



# Interagency Coordinating Committee on the Validation of Alternative Methods

## Adverse Outcome Pathways (AOP)

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U.S. Consumer Product Safety Commission

SACATM meeting

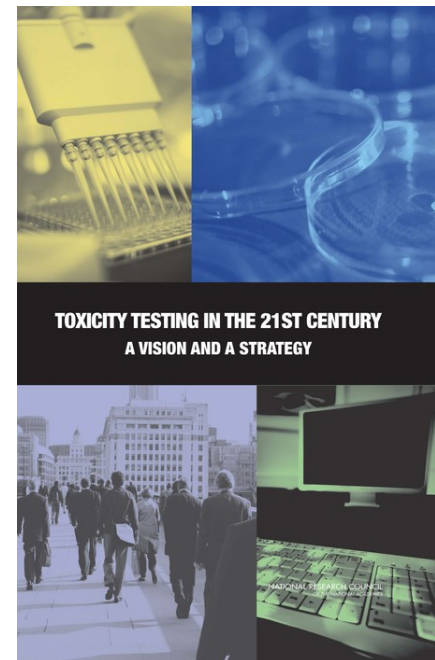
September 24, 2013

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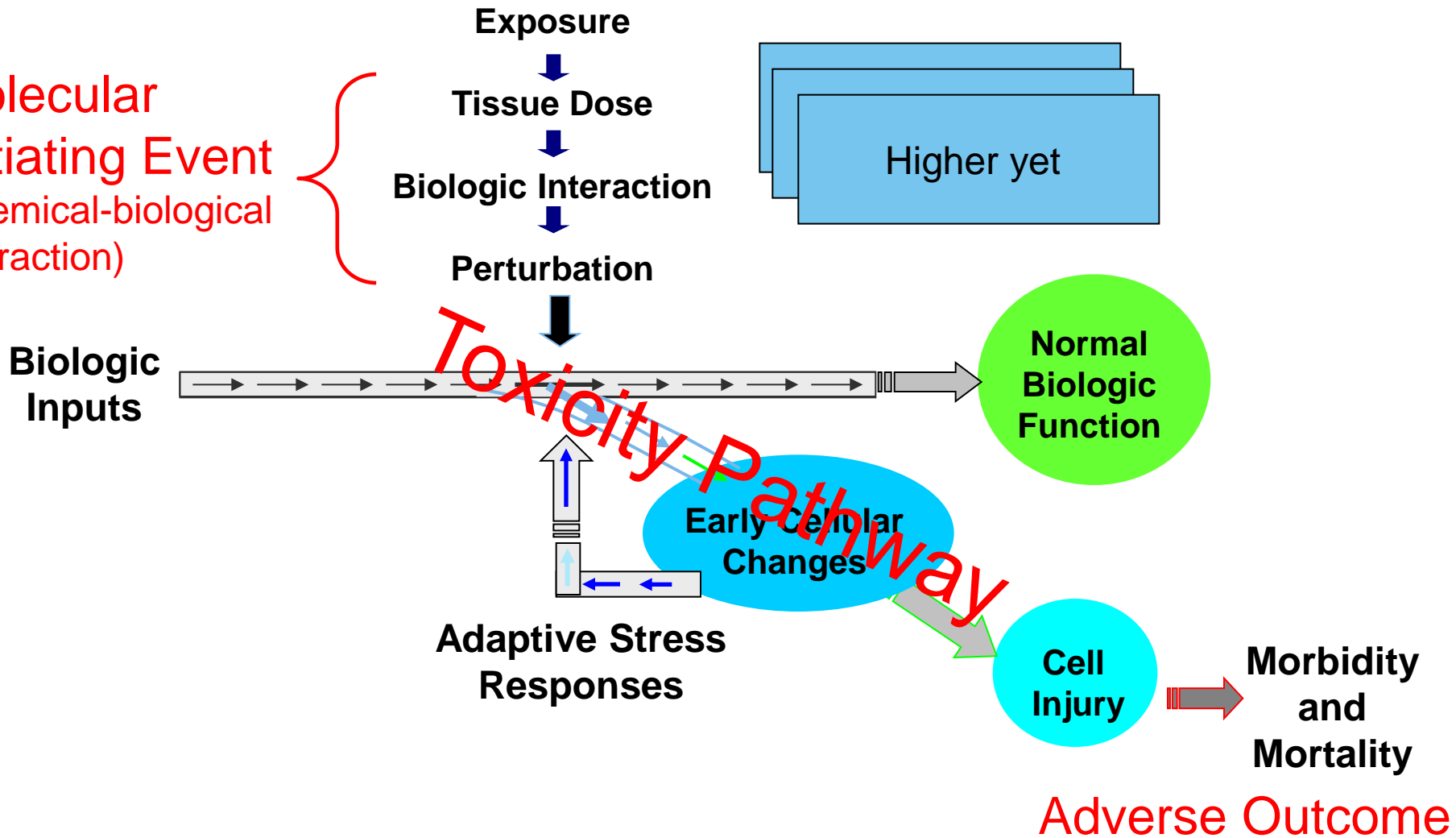
Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture  
Department of Defense • Department of Energy • Department of the Interior • Department of Transportation  
Environmental Protection Agency • Food and Drug Administration • National Institute 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

# AOP Brief Overview

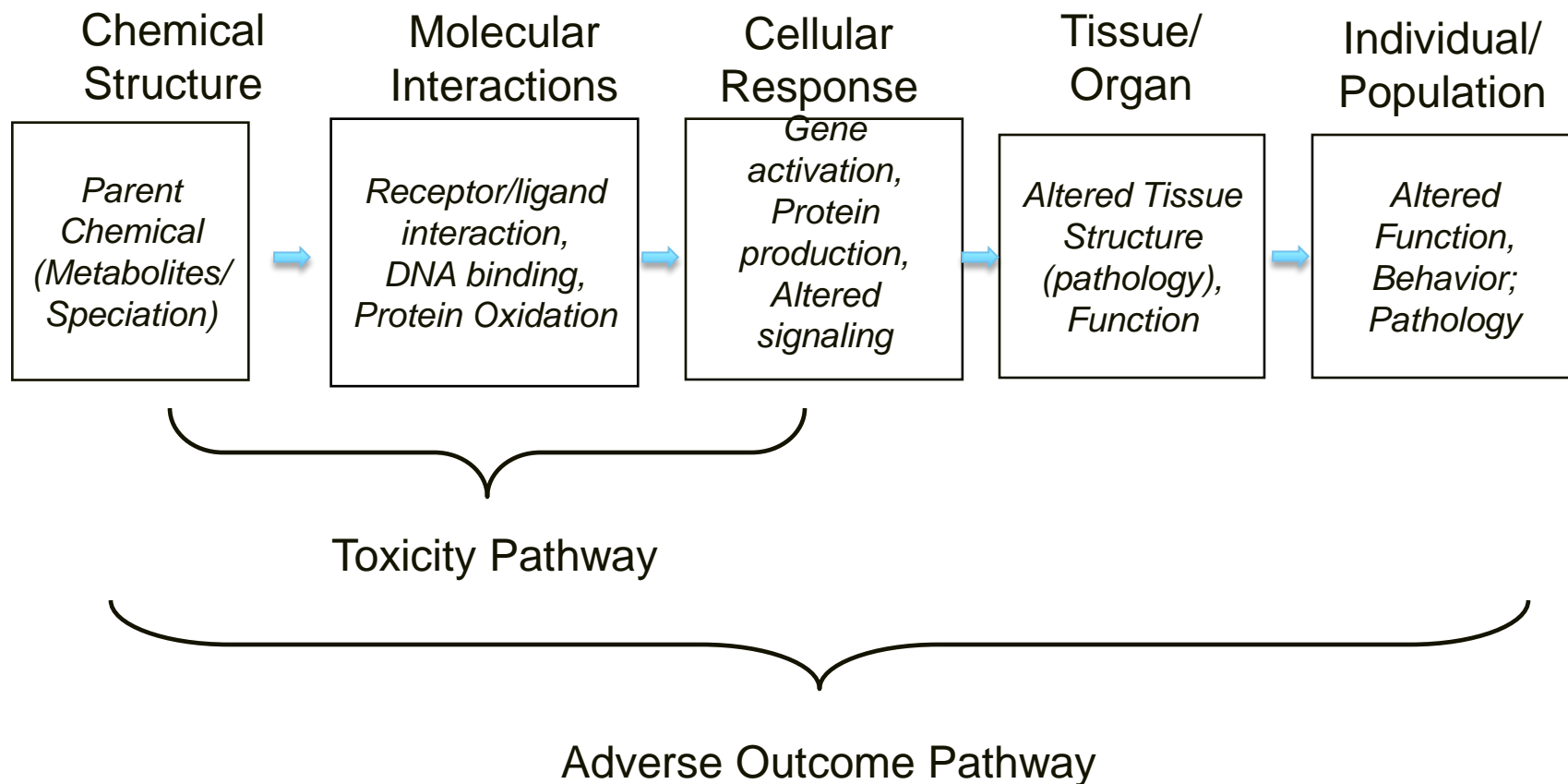
- Conceptual construct outlining the sequence of events from exposure through the adverse effect
- Mechanistic understanding of a chemical's effect at the molecular and cellular level



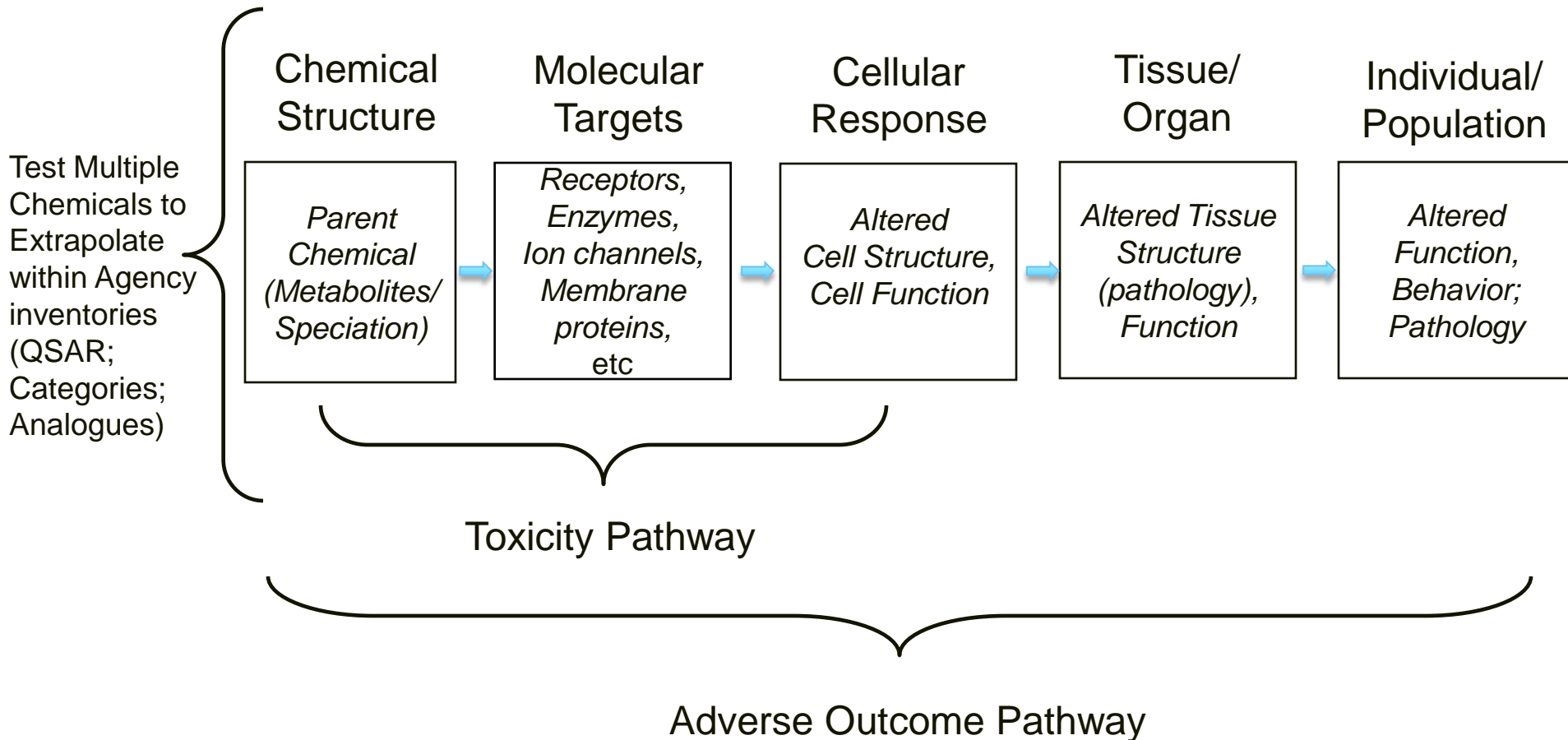
Molecular  
Initiating Event  
(chemical-biological  
interaction)



## General AOP Framework

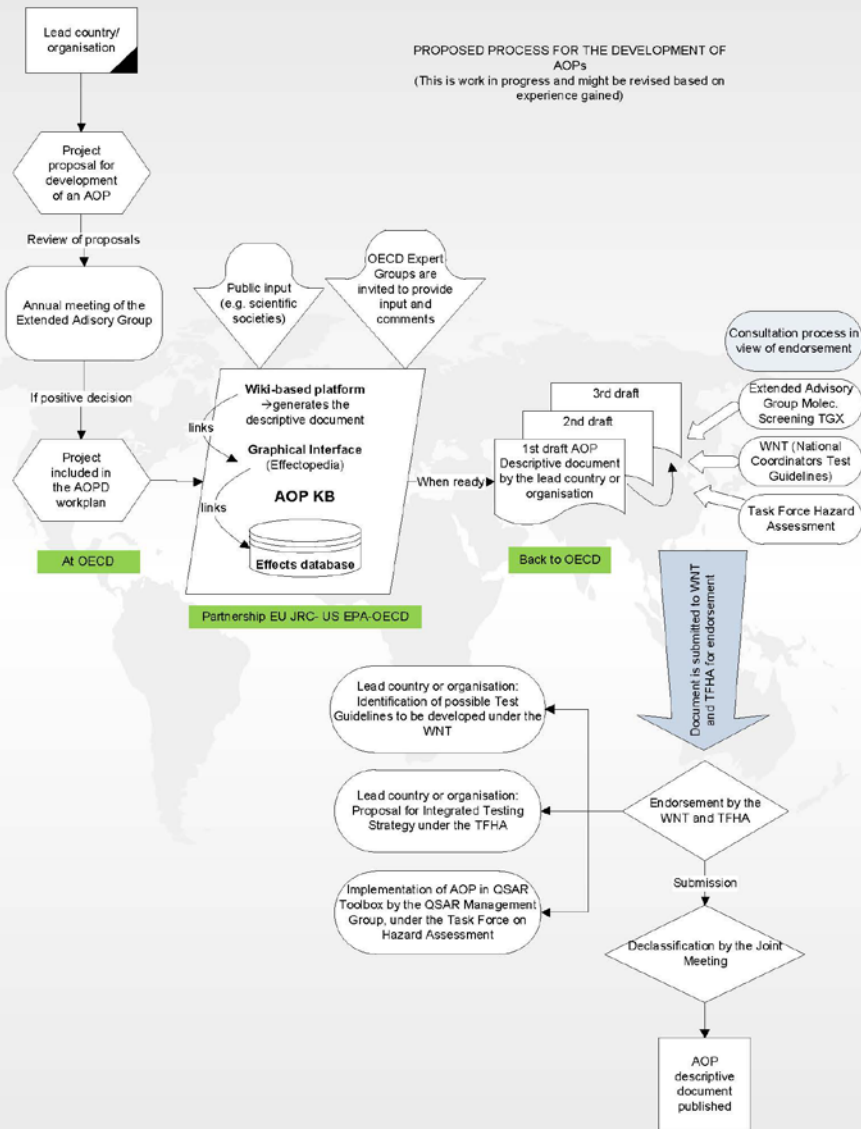


## AOP Applications: Chemical Extrapolation



# AOP Applications

- To develop chemical categories
  - Derive SARs, further develop QSAR toolbox
  - Prioritize chemicals for further assessment
- Inform data gaps for development of *in vitro*, *in silico*, *et. al.*, assays
- To develop integrated approaches to testing and assessment; tiered testing approach
- Increase confidence in chemical hazard and risk assessments



# Projects in the OECD AOP development program work plan

- 1.1 – Skin sensitization initiated by covalent binding to proteins (Secretariat)
- 1.2 – Nonpolar narcosis (US)
- 1.3 – Acetylcholinesterase inhibition (US)
- 1.4 – Cell signaling pathways (5) associated with cell proliferation and differentiation conserved across species (Secretariat)
- 1.5 – Mitochondrial toxicity (2) (Secretariat)
- 1.6 – Embryonic vascular disruption & developmental defects (US)
- 1.7 – Sustained activation of the avian aryl hydrocarbon receptor (Canada, BIAC)
- 1.8 – Mutagenic MOA for cancer (US)
- 1.9 – Upregulation of thyroid hormone catabolism via activation of hepatic nuclear receptors, and subsequent adverse neurodevelopmental outcomes in mammals (US)



# Projects in the OECD AOP development program work plan (cont.)

- 1.10 – Xenobiotic induced inhibition of thyroperoxidase and decreased TH synthesis and subsequent adverse neurodevelopmental outcomes in mammals (US)
- 1.11 – Heritable germ-cell derived disease (3) (Canada)
- 1.12 – AOPs linking aromatase inhibition, androgen receptor agonism, estrogen receptor antagonism, or steroidogenesis inhibition, to impaired reproduction in small repeat-spawning fish species (US)
- 1.13 – Neurotoxicant-induced neuroinflammation: a converging key event (Switzerland)
- 1.14 – Protein alkylation to liver fibrosis (European Commission)
- 1.15 – Neurotoxicity induced by GABAA receptor inhibition (US)
- 1.16 – Hematotoxicity due to nitroaromatics and n-hydroxyl anilines (US)
- 1.17 – CAR and PPAR $\alpha$ -mediated pathways to non-genotoxic rodent liver cancer (US)
- 1.18 – CAR and PXR-mediated pathways to rodent liver hyperplasia (US)

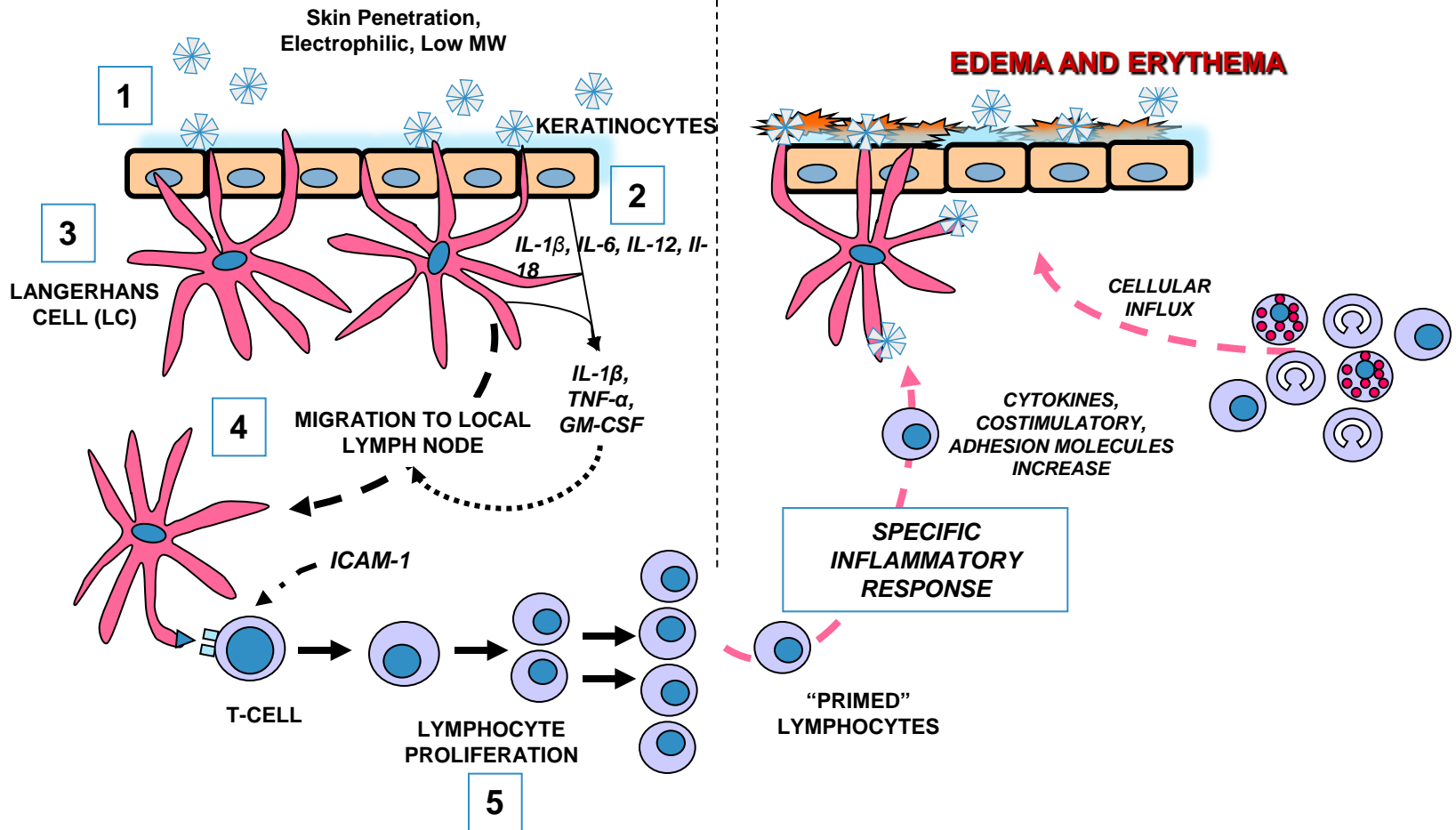
# AOP references

- <http://www.oecd.org/env/ehs/testing/molecularscreeningandtoxicogenomics.htm>
- <http://aopwiki.org/>
  - The AOP Wiki represents one component of a larger effort to build a comprehensive AOP knowledgebase (AOP KB). Other components include an AOP Network tool, being developed by the [US Army Corps of Engineers - Engineering Research and Development Center](#), and Effectopedia, being developed by the [International QSAR Foundation](#). Following completion, an integrated AOP KB will be formed with a focus on formalizing AOP information to facilitate computational modeling.
- [http://www.epa.gov/nheerl/articles/2011/Chemical\\_Safety\\_Assessments.html](http://www.epa.gov/nheerl/articles/2011/Chemical_Safety_Assessments.html)
- Ankley GT 2010, Adverse Outcome Pathways: a conceptual framework to support ecotoxicology research and risk assessment. Environ Toxicol Chem 29(3): 730-741.

# Skin Sensitization Pathway

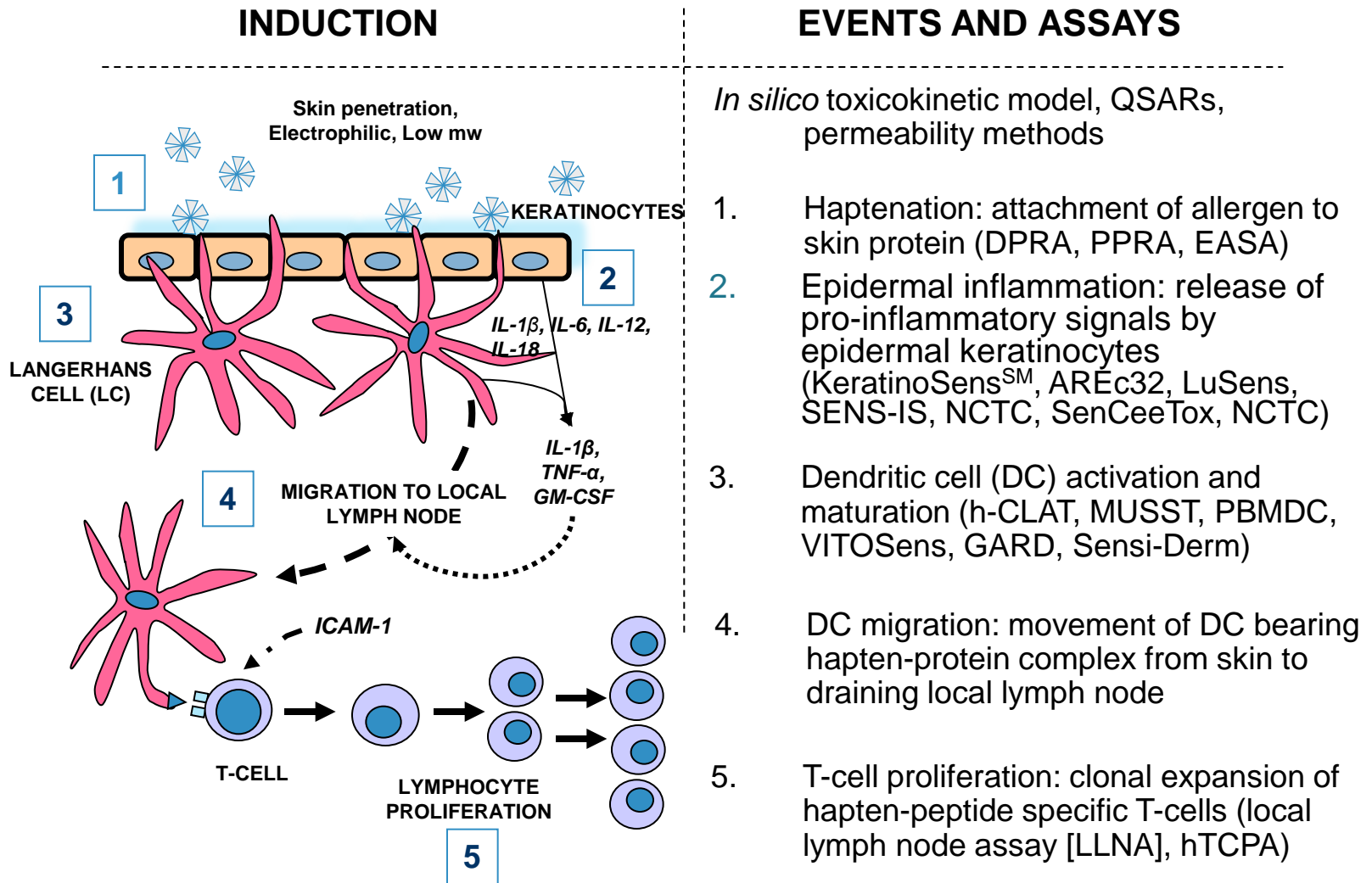
## INDUCTION

## ELICITATION



\*Illustration by D. Sailstad

# Key Events in the Skin Sensitization AOP



\*Illustration by D. Sailstad

## ICCVAM Activities

- Electrophilic Allergen Screening Assay (EASA), nominated by NIOSH; AOP Key event 1
- NICEATM collaboration 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 ITS
- NICEATM evaluation of various high-throughput screening assays in coordination with NIEHS Tox21 activities



Thank you!