

Workflows for Target Organ Toxicity Prediction Implemented into KNIME



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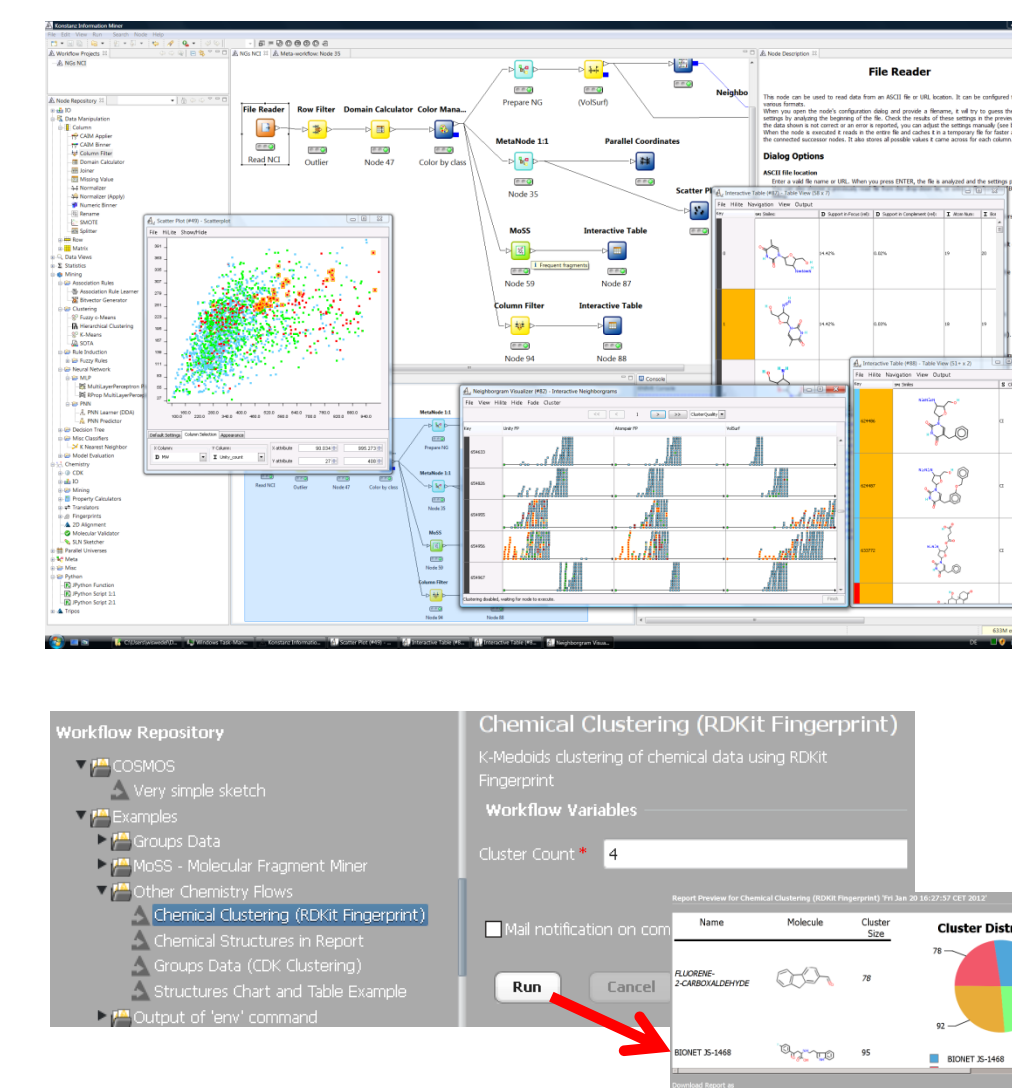
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Introduction and Aims

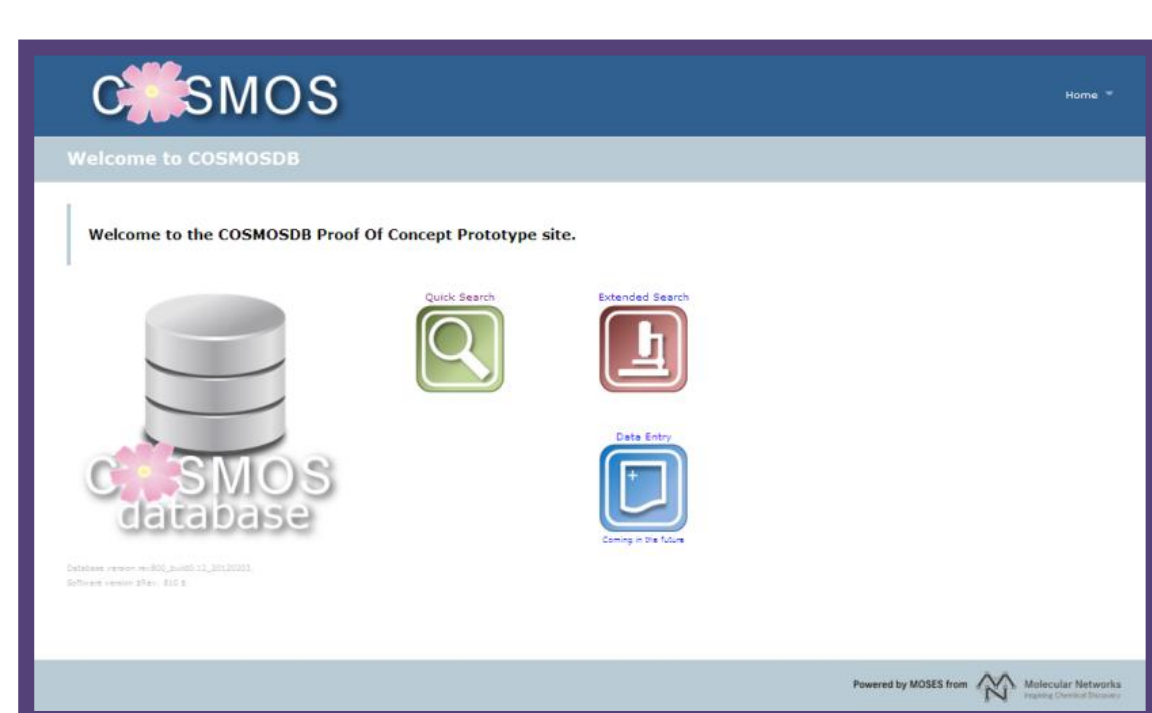
- Open and **flexible platforms** integrating modelling processes are required for the evaluation of the **safety of chemicals**. They should support data capture, storage and retrieval, the link of chemistry to toxicity pathways through Adverse Outcome Pathways (AOPs) as well as modelling.
- COSMOS is developing a novel **computational toxicology workflow system** allowing users greater control and understanding of target organ toxicity prediction.
- The workflows are being built in the open-access KNIME [1] platform which allows pipelining via a graphical user interface.

KNIME Server and Web Portal

- KNIME **workflows integrate** access to chemical inventories/databases, data processing and analysis, modelling approaches, profiling of structures and calculation of properties into building blocks ("nodes") in a flexible way.
- Desktop version** allowing links to additional data sources or updates of the models.
- Web Portal version** for application of workflows without software installation.



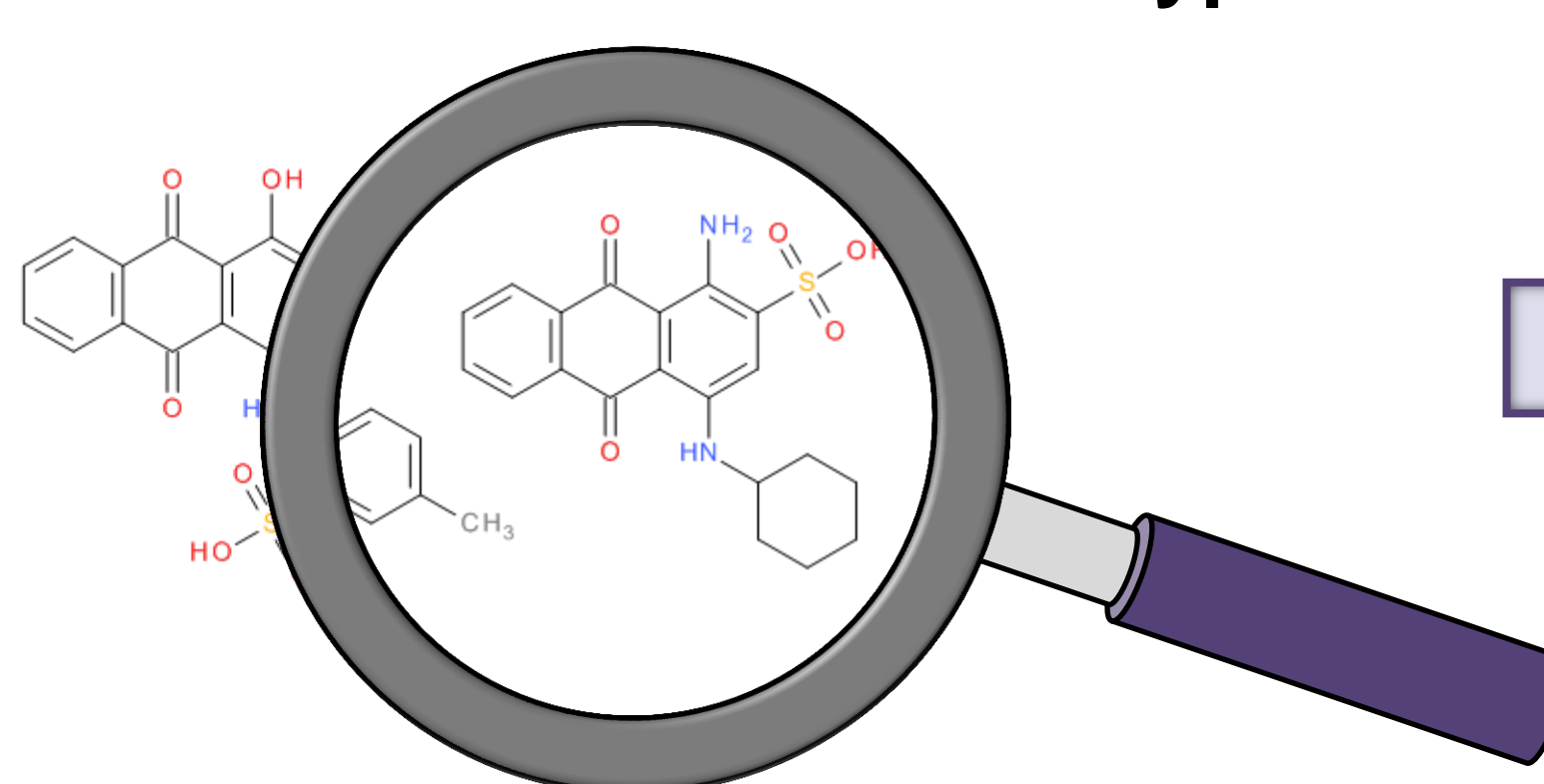
COSMOS Database



COSMOS Cosmetics Inventory
Toxicity data including NOELs

Structural Alerts

Chemotypes



Categories of Chemicals

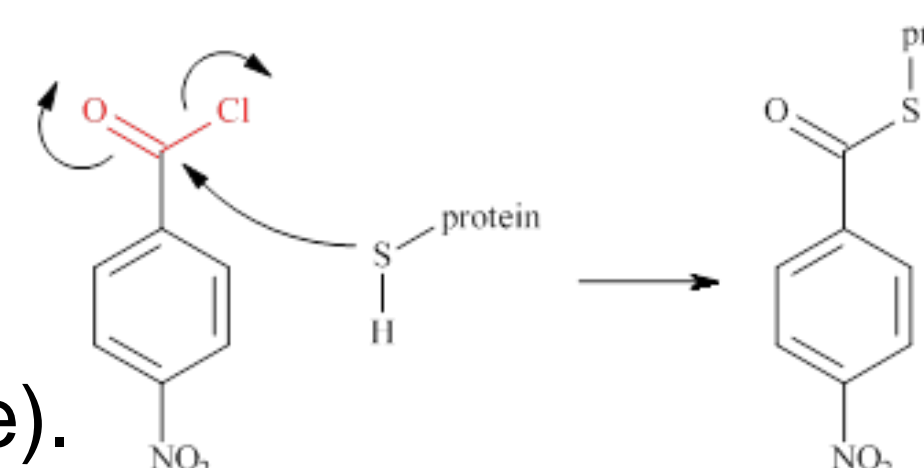
+
Toxicity Data

→ Read-Across
for Toxicity Prediction

108 alerts protein reactivity
85 alerts DNA binding
32 alerts phospholipidosis
16 alerts other liver toxicity

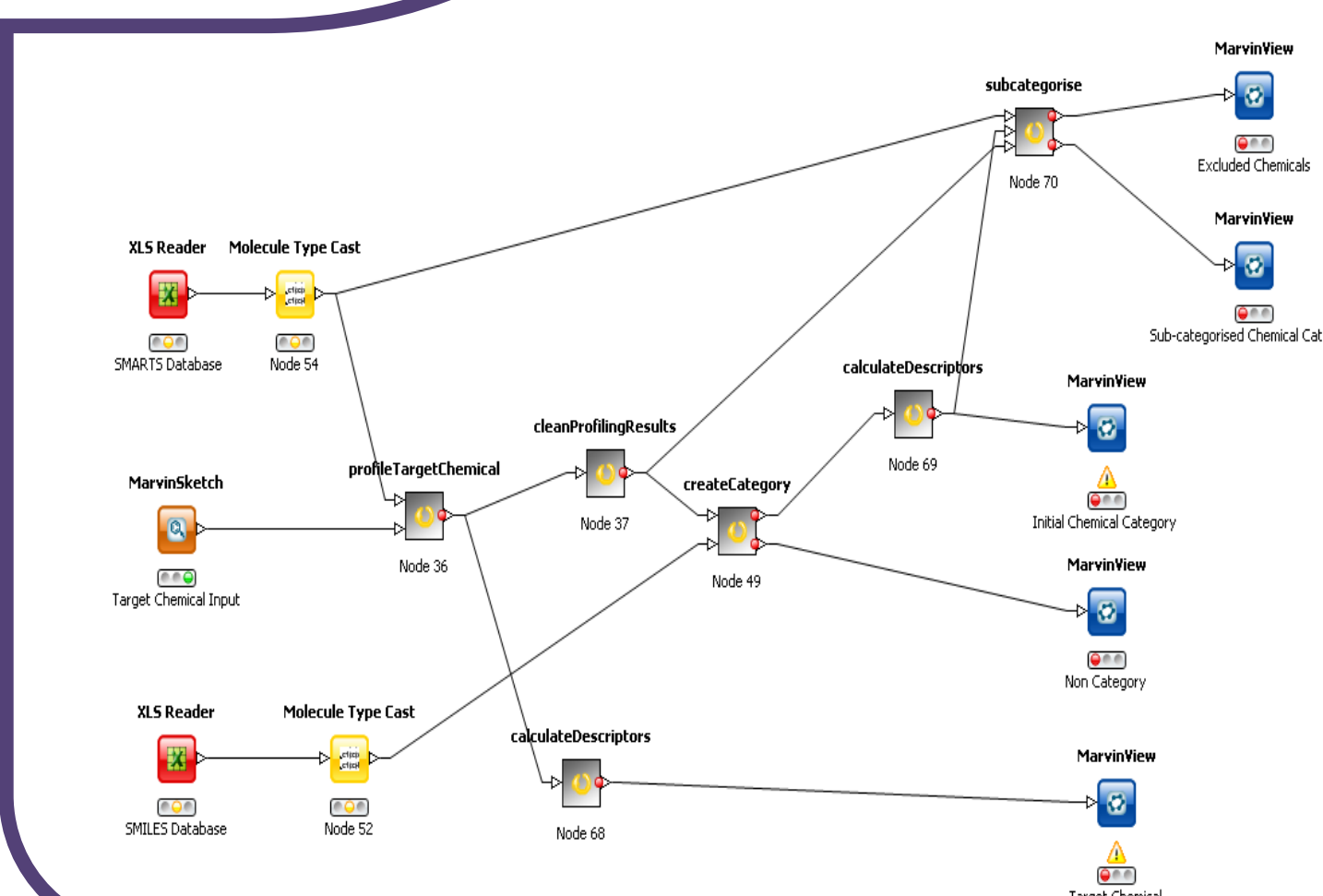
Example: Protein Binding

- The **Molecular Initiating Event (MIE)** is the key initial interaction between a chemical and the biological system resulting in a cascade of biological events to an adverse outcome [2].
- Formation of a covalent bond with proteins: a key MIE for important toxicological endpoints such as **hepatotoxicity**.
- Mechanistic knowledge** relates specific structural features of a chemical to its ability to covalently bind to proteins.
- Structural alert** = fragment of a molecule (electrophile) identified as reacting with a biological nucleophile (as S in cysteine, N in lysine).



KNIME Workflow

- Searches the structure of a chemical for a particular **structural rule**, associated with a mechanism of action.
- Identifies compounds with the same rules from a list of compounds or a database to **form a category**.
- Forms subcategories for categories containing substances with multiple functional groups.
- Retrieves **toxicological data** from the database for read-across.



Screening the COSMOS Cosmetics Inventory with Protein Binding Alerts

- The COSMOS Cosmetics Inventory v1.0, containing 4467 substances, was analysed with **structural alerts for protein binding** as MIE [3].
- 837 of the 4467 chemicals contained a single structural alert related to covalent protein binding. A further 83 chemicals contained more than one structural alert.
- The analysis of the **mechanistic domains** assigned to the chemicals containing a single structural alert is summarised in Table 1.

Mechanistic domain	Number of chemicals
Acylation	78
Michael addition	223
Pre-Michael addition	159
Schiff base formation	159
S _N 2	14
S _N Ar	204

Table 1. Mechanistic analysis of the COSMOS Cosmetics Inventory using covalent protein binding rules [3].

Table 2. Subcategorisation of chemicals assigned to individual structural alerts within the S_N2 mechanistic domain.

Structural alert	Number of chemicals
α-Haloalkenes	1
α-Halobenzyls	1
α-Halocarbonyls	2
Aliphatic-halide	1
Alkyl-diazo	1
Allyl-acetates and related	132
Epoxides	28
Isothiazol-3-ones-(sulphur)	3
N-chloro-sulphonamides	1
Phosphates (incl. thiophosphates)	5
Polarised alkenes with a halogen leaving group	2
Thiols	27

- A mechanistic domain consists of a collection of structural alerts.
- In order to develop **structure-activity relationships** and/or make **read-across predictions**, the chemicals have to be subcategorised into smaller, structurally related groups.
- The categories developed were analysed using the individual structural alerts building each mechanistic domain. The **subcategorisation** of the S_N2 mechanistic domain for the COSMOS Cosmetics Inventory substances is shown in Table 2.

Conclusions

- The workflow shown builds on the COSMOS database, which is profiled using structural alerts representing a MIE, and can be categorised according to mechanistic domains. Toxicological data are retrieved for categories formed for read-across to assist toxicity prediction.
- KNIME is a powerful platform for developing *in silico* tools for predictive toxicology. The flexible and transparent workflows guide users through the prediction making process and thus are useful tools for safety assessment.

References

- [1] www.knime.org
- [2] Schultz TW (2010), Adverse outcome pathways: A way of linking chemical structure to *in vivo* toxicological hazards. In Cronin MTD, Madden JC (eds) *In Silico Toxicology: Principles and Applications*. Royal Society of Chemistry, Cambridge, UK
- [3] Enoch SJ, Ellison CM, Schultz TW, Cronin MTD (2011) A review of the electrophilic reaction chemistry involved in covalent protein binding relevant to toxicity. *Critical Reviews in Toxicology* 41: 783-802

www.cosmostox.eu

Acknowledgements

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