Using Adverse Outcome Pathways to Group Chemicals into Toxicologically Relevant Categories

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(Quantitative) Structure-Activity Relationships ((Q)SARs)

- Relate chemical structure to toxicity

Structural Fragment = Toxicity

Toxic Potency = f (Chemistry)

- Allow for prediction of toxicity from structure
  - Product development
  - Data gap filling

When Does (Q)SAR Work?

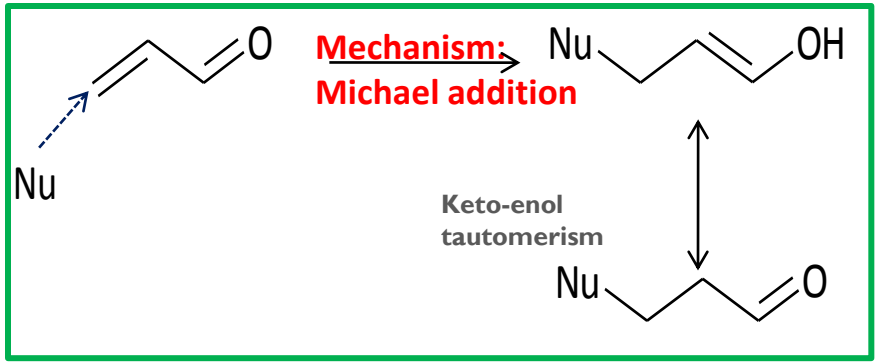
- When a steady state / equilibrium is reached
  - Controlled by a small number of variables
  - Aquatic acute toxicity, but seldom rodent LD_{50}
- When there is a single, definable and rate limiting "initiating event"
  - Receptor binding e.g. HERG
  - Covalent binding e.g. skin sensitisation, genotoxicity
- When it is used intelligently as part of a strategy and /or consensus
  - Limitations and context are understood

When Does NOT (Q)SAR Work?

- Lack of data and mechanistic understanding
- Modelling too complex phenomena
  - Chronic, systemic, reproductive toxicity
- Does not account for ADME
- Statistical goobledygook and over-fitting
  - It is easy to derive an a statistical relationship if you
    1. Ignore biology
    2. Calculate enough descriptors
    3. Accept 75% accuracy

Mechanism and Mode of Toxic Action

- How toxicity is brought about at the molecular level resulting in effects at organ or organism level



- If we understand mechanism and modes, we understand toxicology, predict it and justify predictions

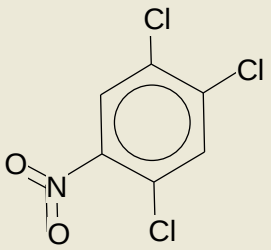
Grouping Chemicals Together Rationally Seen as a Solution to Some of the Problems

- Find similar chemicals to the “target”
  - Various methods to identify similar chemicals
  - Similarity should be based on a rational, preferably mechanistic, basis
- Obtain toxicological data for the similar chemicals
- Interpolate the activity – known as read-across
- The freely OECD QSAR Toolbox helps this process
  - High usage for e.g. REACH dossiers
- A “Toxicologically Relevant Category” is one that groups chemicals according a known mechanism or mode of action

Skin Sensitisation: Electrophilic Reactivity Essential

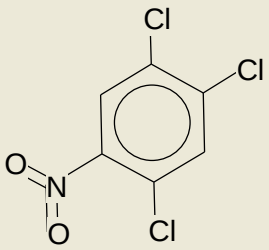
Category Formation for Skin Sensitisation

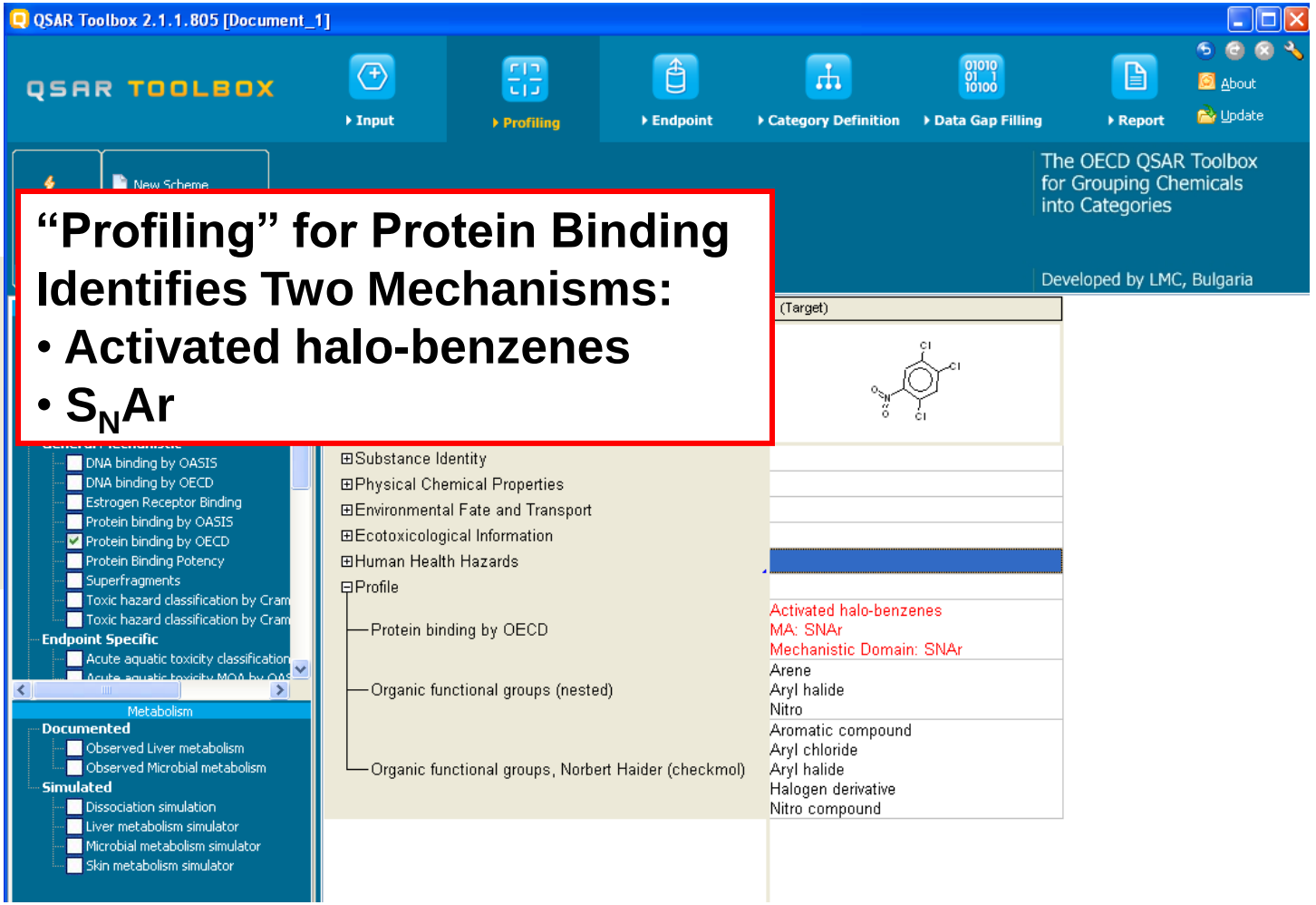
Target



Mechanisms for Grouping

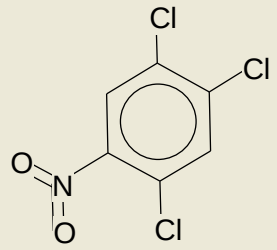
Target





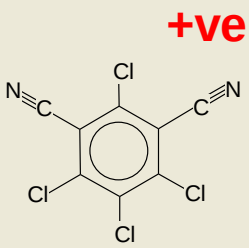
Read-Across for Skin Sensitisation

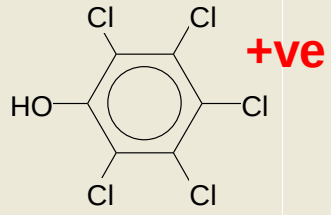
Target

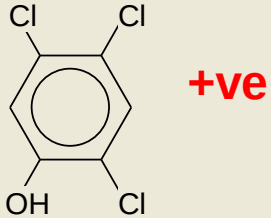


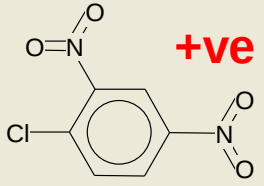
Read-Across:
Positive

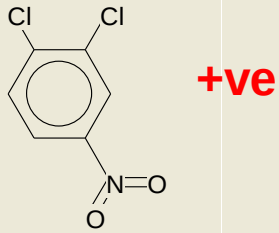
Category

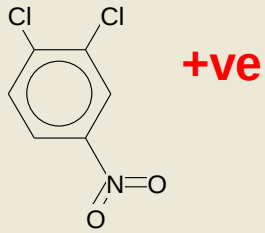


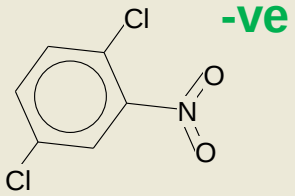


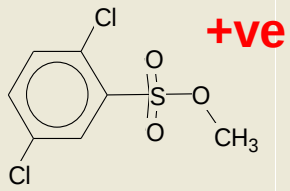


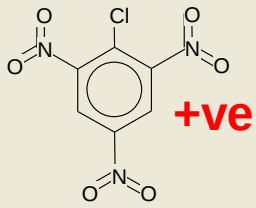








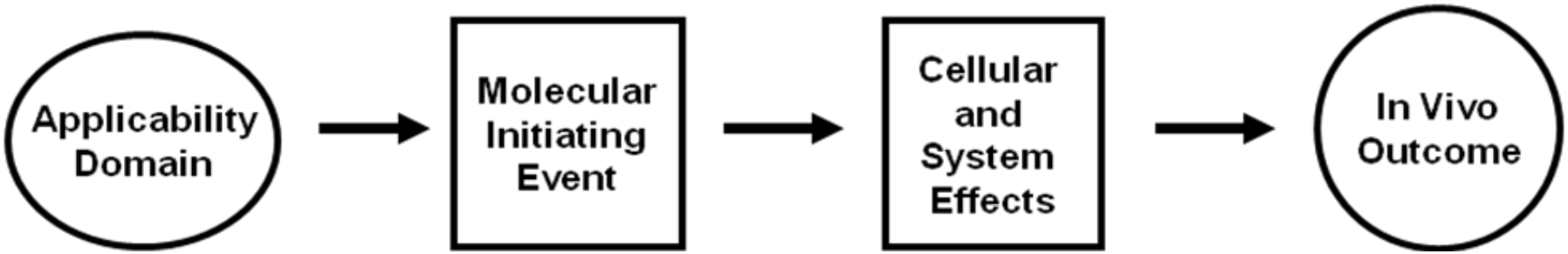




Importance of Mechanistic Category Formation

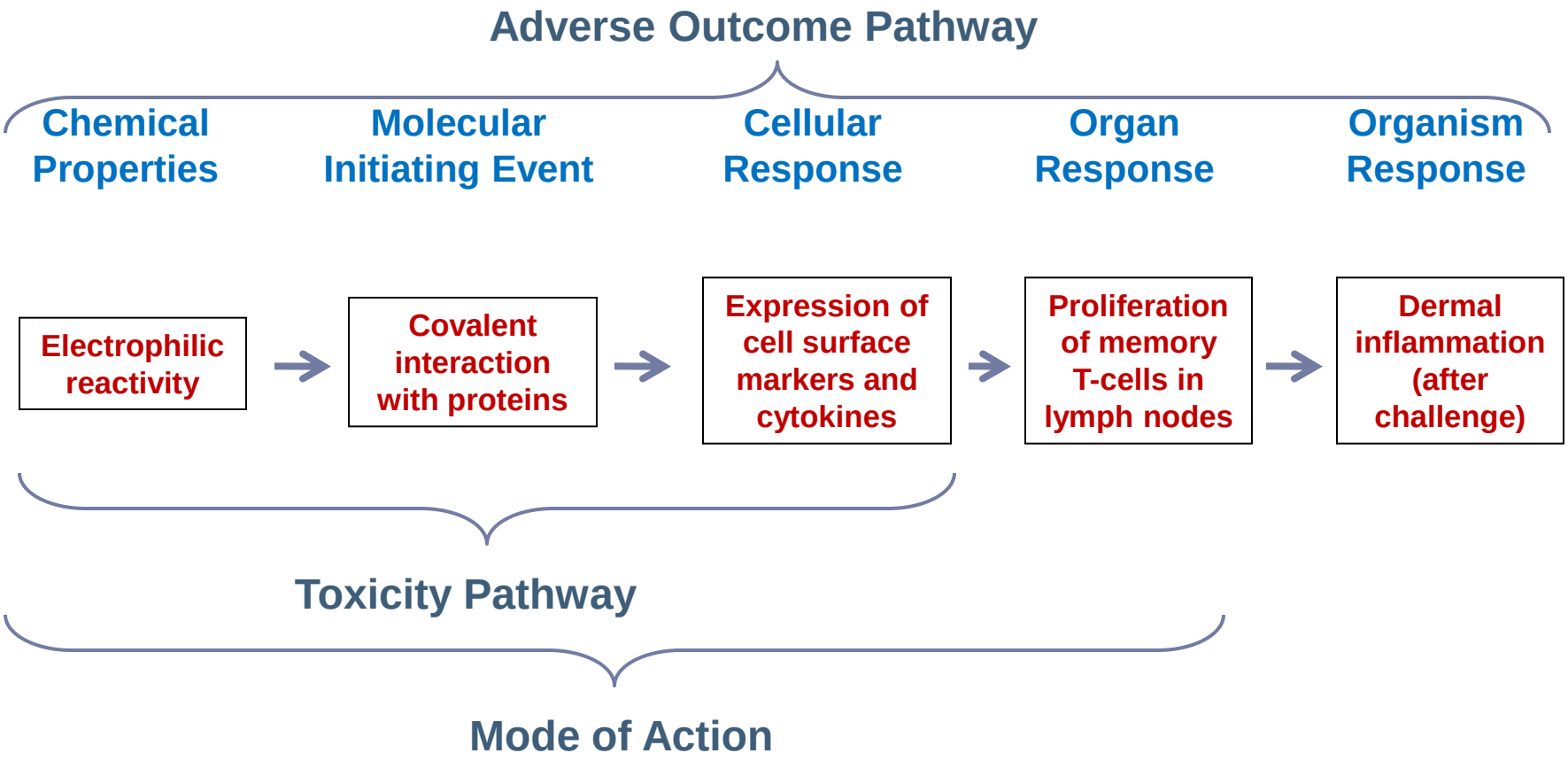
- Demonstrates direct link from chemistry to toxicology
- Enshrined within the OECD Principles for Validation of QSARs
- Makes regulatory submissions more acceptable
- However, more work needed to translate mechanisms to chemistry
- Adverse Outcome Pathways provide a solution, particularly for complex toxicities

Adverse Outcome Pathways (AOPs)



Schultz TW (2010), In Cronin MTD, Madden JC (eds) *In Silico Toxicology: Principles and Applications*, Royal Society of Chemistry. pp. 346-371

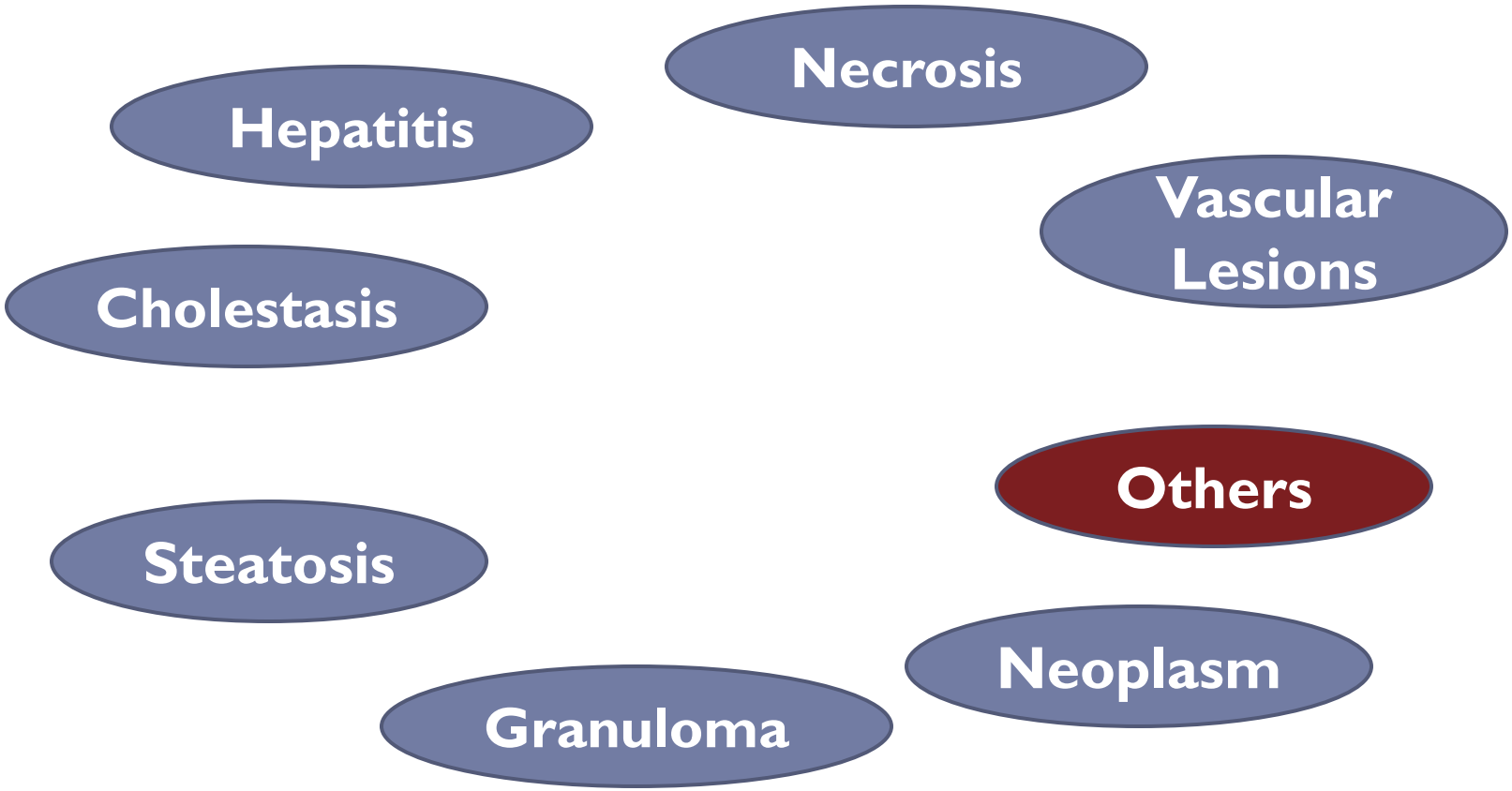
Adverse Outcome Pathways (AOPs): An Example for Skin Sensitisation



Shamelessly adapted from OECD Documentation

Predicting Systemic Toxicity and Organ Level Effects

Modelling Toxicity to the Liver



Traditional QSAR

Find data

[Determine Mechanisms]

Calculate Descriptors

Develop Models

Traditional QSAR

Find data

↓

[Determine Mechanisms]

↓

Calculate Descriptors

↓

Develop Models

Future *In Silico* Modelling QSAR

Define Effects

↓

Determine Mechanisms

↓

Measure (*in vitro*) data

↓

Describe Chemistry

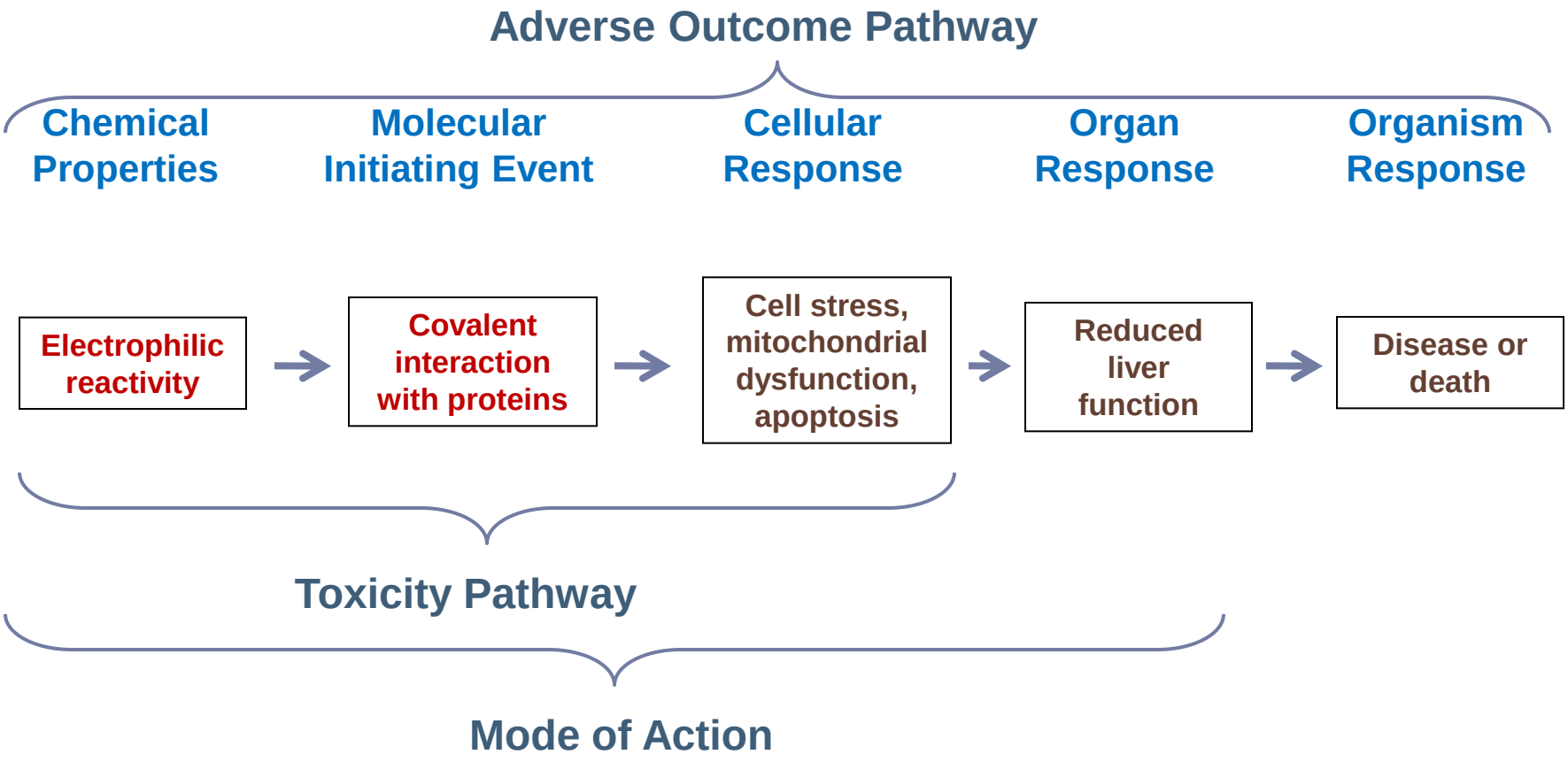
↓

Develop Models

Future *In Silico* Modelling QSAR

Define Effects	Liver toxicity, possible death
Determine Mechanisms	Covalent hepatotoxicity
Measure (*in vitro*) Data	Binding data
Describe Chemistry	Domains of electrophilic reactivity
Develop Models	Groupings of compounds

Adverse Outcome Pathways (AOPs): An Example for Heptatoxicity



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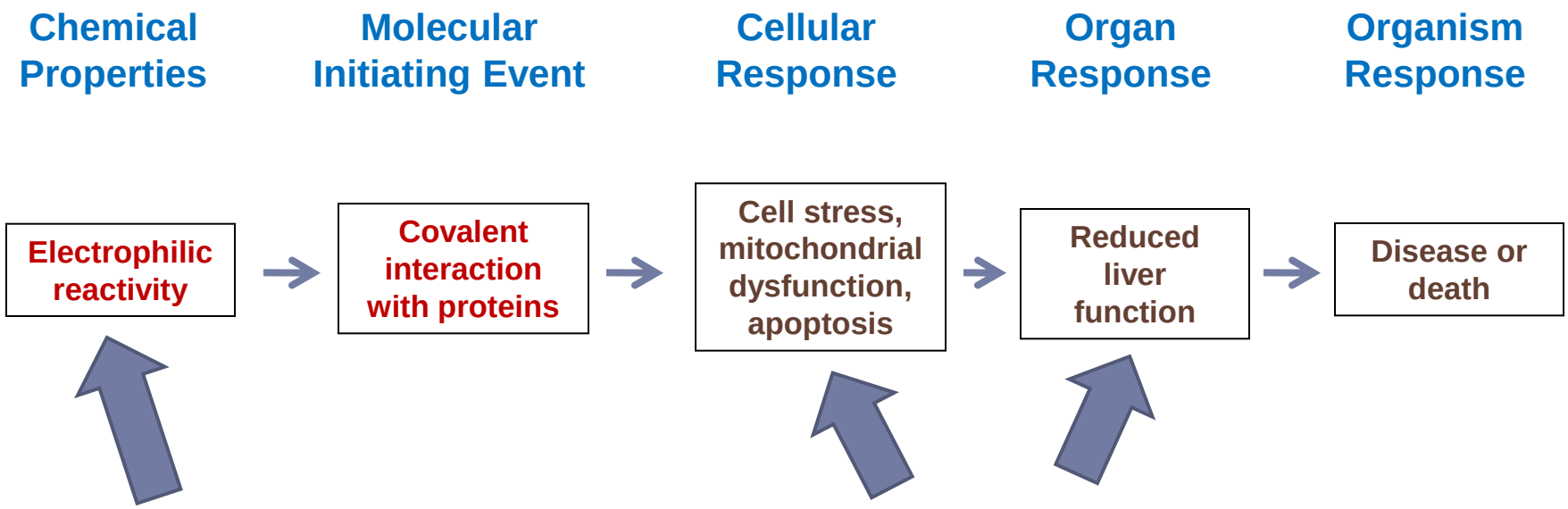
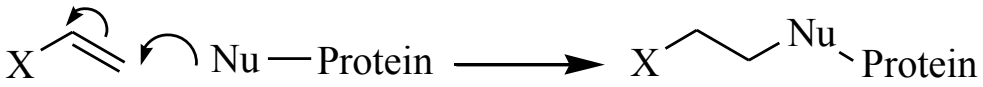
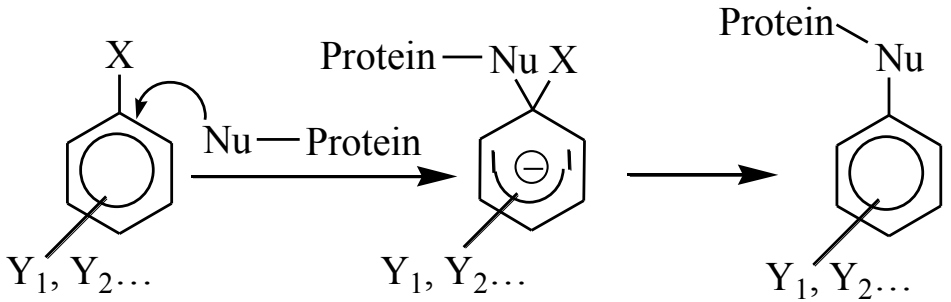
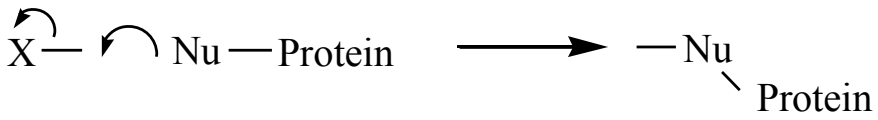
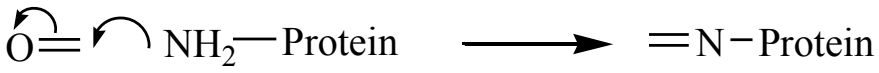
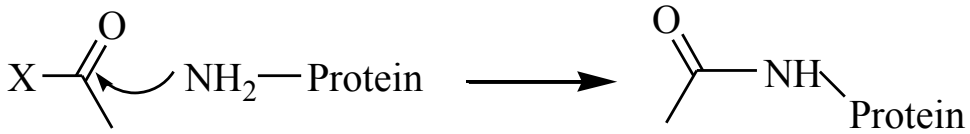


- **Can be defined in terms of chemistry**
- **Chemical definitions can be used to group compounds together**

- **Opportunity to use *in vitro* assays and "intelligent" testing to define chemical space associated with AOP**

Defining Electrophilic Chemistry Related Toxicity

Mechanistic domain	Protein binding reaction	Modified protein
Michael acceptors		
S_NAr electrophiles		
S_N2 electrophiles		
Schiff base formers		
Acylating agents		

Defining Electrophilic Chemistry Related Toxicity

Critical Reviews in Toxicology, 2010; 40(8): 728–748

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REVIEW ARTICLE

A review of the electrophilic reaction chemistry involved in covalent DNA binding

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REVIEW ARTICLE

A review of the electrophilic reaction chemistry involved in covalent protein binding relevant to toxicity

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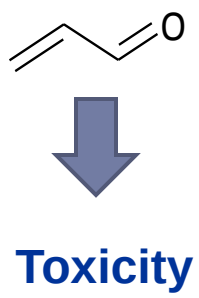
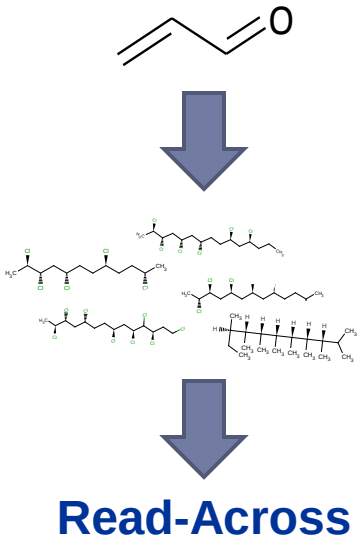
Use of Structural Alerts: SARs vs Grouping / Category Formation

- SARs e.g. Toxtree, Derek Nexus
  - An alert is linked directly to toxicity
  - Much direct toxicological evidence
  - Often highly defined
  - Absence of an alert does not infer safety



- Grouping e.g. OECD QSAR Toolbox
  - Chemistry groups compounds
  - May be loosely defined
  - Category may include negatives
  - Read-across applied by user to make the prediction



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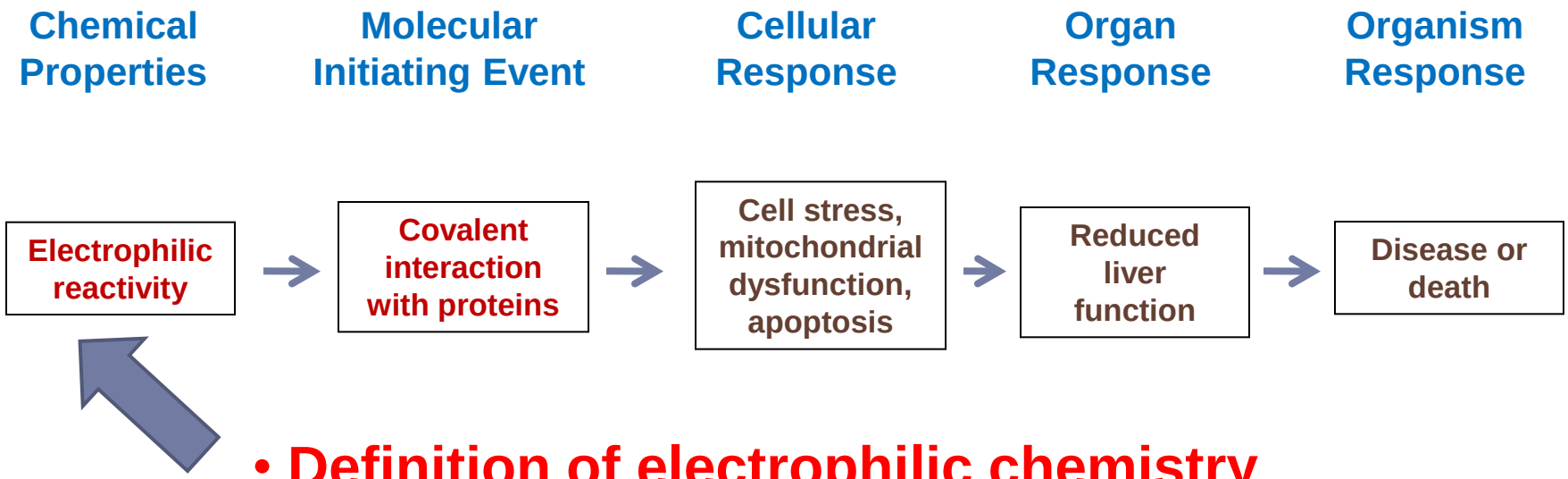
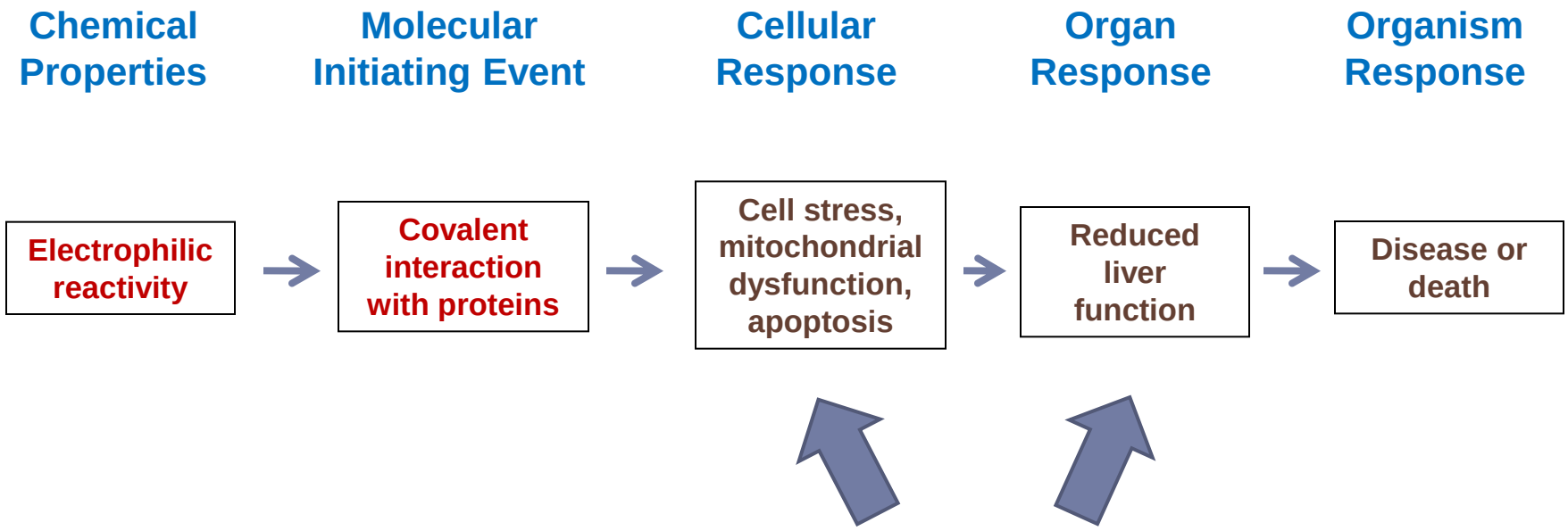


- **Definition of electrophilic chemistry associated with hepatotoxicity required**
- **Few reliable *in vivo* data**

Adverse Outcome Pathways (AOPs): An Example for Heptatoxicity



- **Opportunity to use *in vitro* assays and "intelligent" testing to define chemical space associated with AOP**

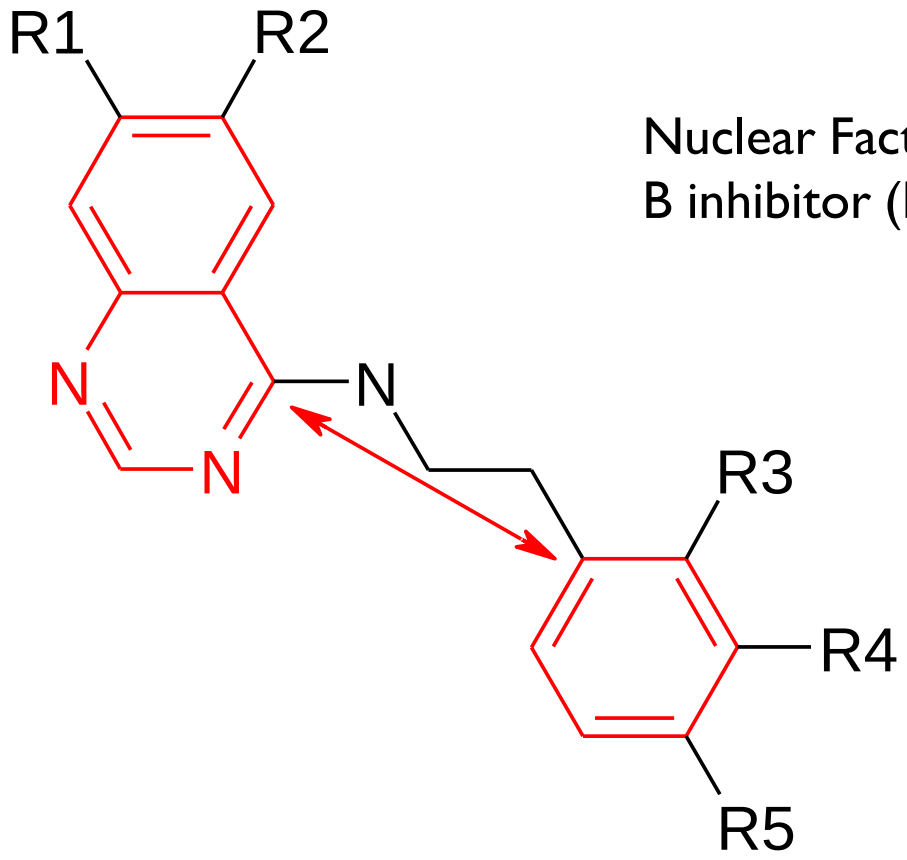
Role of Molecular Biology, *in Vitro* Assays, -omics

- We need mechanism based assays and biomarkers
  - Tox21 / ToxCast
- Support of AOP concept
- Intelligent testing will define “domains” of chemical space

Happy AOPs:
A Category for Every Occasion

- We need information on mechanisms and modes of action
- Molecular initiating events should be established
- Chemical space associated with molecular initiating events should be defined
- Support chemical categories with non-test information
  - Define the boundaries of a category
  - Quantify the potency

Another Key Challenge: Grouping for Receptor Mediated Effects



Nuclear Factor Kappa B inhibitor (NF-K-B)

Define the applicability domain of the structure alert as the generic features of the backbone (toxicophore)

Conclusions

- Predicting chronic toxicity by QSAR is difficult
  - Multiple mechanisms within the same organ, different organ effects and modes
- Following a pathway approach (AOP or otherwise)
  - Provides mechanistic basis and framework
  - Allows for grouping
  - Allows for moderating factors / influencing to be integrated
  - Allows for other non-test information to be included
  - Transparent, more acceptable for regulatory use
  - Can be used with non-test data as part of an ITS
- Needs to make progress are definable

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- Terry Schultz, Bob Diderich, OECD, Paris

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- COSMOS FP7 Project

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