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

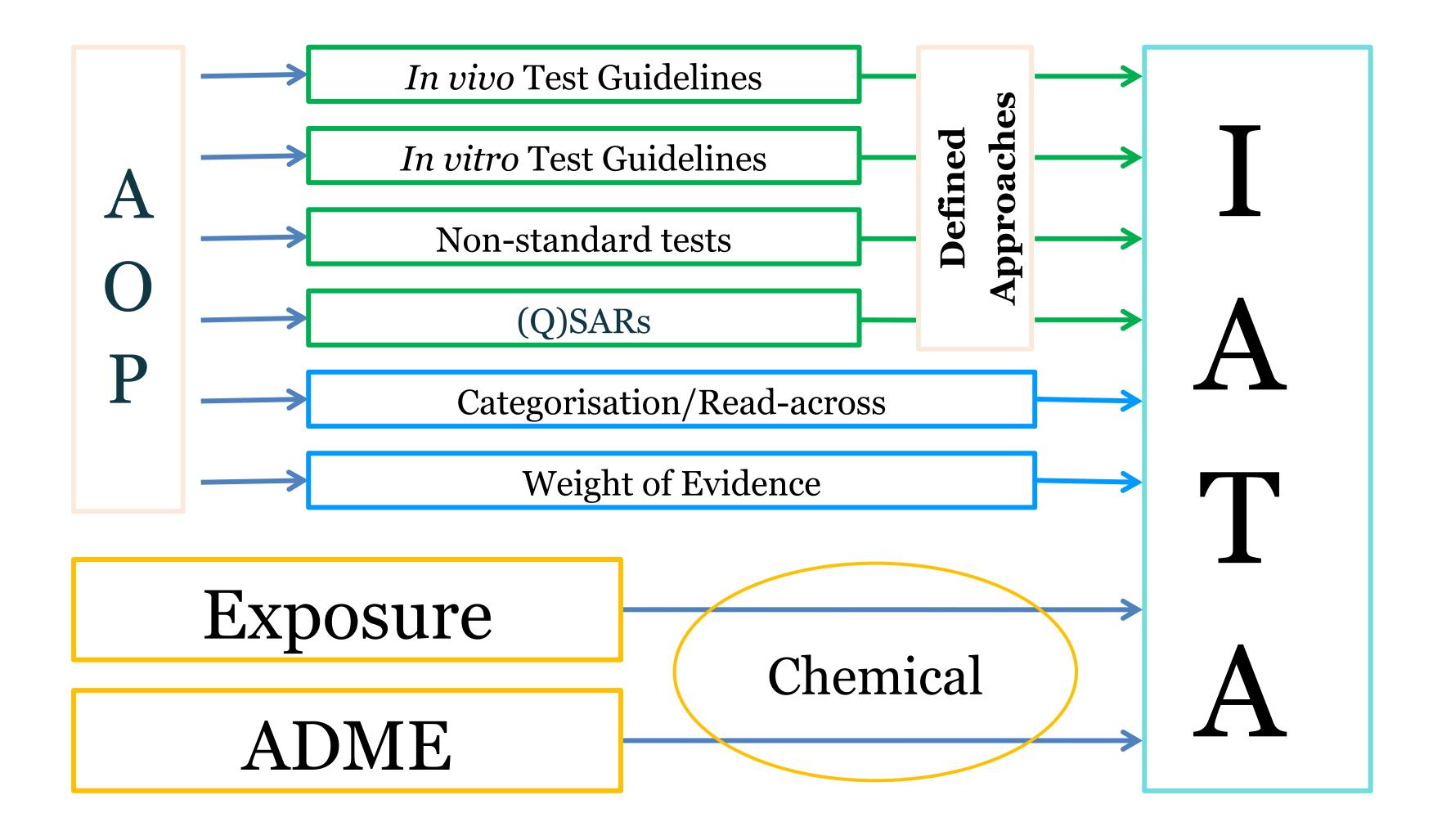
Kristie Sullivan, MPH
Vice President for Research Policy

Physicians Committee

for Responsible Medicine

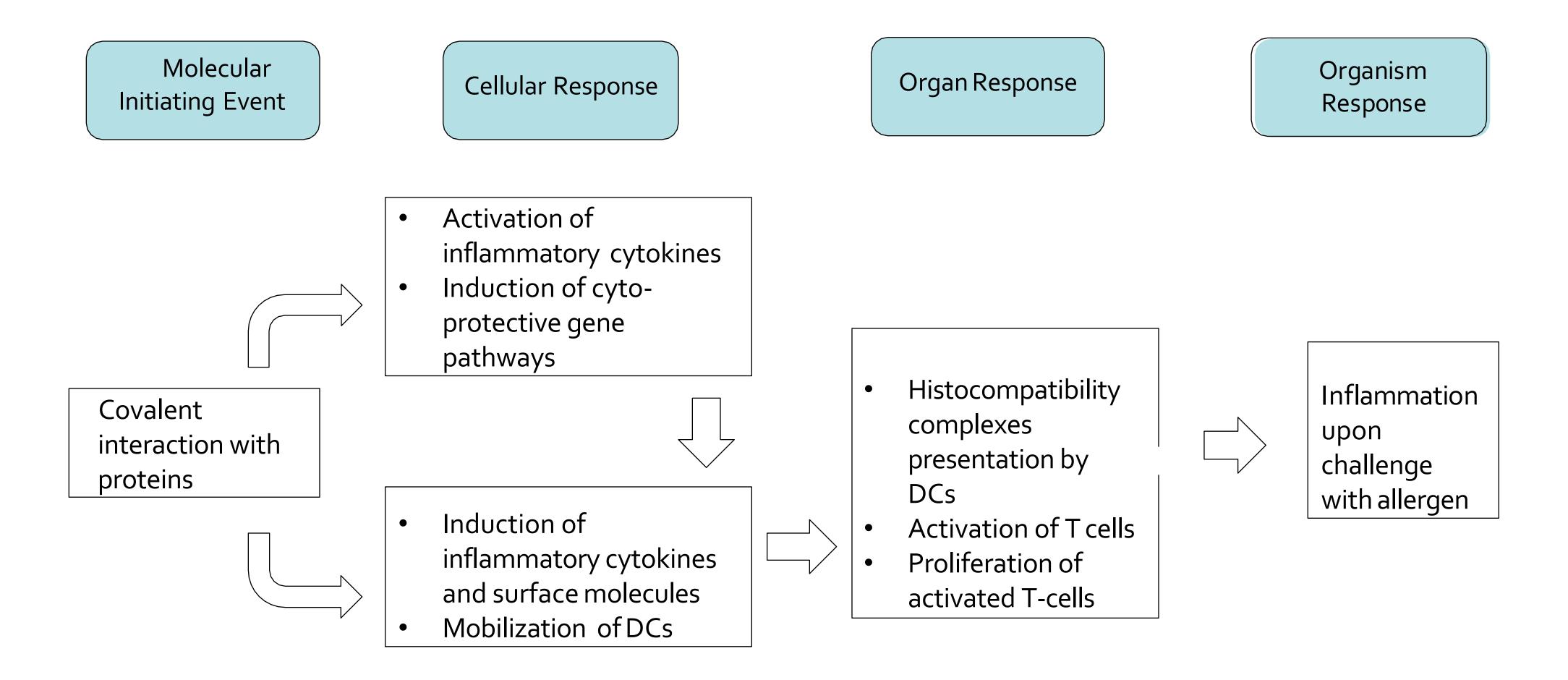


AOPs Inform Evidence and Test Methods



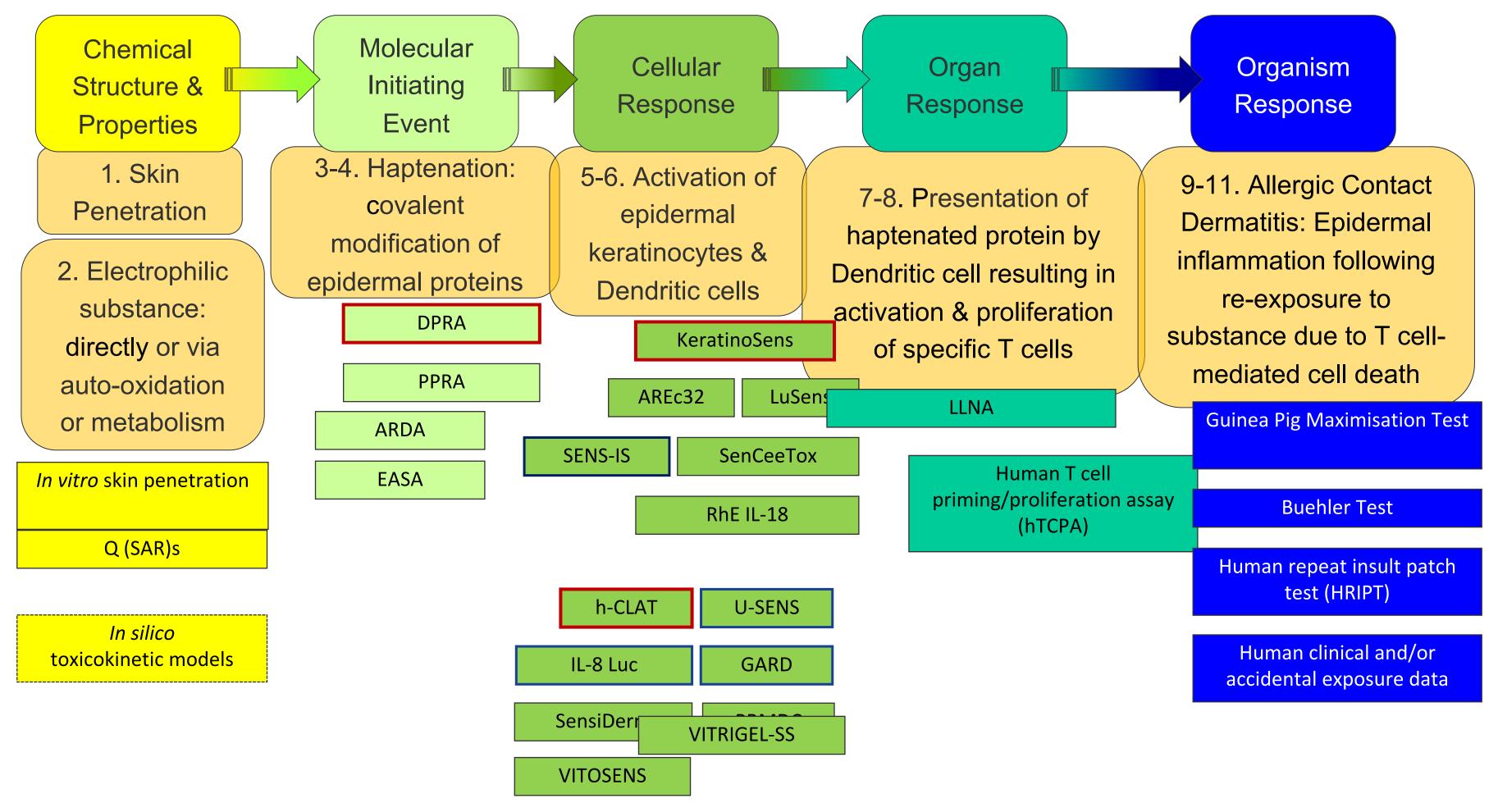
http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm

Skin Sensitization AOP



The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins Part 1: Scientific Evidence Series on Testing and Assessment No.168

Mapping of Information Sources/Test Methods



The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins Part 1: Scientific Evidence Series on Testing and Assessment No.168

- 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

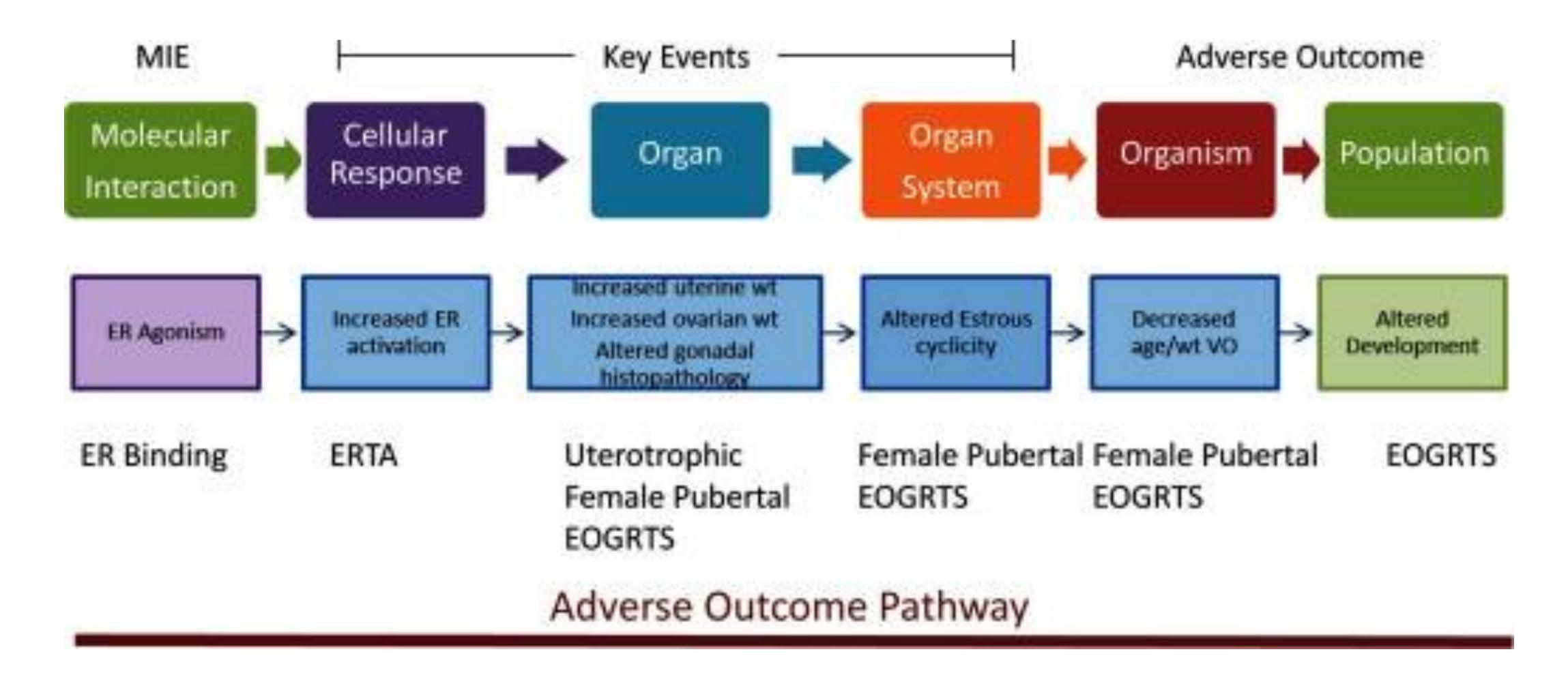
 2016: No. 256 Guidance Document on the Reporting of Defined Approaches and Individual Information Sources to be Used Within Integrated Approaches to Testing and Assessment (IATA) for Skin Sensitisation, <u>Annex 1</u>, <u>Annex 2</u>

• 2018: EPA releases <u>Draft Interim Science Policy</u>: <u>Use of Alternative Approaches for Skin Sensitization as a Replacement for Laboratory Animal Testing</u>

Ongoing project to adopt a Defined Approach test guideline at OECD

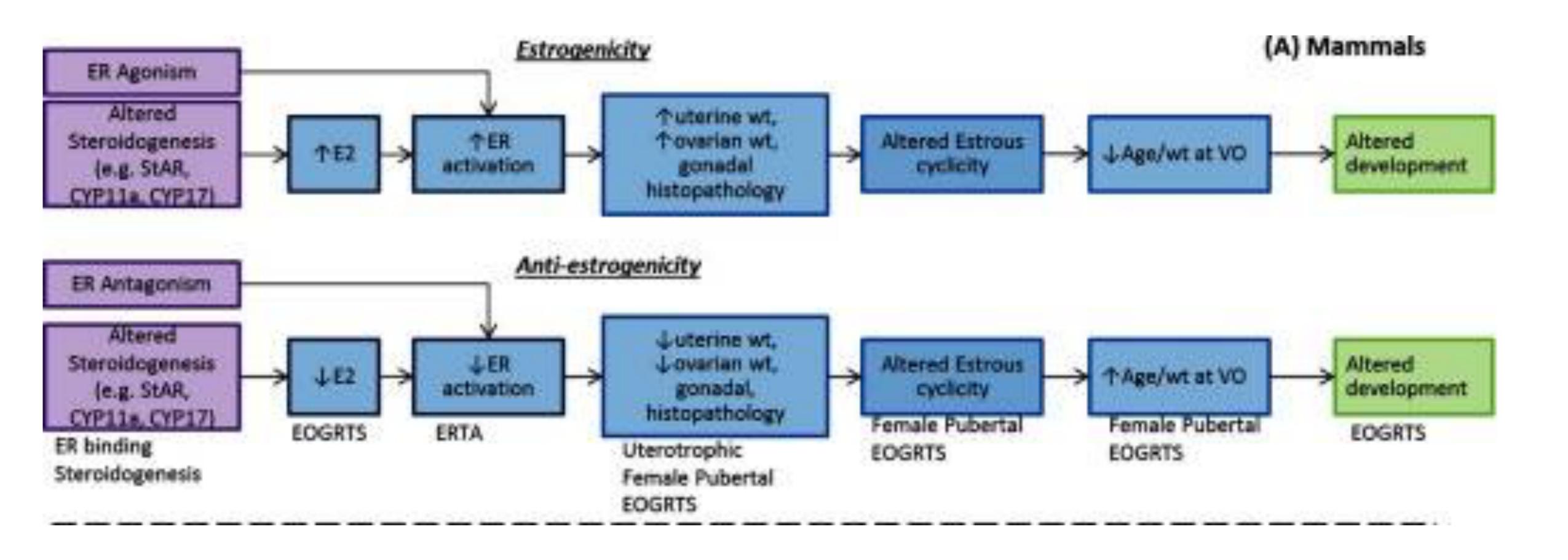


Endocrine Disruption: EPA EDSP



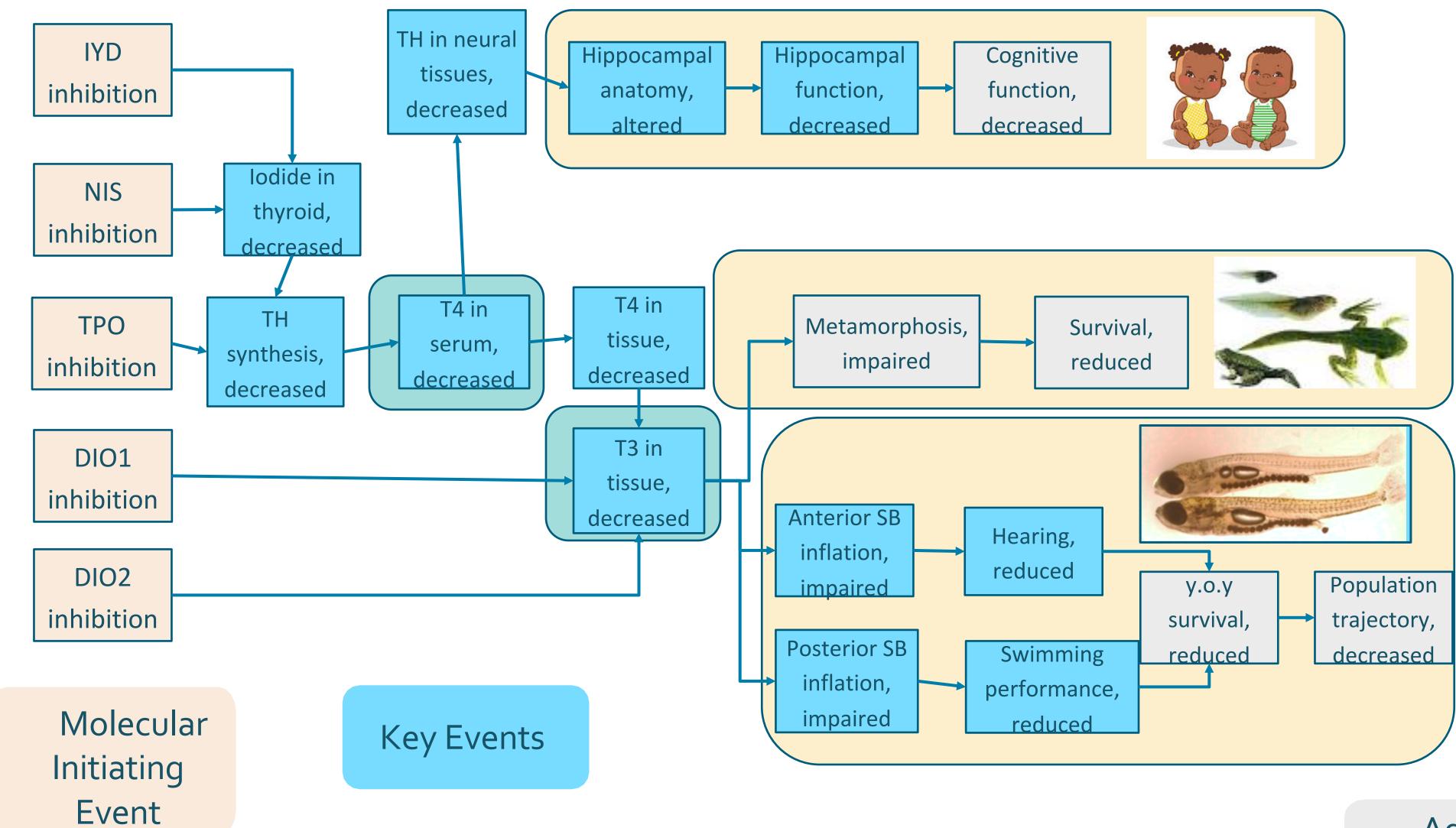
Browne P, Noyes PD, Casey WM, Dix DJ. Application of Adverse Outcome Pathways to U.S. EPA's Endocrine Disruptor Screening Program. *Environ Health Perspect*. 2017;125(9):096001. Published 2017 Sep 1. doi:10.1289/EHP1304

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. doi:10.1289/EHP1304

AOP ELEMENTS: THYROID AOP NETWORK



Adverse Outcome (s)

- 2012: EDSP21 launched to transition in the project to a mechanistic approach
- EPA develops Estrogen and Androgen receptor bioactivity predictive models
 - <u>Development and Validation of a Computational Model for Androgen Receptor Activity</u> Kleinstreuer NC et al. Chem Res Toxicol. 2017 Apr 17;30(4):946-964. doi: 10.1021/acs.chemrestox.6b00347.
 - <u>Screening Chemicals for Estrogen Receptor Bioactivity Using a Computational Model.</u>
 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: <u>Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption</u>
- Steroidogenesis and Thyroid models under active development and review



ENVIRONMEN

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

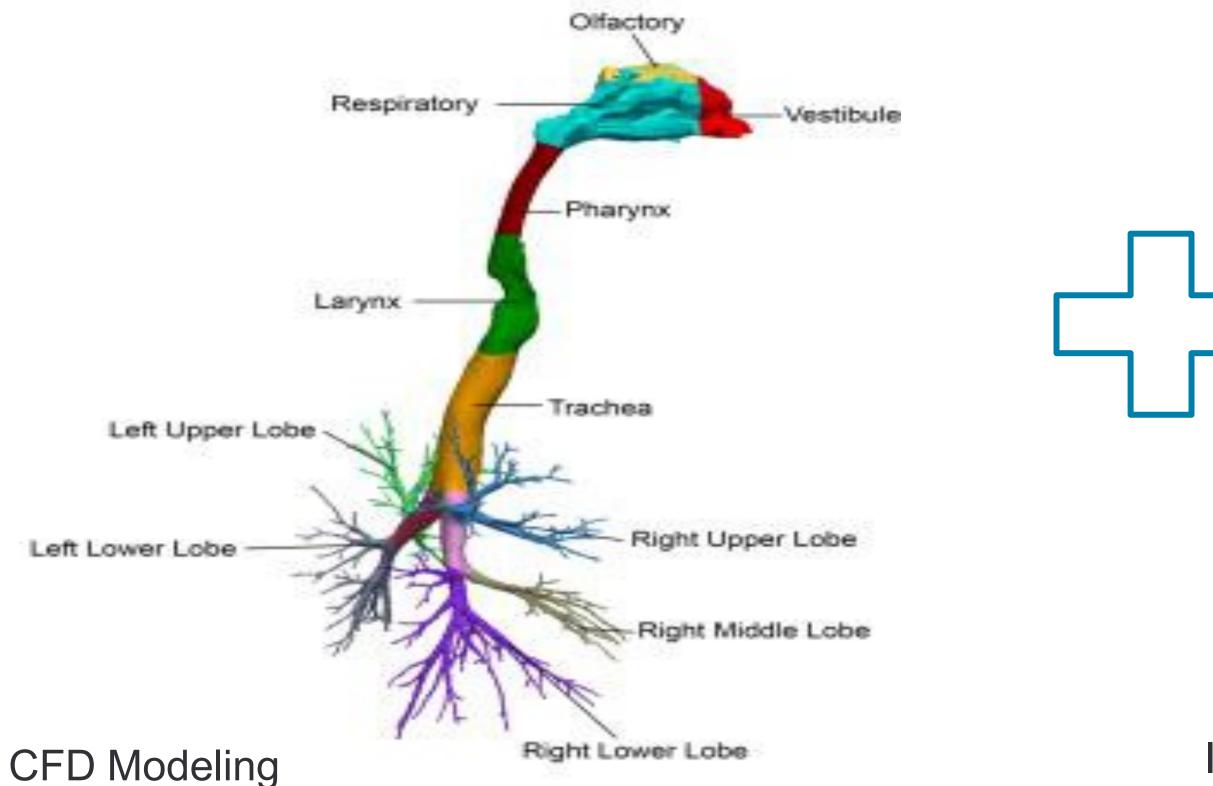
Necrotic injury to luminal respiratory epithelial cells Loss of surface epithelium Repeated injury Basal stem cell reprogramming Respiratory epithelium changes to squamous cells Squamous cell metaplasia

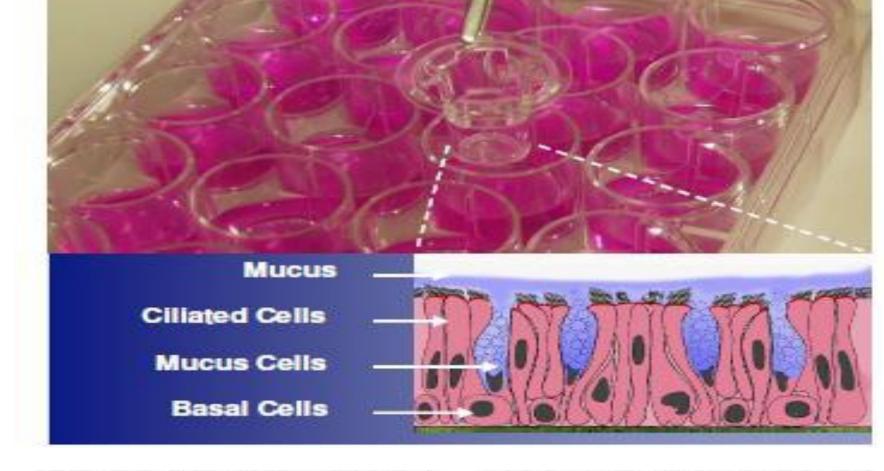
ENVIRONMENTAL PROTEC **Evaluation of a Proposed Approach to Refine Inhalation Risk Assessment for Point of Contact Toxicity:**

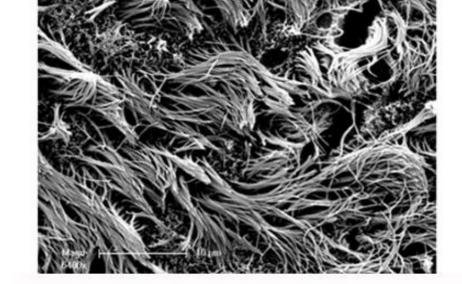
A Case Study Using a New Approach Methodology (NAM)

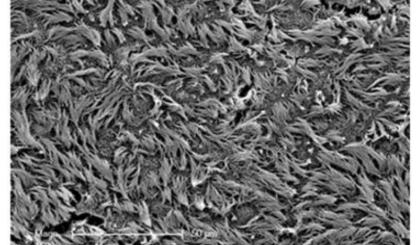
EPA FIFRA Science Advisory Panel meeting December 2018

Report expected April 2019

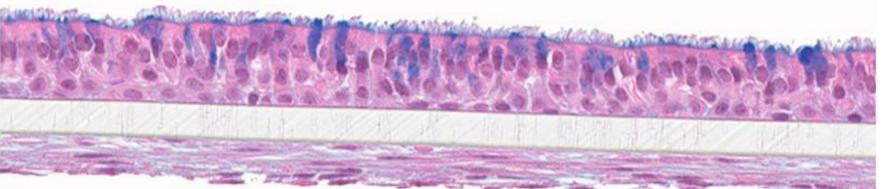








UNITED STA





Finding AOPs and AOP info in the AOP Wiki

Entering information into the AOP Wiki

Adding a diagram

OECD AOP Wiki: AOP Wiki: https://aopwiki.org

AOP Training Wiki

https://training.aopwiki.org

User name: author@epa.gov

Password: AOPtraining4@!!













Request Access to AOP Wiki: www.saaop.org

Developer's Handbook:

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

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