverage of Chemical Space

- Most chemicals used in the validation of non-animal test methods are cosmetics ingredients

- NTP supporting testing of expanded chemical space in three alternative test methods: DPRA, LuSens, GARD

- Compiling chemical nominations from ICCVAM agencies
  - Chemicals with existing LLNA data (e.g. pesticides, agrochemical formulations, dermal excipients, etc.)

- NTP has procured 48 chemicals for initial testing phase (late 2016), with additional testing to follow in 2017

ICATM Workshop on Skin Sensitization

- October 4-5, 2016; hosted by EURL-ECVAM, Ispra, Italy
  - Identify available non-animal approaches accepted in each country/region
  - Identify the current regulatory requirements for skin sensitization in different regions that could be satisfied with non-animal approaches
  - Define a set of performance based criteria for regulatory use of defined approaches
  - Issue recommendations for specific regulatory applications in defined chemical sectors