ICCVAM Roadmap for Skin Sensitization Testing

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CPSC

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Research Triangle Park, NC
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

<table>
<thead>
<tr>
<th>US Statute/Regulations</th>
<th>Agency</th>
</tr>
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<tbody>
<tr>
<td>Federal Hazardous Substances Act (FHSA) (1964): 16 CFR 1500.3: <strong>Consumer Products</strong></td>
<td>CPSC</td>
</tr>
<tr>
<td>Federal Food, Drug, and Cosmetic Act (1938): <strong>Cosmetics</strong></td>
<td>FDA</td>
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<tr>
<td>Federal Food, Drug, and Cosmetic Act (1938): <strong>Pharmaceuticals</strong></td>
<td>FDA</td>
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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**

- **Pesticides**
  - LLNA

- **Household Products**
  - LLNA

- **Dermatological Products**
  - GPMT

**Classification Criteria**

- **Potency**
  - NS, S, SS

- **Hazard**
  - NS, S
## Accuracy of Animal Test Methods Compared to Human Data

<table>
<thead>
<tr>
<th>Method</th>
<th>Hazard</th>
<th>Potency</th>
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<tr>
<td>LLNA</td>
<td>~75%</td>
<td>~60%</td>
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<tr>
<td>GPMT / Buehler</td>
<td>~72%</td>
<td>~60%</td>
</tr>
</tbody>
</table>

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

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 now 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%
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