The Role of Adverse Outcome Pathways in Streamlining Hazard and Risk Assessment

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Outline

- The need for a new approach to toxicology
- The Adverse Outcome Pathway concept
- Examples in progress
- Strategies for the future

The argument for a new approach

- **Pharmaceuticals:**
  - 92% of drug candidates fail in clinical studies
  - Need to assess novel chemistries (i.e. nanomaterials)
- **Industrial chemicals:**
  - Growing concern over lack of data for possibly tens of thousands of chemicals on the market and in the environment world-wide
  - REACH (EU, China, S.Korea)
- **Pesticides:**
  - Registration requires the use of approximately 10,000 animals, millions of USD, and many years (decades)
  - Need to identify “greener” chemistries
- **Cosmetics**
  - European Cosmetics Directives ban on animal testing
  - Consumer concern over safety and animal testing worldwide

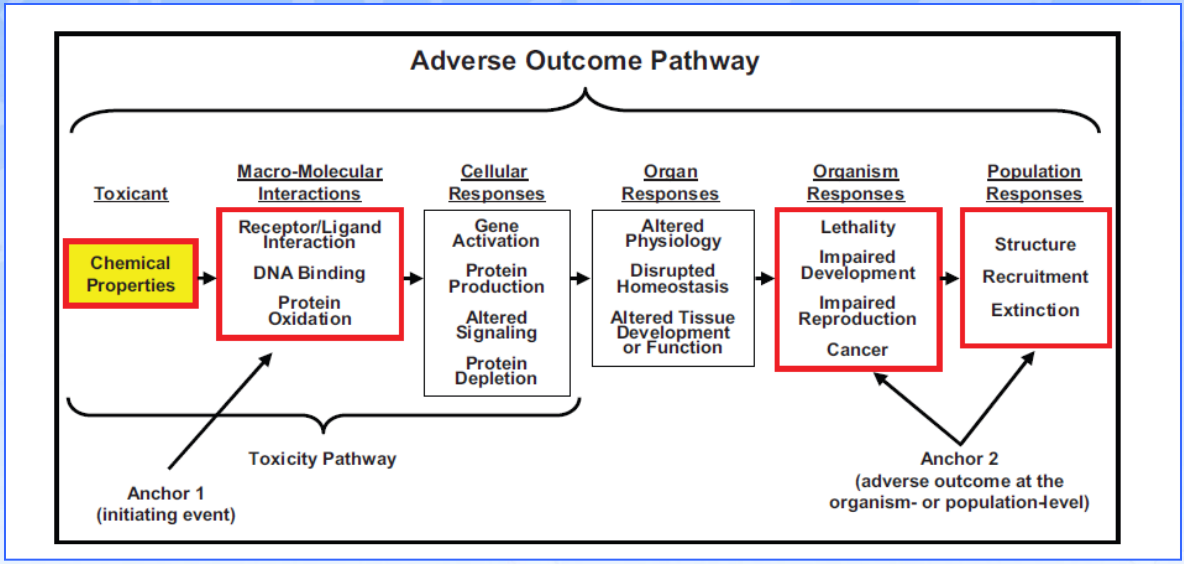
The argument for a new approach

- Capitalize on advances in chemistry, biology, and engineering
- Fully utilize all existing knowledge
- Increase relevance to humans
- Increase assessment capacity (through-put)
- Increase efficiency (benefit/cost)
- Better *predictivity*

National Research Council (2007). Toxicity testing in the 21st century: A vision and a strategy. National Academy of Sciences, Washington, DC.

The Adverse Outcome Pathway Concept

- A **chemical and biological description** of what occurs when a substance interacts with a living organism and results in an adverse reaction
- A **biological map** from the **molecular initiating event** through the resulting **adverse outcome** that describes both mechanism and mode of action.



From: Ankley et al. Environ.Toxicol.Chem. 2010. 29 (3): 730–741.

The Adverse Outcome Pathway Concept

Human Relevance Frameworks*

- Characterize MoA of each class of carcinogens
- Determine which rodent MoA is possible relevant to humans
- Built using case studies

DNA reactive vs non-DNA reactive (epigenetic)

– Genotox battery

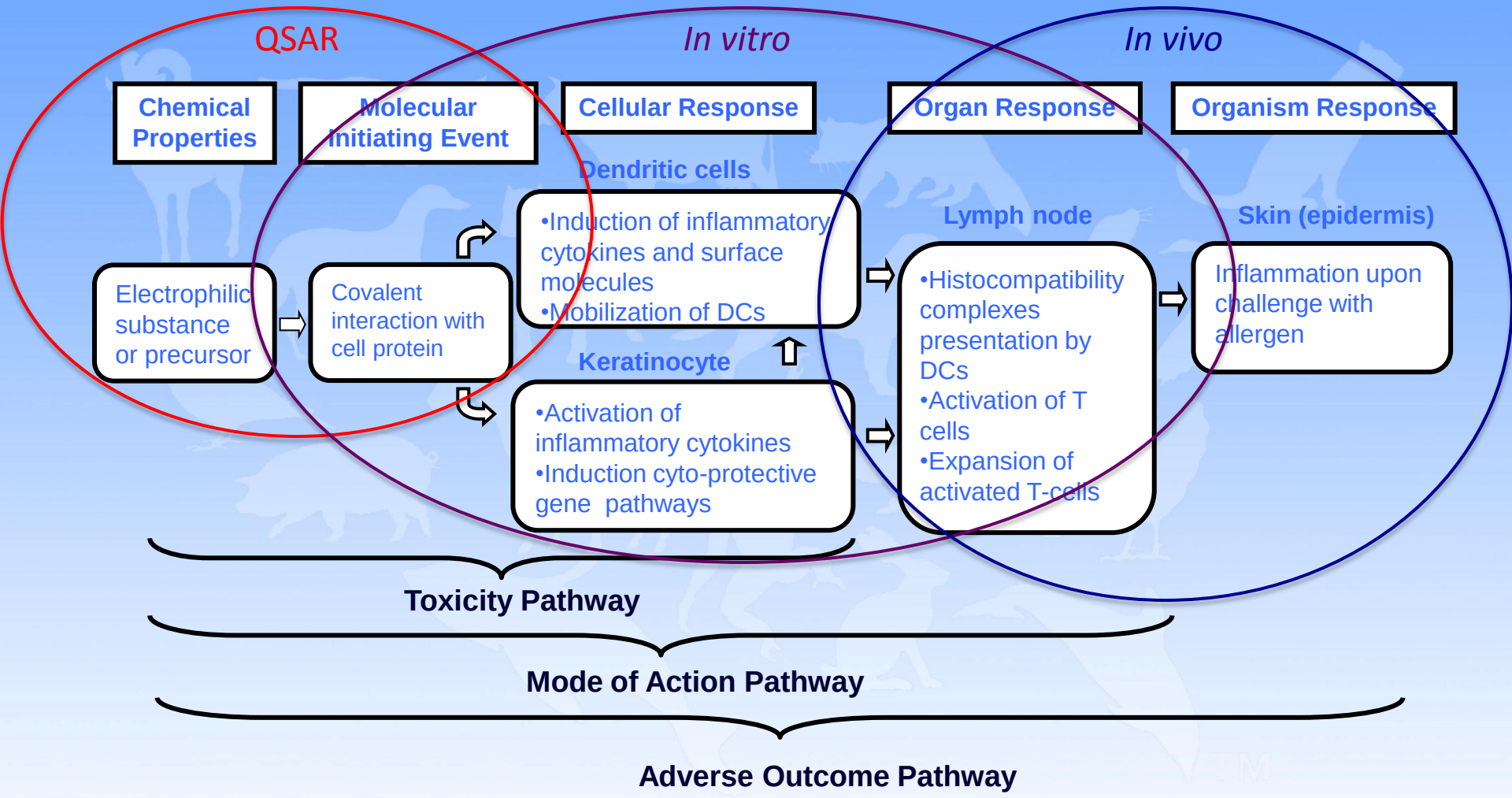
– Cell transformation assays

*Boobis, et al. IPCS framework for analyzing the relevance of a noncancer mode of action for humans. Crit Rev Toxicol. 2008;38(2):87-96.

Case examples of AOPs

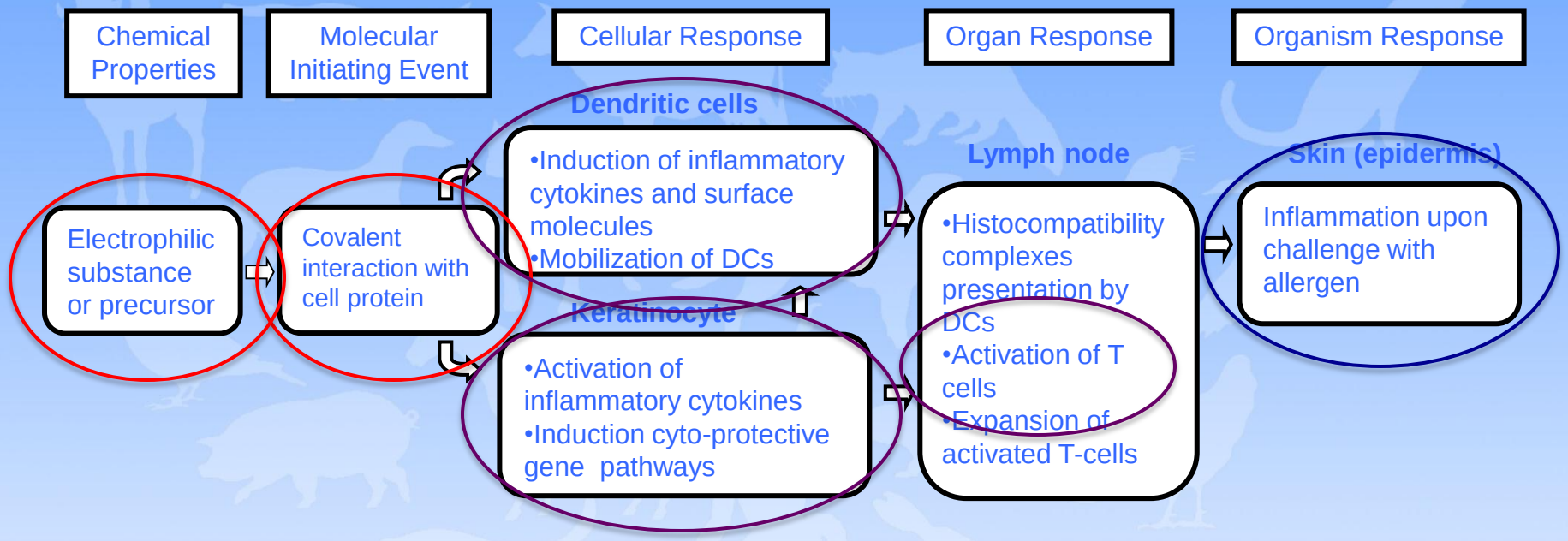
- OECD skin sensitisation project
- Estrogen receptor-mediated effects
- Thyroid hormone pathway

OECD sensitization project



OECD 2012. The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins

OECD sensitization project



Aeby et al. (2010). *Toxicol In Vitro* 24, 1465 – 1473

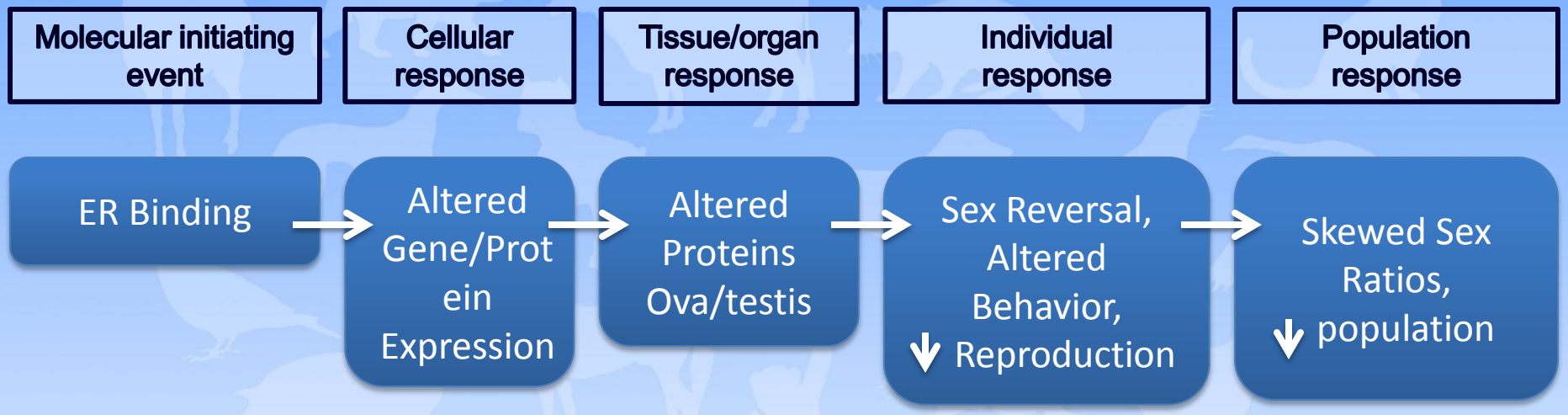
Bauch et al. (2011). *Toxicol In Vitro* 25, 1162–1168

European Union, 7th Framework Programme Sens-it-iv: http://www.sens-it-iv.eu

Lambrechts et al. (2010). *Tox Sci* 116(1),122–129.

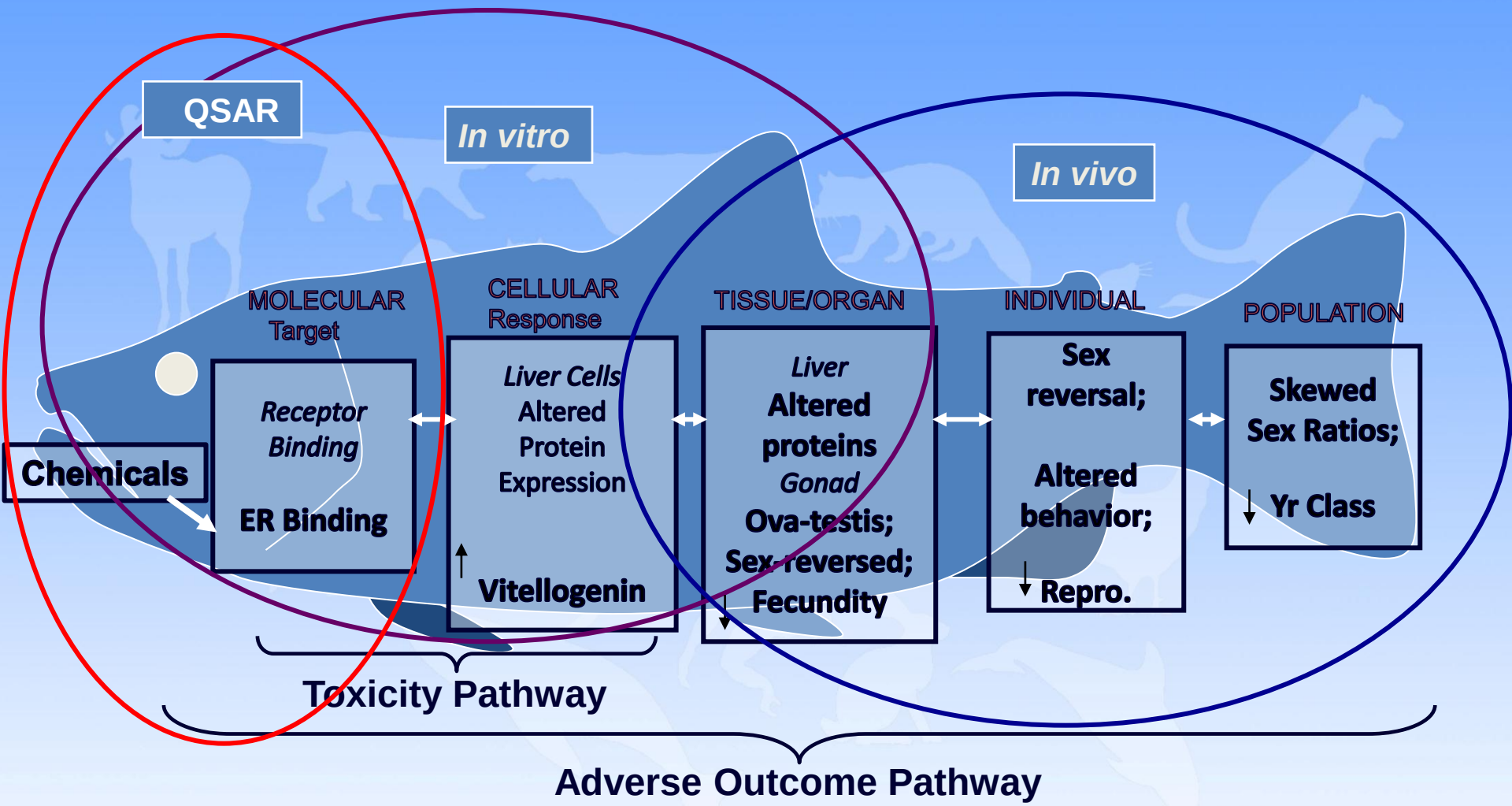
McKim et al. *Cutan Ocul Toxicol* Apr 12. [Epub ahead of print]

ER-mediated reproductive impairment



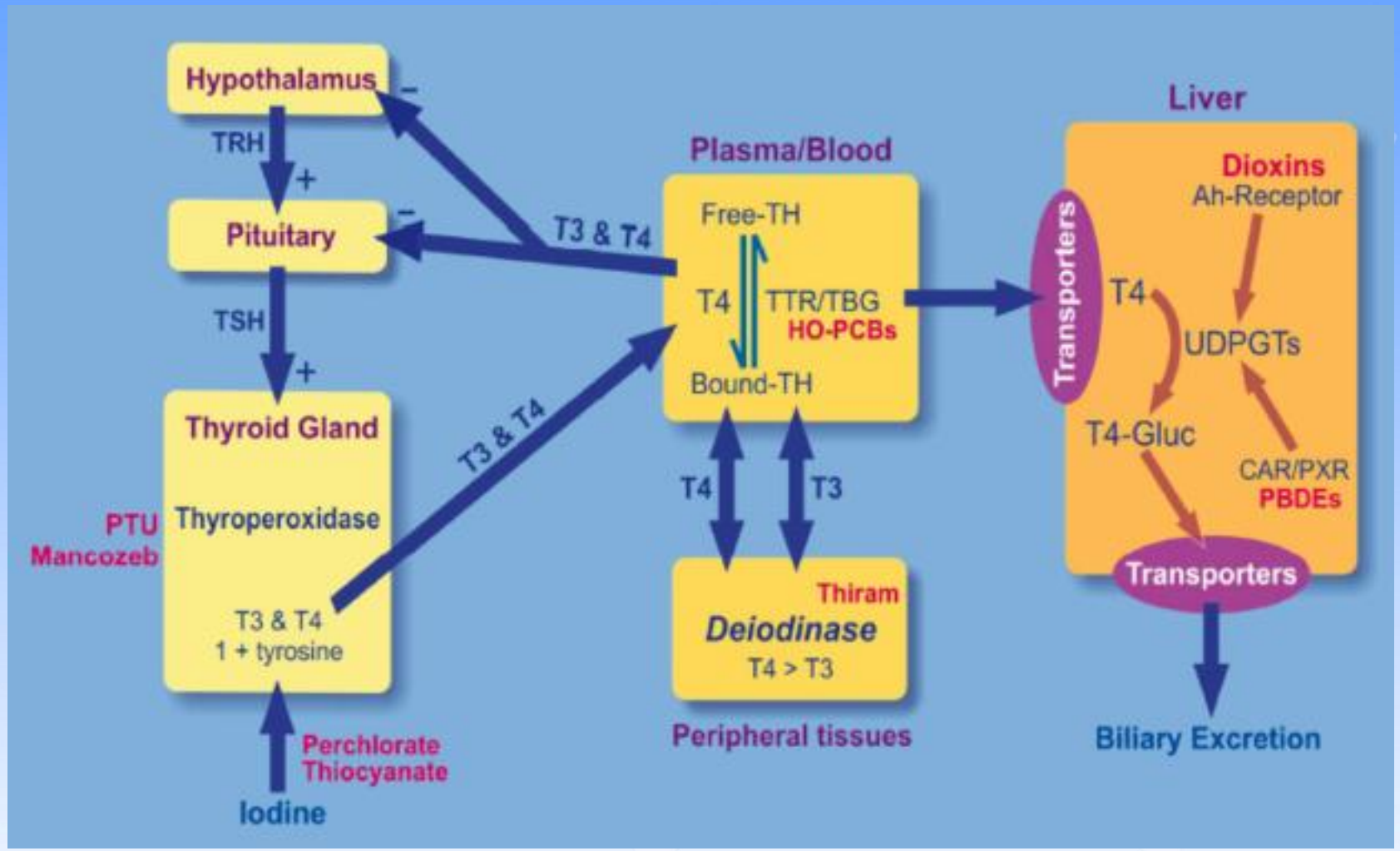
OECD, 2011. Report of the Workshop on Using Mechanistic Information on Forming Chemical Categories ENV/JM/MONO(2011)8. 18-May-2011 176 pp.

ER-mediated reproductive impairment



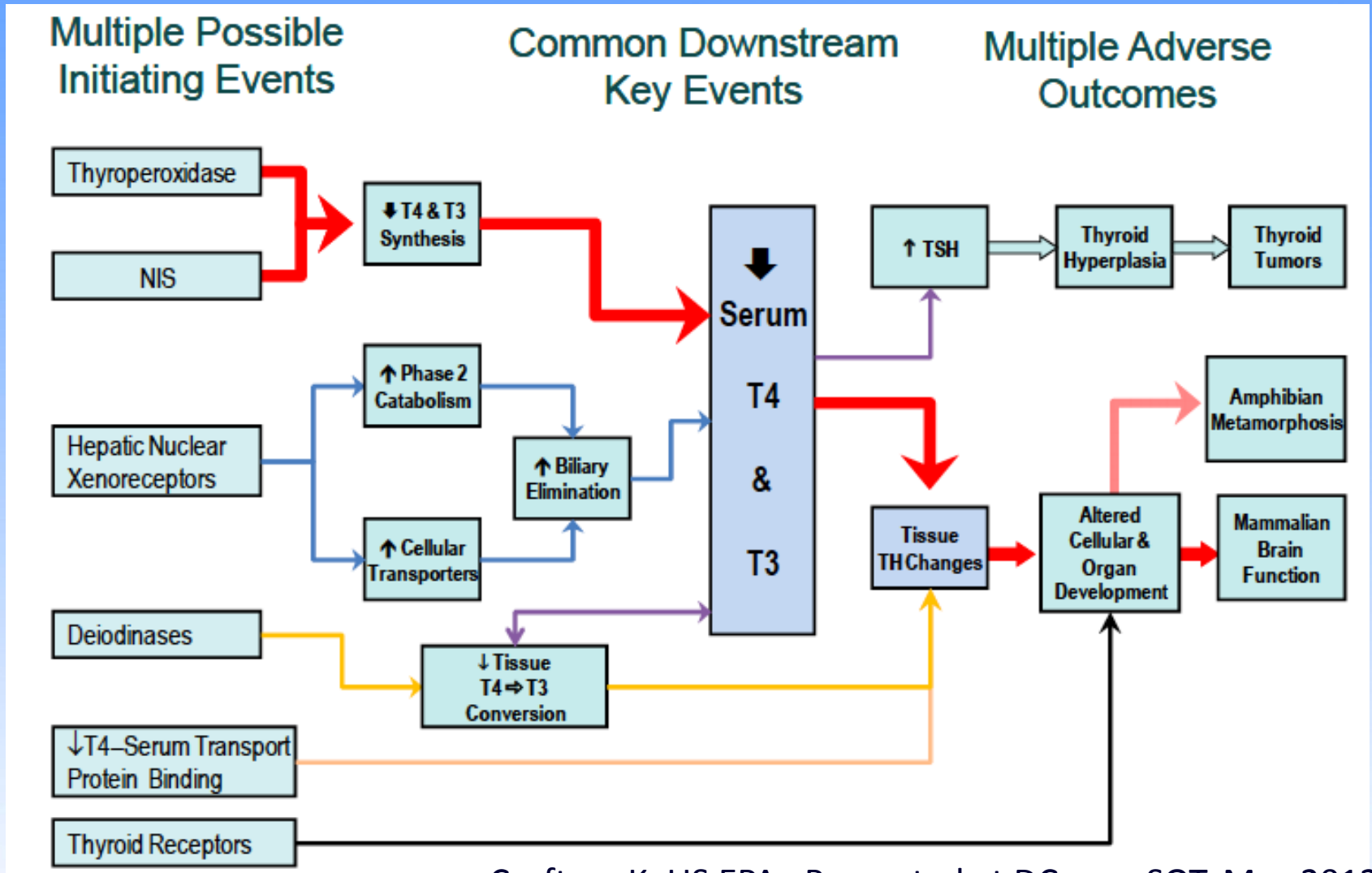
OECD, 2009. Report of the Expert Consultation to Evaluate an Estrogen Receptor Binding Affinity Model for Hazard Identification. Task Force on Hazard Assessment. ENV/JM/HA/RD(2009)1. 2-March-2009 107 pp.

Thyroid hormone pathway(s)



Crofton, K. US EPA. Presented at DC area SOT, May 2012.

Thyroid hormone pathway



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The Adverse Outcome Pathway Concept

Near-term use:

- Inform chemical categories and structure activity relationships
- Increase certainty of interpretation of both existing and new information
- Develop integrated testing strategies that maximize useful information gained from minimal testing

Longer-term use:

- Identify key events for which non-animal tests can be developed, thereby facilitating mechanism-based, non-animal chemical assessment
- Create predictive toxicological assessments with low uncertainty and high human relevance
- Eventually without the use of animals

Strategy for the future

- Build Biological and adverse-outcome “pathways”
  - OECD integration of AOPs into the Test Guidelines program
  - Guidance
- Improve predictive tools
  - NIH National Center for Advancing Translational Sciences
  - EPA’s Computational Toxicology Research
  - OECD QSAR tool box
  - Hamner Institute
- Develop assessment systems for complex endpoints
  - Reconstructed tissues and organ systems
    - Human skin, eye, lung
    - Liver-on-a-chip
    - Stem-cell derived
- Integrate absorption, metabolism and distribution information
  - QSAR
  - Liver cells, tissues, extracts, reconstructed tissues
- Integrated databases and “knowledge bases”
  - **ACToR and MetaPath:** EPA – all available chemical toxicity data on over 500,000 environmental chemicals searchable by chemical name and structure
  - **Kegg pathway database**: collection of manually drawn pathway maps representing current knowledge on the molecular interaction and reaction networks
  - **Effectopedia**: open knowledge aggregation and collaboration tool that provides a means of describing adverse outcome pathways in an encyclopedic manner.

Strategy for the future

Effectopedia

- an open source knowledge aggregation and collaboration tool that provides a means of describing adverse outcome pathways in an encyclopedic manner

- creates a common organizational space that
  - (1) helps experts identify exactly where more detailed knowledge is needed in order to extend the causal linkages of biological responses and
  - (2) creates a web-based conference room for dialogue and synthesis by experts with interest in a specific AOPs.

This kind of common, encyclopedic resource is necessary for forming the framework to establish the **quantitative** linkages required for true use of AOPs in risk assessment.

www.effectopedia.org

Human Toxicology Project **Consortium**

Articulating the Vision:

Communicating the purpose and goals of TT21C

Implementation:

facilitating scientific and technical approaches to accomplishing the vision globally

Lobbying/Funding:

in the US and internationally

Thank You

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