SESSION 3: SCIENCE, DATA, EVIDENCE FOR DECISION-MAKING

The AOP Framework Experience

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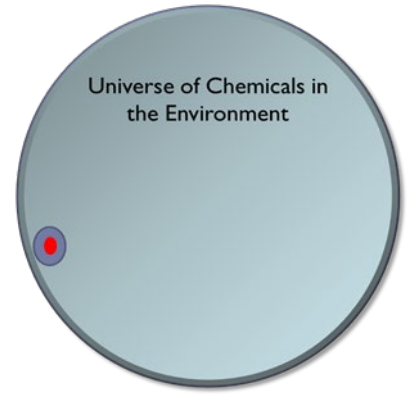
BETTER POLICIES FOR BETTER LIVES

Challenges in chemical safety assessment

01 High number of untested chemicals

To close this data gap with the current approach that relies almost completely on animal testing is not achievable



02 Research innovation

Development of cutting edge cellular models, computational methods, and technologies could advance chemical safety assessment

03 Storage and dissemination of mechanistic knowledge

Currently through peer-reviewed journals, text books, reports, laboratory notebooks, agency archives, institutional and government databases

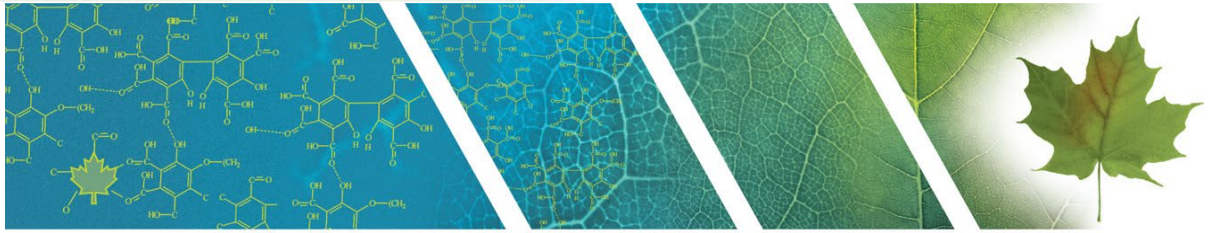
Countries are improving their legislation to assess more chemicals in a shorter time frame

Chemical Substances Control Law

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

IMAP
ACCELERATED ASSESSMENT OF INDUSTRIAL CHEMICALS IN AUSTRALIA

K-REACH



CHEMICALS MANAGEMENT PLAN

PLAN DE GESTION DES PRODUITS CHIMIQUES

Transformation in Standard Toxicity Testing

5000 animals / chemical

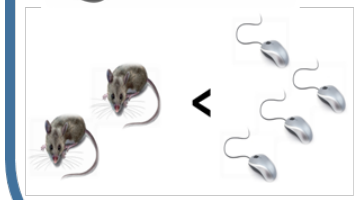
Test duration
30 – 720 days

Costs
€2,000 - €2,000,000

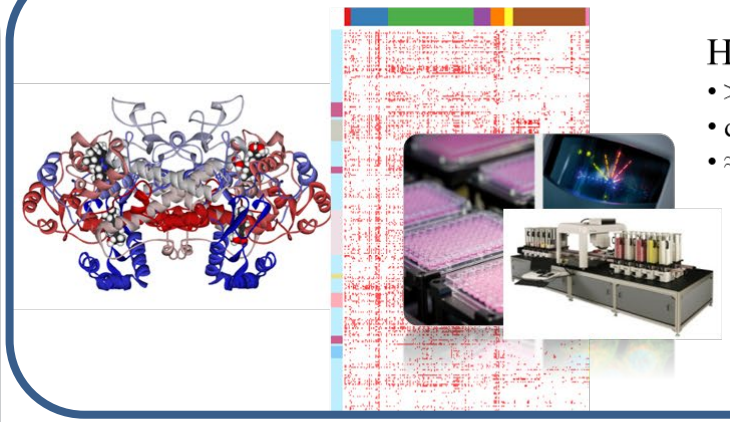
Avian reproduction study (OECD TG 206)
Animals: > 200
Test duration: > 30 weeks
Cost: > $250,000

Toxicity Testing in the 21st Century:

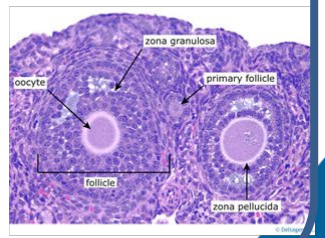
- ***In vitro* and *in silico* methods**
  - **Pathway-based approaches**
  - **Focus on disturbance of the biological pathway**
    - **Predictive of the observable toxic effects**



New Approach Methods (NAMs)



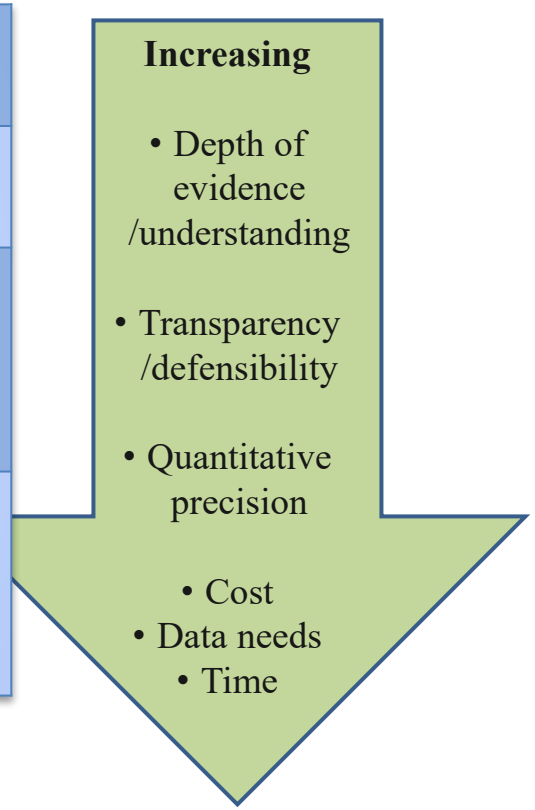
High throughput toxicology
- > 600 in vitro assays
- days
- ≈ $ 20,000



- **Validation of NAMs for confidence in decision-making**
- **Diverse data streams need integration**

Stages of AOP Development

Stages of AOP Development	Characteristics
Putative AOPs:	Hypothesized set of KEs and KERs primarily supported by biological plausibility and/or statistical inference
Formal AOPs:	Include assembly and evaluation of the supporting weight of evidence – developed in AOP knowledgebase in accordance with internationally-harmonized OECD guidance
Quantitative AOPs:	Supported by quantitative relationships and/or computational models that allow quantitative translation of key event measurements into predicted probability or severity of adverse outcome

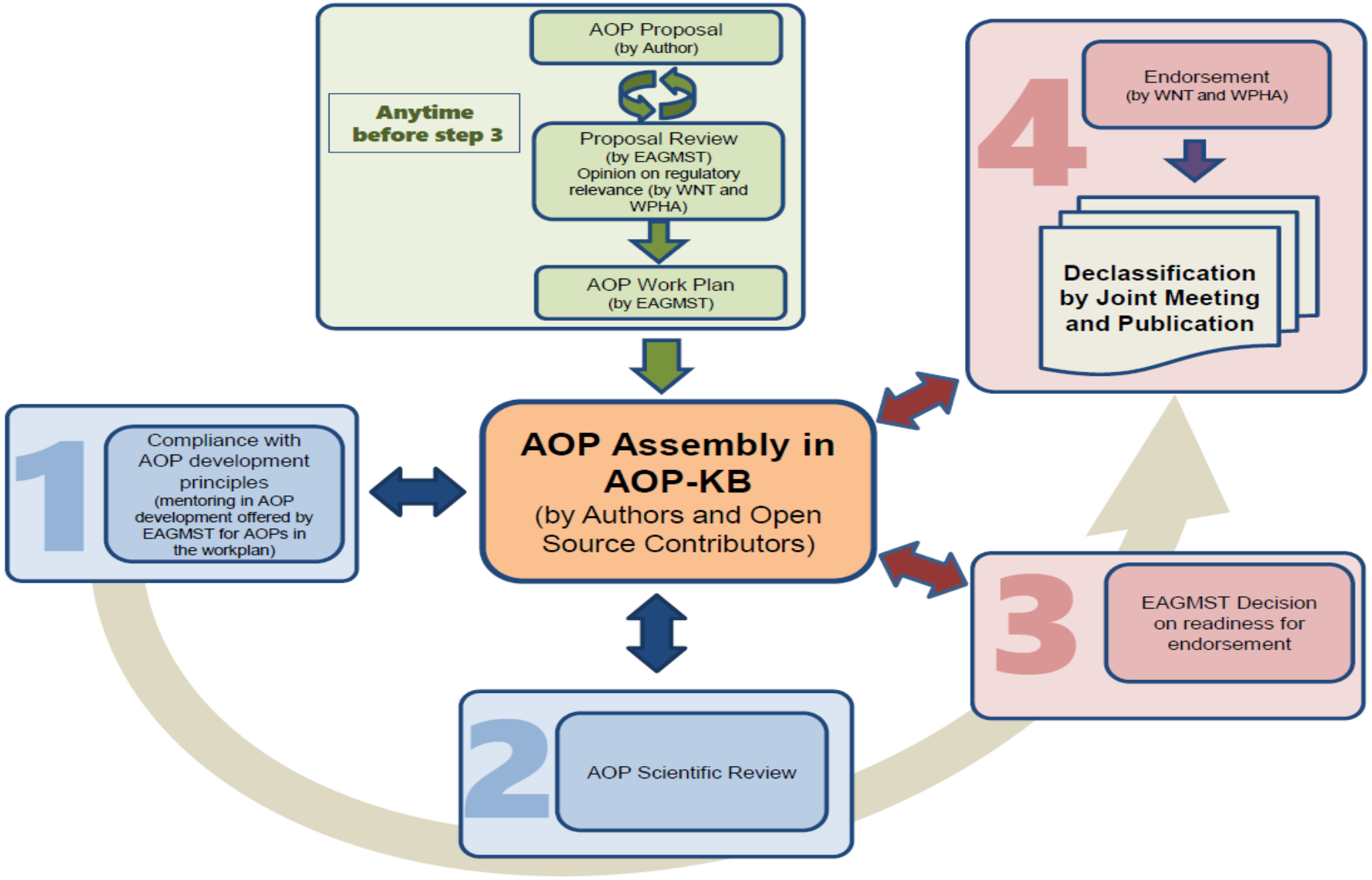


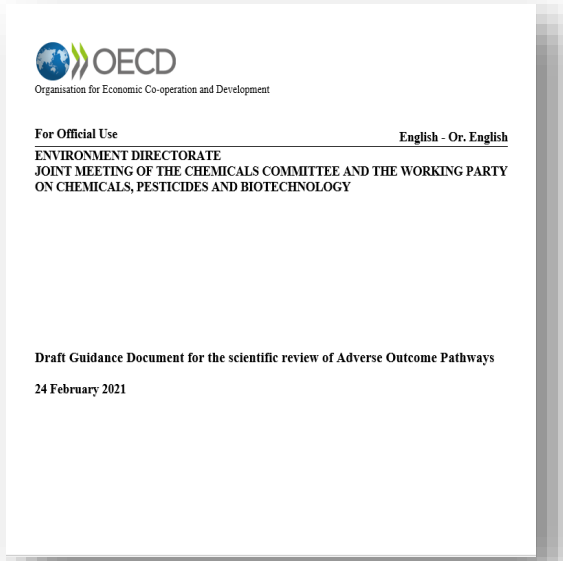
- All stages have potential utility
- Level of development desired/required depends on the application

Evaluating the Strength of Evidence for an AOP

1. Strength of association
2. Consistency
3. Specificity of association
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experimental evidence
9. Analogy

Detailed description of the AOP development process





OECD

Organisation for Economic Co-operation and Development

For Official Use — English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY
ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

Draft Guidance Document for the scientific review of Adverse Outcome Pathways

24 February 2021

The virtuous circle of collaboration

Increased usefulness and use by regulators

Increased awareness of the AOP programme

Increased collaboration of scientists / crowdsourcing

Increased number of AOPs developed and published

Increased number of AOP networks

AOP Knowledge Base

Collaboration with journals as an accelerator of the cycle

Application of the AOP Framework

- Enhance use of mechanistic data in regulatory decision-making
- Support hypothesis-driven testing - target in vivo testing on endpoints of concern
- Inform appropriate cross-species extrapolation & focus testing on species, life-stages, taxa of concern
- Aid a strategic, knowledge-driven approach to evaluating complex mixtures
- Identify critical knowledge & evidence gaps that impede application

CASESTUDIES

From IATA to DAs

IATA	Defined Approaches
Designed in response to problem formulation	Designed to address pre-defined endpoint/prediction
Inputs are defined by user	Defined information sources
Sequence of input, next steps, decision context defined by user	Sequence defined and next steps are rule-based
Expert judgement for weighting data, interpreting data	Fixed data interpretation procedure
Conclusion may be open to interpretation	Regulatory conclusion is clear

- Defined approaches:
  - Remove expert judgement
  - Are **not flexible** and **are suitable** for harmonisation
- **OECD has the first approved Defined Approach that would be covered by mutual acceptance of data (MAD)**

AOP for Skin Sensitization

OECD (2014)

Chemical Structure & Properties → Molecular Initiating Event → Cellular Response → Organ Response → Organism Response

Metabolism
Penetration

Electrophilic substance

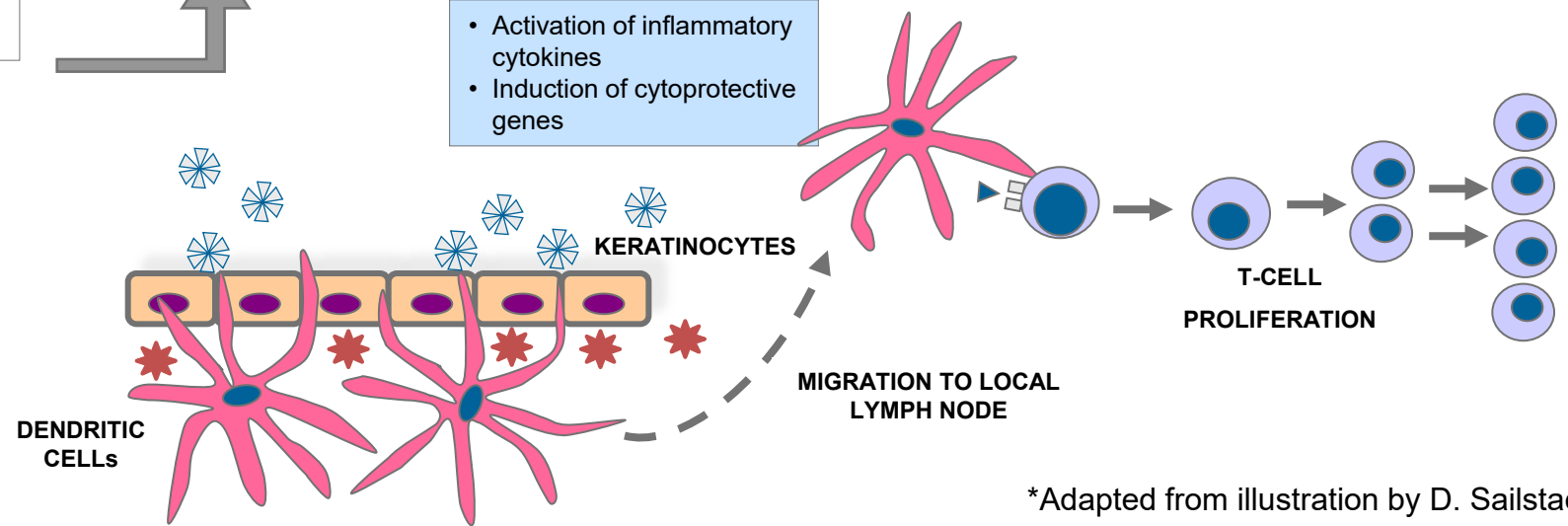
Key Event 1
Covalent interaction with skin proteins

Key Event 3
Dendritic Cells (DCs)
- Induction of inflammatory cytokines and surface molecules
- Mobilisation of DCs

Key Event 2
Keratinocytes responses
- Activation of inflammatory cytokines
- Induction of cytoprotective genes

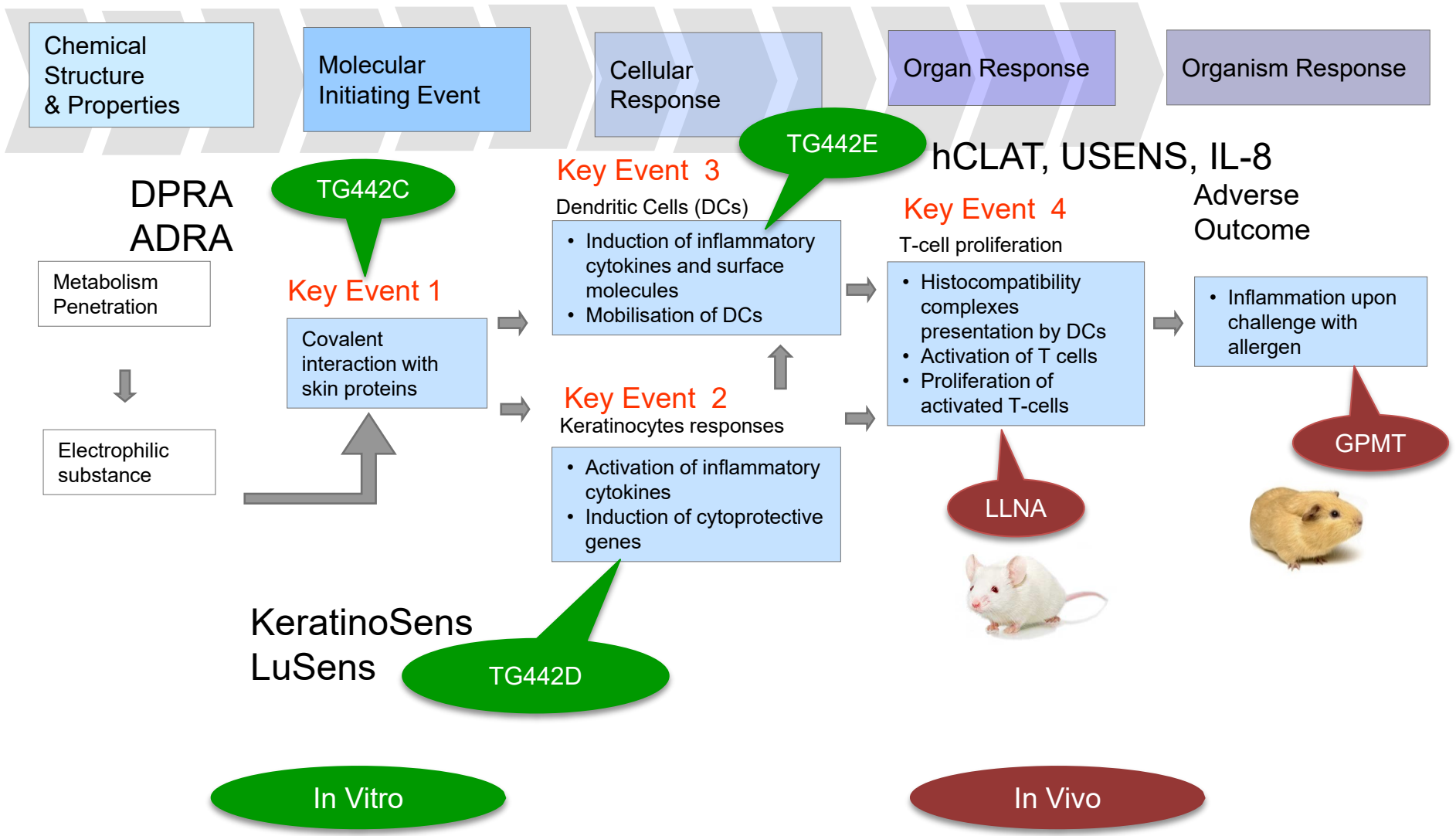
Key Event 4
T-cell proliferation
- Histocompatibility complexes presentation by DCs
- Activation of T cells
- Proliferation of activated T-cells

Adverse Outcome
- Inflammation upon challenge with allergen



*Adapted from illustration by D. Sailstad

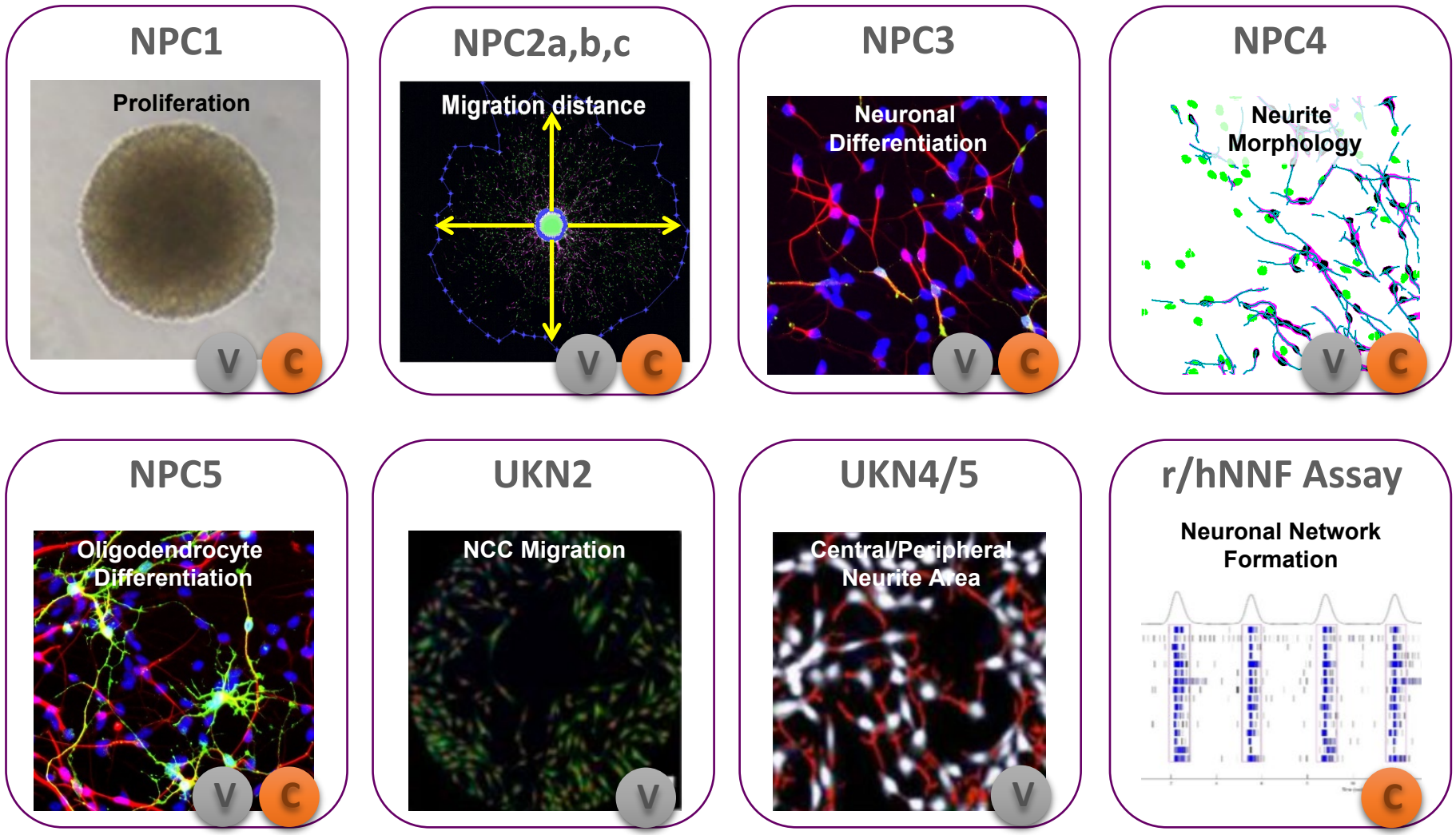
Test Methods Mapped to AOP



OECD Defined Approaches SS Guideline

- Extensive curation efforts undertaken to build reference databases (LLNA, Human)
- Applicability Domain and DA Confidence defined
- Final draft guideline was approved on April 2021
- DA GL will meet regulatory requirements of:
  - DAs that discriminate skin sensitisers from nonsensitisers
  - DAs that discriminate strong from moderate/weak sensitisers (GHS potency categories)
- Future work will cover DAs that address regulatory needs of quantitative risk assessment

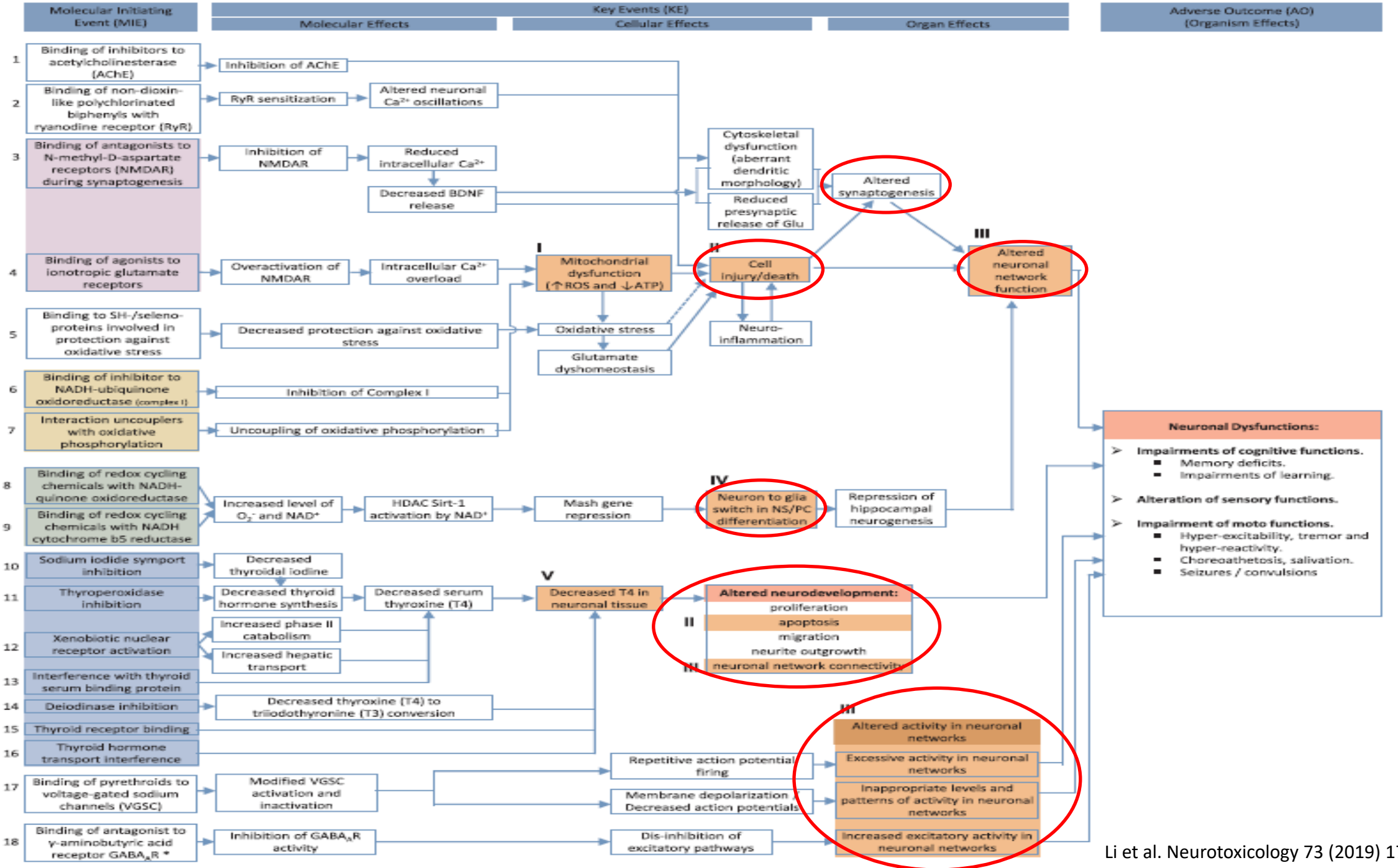
DNT *In Vitro* Battery



V Viability C Cytotoxicity

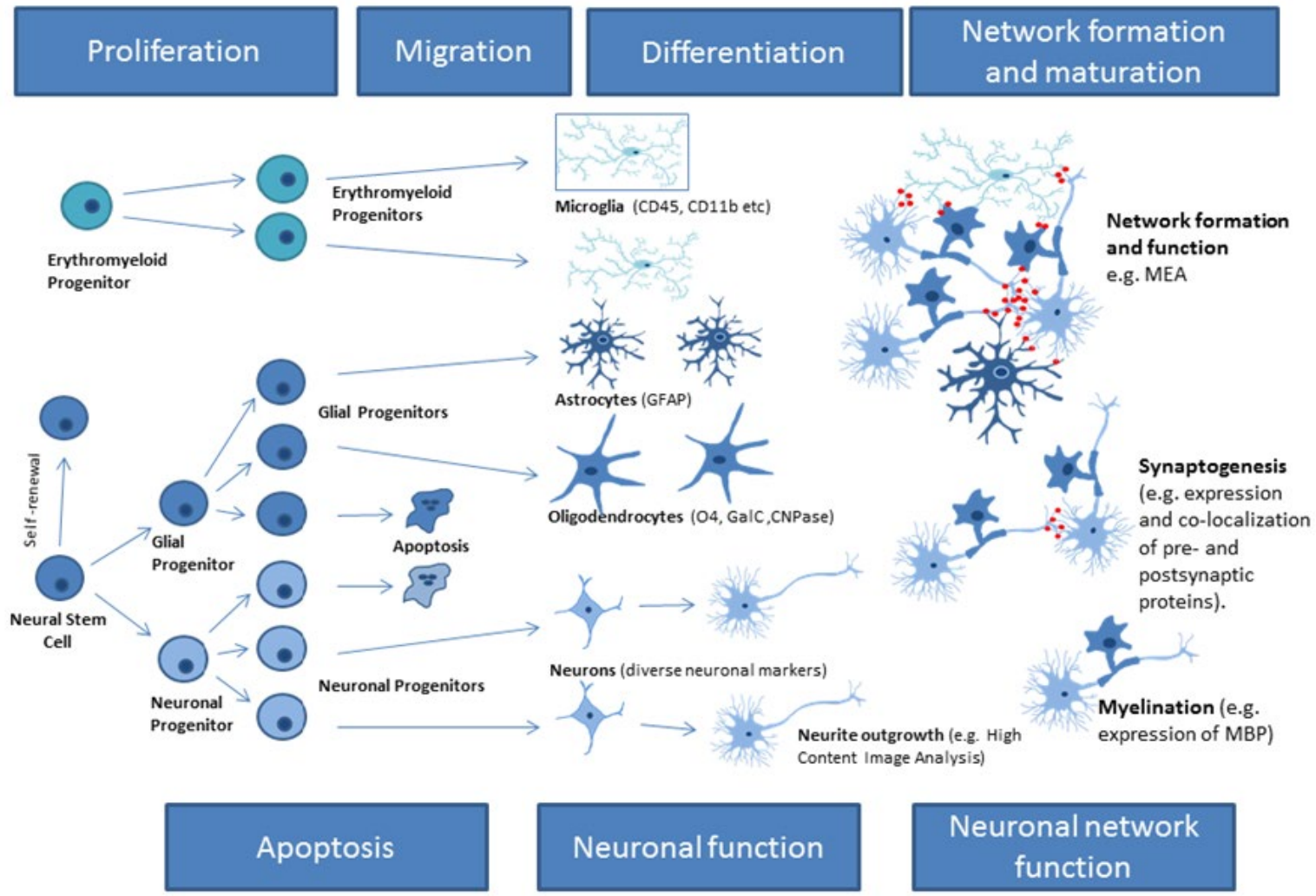
Masjosthusmann et al. 2020

Graphic representation of 18 DNT-related AOPs

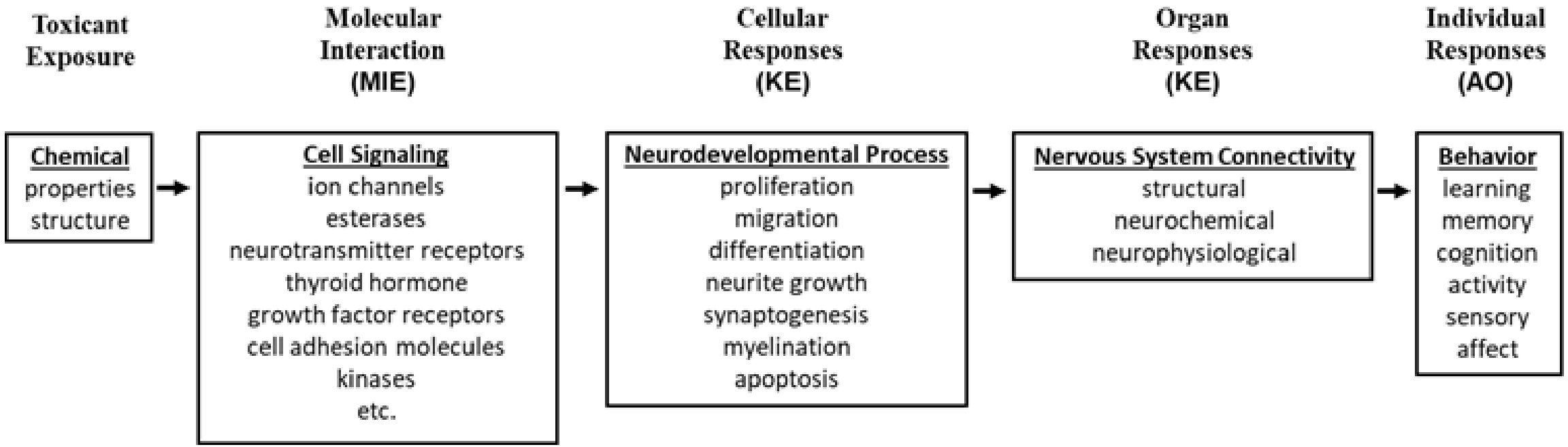


Li et al. Neurotoxicology 73 (2019) 17–30

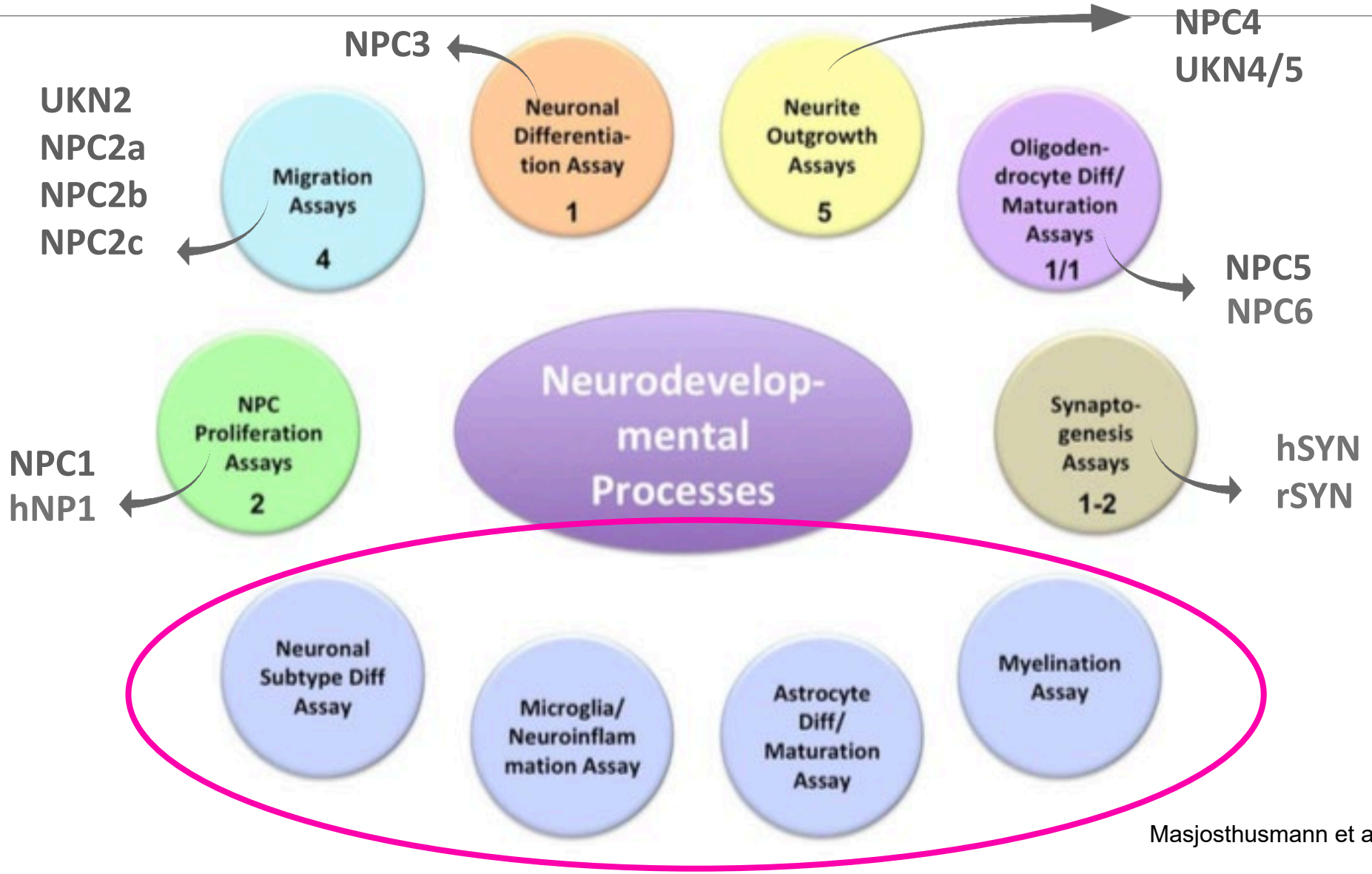
Key neurodevelopmental processes and DNT *In Vitro* Battery



Key neurodevelopmental processes in AOPs

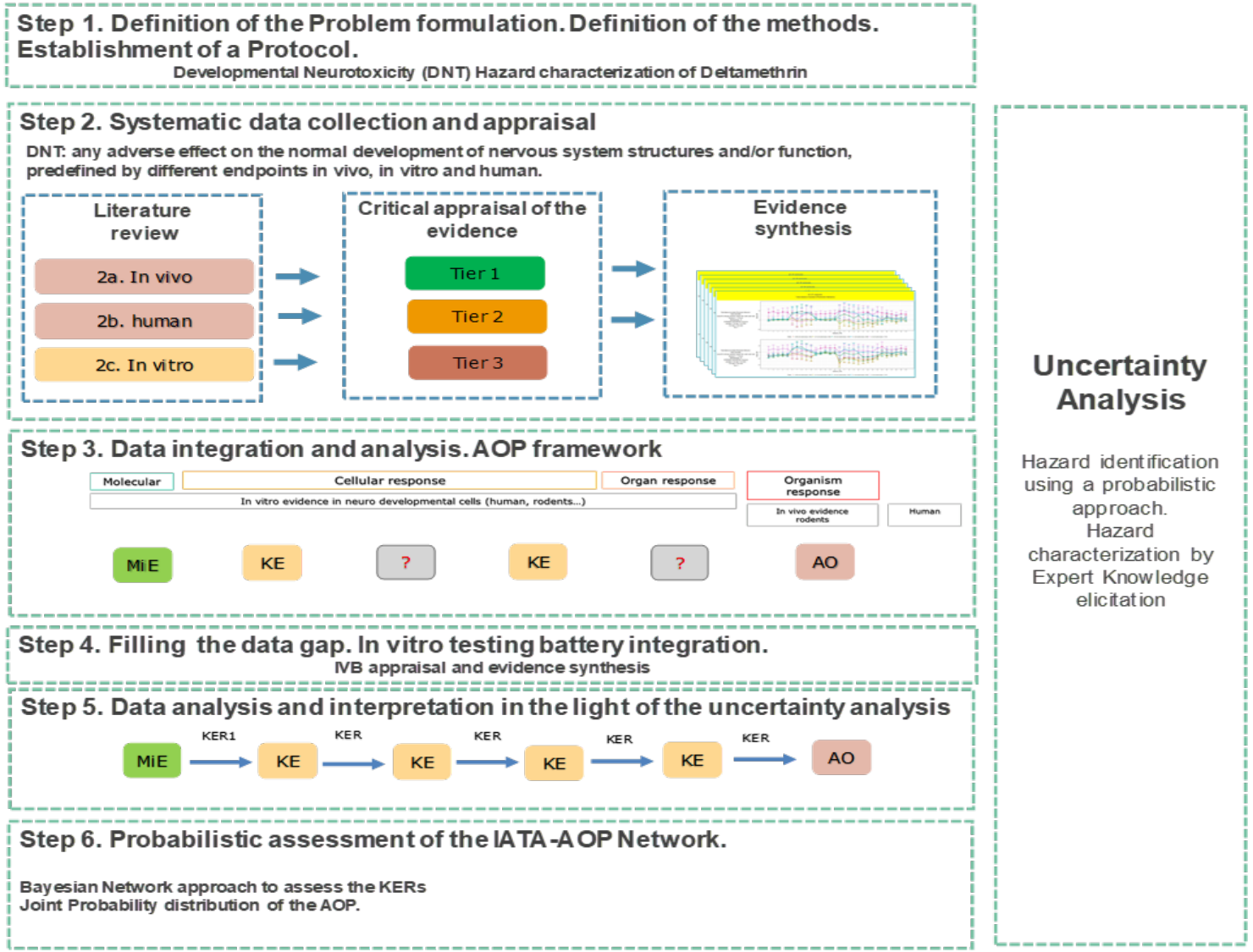


Gap analysis



Masjosthusmann et al. 2020

AOP informed IATA for DNT

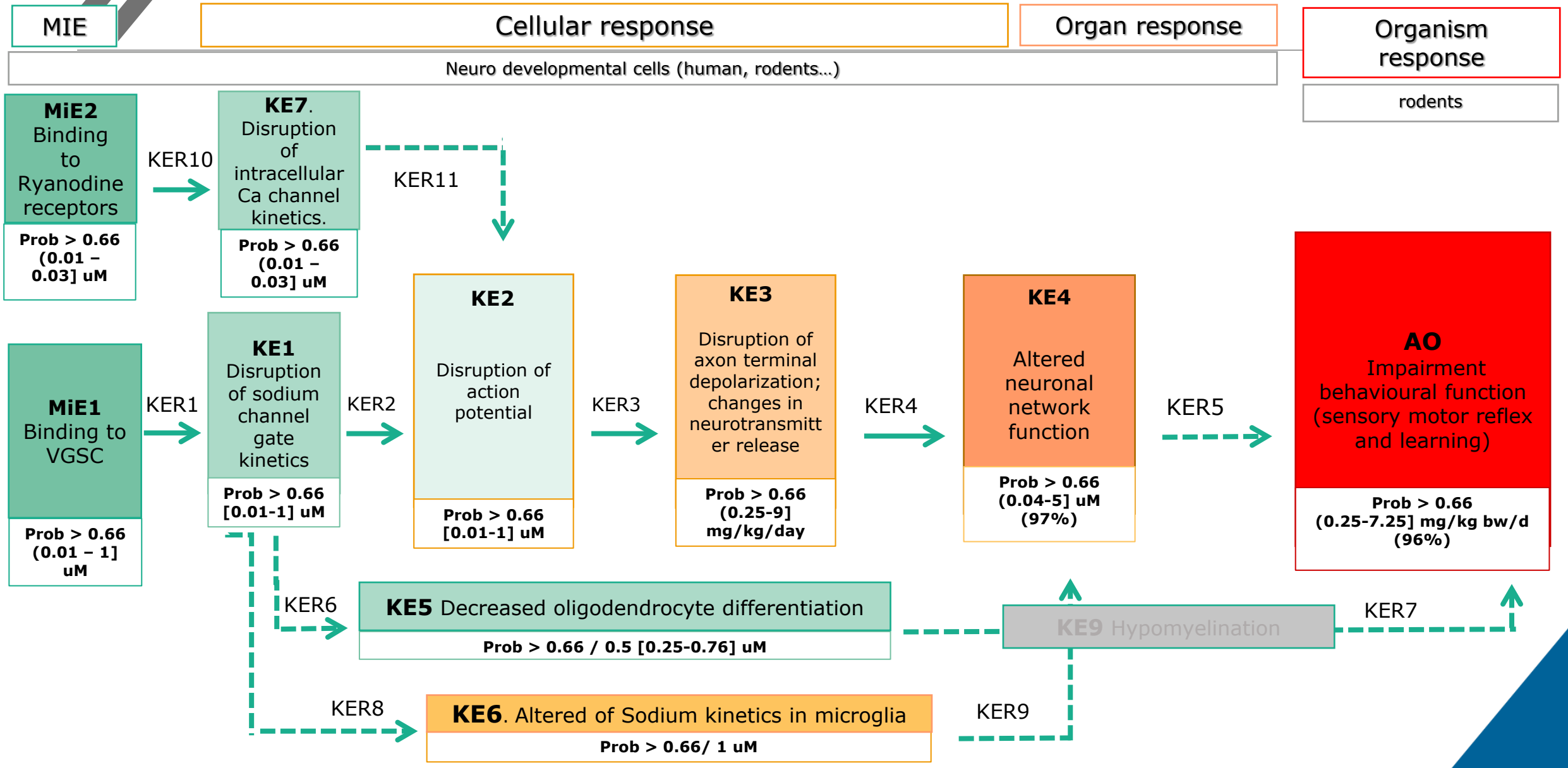


IATA workflow

Key words:

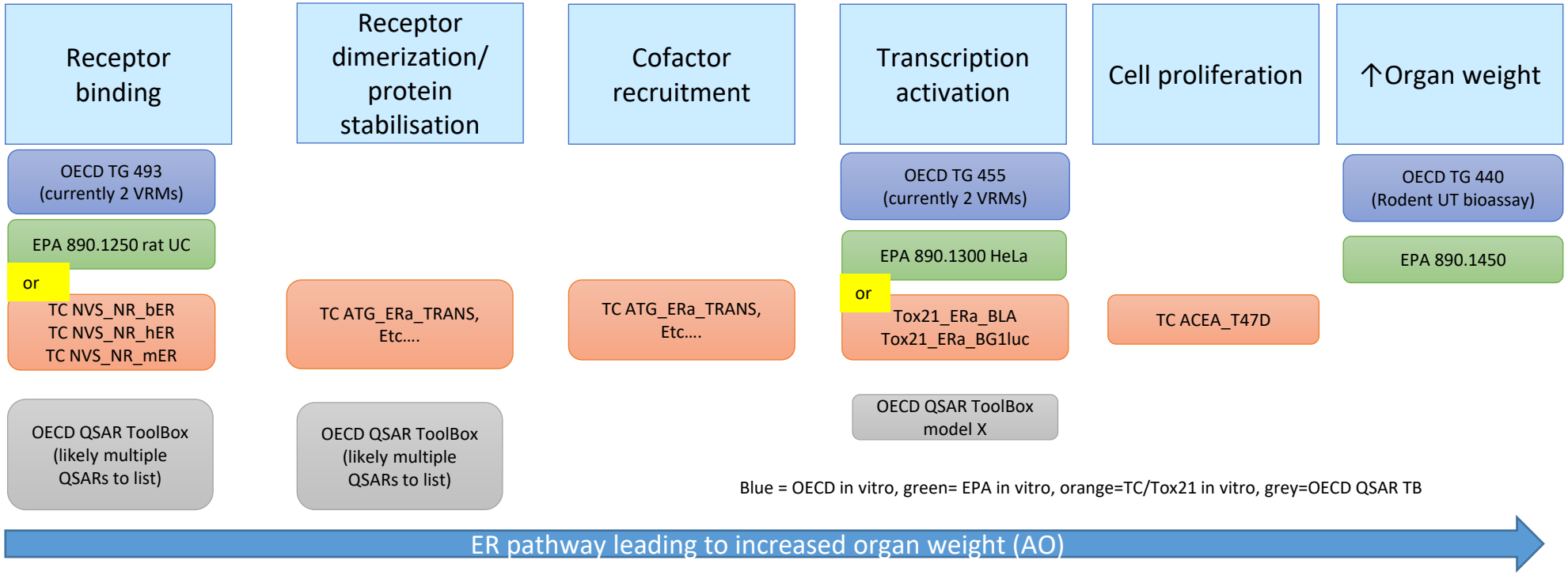
- Problem formulation
- Stressor based AOP
- Evidence based
- Systematic approach
- Uncertainty analysis

Stressor-based putative AOP Network

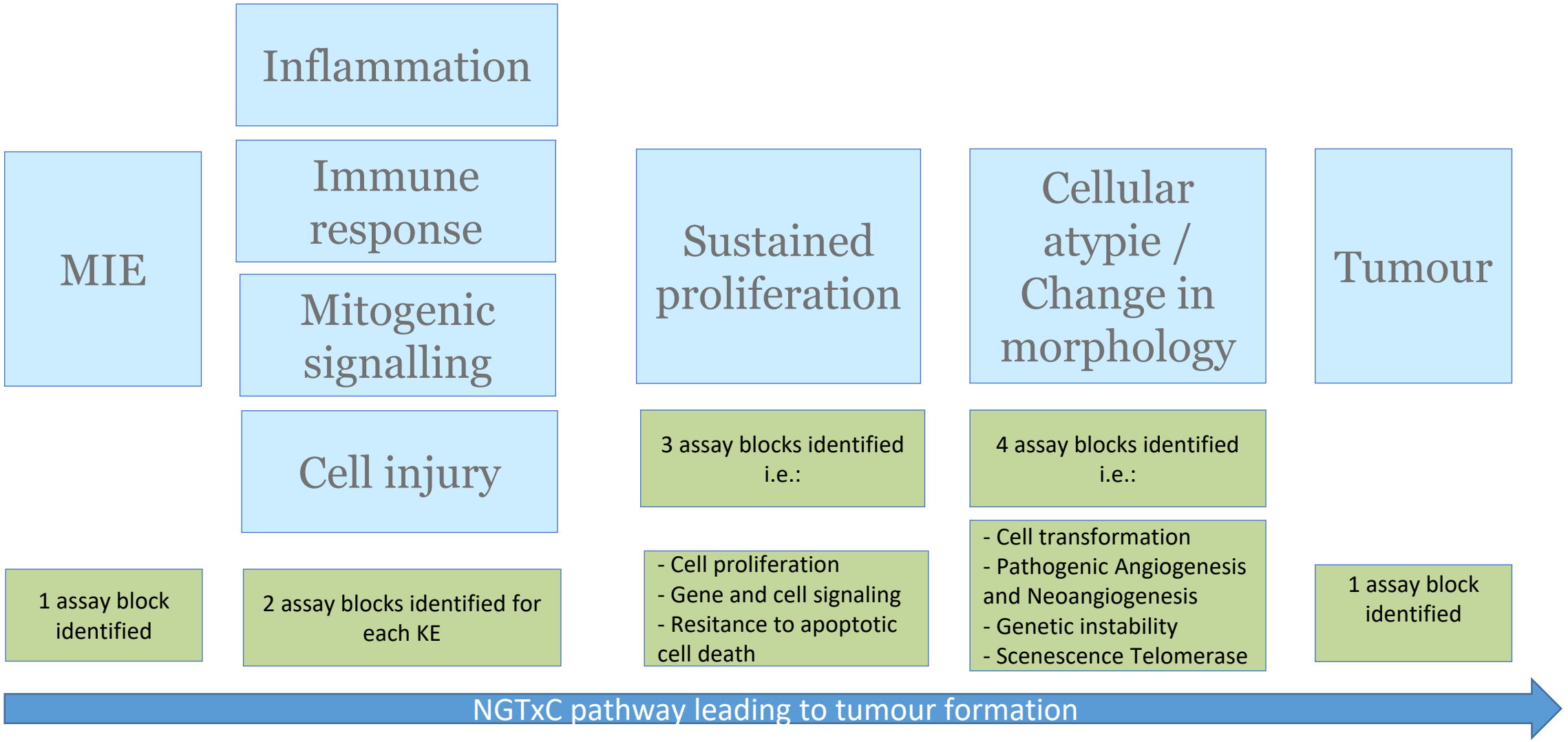


IATA-related endocrine projects: Estrogen receptor active chemicals

- IATA case study project
  - Led US
  - Considered with a defined approach
  - Combines results form ≥ 4 in vitro assays to predict the rodent in vivo uterotrophic response



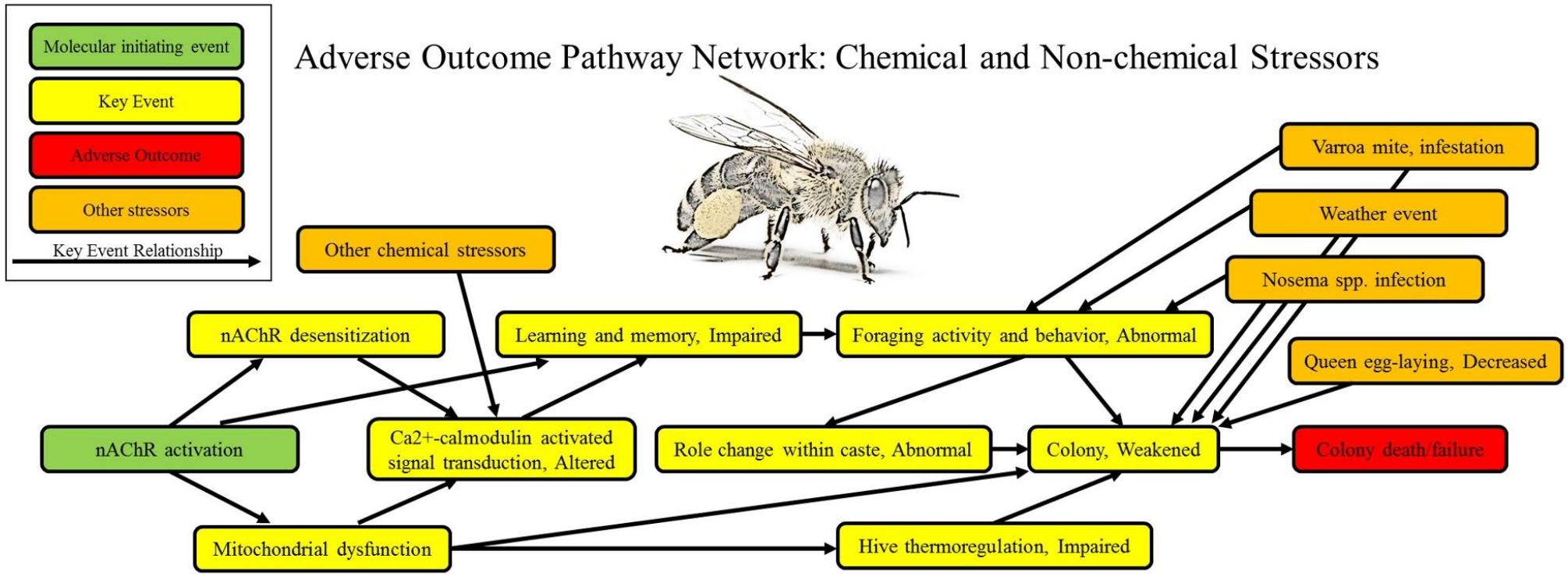
Simplified Non-genotoxic carcinogenicity AOP flow



AOP conceptual framework, a useful tool for Human Health Risk Assessment

- Contextualise the NAMs
- Understanding what are you testing for
- Avoid additional testing
- Identify data gaps and perform targeted testing
- Use human data rather than rodent data in the process of hazard characterization

Pollinator Health



Identification of knowledge gaps
Multiple contributors weaken the colony
Nodes impacted by multiple stressors

Understanding Contributed to Mitigation Policy

U.S. ENVIRONMENTAL PROTECTION AGENCY'S POLICY TO MITIGATE THE ACUTE RISK TO BEES FROM PESTICIDE PRODUCTS

U.S. Environmental Protection Agency

Office of Pesticide Programs

January 12, 2017

Developmental and Reproductive Toxicology/Endocrine Activity

Opportunity to replace with high throughput in vitro screening

- Median estimated cost: $75,000 [OECD 2012; ENV/JM/MONO(2012)22]
- Animal use: ≈ 320 tadpoles per test
- Time: 21 d test; histology; husbandry and staging

Thyroid AOP Network

- identification of MIE space to cover in a HTS battery

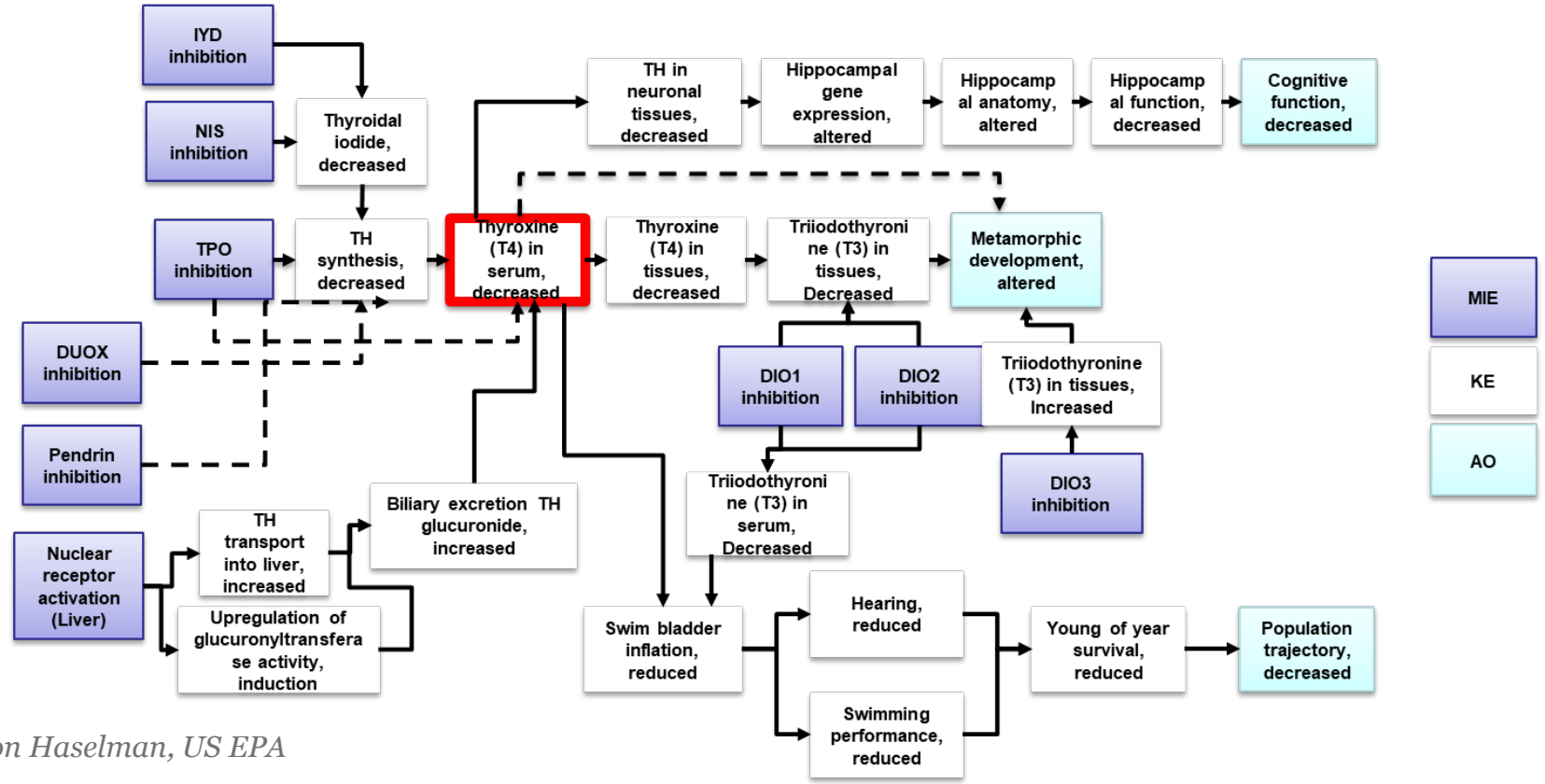
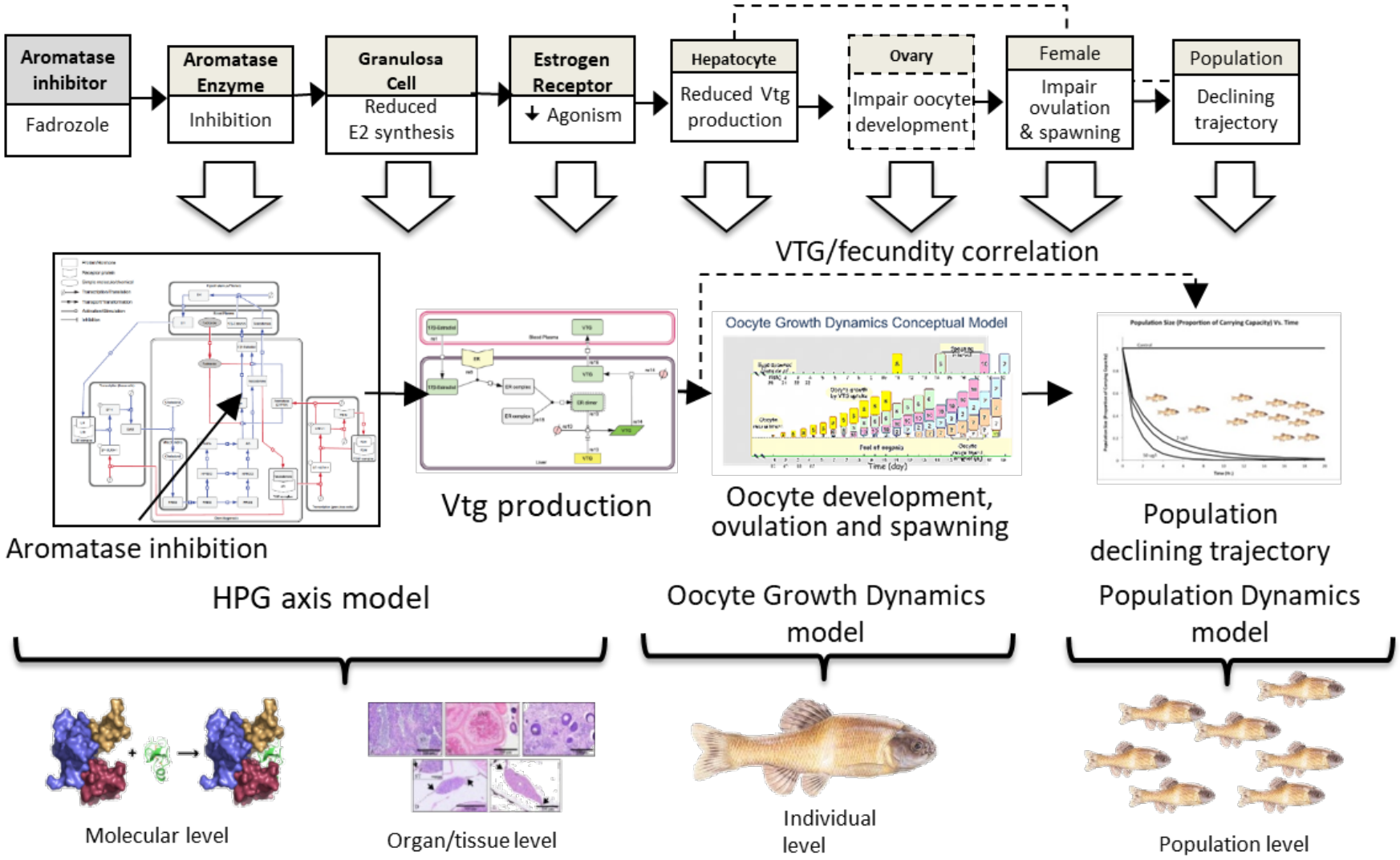


Figure courtesy of Jon Haselman, US EPA

Directly translating mechanistic data directly into predicted adverse outcomes for relevant exposure scenario

Quantitative Prediction of Reproductive/Population Effects



Review Challenges to Uptake of the AOP Framework

- Not enough AOPs to adequately cover biological space (example)
- Time consuming as information is spread in many journals
- Additional quality evaluation is required
- Scarce regulatory feedback on application of AOPs