

Introduction to Adverse Outcome Pathways (AOPs) for Toxicity: Description, Practical Application and Use

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Content

- Definition of AOPs including their history and development
- Description and illustration of molecular initiating events, key events and their relationships to an adverse effect
- Examples of AOPs and how they may be applied
- International efforts in AOP development
- Importance of the AOP concept in 21st Century Toxicology

Learning Objectives

- To understand the definition of an Adverse Outcome Pathway (AOP) and the link with mechanisms and mode of toxic action
- To identify the main components of an AOP
- To appreciate the role of AOPs in 21st Century Toxicology
- To utilise the information from a Molecular Initiating Event for category formation and understand how this may be supported by knowledge from assays representing the key events

Adverse Outcome Pathway

- A means of organising information relating to how a chemical causes an adverse effect
- Ultimately a means of supporting risk assessment of chemicals
- An AOP is not a method or toxicity test!

Put These in a Logical Order

Interaction
Between Chemical
and Target
Organism

Up / Down
Regulated
Genes

Death

Reduced
Population
Viability

Adverse
Effect on
Organ

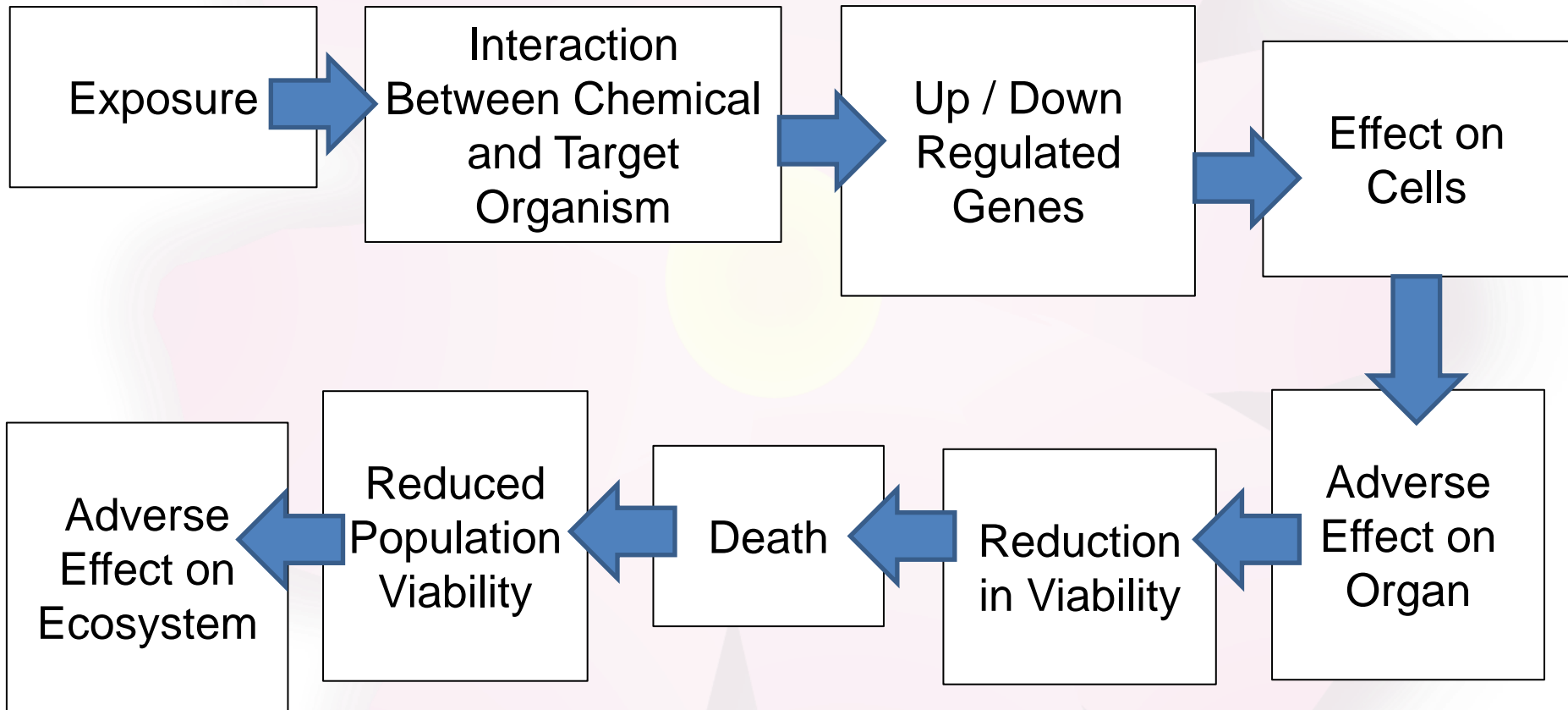
Reduction
in Viability

Adverse
Effect on
Ecosystem

Effect on
Cells

Exposure

A Logical Order?



Where Do These Terms Fit?

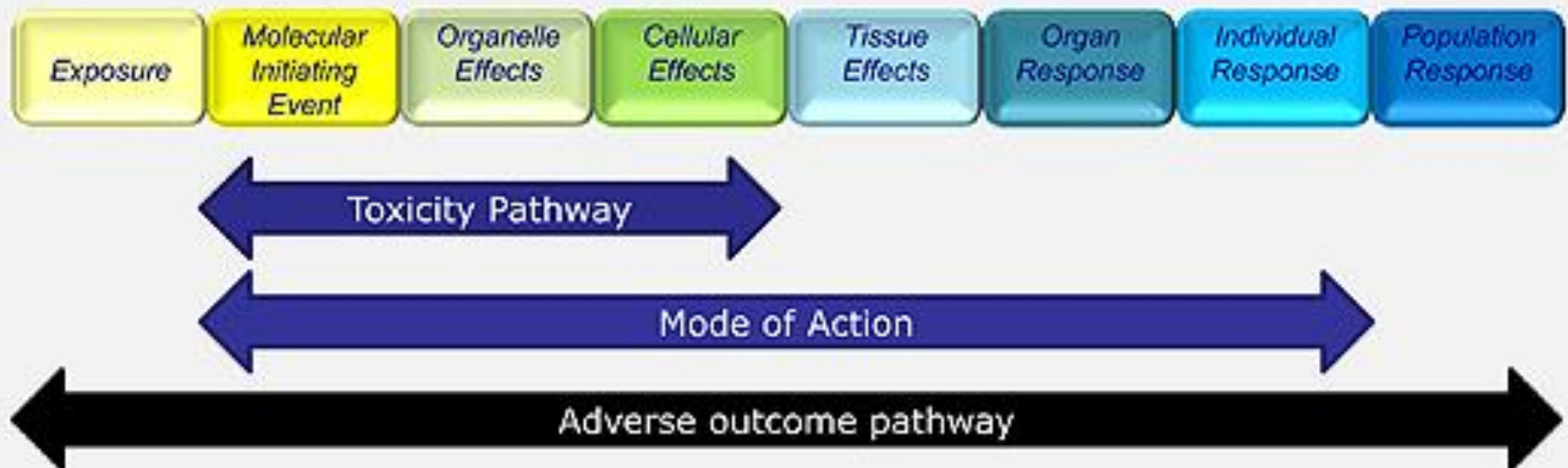
Pathway

Mechanism

Adverse Outcome
Pathway

Source to
Outcome
Pathway

Mode

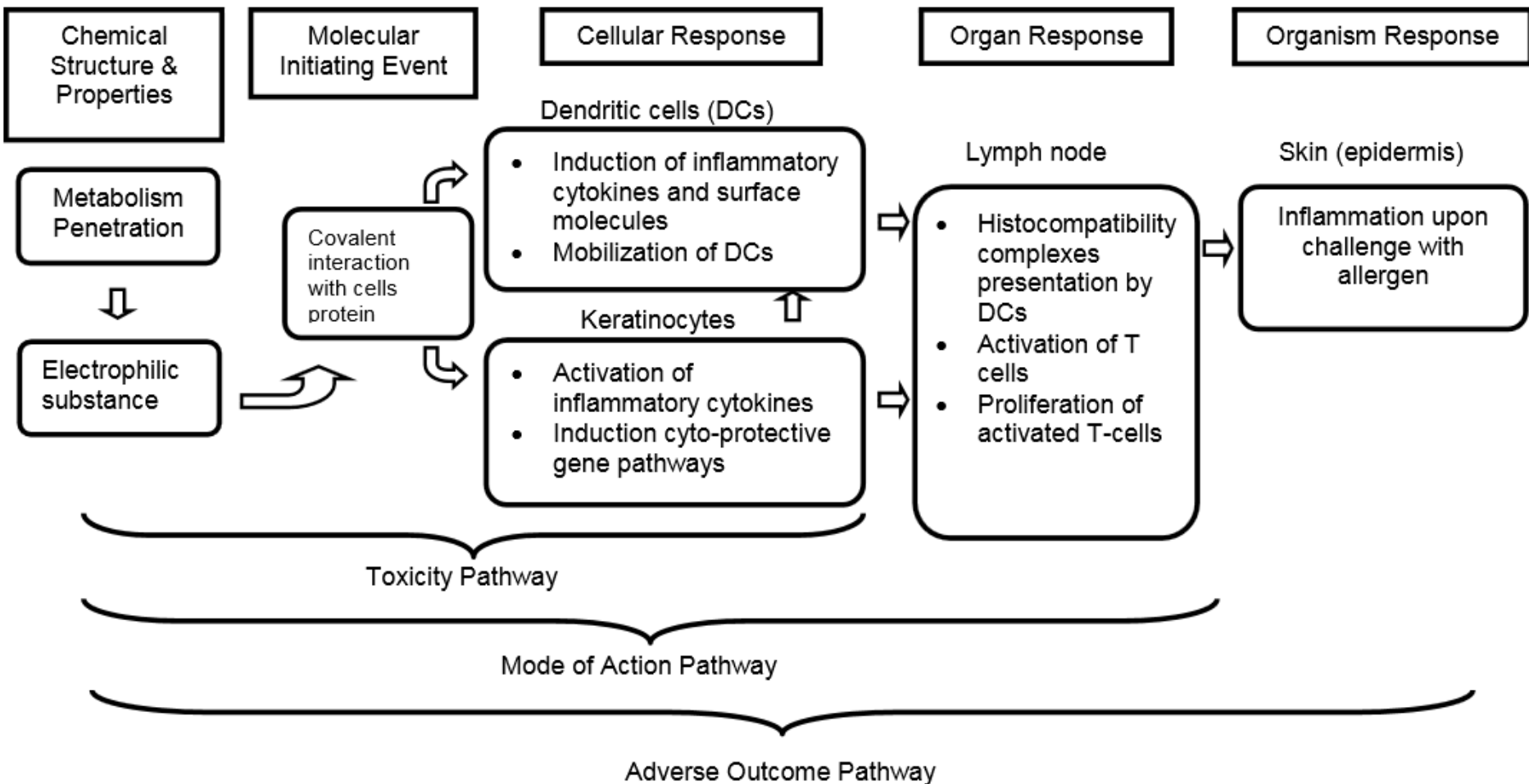


Taken from Prof Maurice Whelan, EC JRC

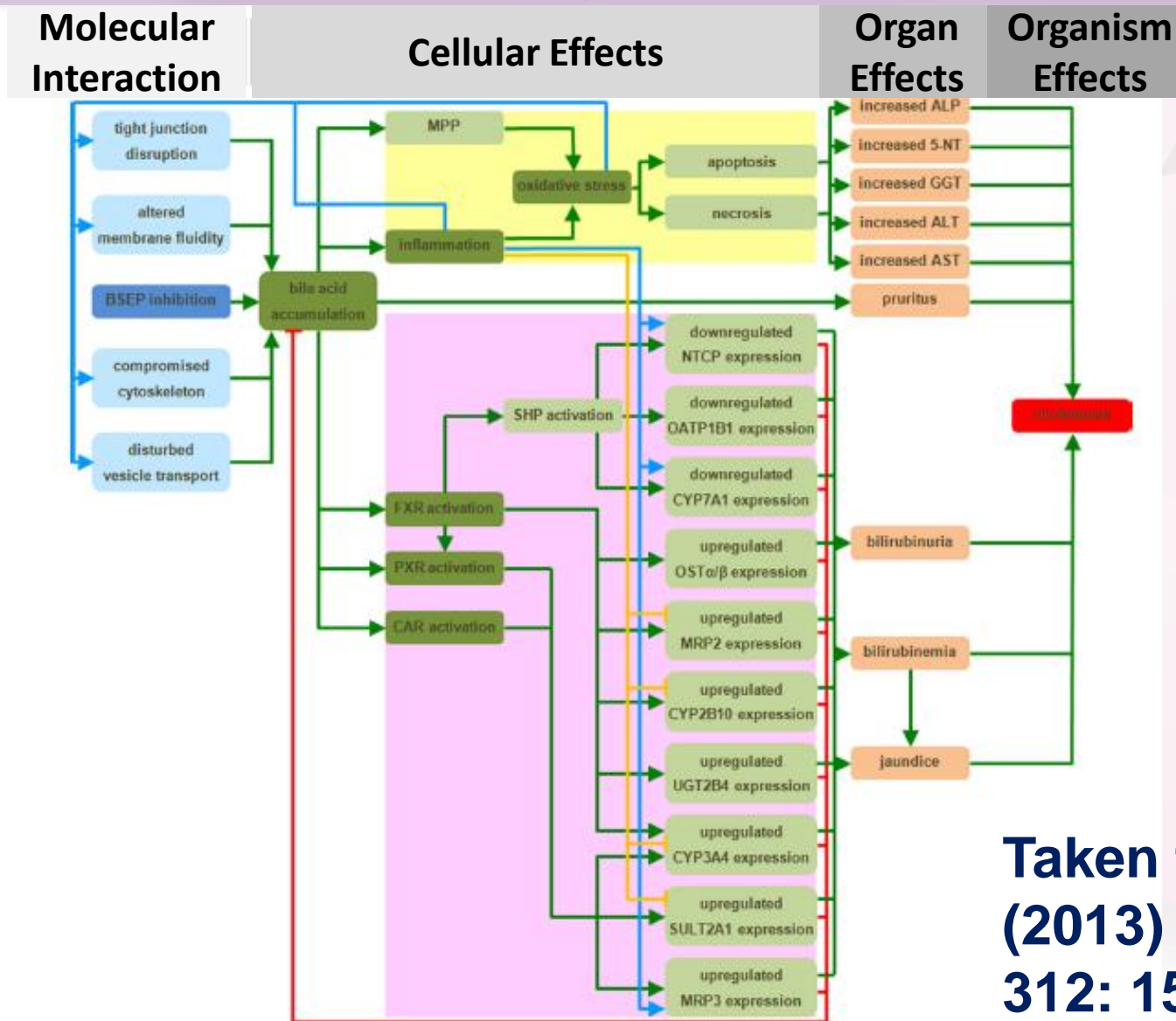
Important Definitions

- **Molecular Initiating Event** - The initial point of chemical-biological interaction within the organism that starts the pathway
- **Key events** are intermediate events (ones between the molecular initiating event and the apical outcome) that are toxicologically relevant to the apical outcome and experimentally quantifiable
- **Adverse effect**: A change in morphology, physiology, growth, development, reproduction, or life span of a cell or organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences

OECD AOP for Skin Sensitisation



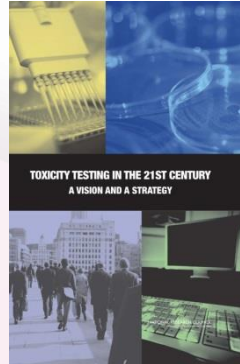
An Adverse Outcome Pathway (AOP) for Cholestasis: Putting the Pieces Together



Taken from Vinken M
(2013) *Toxicology*
312: 158-165

History

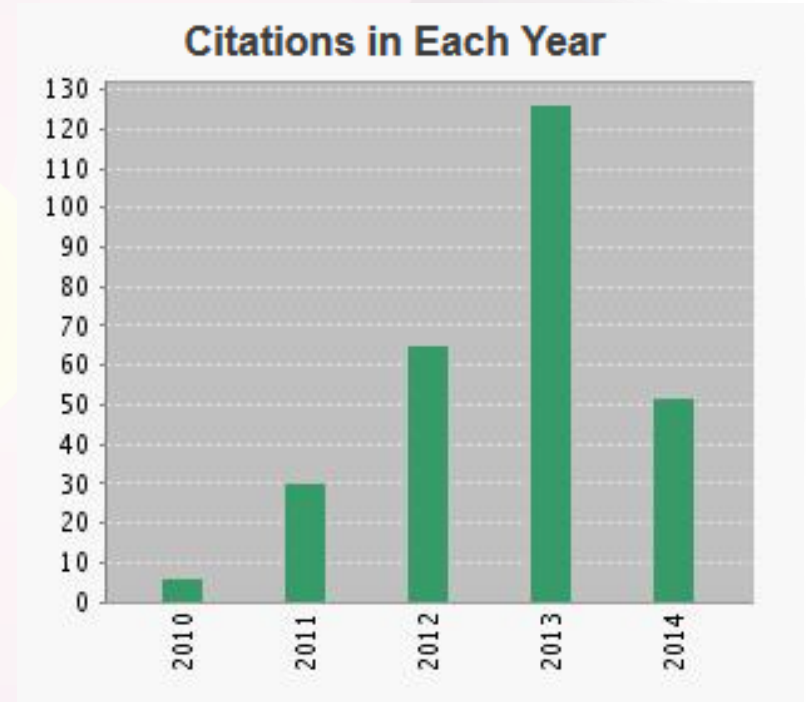
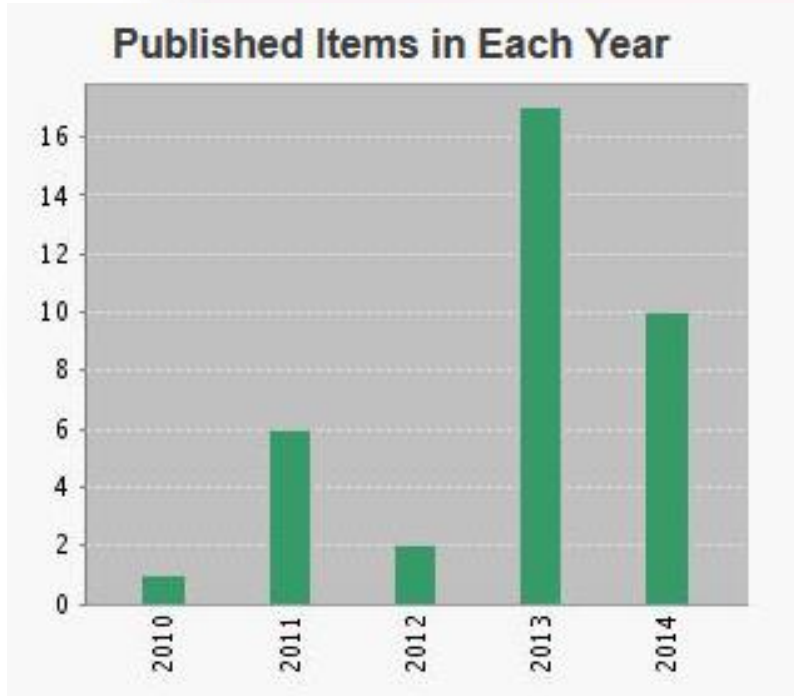
- Toxicity Pathways NRC Report (2010)
- WHO / IPCS Mode of Action Framework (Meeke et al 2013)
- 3Rs Pressures
 - Better ways of doing risk assessment
 - “Big Projects” e.g. SEURAT-1, ToxCAST, ChEMBL, molecular biology



Why Important?

- AOPs provide the linkage from chemistry, through the MIE to Adverse Effect
- Data from key events provides support to read-across especially for regulatory acceptance
- Data from key events will support definition of domains for MIEs
- Part of an ITS or IATA for risk assessment

How Many Publications?



- Search “Adverse Outcome Pathway” in Web of Science, 5 June 2014: 36 references

Key Information Source: OECD

<http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm>

Adverse Outcome Pathways, Molecular Screening and Toxicogenomics

- [What is an Adverse Outcome Pathway](#) [in-page link]
- [Documents](#) [in-page link]
- [How to make a project proposal?](#) [in-page link]
- [Process for the development of AOP at OECD](#) [in-page link]
- [List of projects on the AOP development programme workplan](#) [in-page link]
- [AOP wiki](#) [in-page link]

[Other activities on Molecular Screening and Toxicogenomics](#)

What is an Adverse Outcome Pathway

In 2012, the OECD launched a new programme on the development of Adverse Outcome Pathways. An Adverse Outcome Pathway (AOP) is an analytical construct that describes a sequential chain of causally linked events at different levels of biological organisation that lead to an adverse health or ecotoxicological effect (see figure). AOPs are the central element of a toxicological knowledge framework being built to support chemical risk assessment based on mechanistic reasoning.

Documents

Guidance, template, format available

[AOP project proposal form](#)

[Guidance document and a template for developing and assessing adverse outcome pathways](#)
(Series No. 84, Series on Testing and Assessment)

[AOP for skin sensitisation: Part 1](#)

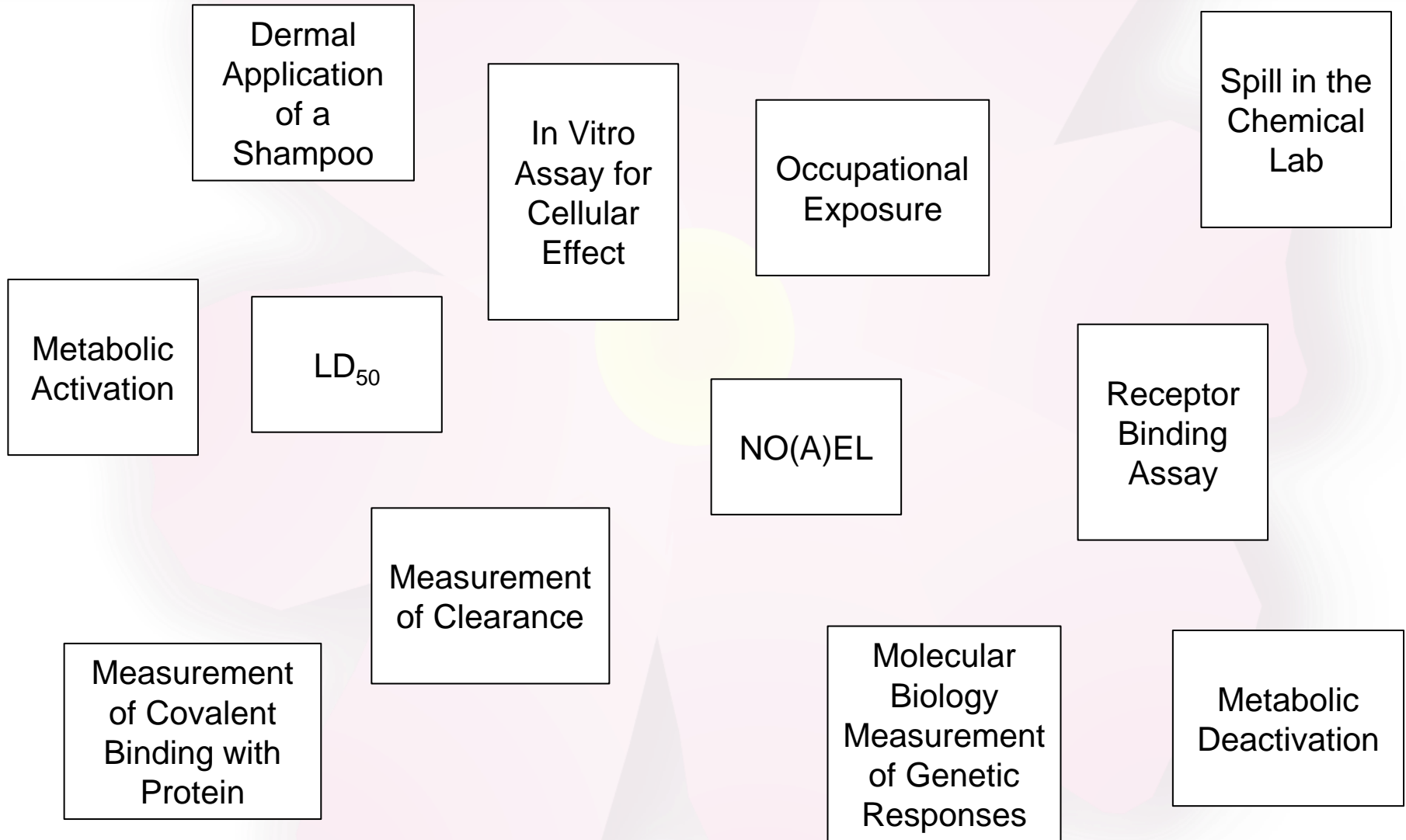
[AOP for skin sensitisation: Part 2](#)

(Series No. 168, Series on Testing and Assessment)

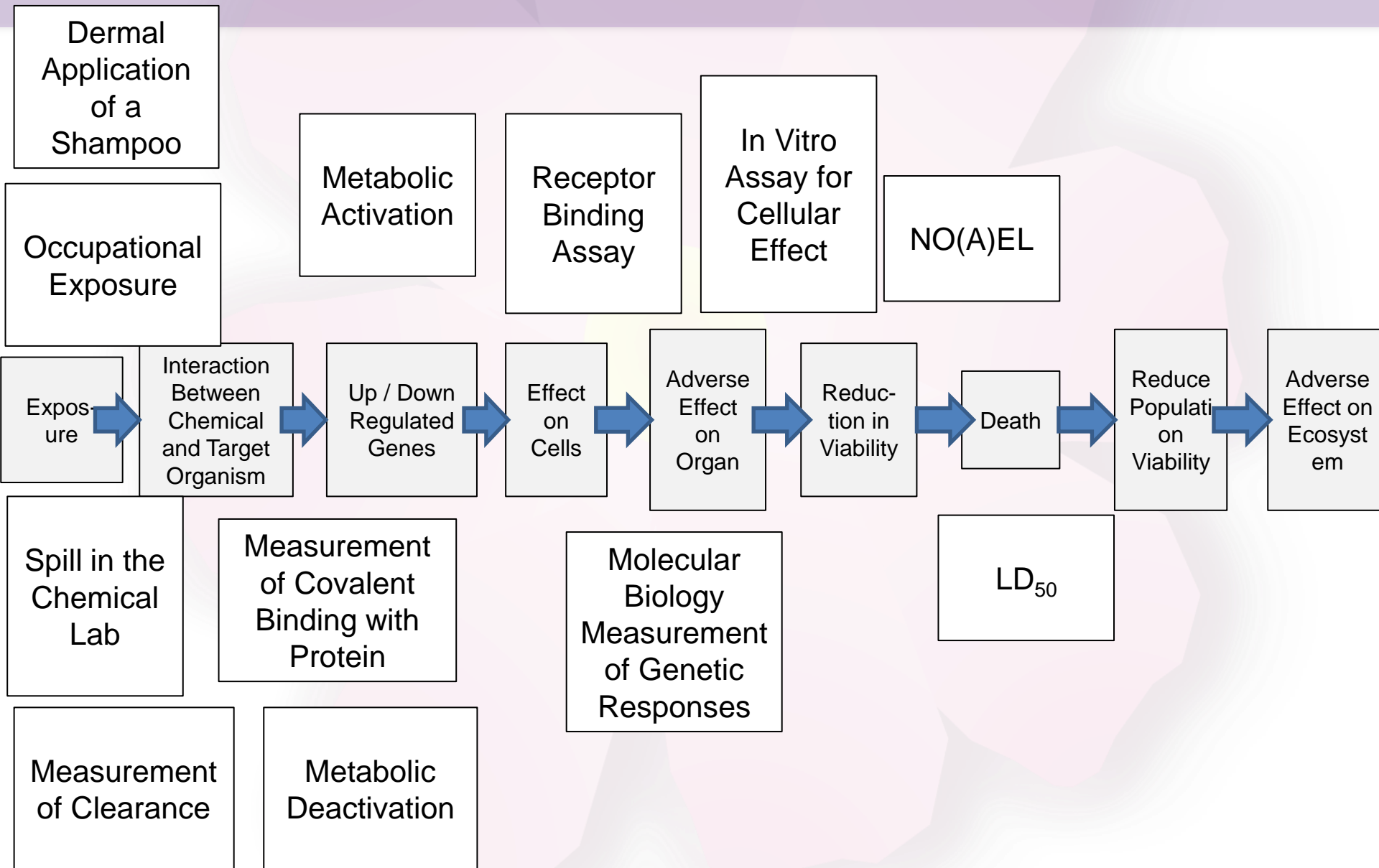
Key Reference Sources

- SEURAT-1 Annual Reports: <http://www.seurat-1.eu/pages/library/seurat-1-annual-report.php>
- GT Ankley et al (2010) Adverse Outcome Pathways: A conceptual framework to support ecotoxicology research and risk assessment. *Environ. Toxicol. Chem.* 29: 730-741 [More than 150 citations]
- Vinken M et al (2013) Development of an Adverse Outcome Pathway From Drug-Mediated Bile Salt Export Pump Inhibition to Cholestatic Liver Injury. *Toxicol. Sci.* 136 : 97-106
- Vinken M (2013) The adverse outcome pathway concept: A pragmatic tool in toxicology. *Toxicology* 312: 158-165
- Gutsell S, Russell P (2013) The role of chemistry in developing understanding of adverse outcome pathways and their application in risk assessment. *Toxicol. Res.* 2: 299-307
- Sakuratani Y et al (2013) Categorization of nitrobenzenes for repeated dose toxicity based on adverse outcome pathways. *SAR QSAR Environ. Res.* 24: 35-46
- Yamada T et al (2013) A category approach to predicting the repeated-dose hepatotoxicity of allyl esters. *Reg. Toxicol. Pharmacol.* 65: 189-195.

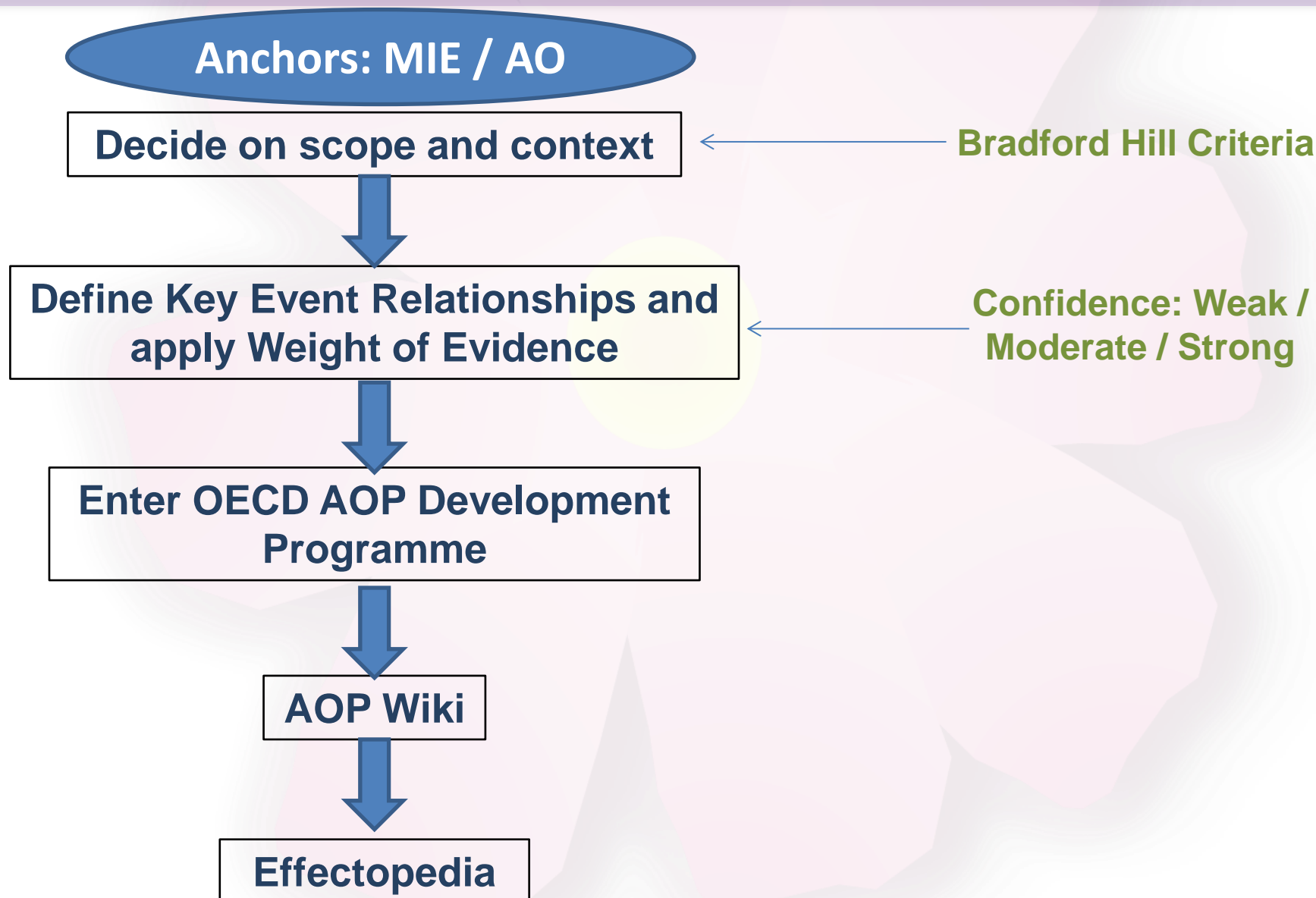
Where Do These Fit Around the AOP?



Information Feeding into an AOP



Process for Developing an AOP



Two Publicly Available Web-Based Tools

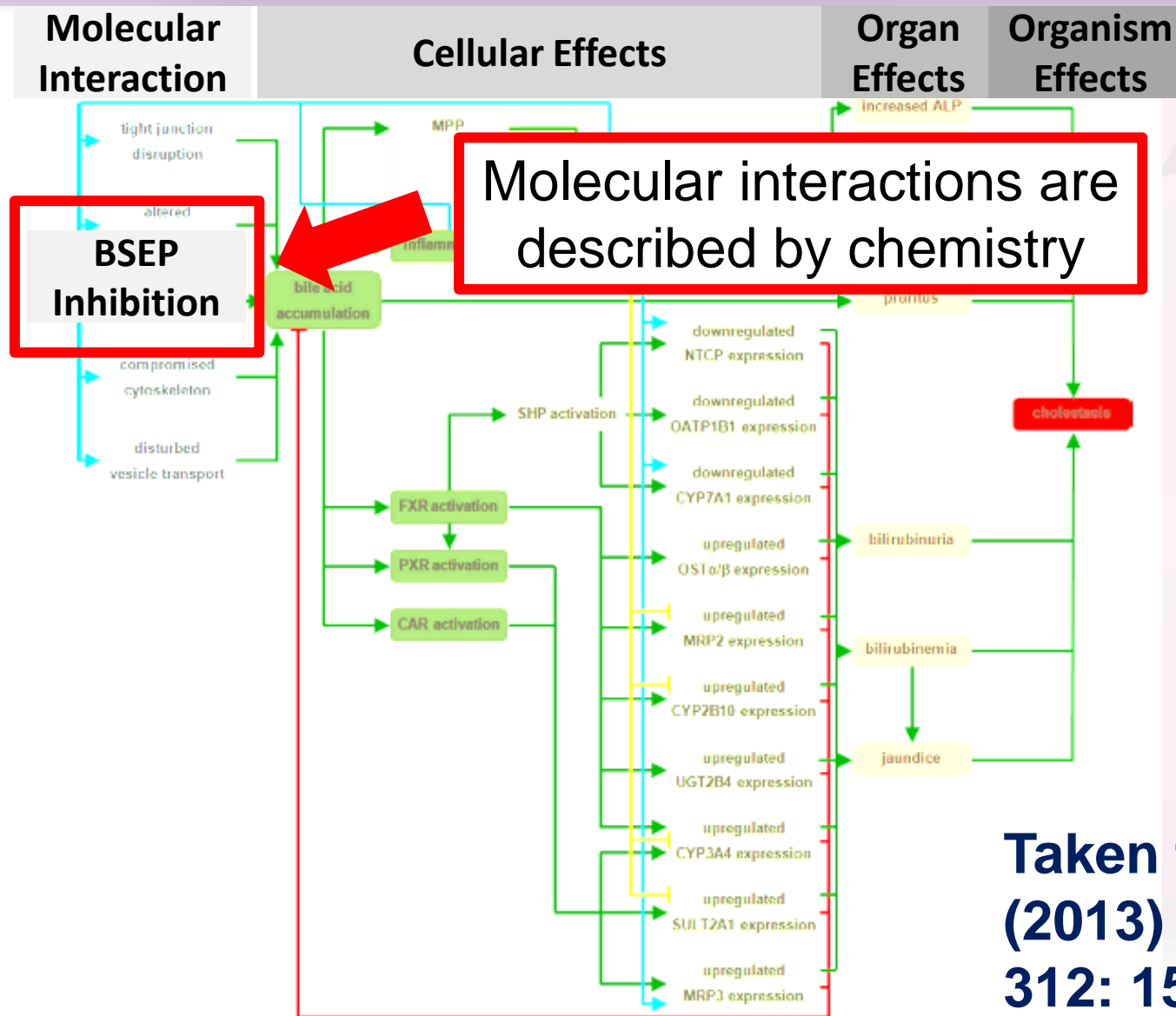
- AOP wiki: An IT system to develop and evaluate Adverse Outcome Pathways
 - Crowd sourcing platform to develop AOPs
- Effectopedia is an open knowledge aggregation and collaboration tool that provides a means of describing Adverse Outcome Pathways (AOPs) in an encyclopaedic manner
 - More complex than wiki
 - Visual and quantitative



Uses of the AOP

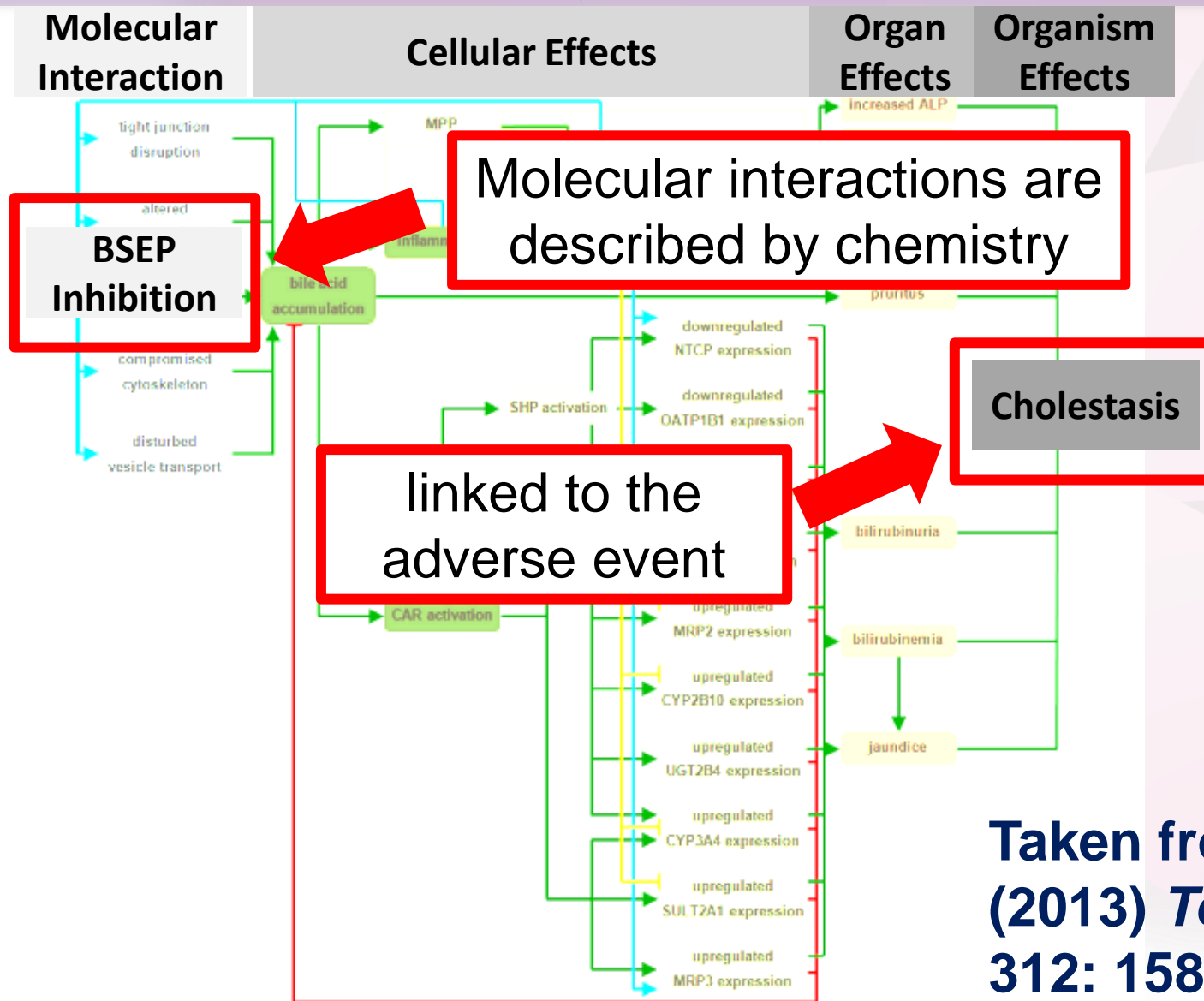
- The framework fixes mechanistic basis to adverse effects
- Provides a basis to link chemistry (from description of MIE) to adverse effect
- Will support grouping and read-across
 - Definition of domains of AOPs through intelligent testing
- Identification of where

An Adverse Outcome Pathway (AOP) for Cholestasis: Putting the Pieces Together



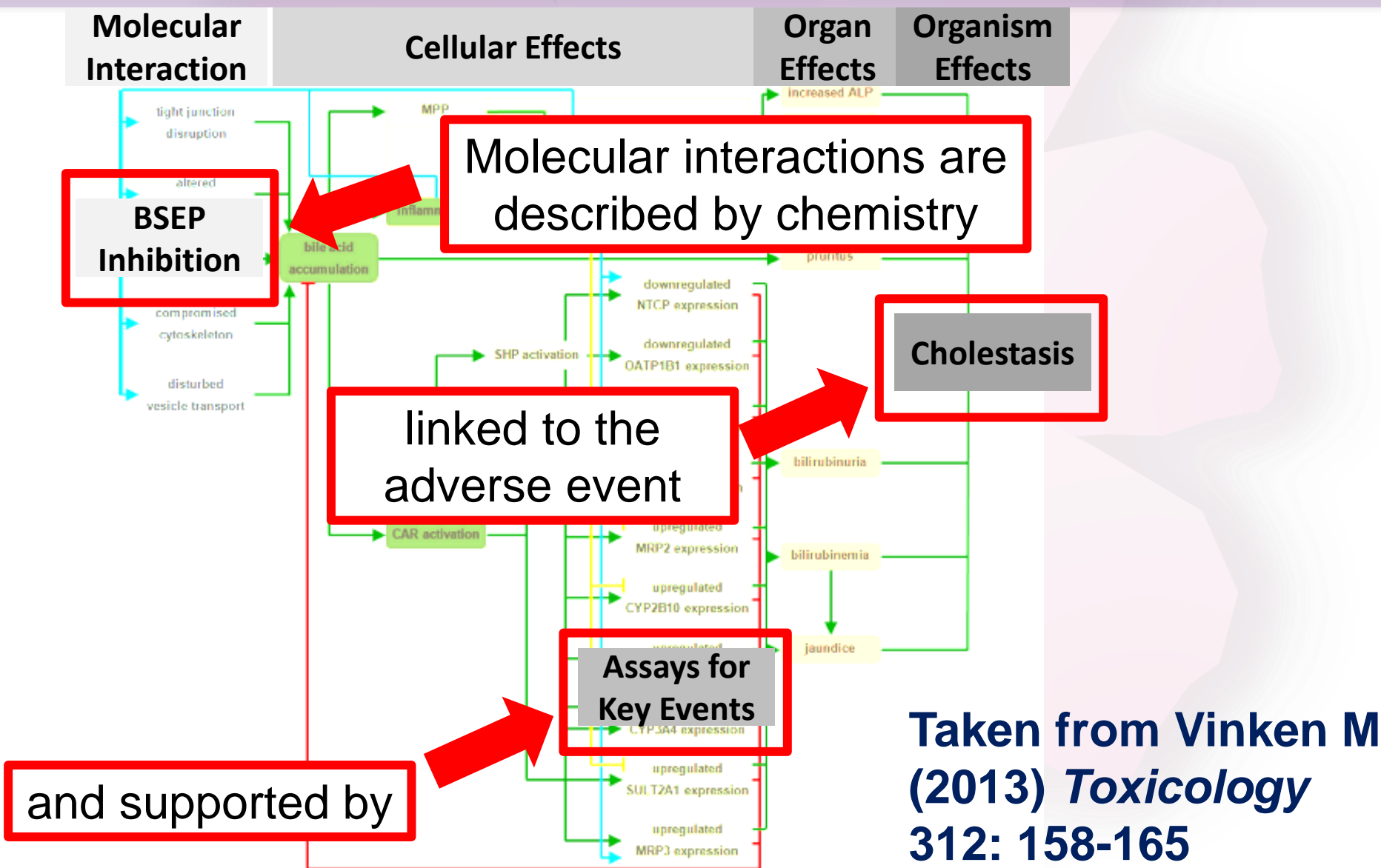
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Conclusion

- AOPs provide a “modern” framework for organising information
 - Chemical
 - *In vitro*
- Provide a linkage and justification from exposure, chemistry to adverse effect at individual, population or ecosystem
- Flexible and fashionable...

Acknowledgements



The research leading to these results has received funding from the European Community's Seventh Framework Program (FP7/2007-2013) COSMOS Project under grant agreement n° 266835 and from Cosmetics Europe.

