

Strategies to Form Chemical Categories from Adverse Outcome Pathways

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Introduction and Aims

- Read-across is increasingly being seen as a solution in toxicity prediction.
- Read-across follows from the formation of groups, or categories, of similar compounds.
- Grouping compounds, relevant to the prediction of human organ level toxicity, is the use of **reactive fragments** associated with known mechanisms of toxicity e.g. reactive hepatotoxicity.
- The aim of this study was to illustrate how categories can be formed and linked to Adverse Outcome Pathways (AOPs). This method is also used to prepare training sets for (Q)SAR work.

Chemotypes

- The chemotype is the molecular fragment or sub-structure associated with a Molecular Initiating Event (MIE).
- Chemotypes can be a combination of a structural fragment and physico-chemical properties (such as logP).
- For liver toxicity, reactive hepatotoxicity is a MIE.
- The chemotypes for specific endpoints, e.g., hepatotoxicity, are also coded as SMARTS and/or CSRML. Some chemotypes can be used as chemical Mode of Action (MoA) classifiers.

Adverse Outcome Pathways

- AOPs record information relating to the perturbation of biochemical pathways which may result in an adverse effect.
- AOPs provide a means of organising toxicological information.

Toxicant	Macro-Molecular Interactions	Cellular Responses	Organ Responses	Organism Responses	Population Responses
Chemical Properties	Receptor/Ligand Interaction DNA Binding Protein Oxidation	Gene activation Protein production Altered signaling	Altered physiology Disrupted homeostasis Altered tissue development/function	Lethality Impaired Development Impaired Reproduction	Structure Recruitment Extinction

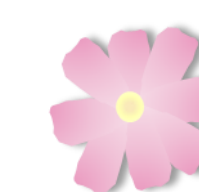
- The Molecular Initiating Event of the AOP can be defined in terms of identifiable chemistry to provide the “domain” of the AOP.

Conclusions

- A strategy is presented to allow molecular initiating events (from AOPs) to guide category formation for cosmetic ingredients.
- The workflow will be available in KNIME as a computational tool to make *in silico* assessments of chronic toxicity. The COSMOS database (or any other database) can be searched via the KNIME workflow and toxicological data can be retrieved.

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COSMOS Inventory

- The workflow is able to search the inventory of cosmetic ingredients developed by the COSMOS project.
- The COSMOS Inventory provides access to “high quality” chemical structures related to names and other identifiers.



COSMOS Database

- The COSMOS database (db) provides access to toxicological information on relevant chemicals.
- COSMOS db retrieves toxicological information for the chemical of interest and likely analogues.
- Access is provided to external toxicological databases to support the retrieval of information on analogues.



In Silico Predictions of Toxicity

- Predictions** can be made from chemotypes directly, although this is over-predictive.
- Selection of compounds with the same chemotype forms a group (or category). **Read-across** can then be performed.
- With sufficient data at aggregated pathways level, **descriptors** can be calculated in the workflow from freely available software. Along chemotypes MoA QSARs can then be developed.



COSMOS KNIME Workflow

- The KNIME software provides an open access platform to integrate the technologies in the workflow.
- Chemotypes have been identified and coded (either as SMARTS or CSRML) into a KNIME workflow.
- The KNIME workflows are transparent and adaptable according to the users requirements.

