

US EPA ARCHIVE DOCUMENT

OECD Dermal Sensitization AOP Regulatory Perspective

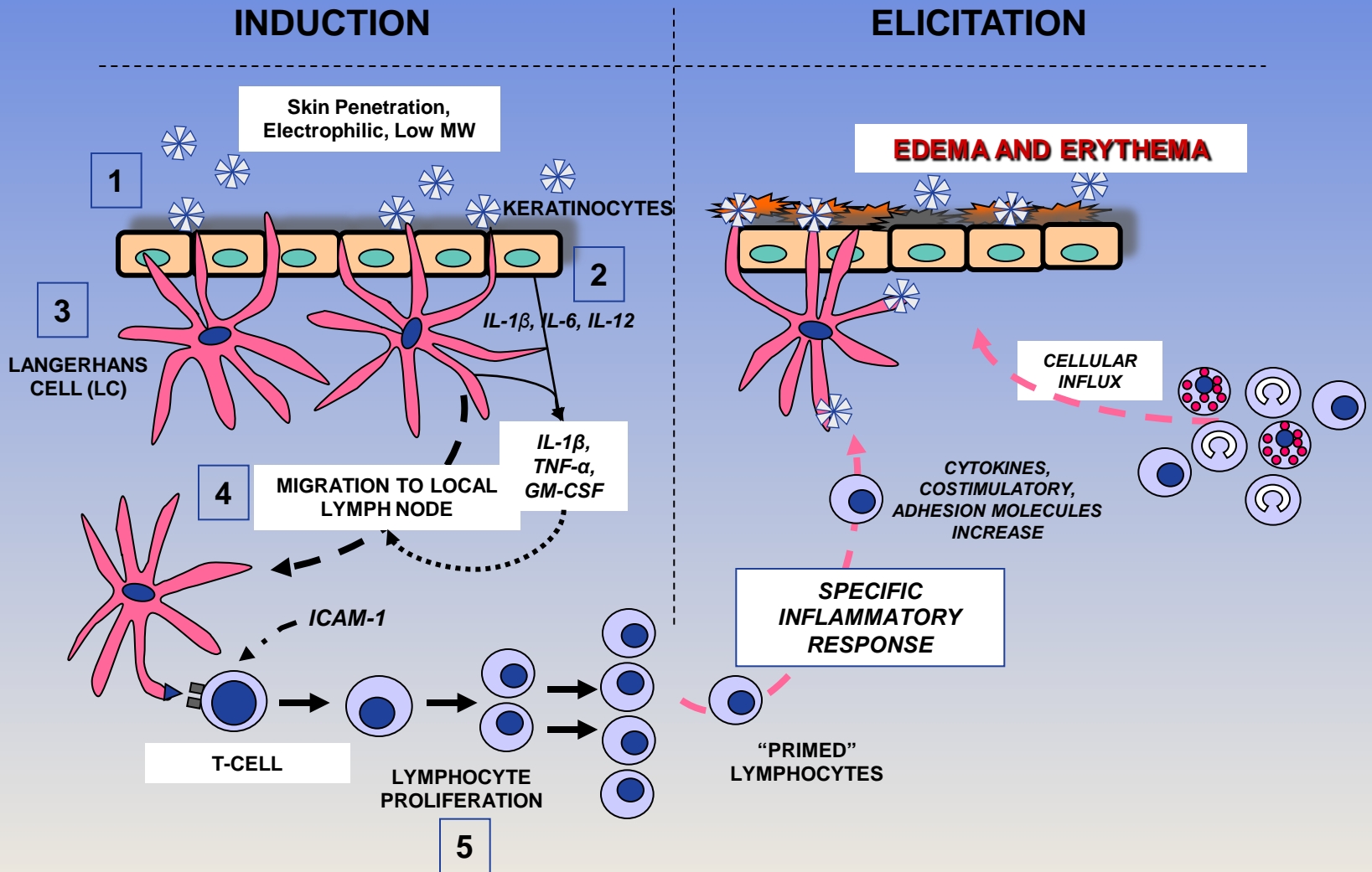
Joanna Matheson
U.S. Consumer Product Safety Commission

This presentation reflects the views of the author, has not been reviewed or approved by, and may not necessarily reflect the views of the U.S. Consumer Product Safety Commission.

Sensitization

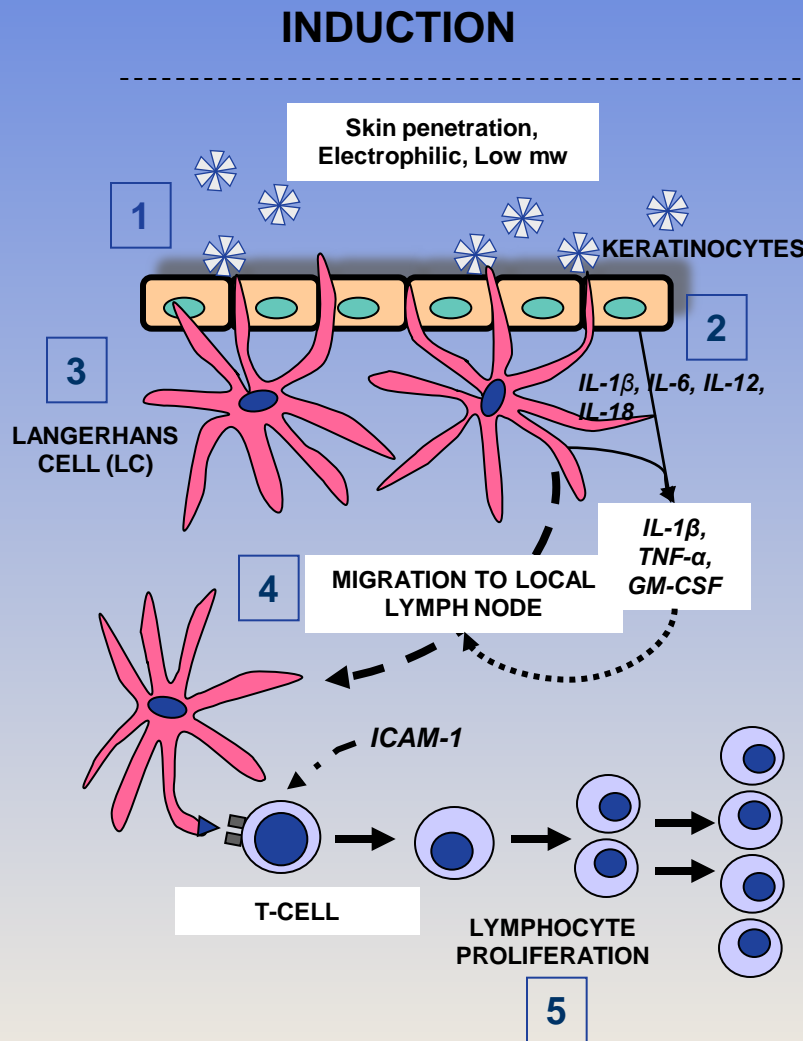
- ICCVAM: Interagency Coordinating Committee on the Validation of Alternative Methods, 15 Federal regulatory and research agencies
 - NICEATM: NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
- EURL-ECVAM: European Union Reference Laboratory for Alternatives to Animal Testing
- ICATM: International Cooperation on Alternative Test Methods
 - ICCVAM, EURL-ECVAM, JaCVAM, KoCVAM
- Cosmetics Europe (COLIPA)
- U.S. regulatory agencies that have needs and/or requirements for sensitization testing:
 - EPA, FDA, OSHA, CPSC

Skin Sensitization Pathway



*Illustration by D. Sailstad

Key Events in the Skin Sensitization AOP



EVENTS AND ASSAYS

In silico toxicokinetic model, QSARs, permeability methods

1. Haptenation: attachment of allergen to skin protein (DPRA, PPRA, EASA)
2. Epidermal inflammation: release of pro-inflammatory signals by epidermal keratinocytes (KeratinoSensSM, AREc32, LuSens, SENS-IS, NCTC, SenCeeTox, SensiDerm, NCTC)
3. Dendritic cell (DC) activation and maturation (h-CLAT, MUSST, PBMDc, VITOSens, GARD)
4. DC migration: movement of DC bearing hapten-protein complex from skin to draining local lymph node
5. T-cell proliferation: clonal expansion of hapten-peptide specific T-cells (local lymph node assay [LLNA], hTCPA)

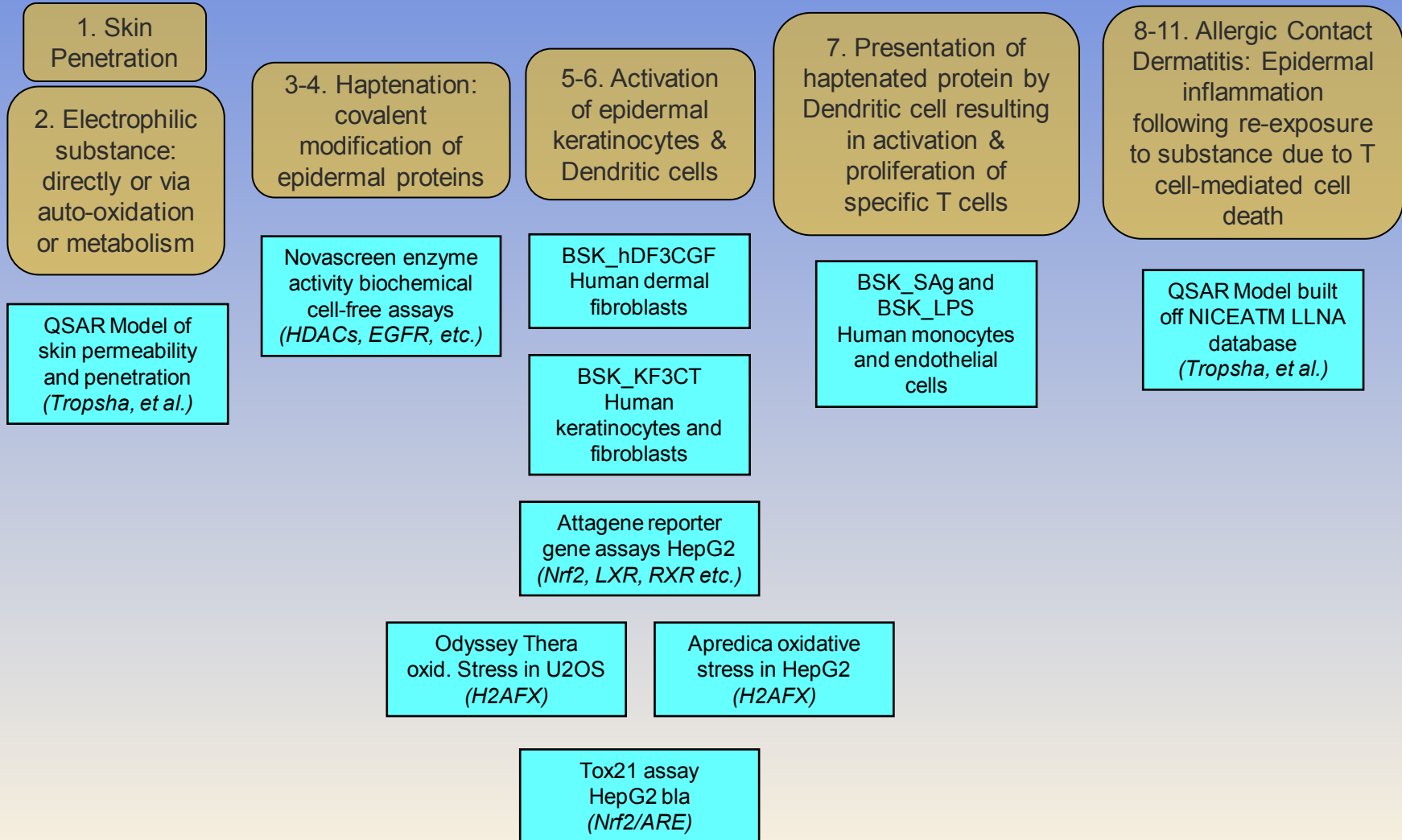
Integrated Testing Strategy (ITS) for Skin Sensitization

- NICEATM developed a strategy that uses:
 - A structural assessment of reactivity (Safford et al. 2011)
 - Direct peptide reactivity assay (DPRA) data
 - rLLNA data
- NICEATM collaboration with UNC-CH: developed multiple QSAR models (using multiple 2D chemical descriptors and Random Forests) with 262 substances from the original rLLNA database.
- NICEATM collaboration with Dr. Joanna Jaworska (P&G) developing open-source Bayesian network that uses physicochemical, *in silico*, *in chemico* and *in vitro* inputs to predict skin sensitization.
 - Probabilistic graphical models
 - Probability of potency category

Integrated Testing Strategy (ITS) for Skin Sensitization

- High throughput systems, Tox21 Assays
- Relevant assays which may predict skin sensitizing activity
 - EPA's ToxCast:
 - Evaluating activity signatures across the 700+ assays of EPA's ToxCast to determine the ability to predict reference immunotoxicity endpoints
 - 52 substances nominated by the NTP based on immunological relevance and correspondence to the AOP
 - NTP's High Throughput Screening program with the National Human Genome Research Institute's NIH Chemical Genomics Center (NCGC), with a library of 10,000+ compounds

Tox21 Assays aligned to AOP key events



Nomination Steps to ICCVAM

Sponsor submits test method nomination to NICEATM and ICCVAM

NICEATM conducts preliminary evaluation of nomination to assess the extent to which it addresses prioritization criteria

ICCVAM considers NICEATM preliminary evaluation and drafts recommended review activity and draft priority

ICCVAM solicits additional relevant data and comments from **public**

Public meeting of SACATM: SACATM provides comments; another opportunity for **public** comment

Final ICCVAM recommendations on priority/activities by ICCVAM (**workshops/evaluations**) or stakeholder organizations with resources (validation studies)