

# Application of the AOP framework to make regulatory decisions: Early case studies

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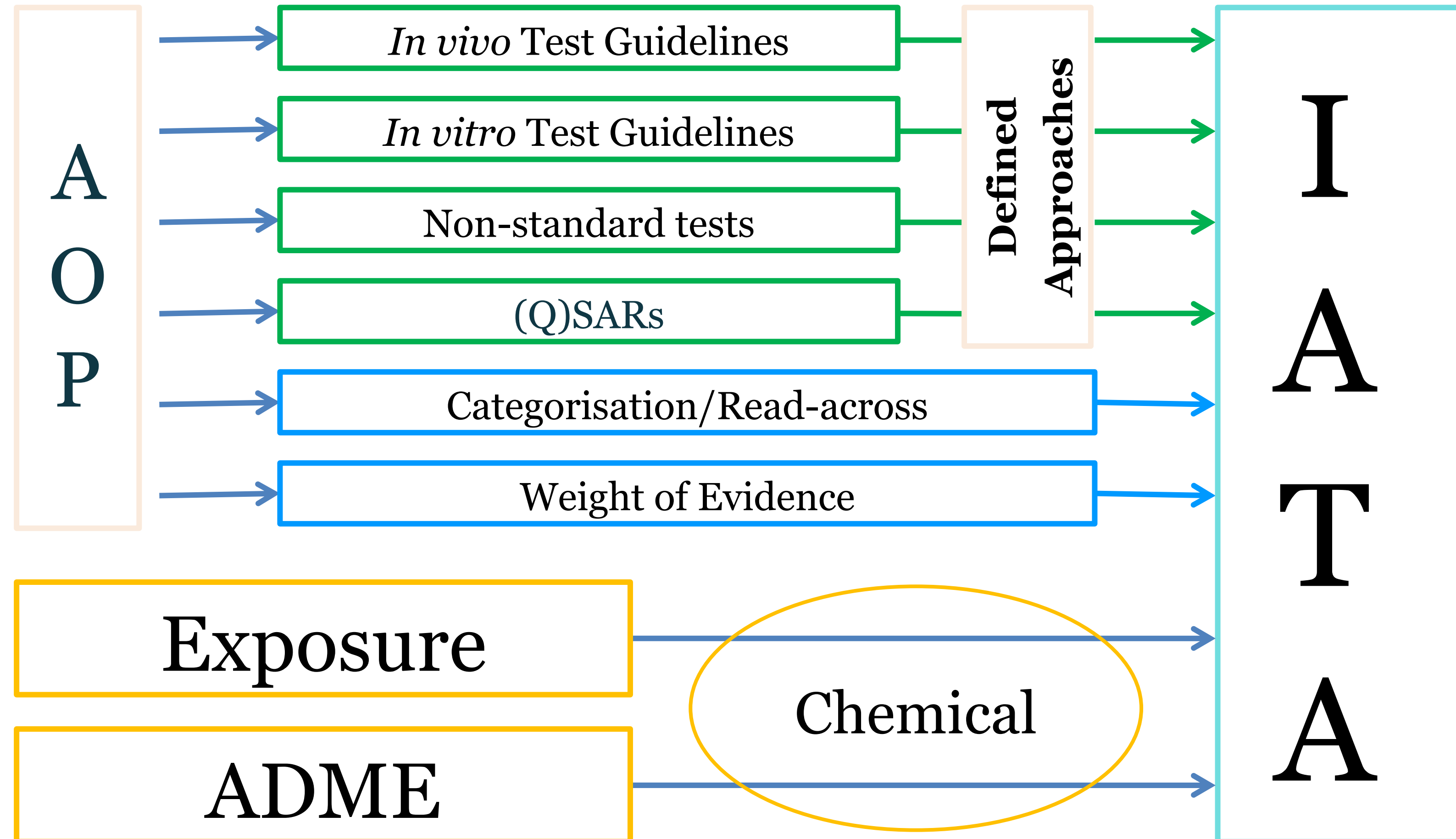
Vice President for Research Policy

PhysiciansCommittee  
for Responsible Medicine



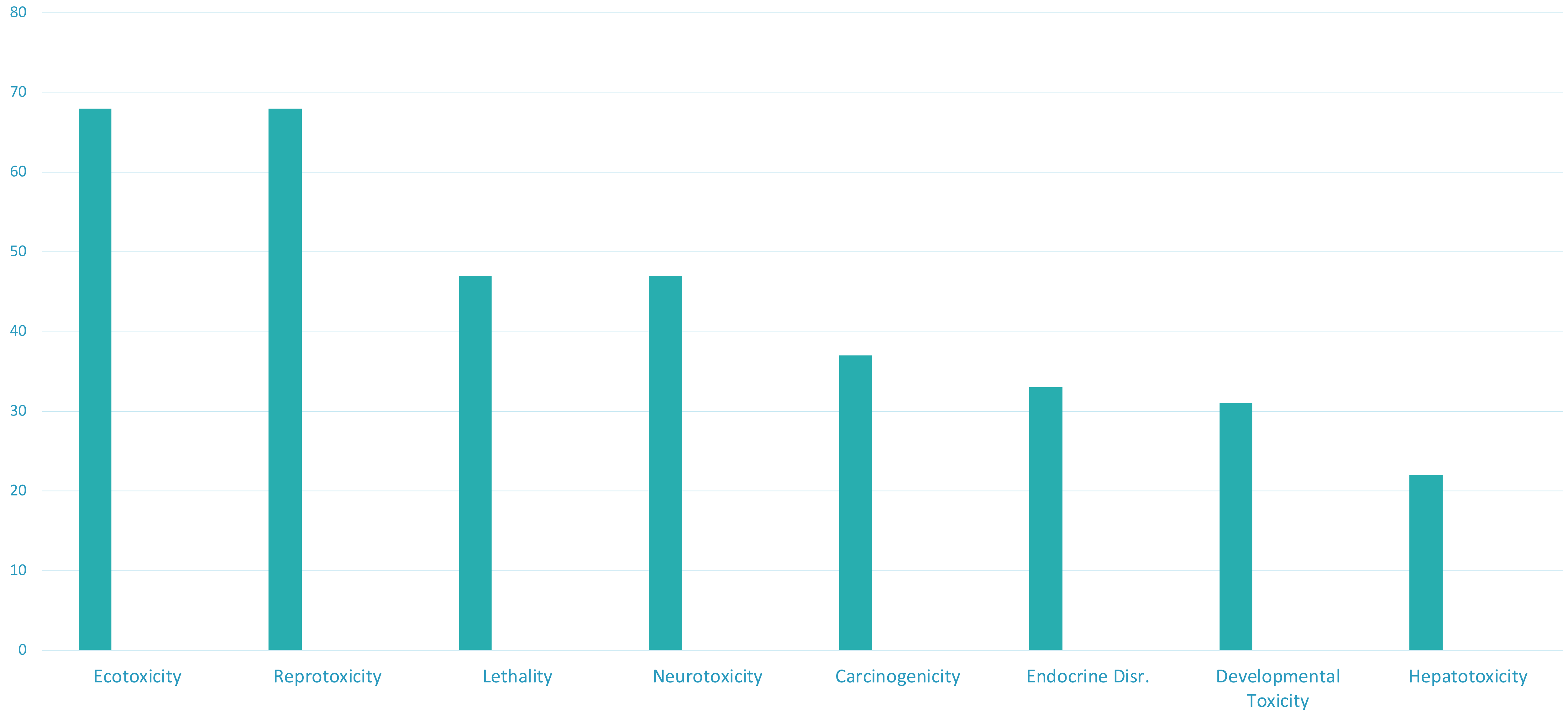


# AOPs Inform Evidence and Test Methods



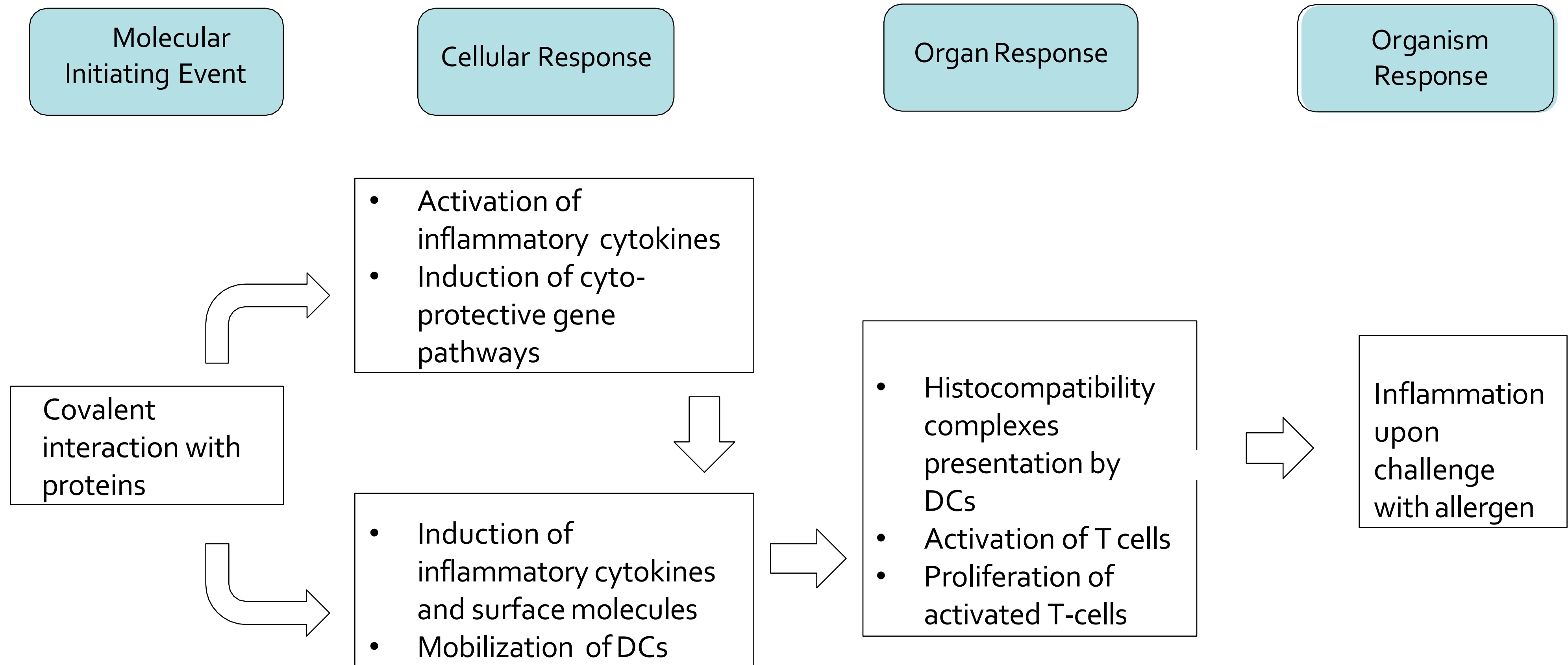


# AOP Wiki endpoint coverage



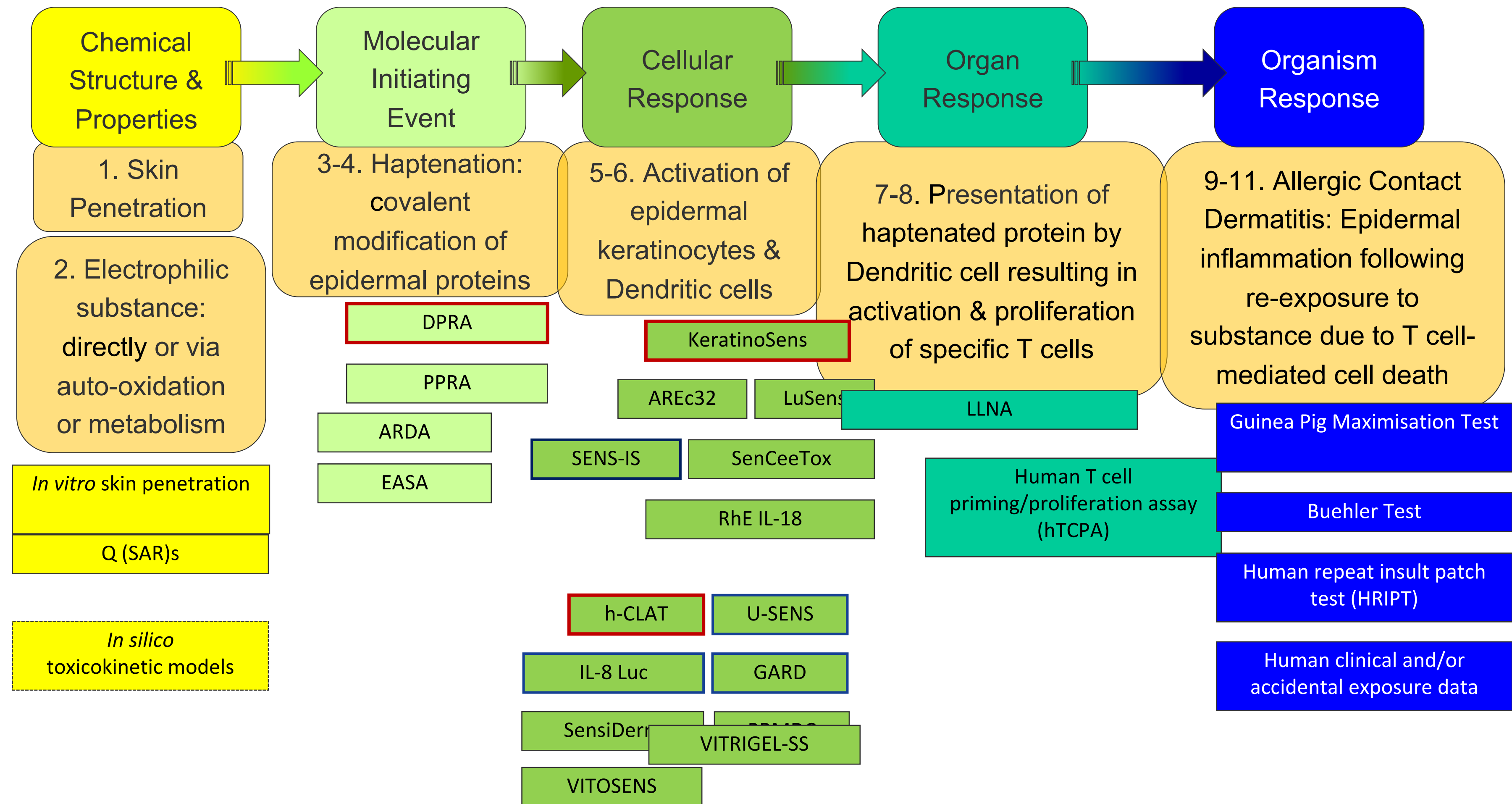


# Skin Sensitization AOP





# Mapping of Information Sources/Test Methods





- 2012: Skin Sensitization AOP published
- Test Guidelines published and updated each year
  - **Test No. 442C: In Chemico Skin Sensitisation:** *Direct Peptide Reactivity Assay (DPRA)*
  - **Test No. 442D: In Vitro Skin Sensitisation:** *ARE-Nrf2 Luciferase Test Method*
  - **Test No. 442E: In Vitro Skin Sensitisation:** *In Vitro Skin Sensitisation assays addressing the Key Event on activation of dendritic cells on the Adverse Outcome Pathway for Skin Sensitisation*

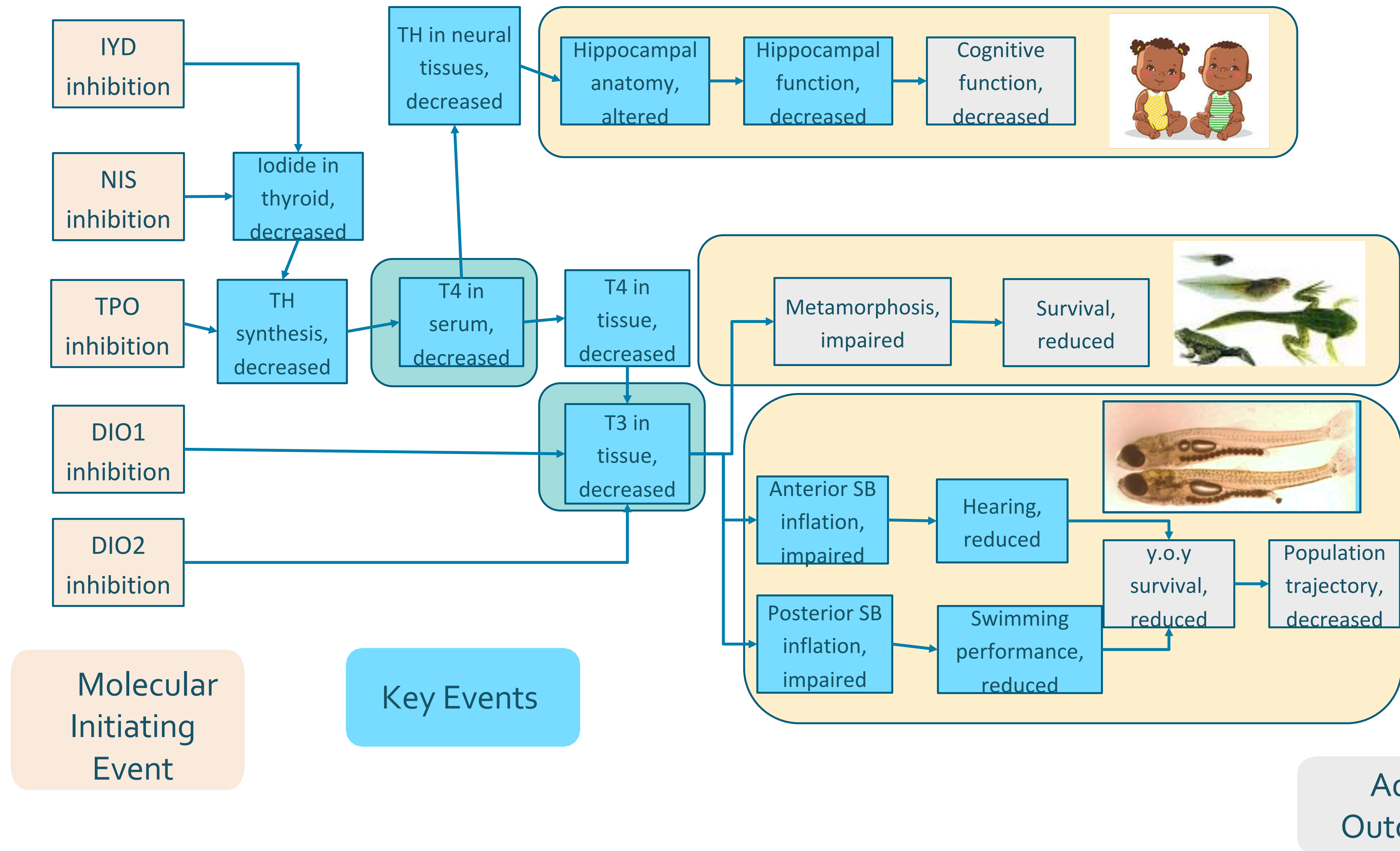


- 2016: [No. 256](#) Guidance Document on the Reporting of Defined Approaches and Individual Information Sources to be Used Within Integrated Approaches to Testing and Assessment (IATA) for Skin Sensitisation, [Annex 1](#), [Annex 2](#)
- 2018: EPA releases [Draft Interim Science Policy: Use of Alternative Approaches for Skin Sensitization as a Replacement for Laboratory Animal Testing](#)
- Ongoing project to adopt a Defined Approach test guideline at OECD



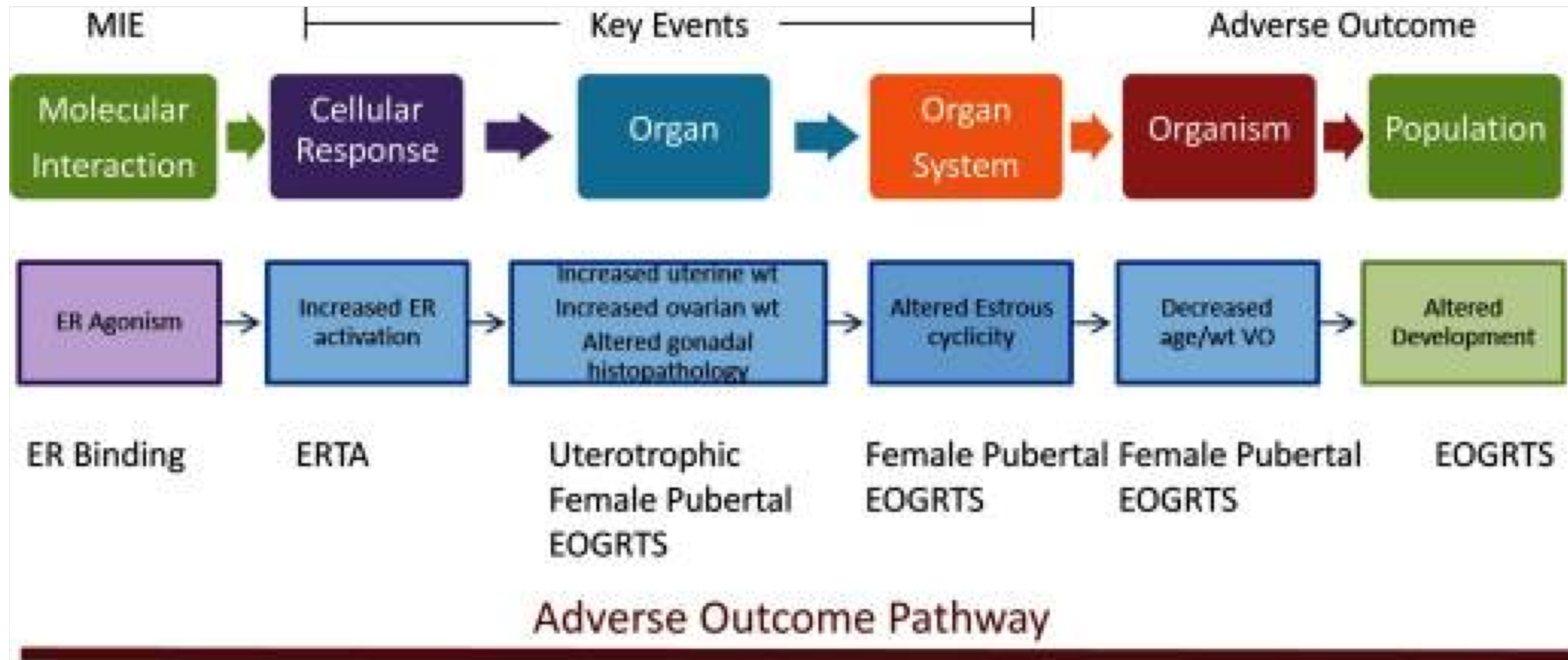


# AOP ELEMENTS: THYROID AOP NETWORK





# Endocrine Disruption: EPA EDSP

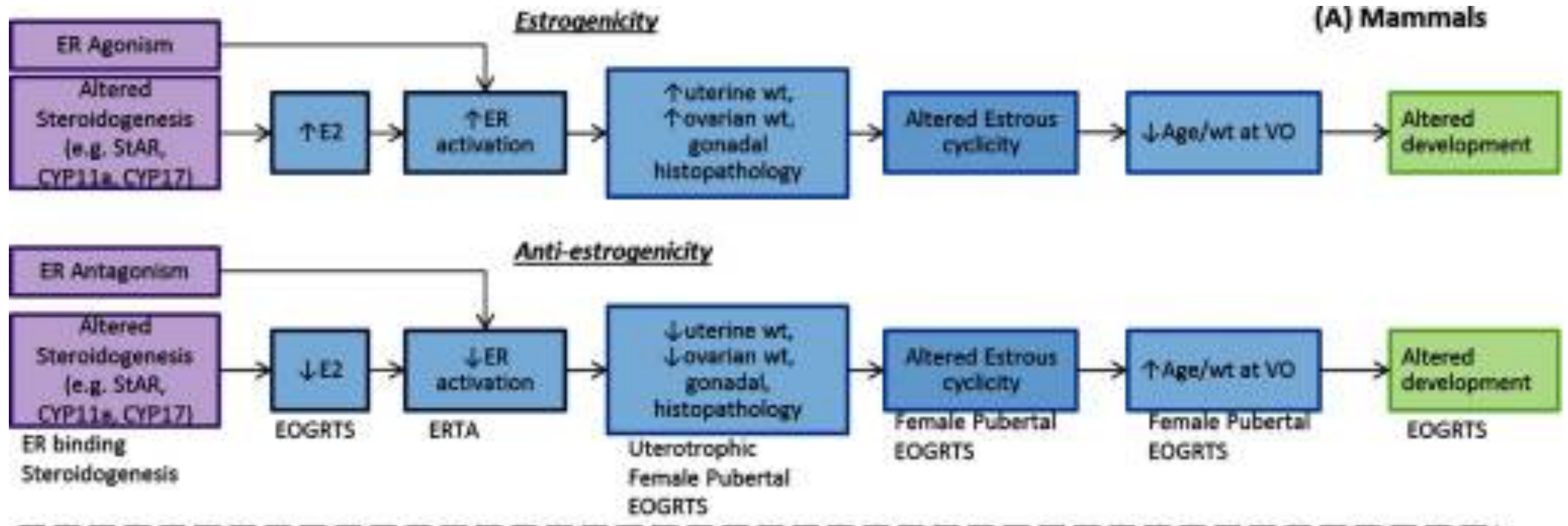


Browne P, Noyes PD, Casey WM, Dix DJ. Application of Adverse Outcome Pathways to U.S. EPA's Endocrine Disruptor Screening Program. *Environ Health Perspect*. 2017;125(9):096001. Published 2017 Sep 1.

doi:10.1289/EHP1304



# Endocrine Disruption: EPA EDSP



Browne P, Noyes PD, Casey WM, Dix DJ. Application of Adverse Outcome Pathways to U.S. EPA's Endocrine Disruptor Screening Program. *Environ Health Perspect.* 2017;125(9):096001. Published 2017 Sep 1.

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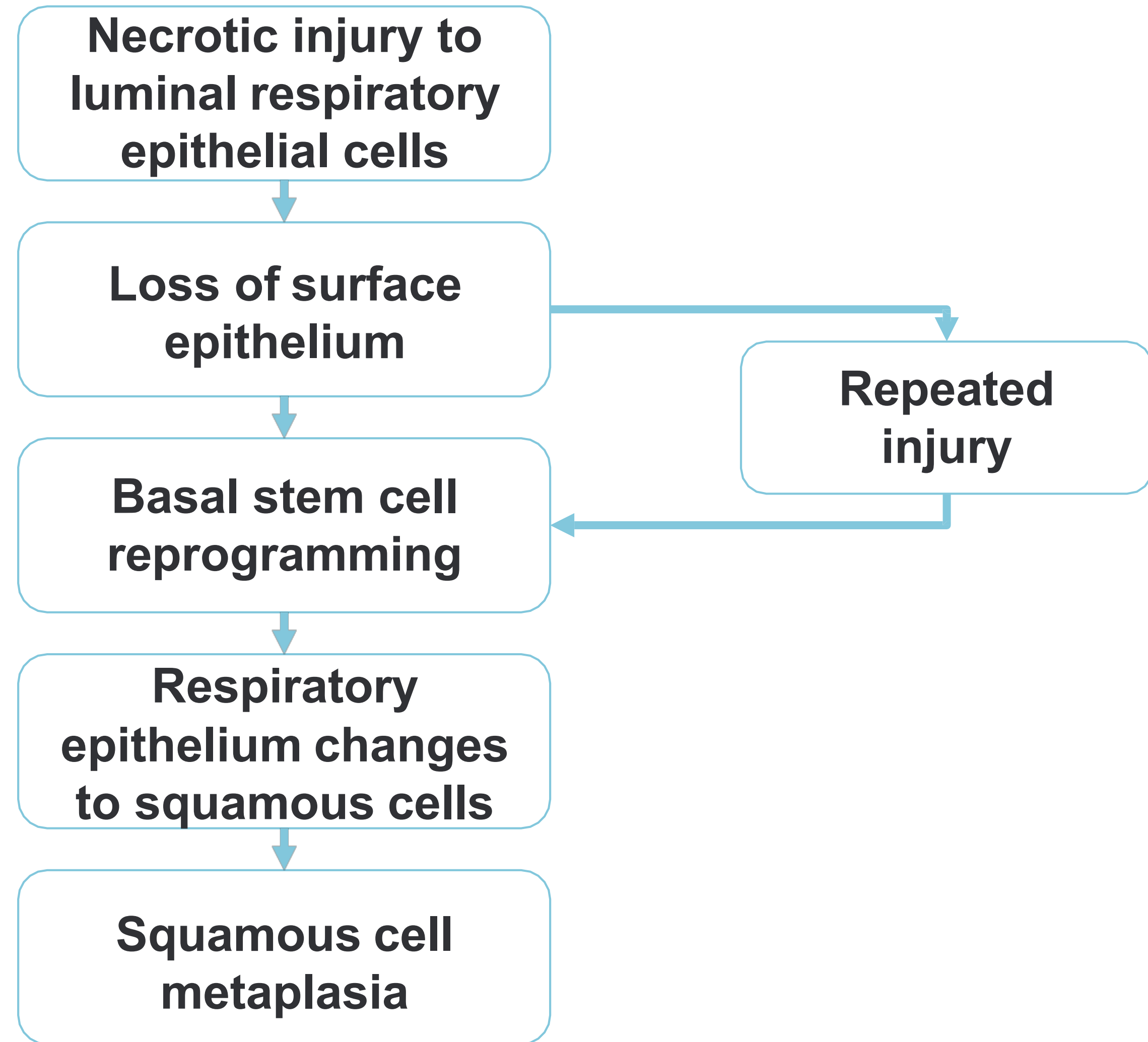
- 2012: EDSP21 launched to transition in the project to a mechanistic approach
- EPA develops Estrogen and Androgen receptor bioactivity predictive models
  - [Development and Validation of a Computational Model for Androgen Receptor Activity](#)  
Kleinstreuer NC et al. Chem Res Toxicol. 2017 Apr 17;30(4):946-964. doi: 10.1021/acs.chemrestox.6b00347.
  - [Screening Chemicals for Estrogen Receptor Bioactivity Using a Computational Model.](#)  
Browne P et al. Environ Sci Technol. 2015 Jul 21;49(14):8804-14. doi: 10.1021/acs.est.5b02641.
  - Science Advisory Panel reviews in 2014 and 2017
- [Endocrine Disruptor Screening Program \(EDSP\) Estrogen Receptor Bioactivity results and EDSP21 Dashboard](#)
- 2018: [Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption](#)
- Steroidogenesis and Thyroid models under active development and review



# Adverse Outcome Pathway for squamous cell metaplasia of the larynx

Adapted from: Renne R, Brix A, Harkema J, Herbert R, Kittel B, Lewis D, March T, Nagano K, Pino M, Rittinghausen S, Rosenbruch M, Tellier P, Wohrmann T (2009) Proliferative and Nonproliferative Lesions of the Rat and Mouse Respiratory Tract, Tox Path, 37:5D-73S

\*Slide from: Syngenta Crop Protection, December 2018 FIFRA SAP meeting presentation



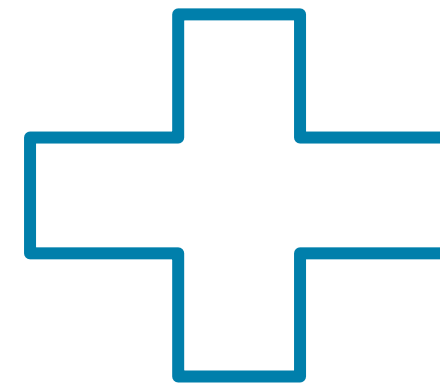
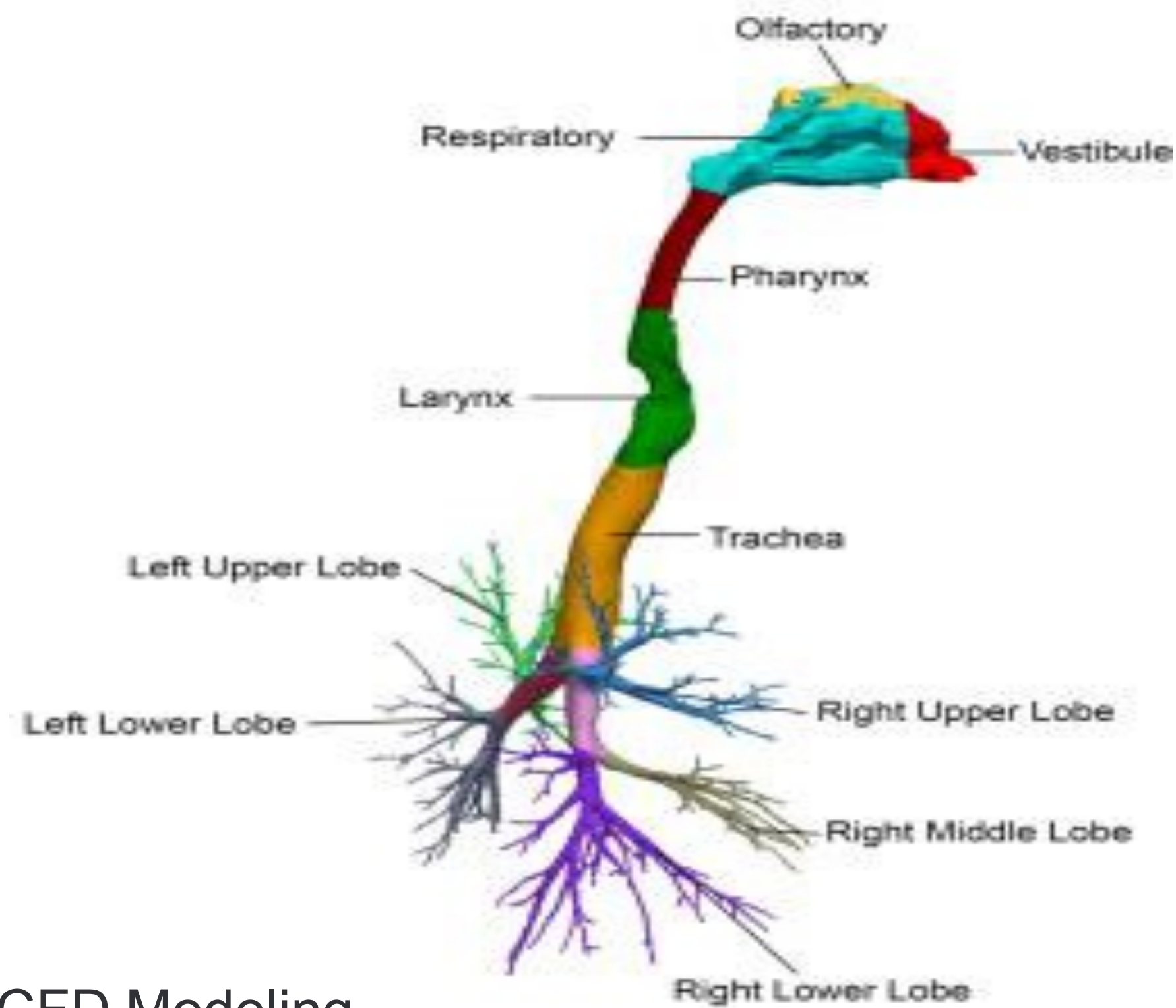




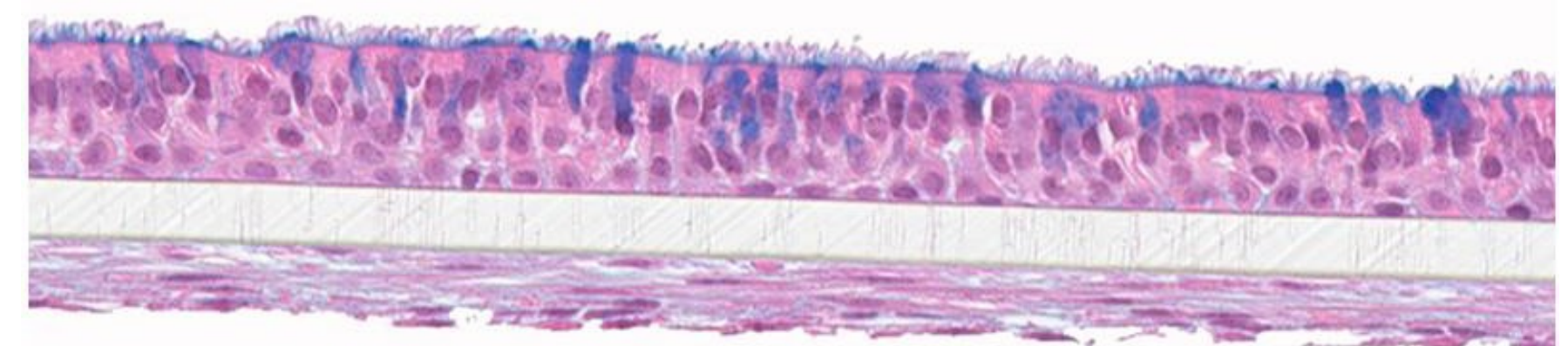
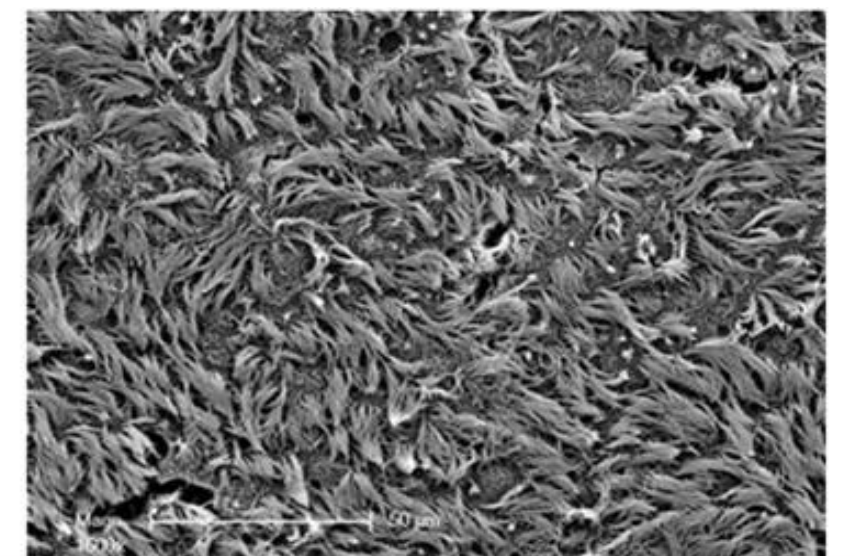
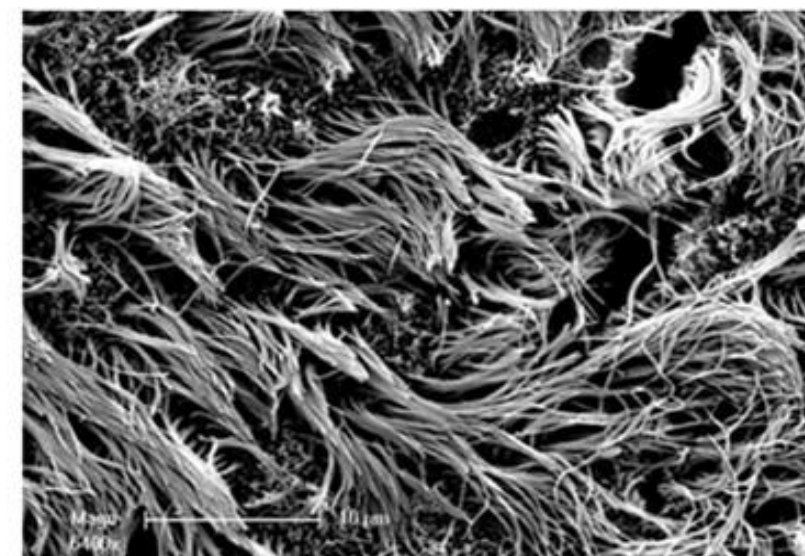
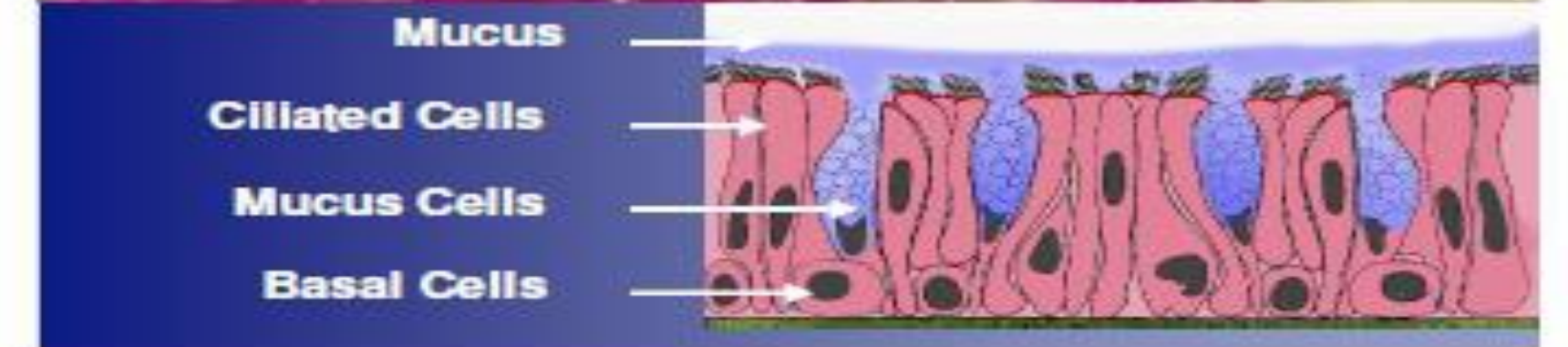
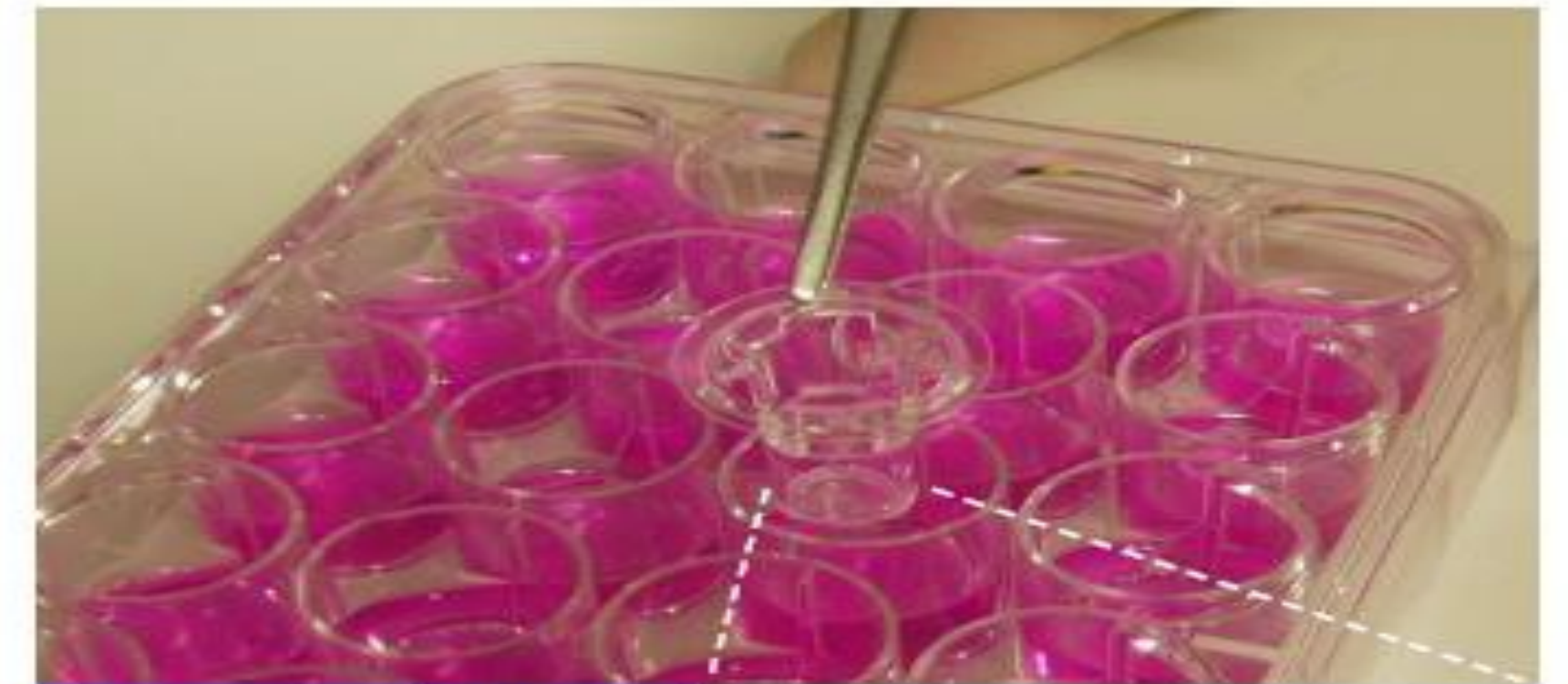
## Evaluation of a Proposed Approach to Refine Inhalation Risk Assessment for Point of Contact Toxicity: A Case Study Using a New Approach Methodology (NAM)

EPA FIFRA Science Advisory Panel meeting December 2018

Report expected April 2019



CFD Modeling



In vitro Testing





# AOP Wiki demonstration and hands-on activity





Finding AOPs and AOP info in the AOP Wiki

Entering information into the AOP Wiki

Adding a diagram





Endorsed AOPs: <https://doi.org/10.1787/2415170X>

OECD AOP Portal: <https://aopkb.oecd.org>

AOP Wiki: <https://aopwiki.org>





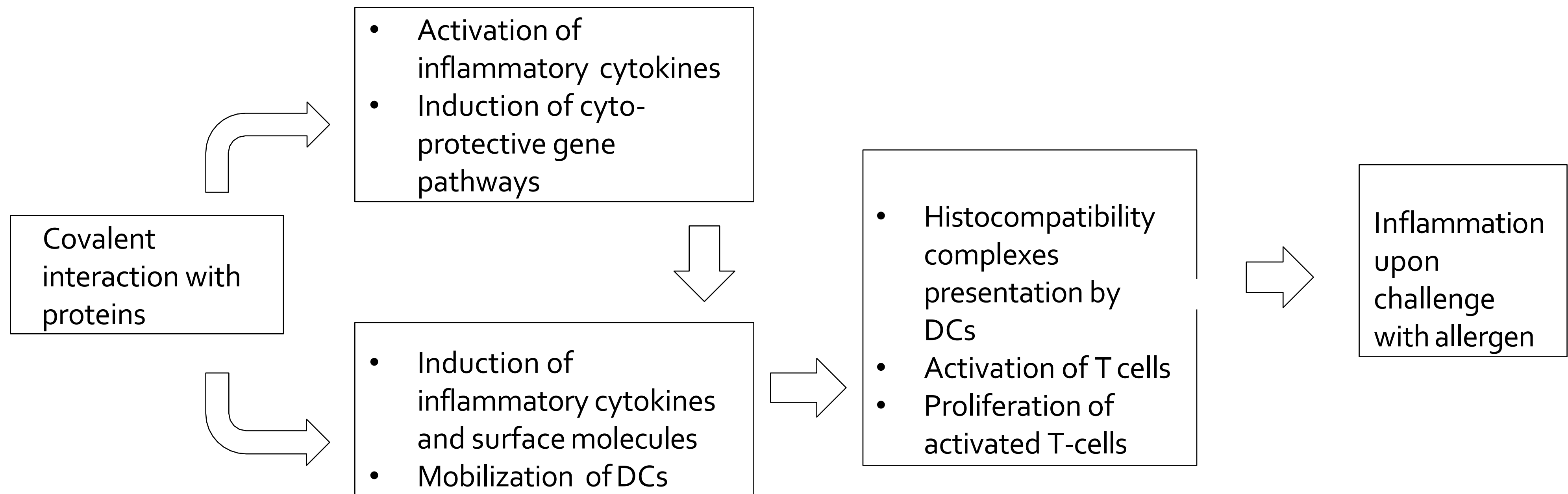
# AOP Training Wiki

<https://training.aopwiki.org>

User name: [author@epa.gov](mailto:author@epa.gov)

Password: AOPtraining4@!!









Request Access to AOP Wiki:

[www.saaop.org](http://www.saaop.org)

Developer's Handbook:

[https://one.oecd.org/document/ENV/JM/MONO\(2016\)12/en/pdf](https://one.oecd.org/document/ENV/JM/MONO(2016)12/en/pdf)