QSAR TOOLBOX

The OECD QSAR Toolbox for Grouping Chemicals into Categories

Future Developments

The OECD Perspective

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Workshop on the use of the QSAR Toolbox

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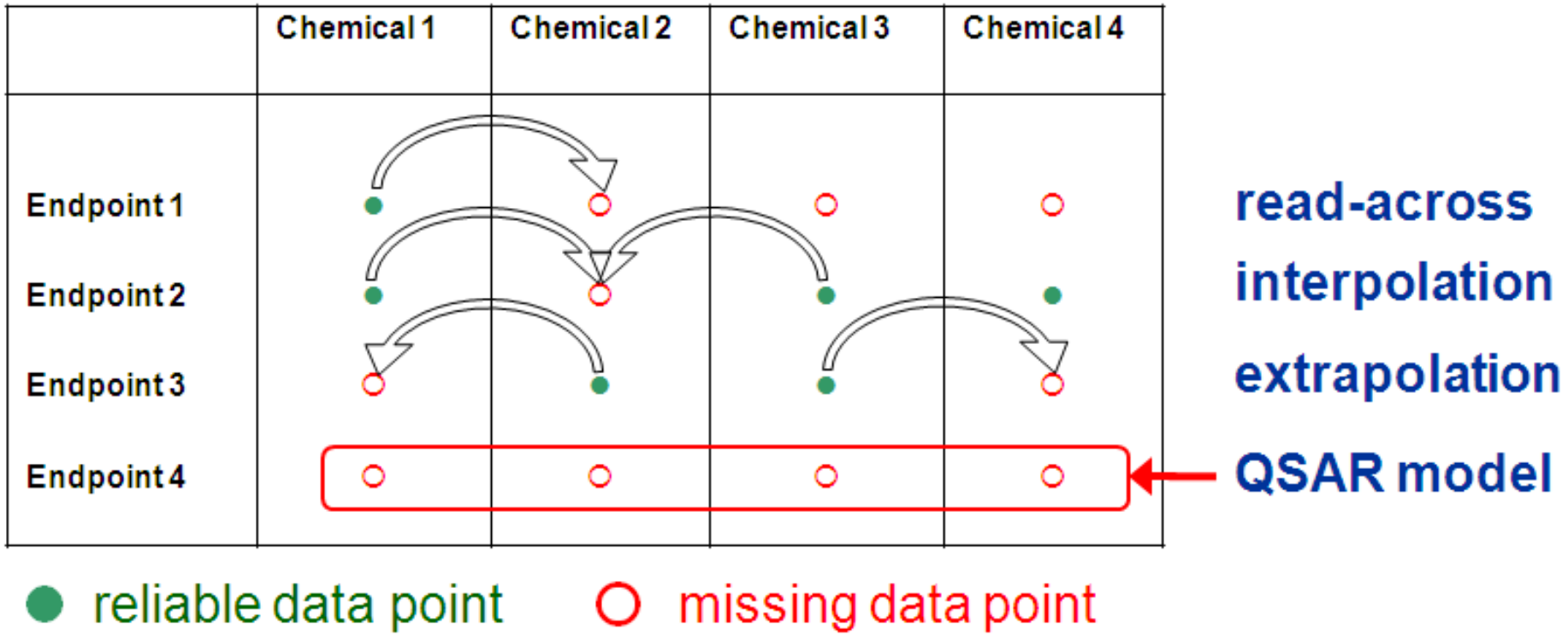
Philosophy

- Implement into a flexible software the OECD Guidance on Grouping of Chemicals
- http://appli1.oecd.org/olis/2007doc.nsf/linkto/env-jm-mono(2007)28
- Facilitate the regulatory use of QSAR approaches by using structure-activity methodologies for the formation of toxicologically meaningful categories allowing to fill data gaps by read-across or trend analysis

Chemical Categories

- A chemical category is a group of chemicals whose physical-chemical and toxicological and/or ecotoxicological properties and/or environmental fate properties are likely to be similar or follow a regular pattern because of their similar chemical structure.
- Using this so-called category approach, not every chemical needs to be tested for every endpoint because the available test results for the members of the category allow an estimation of the results for the untested endpoints.

Chemical Categories



Workflow

- Identification of structural and mechanistic features of a target chemical (Profiling).
- Identification of other substances with the same structural and mechanistic features (Category Definition).
- Use of existing experimental results to fill the data gap (Filling Data Gap).

Long-term objectives

- To ensure that the categories approach to filling data gaps works uniformly for all discrete organic chemicals and for all regulatory endpoints
- “provide (Q)SAR tools that can group chemicals into (eco)toxicologically meaningful categories and that (eco)toxicologists recognise as being relevant for the regulatory endpoint for which read-across is proposed”

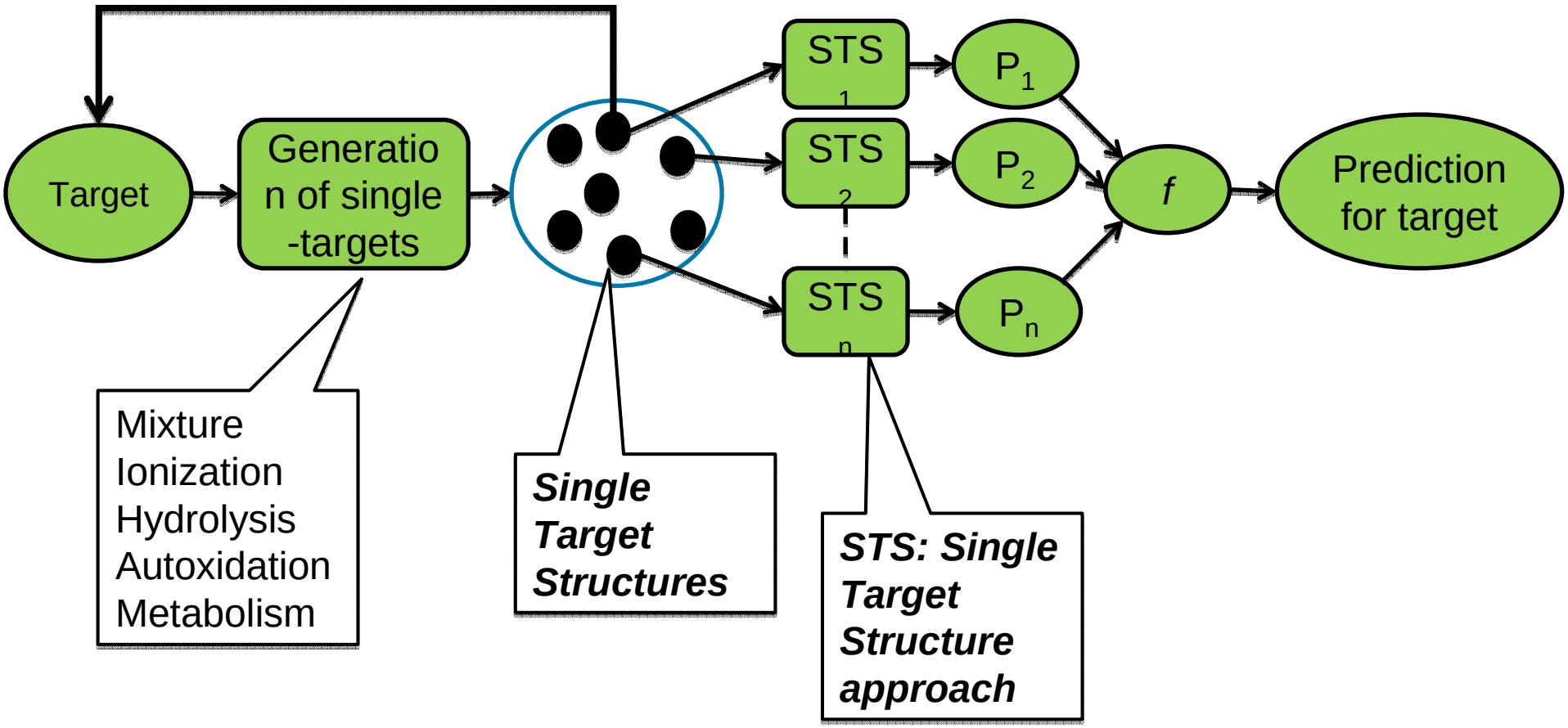
Main improvements of version 2

- Server version in addition to stand-alone version
- Quality assurance of chemical IDs
- Data exchange with IUCLID 5
- Automatic generation of reports
- Additional databases
- Additional profilers and revision of existing profilers

Focus of development work for version 3.0

- Tautomers
- Transformation
  - Ionisation
  - Metabolism
  - Hydrolysis
  - Autooxidation
  - Degradation
- Assessment of mixtures of known composition
- Proof-of-concept implementation of adverse outcome pathways

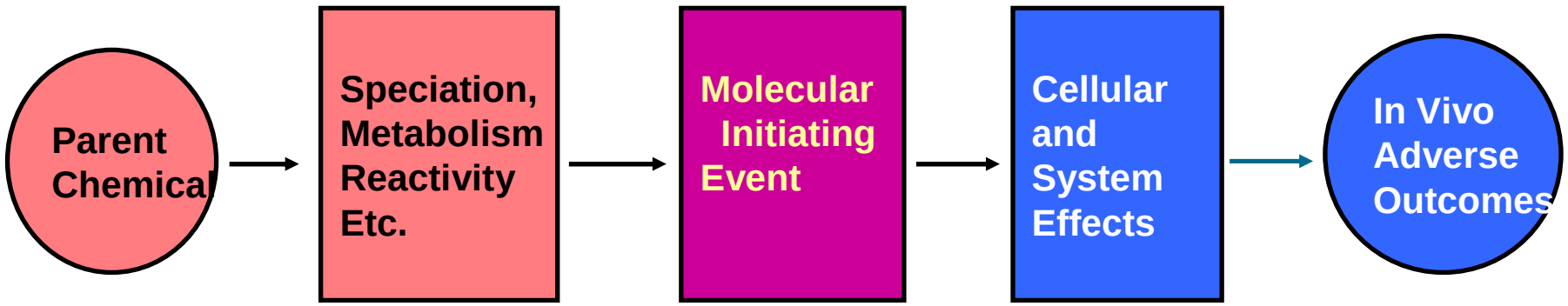
Structure of multiplication scheme in Toolbox



Adverse Outcome Pathways

- Description of causal linkages that illustrate how a chemical interaction with a biological system at the molecular level causes biological effects at the cellular, tissue, organ and animal levels of observation.
- A means of forming categories based on both chemical and biological activity and evidence supporting the robustness of the categories.

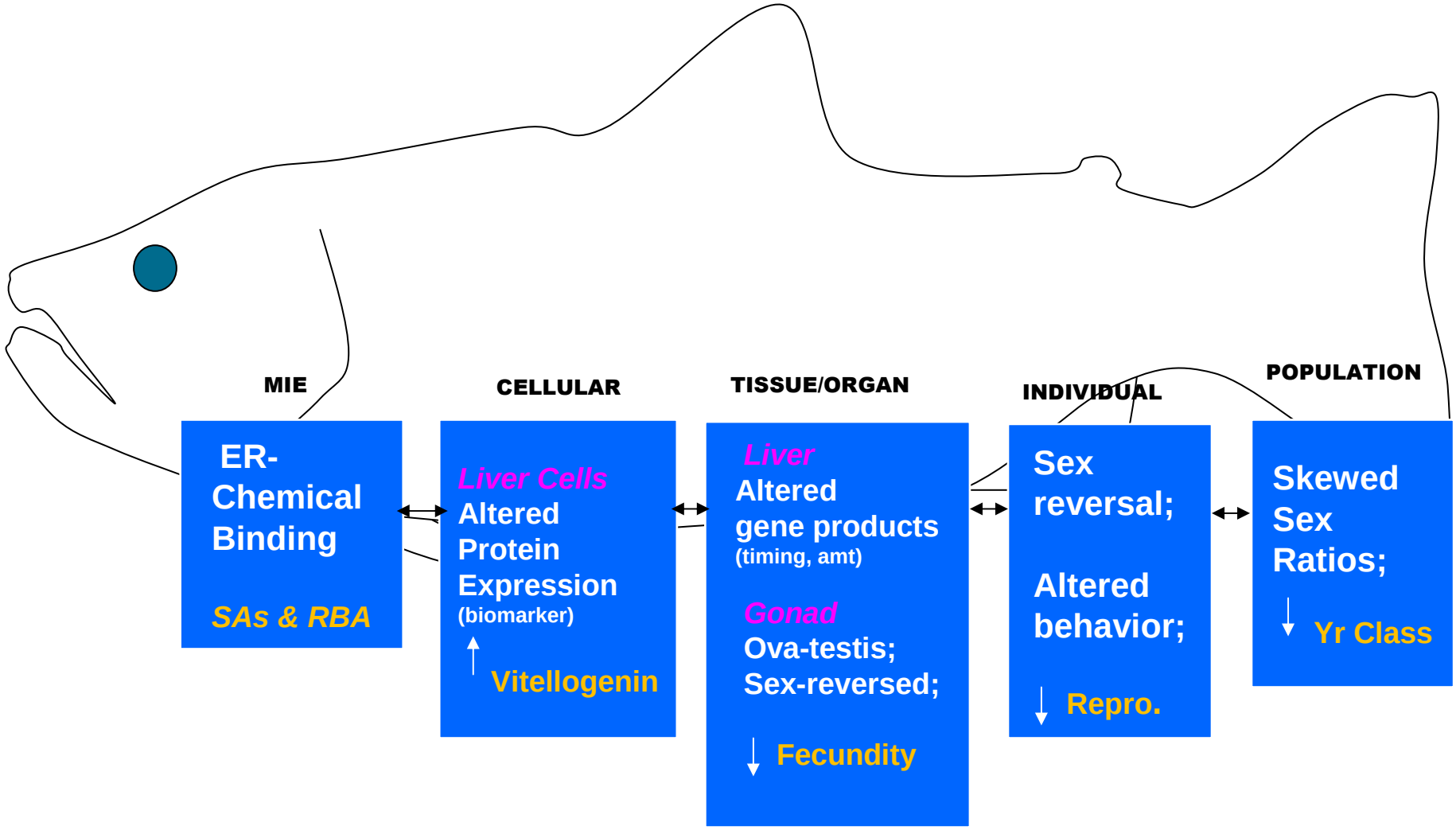
Adverse Outcome Pathway



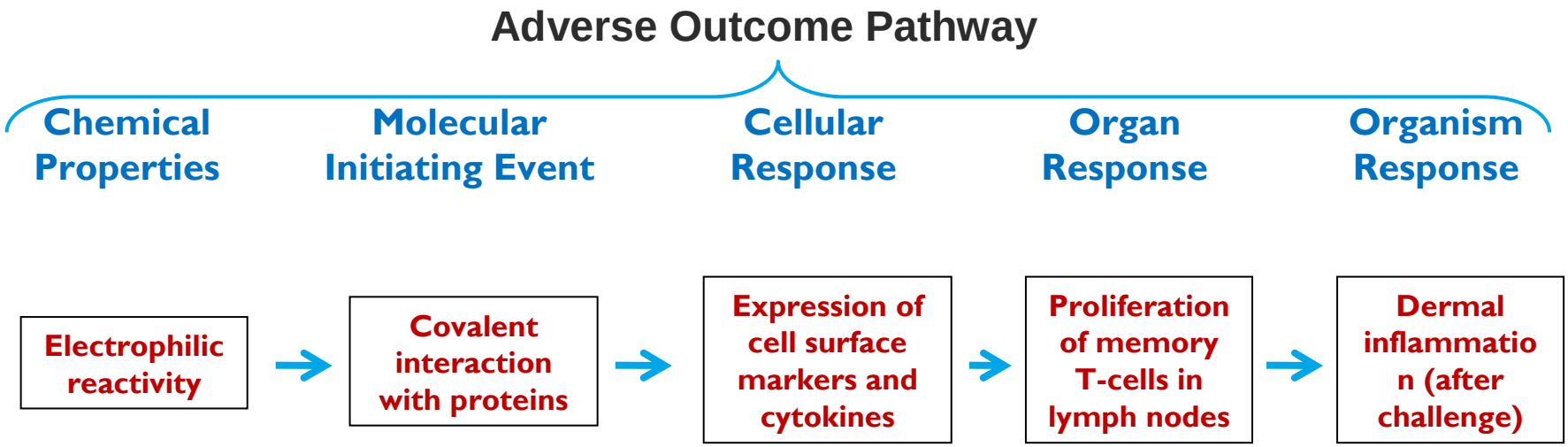
Up-Stream
CHEMISTRY
Structure-Activity

Down-Stream
BIOLOGY
Levels of Organization

AOP for ER-mediated Reproductive Impairment



AOP: An example for skin sensitisation



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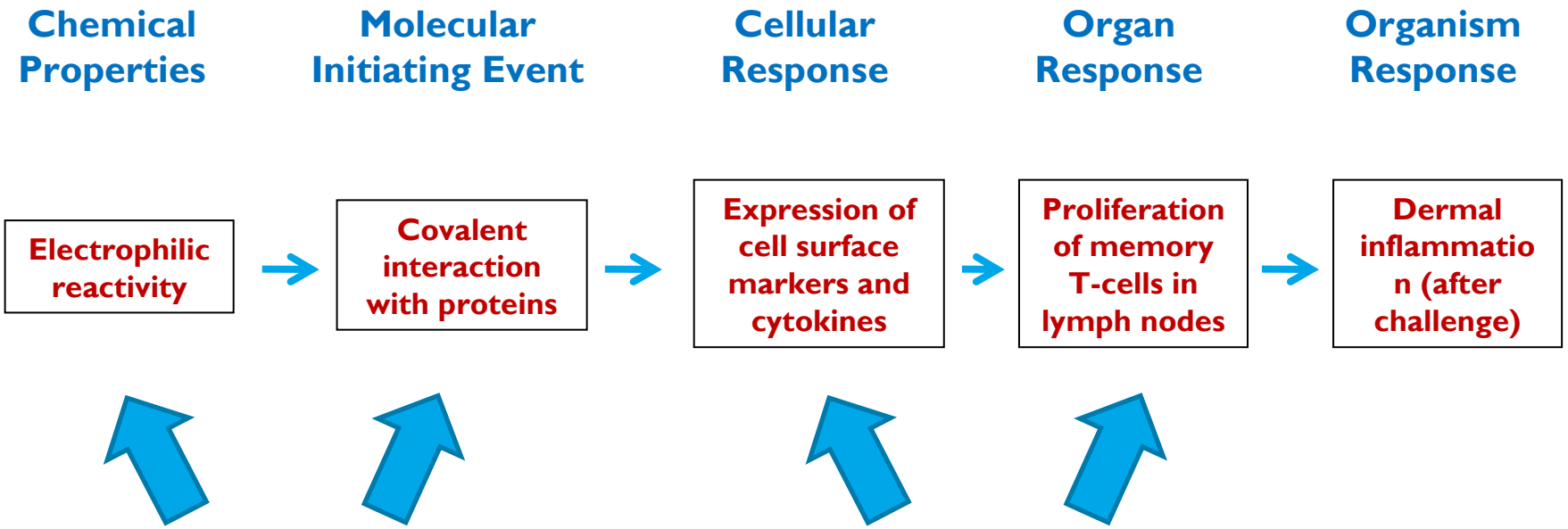
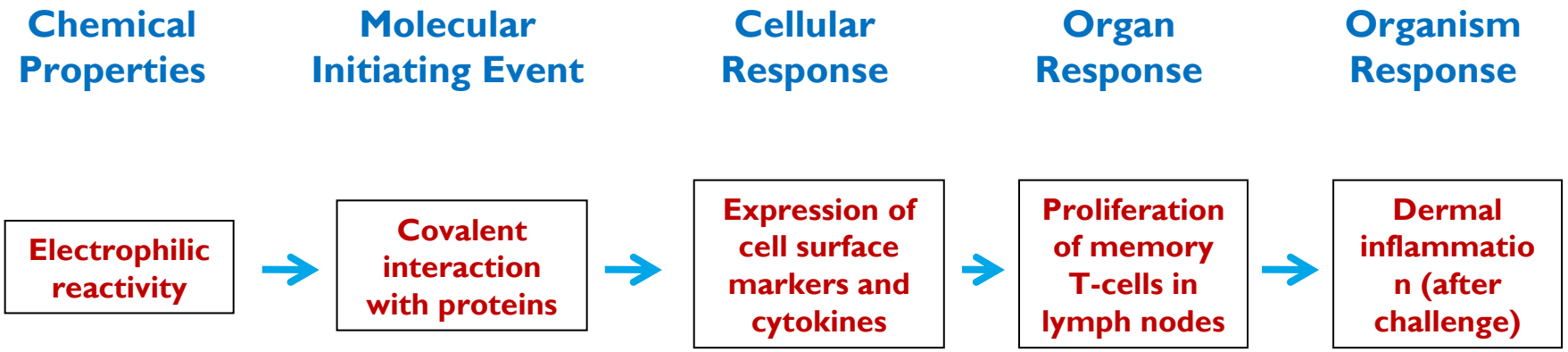
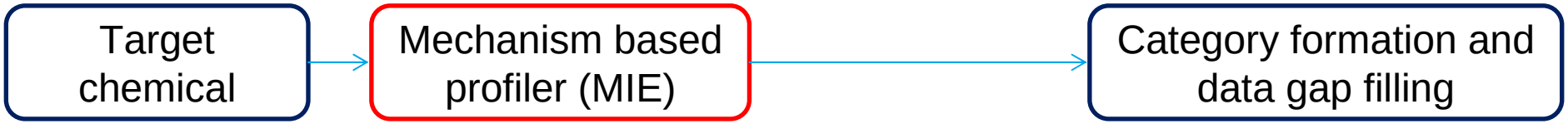


- **Chemistry**

- **Molecular biology**
- ***In vitro* assays**
- **Other non-test data**

AOP: An example for skin sensitisation





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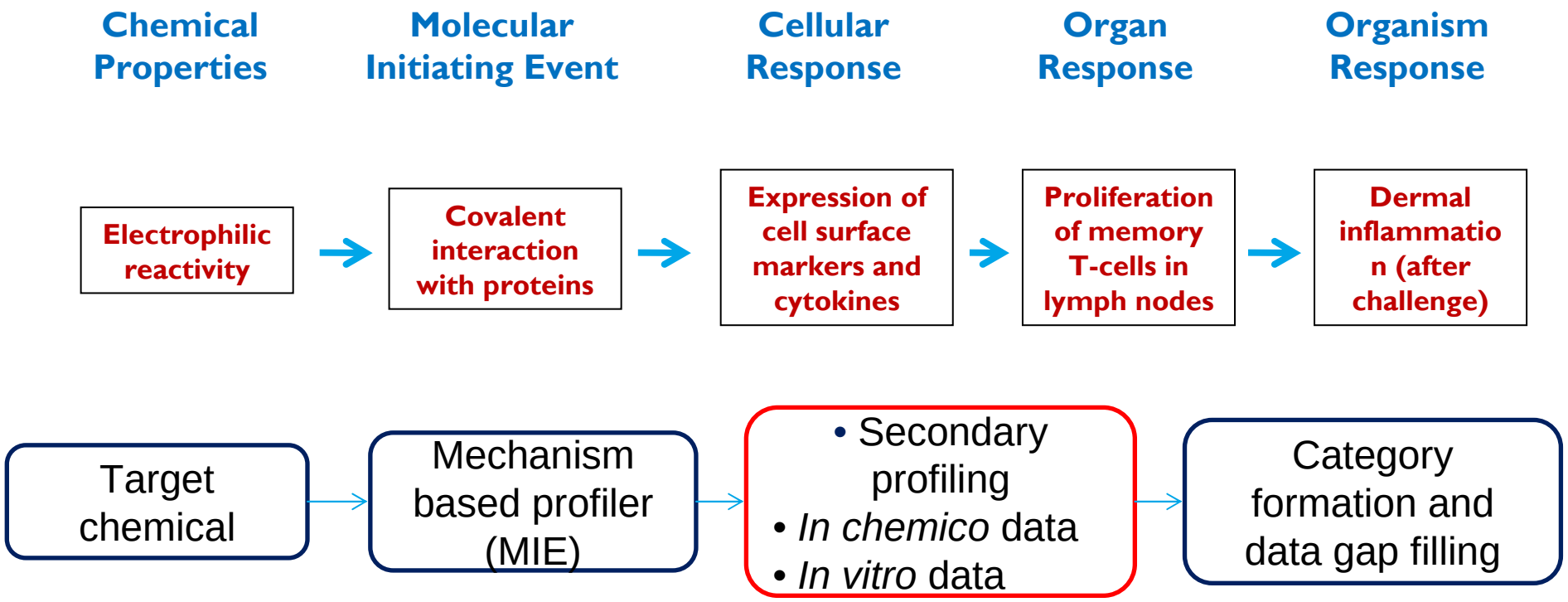

AOPs: what's to be achieved by end of 2012

- Finalisation of the AOP for skin sensitisation
- Finalisation of AOPs for several cellular signalling pathways associated with cellular proliferation and differentiation that are conserved across species and linked to developmental toxicity.
- Drafting of working guidance on the development of AOPs.
- Identification of a first limited set (2-5) of QSARs for predicting molecular initiating events and implementation as profilers in the QSAR Toolbox.
- Implementation of one or two AOPs in version 3.0 of the QSAR Toolbox as a proof-of-concept.
- Development of a work plan for the development of AOPs after 2012 and identification of lead countries/organisations.

AOPs: What's to be achieved in 2013-1016

- Development of AOPs in accordance with the work plan developed in 2012.
- Implementation of the AOPs into the QSAR Toolbox.
- Compilation of a series of molecular initiating events, identification of the structural boundaries and implementation into the Toolbox as profilers