

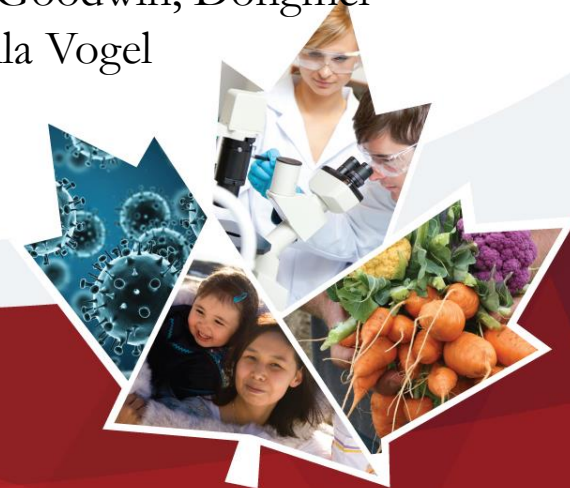
'Omics' and Adverse Outcome Pathways: tools for risk assessment of nanomaterials

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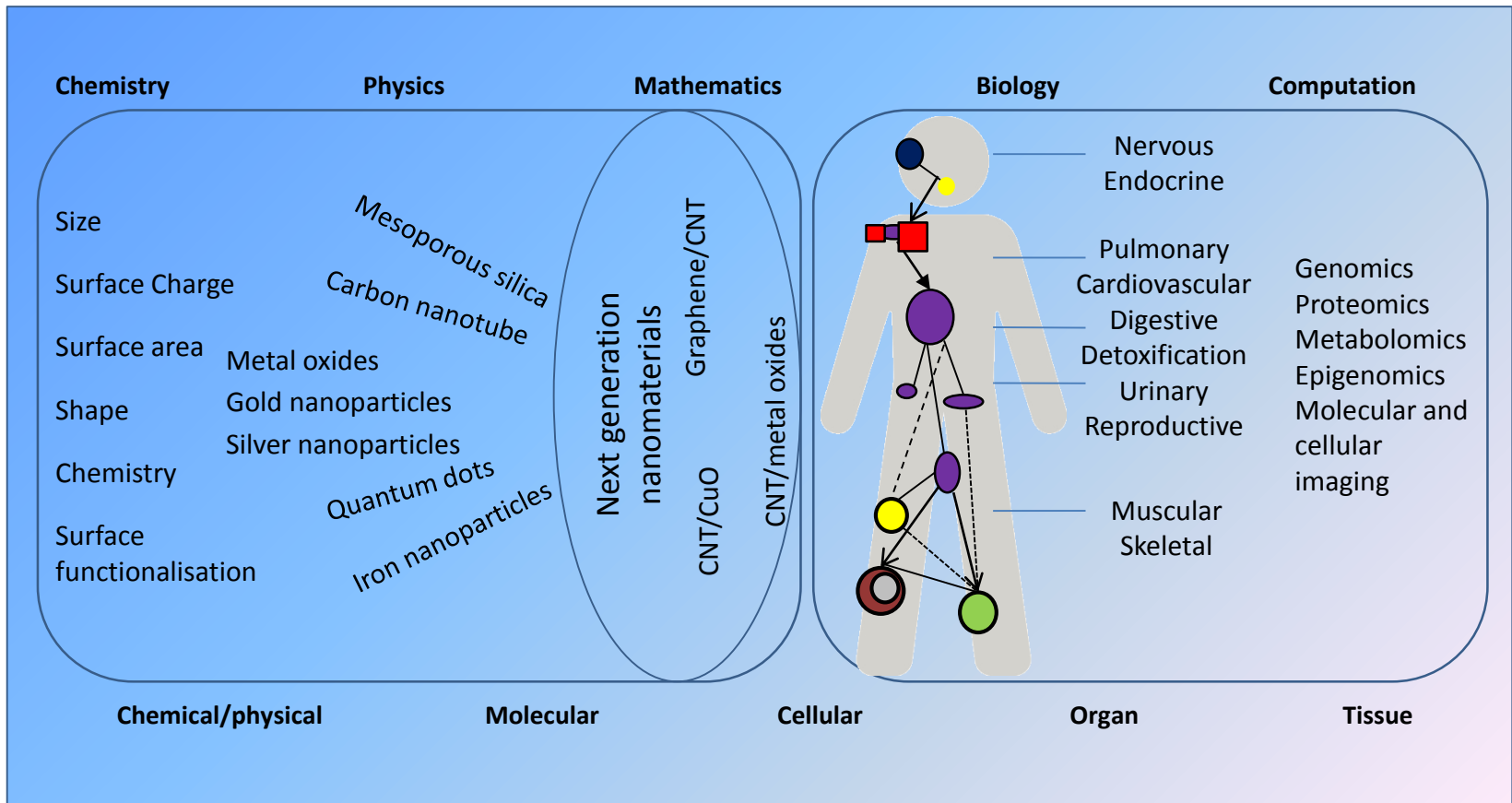
Environmental Health Science and Research Bureau, Health Canada, Canada

Jake Nikota, Sarah Labib, Allyson Banville, Laura Rose Goodwin, Dongmei Wu, Andrew Williams, Håkan Wallin and Ulla Vogel



Systems Biology for Nanotoxicology

'Omics' – an important platform



Effective safety assessment strategy for nanomaterials will require cross-disciplinary collaborations and integration of data from the various sources enabling comprehensive understanding of the material properties and behaviours at different levels of biological organization.

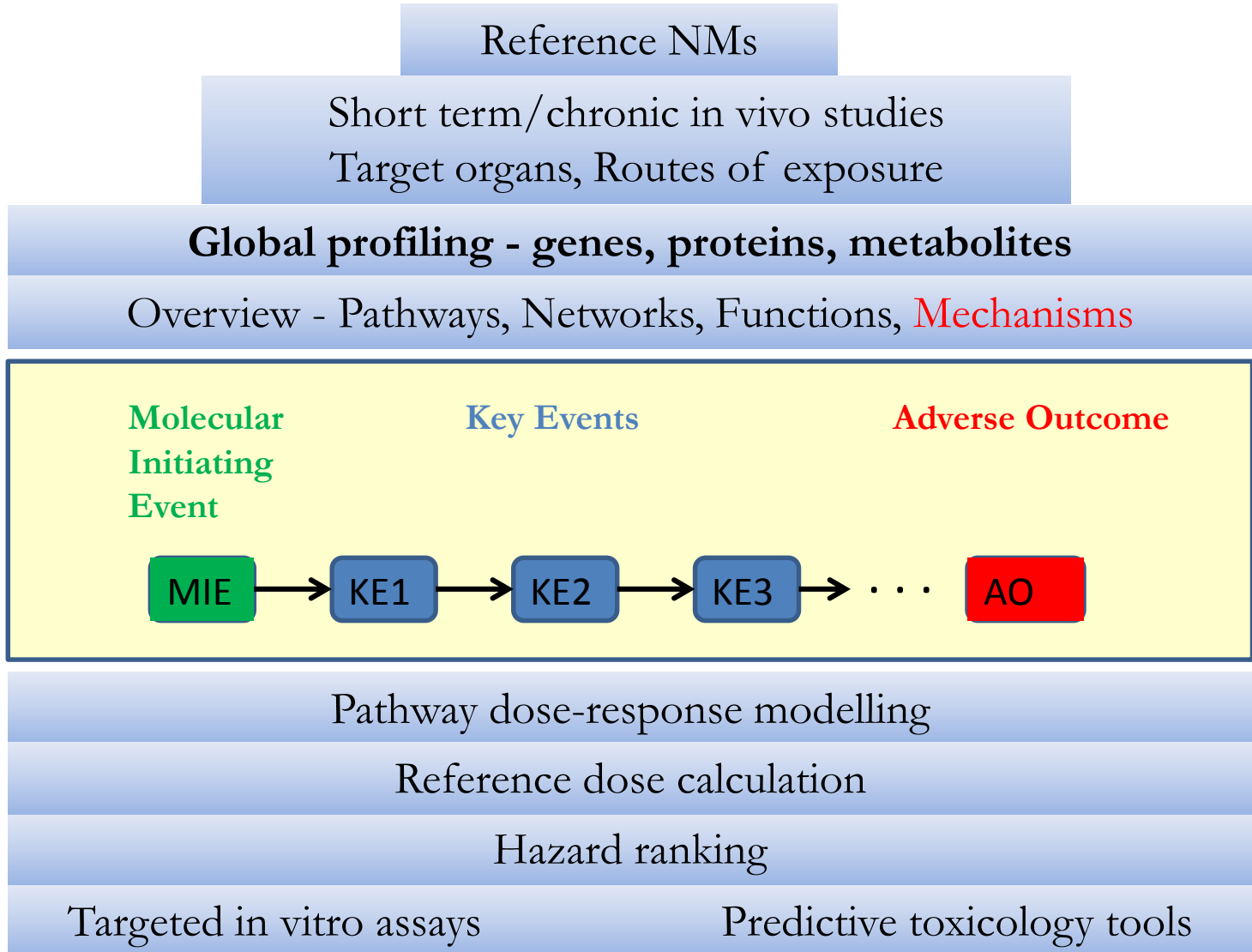
'Omics' – informing the risk assessment process

Physical-chemical characterisation

Exposure

Hazard

Dose-response

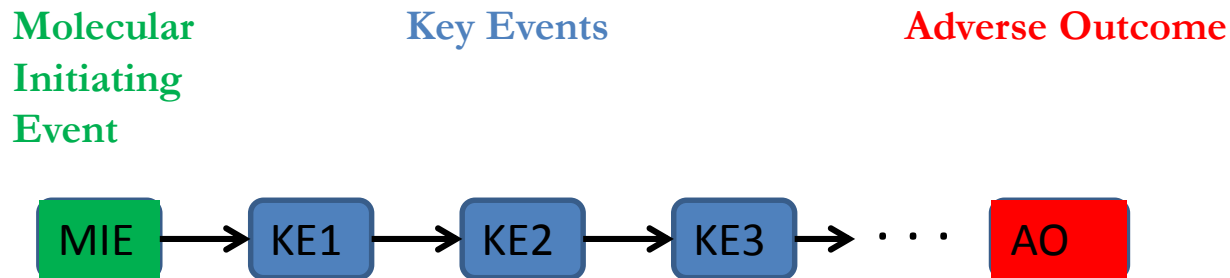


Risk characterisation

Adverse outcome pathways (AOPs)

- ‘Conceptual constructs that portray existing knowledge concerning the linkages between a direct molecular initiating event and an adverse outcome at a biological level of organization relevant to risk assessment’

(Ankley et al 2010, Environ. Toxicol. Chem., 29(3): 730-741).

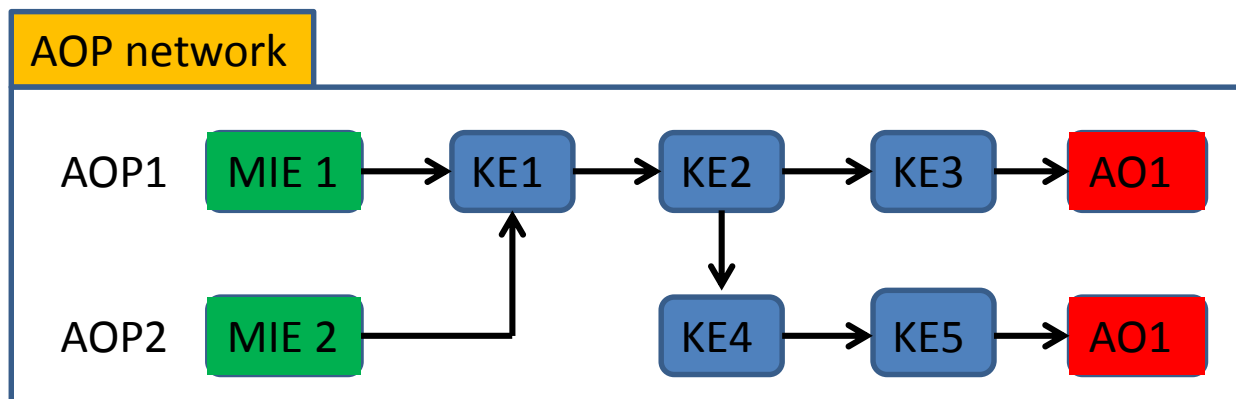


- Systematic organization - simplified representation
- **Measurable** or **observable** biological/chemical changes that are **essential** for toxicity
- Quantitative Key Event Relationships (KER) – \longrightarrow supported by biological plausibility and empirical evidence

(Villeneuve et al 2014, Toxicological Sciences, 142(2), 312–320)

Core principles of AOPs

- AOPs are not chemical specific
- AOPs are modular, components of AOPs (KEs and KERs) can be reused
- An individual pathway composed of **a single linear sequence of KEs and KERs**
- One can develop multiple AOPs that share common KEs and KERs – networks of AOPs or add branches. These will be used to represent the complexity of the toxicity – have better predictive value
- AOPs are living documents



AOPs for nanomaterials/chemicals under development

AOP proposals submitted to EAGMST committee, OECD

Project 1.25: Induction of Secretion of Inflammatory Cytokines Leading to Lung Emphysema – Canada Lead

Project 173: Pulmonary Injury Leading to Fibrosis – Canada Lead

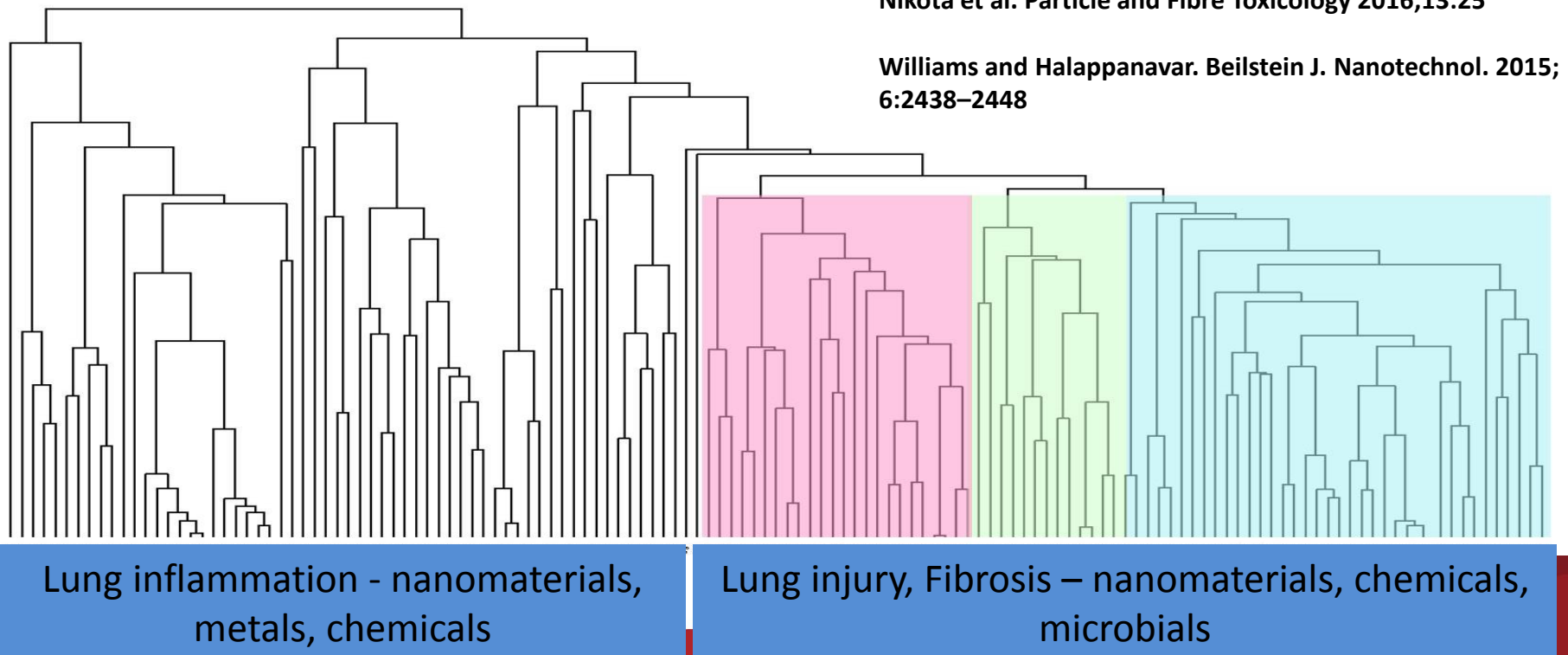
ENV/CHEM/NANO/2016/2222 : Advancing Adverse Outcome Pathway (AOP) Development for Nanomaterial Risk Assessment and Categorization – Canada Lead, coordinated by Vireo Advisors

Project 173: Pulmonary Injury Leading to Fibrosis

Step-1: identify key events or an adverse outcome and the underlying mechanism/s

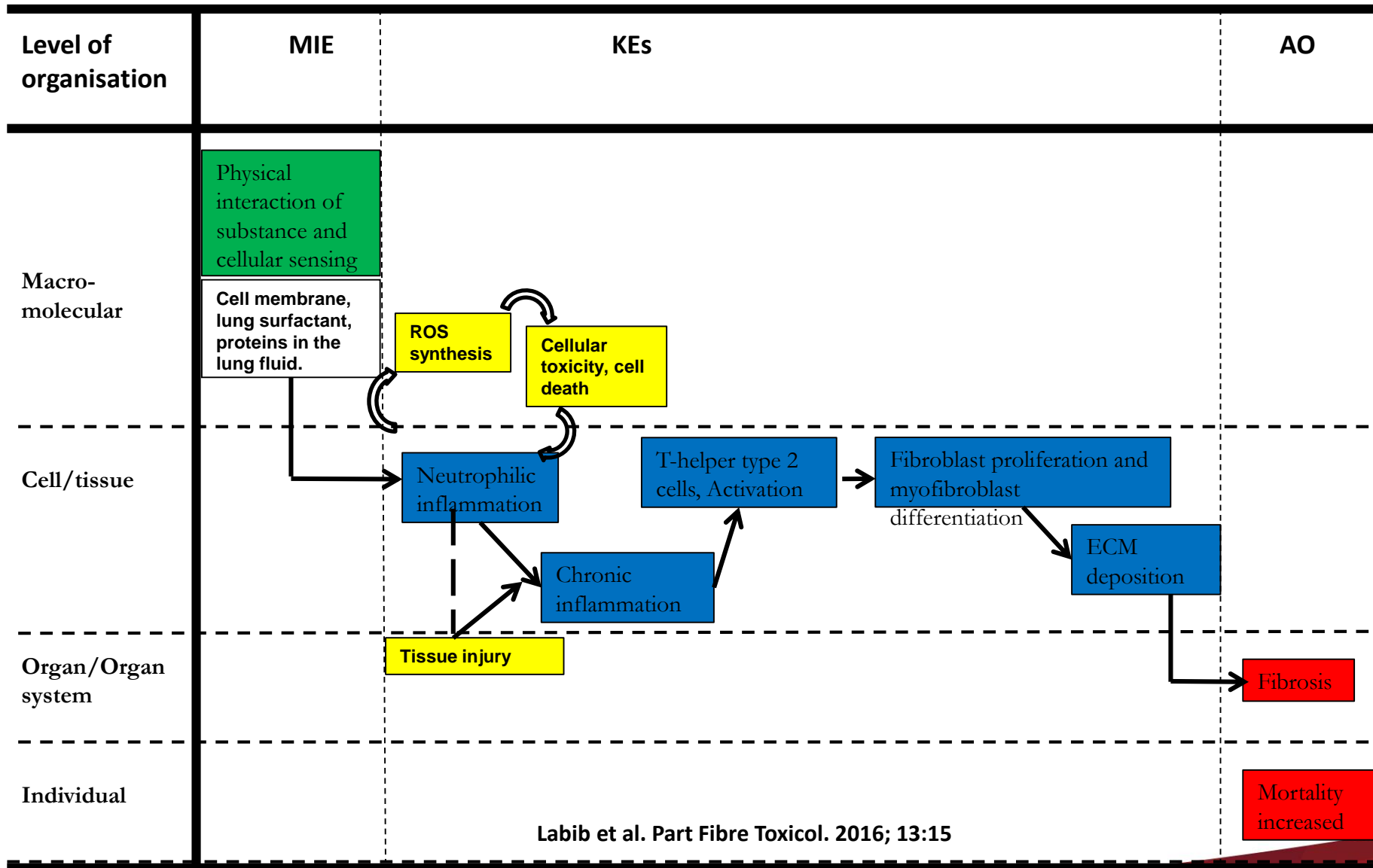
- Lung inflammation is commonly observed
- Lung fibrosis is a predominantly observed adverse outcome following CNT exposure
- In-house and external data sets describing pulmonary diseases induced by bacterial infection, cytokine-induced lung injury, chemicals....
- Meta analysis - ~ 50 individual datasets, more than 2000 arrays

Hierarchical clustering of differentially expressed genes –



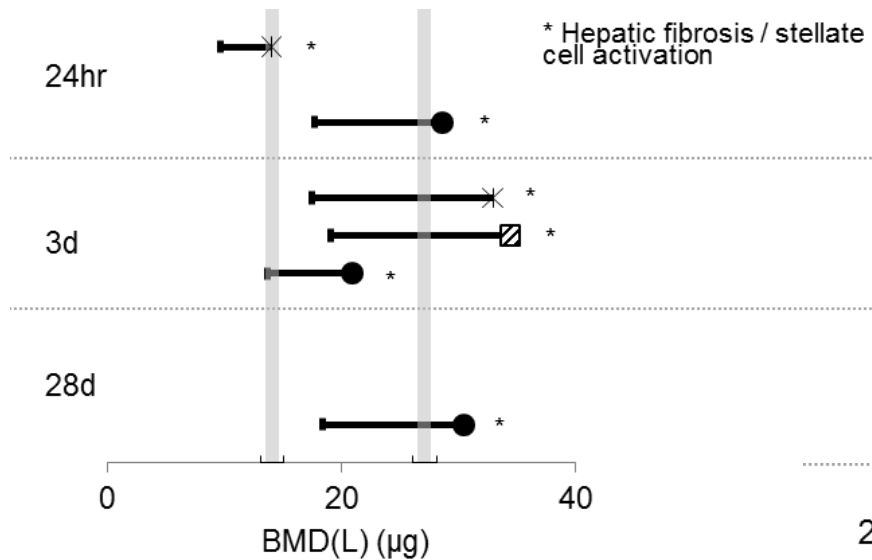
Project 173 Pulmonary injury leading to fibrosis

Step-2: build an AOP

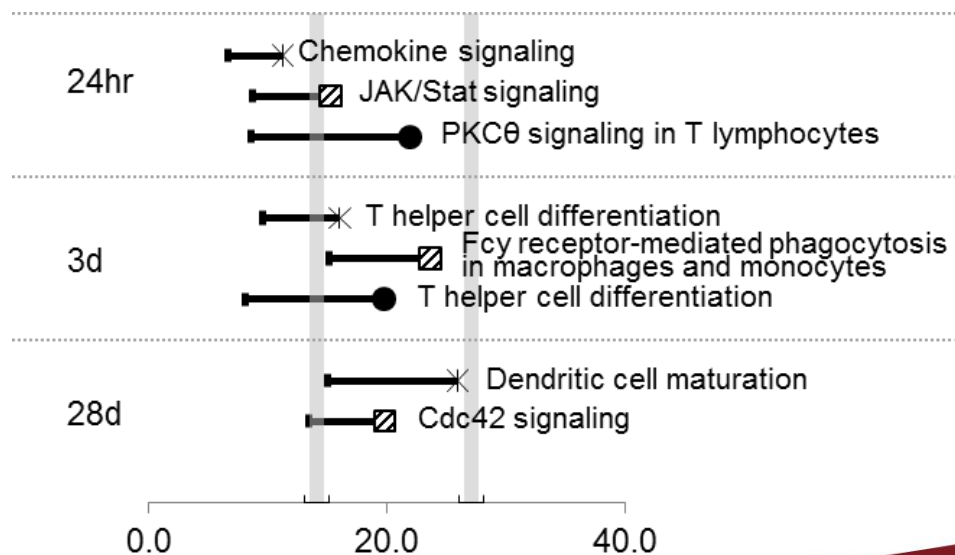


Step-3 : identify pathways associated with key events – POD calculation

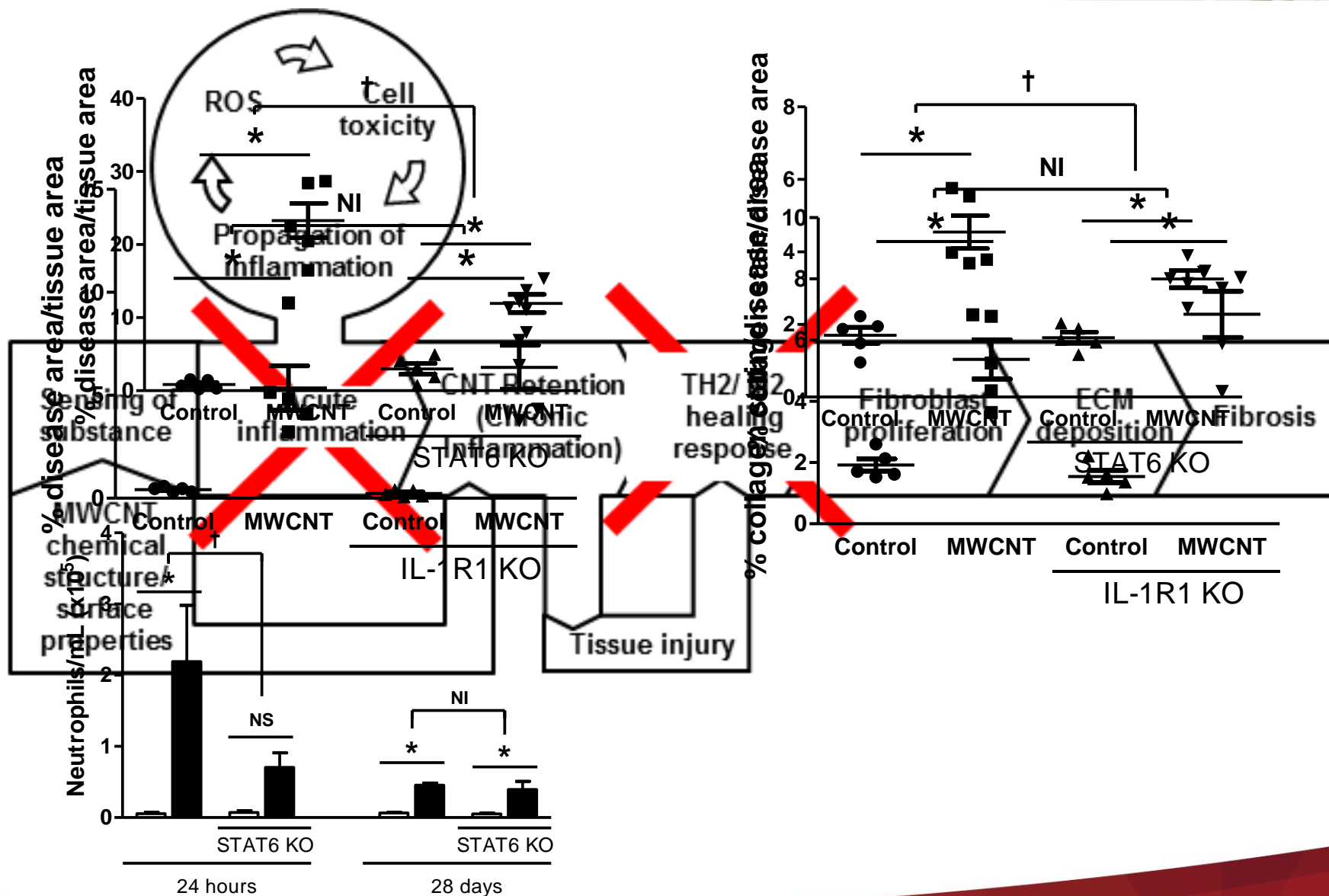
Adverse outcome – associated pathway



T-helper type 2 cells, Activation

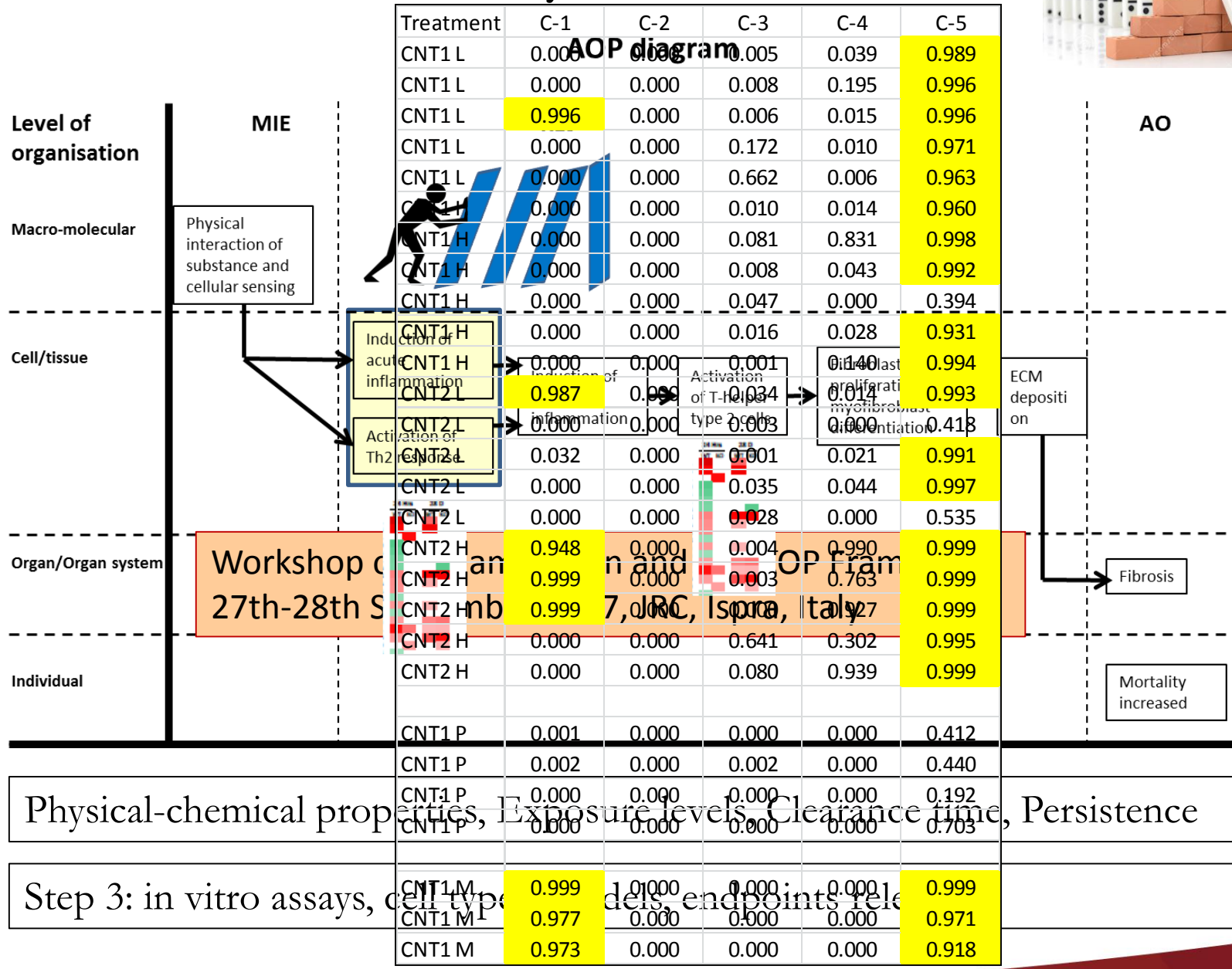


Step 2A: Validation of AOPs – essentiality of KEs



Gene classifiers – predicting lung fibrosis

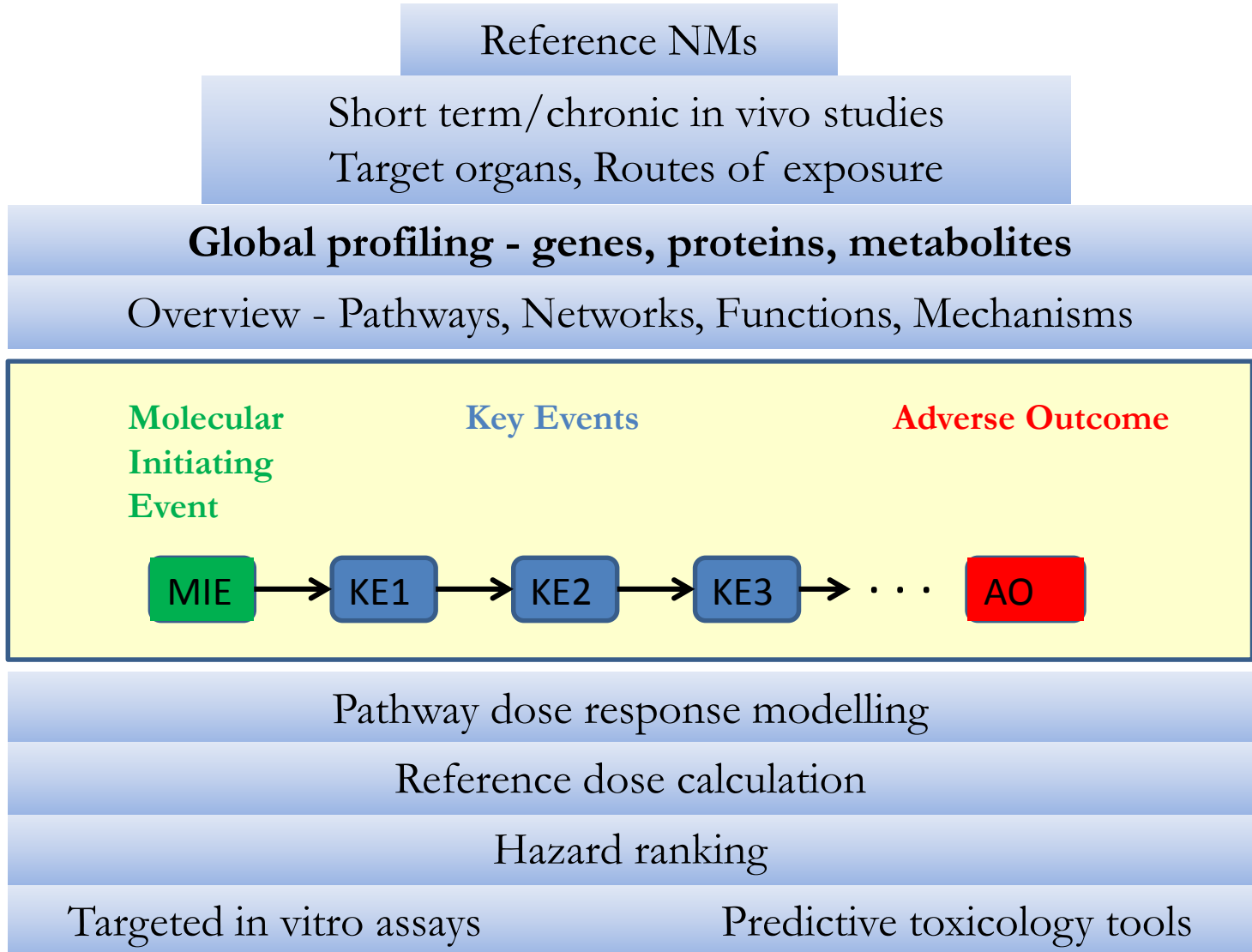
Validation of AOPs – essentiality of KEs



Conclusions

Physical-chemical characterisation

Exposure
Hazard
Dose-response



Risk characterisation

Acknowledgements

Health Canada

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Dongmei Wu

Allyson Banville

Laura Goodwin

Andrew Williams

National Research Center for the Working Environment

Ulla Vogel

Hakan Wallin

Funding



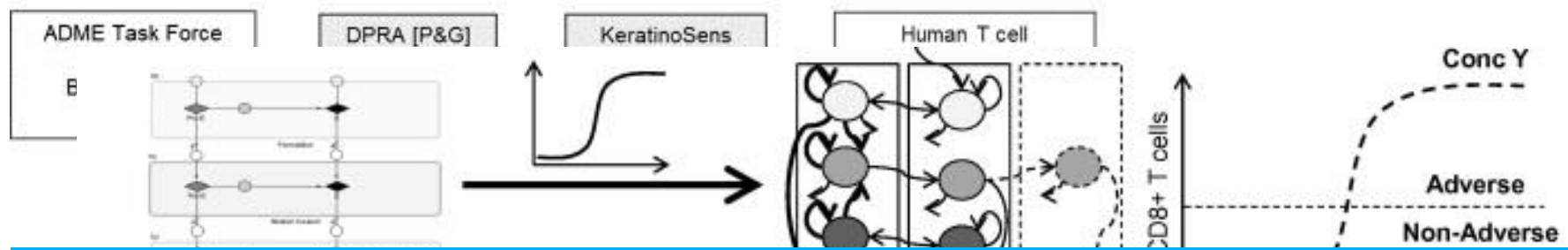
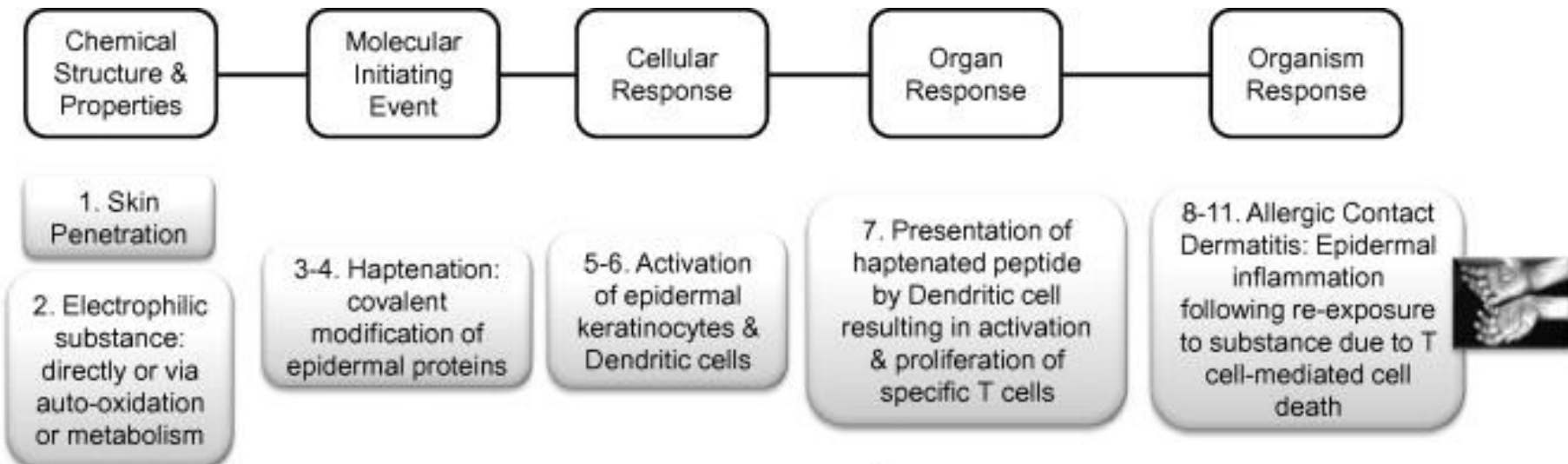
Health
Canada

Santé
Canada

Chemicals Management Plan Nano

Genomic Research and Development
Initiative

Skin sensitization adverse outcome pathway – an example



OECD TGs developed for individual in vitro assays

New Performance Based Test Guideline (PBTG) for defined approaches and test methods for skin sensitisation

SensiDerm [Proteome Sciences]