

COSMOS: An International Cooperative Project Developing Computational Models for Repeated Dose Toxicity



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Introduction

- There is a need for **alternatives to animal testing** for chemical risk assessment, because of legal requirements, e.g. through the Cosmetics Directive and REACH, as well as for ethic and economic reasons.
- Although legislation varies in different countries in the world, the safety of the substances, used globally, is of universal concern.
- Therefore the **international dimension** is important for the development and especially regulatory acceptance of the models proposed.
- The COSMOS project is taking up the challenge of developing **computational models to predict repeated dose toxicity** within an international consortium. The outset and first results are described in the following.



In Silico Models Contributing to the 3Rs

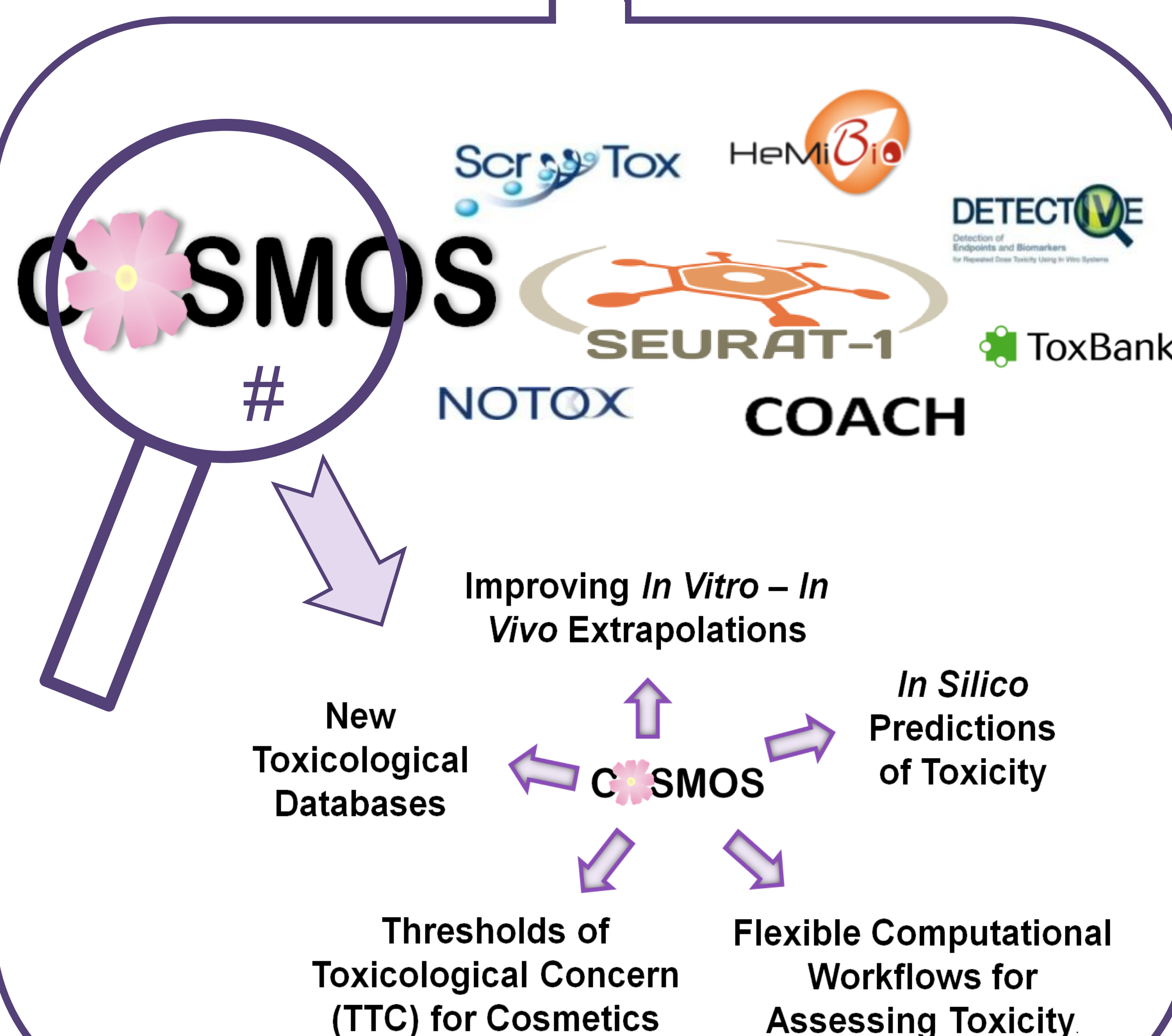
- Chronic, organ level toxicity involves complex mechanisms, thus it cannot be predicted by a single simplified *in silico* model. COSMOS is taking an innovative approach integrating different methods and models.
- Special emphasis is on the mechanistic basis of the models considered. **Adverse Outcome Pathways** (AOPs) provide a framework for organising relevant information at the chemical : biological interface.
- COSMOS computational workflows as well as a new comprehensive database with reliable structures and repeated dose toxicity data will be **freely available to support safety assessment** without the use of animals and will thus **contribute to the 3Rs**.

International Perspective

- Research institutes, industry, small/middle-sized companies, regulatory agencies and NGOs **from across Europe and the US** are involved in the COSMOS project either directly as one of the 15 project partners or as advising external experts. They contribute with a broad interdisciplinary expertise including computational chemistry, toxicology, database governance, chemo-informatics and toxicokinetics.
- COSMOS is part of an even larger international cooperation effort for **Safety Evaluation Ultimately Replacing Animal Testing** (SEURAT), SEURAT-1 comprising six research projects working together on an innovative concept for repeated dose systemic toxicity testing.

First Results

- Database** framework to capture repeated dose toxicity, as well as dermal absorption / metabolism data.
- Comprehensive **COSMOS inventory** of cosmetic ingredients with over 4,400 well-defined, unique chemical structures, compiled from the European Commission CosIng and the US Personal Care Products Council lists.
- New non-cancer **COSMOS TTC dataset**, enriched with cosmetic ingredients and more suitable toxicity data, to assist extension of the Threshold of Toxicological Concern (TTC) approach to cosmetics.
- The inventory / dataset compiled were assessed for their representation of the **chemical space of cosmetic ingredients**.
- Integration of the access to databases and modelling approaches into **flexible computational workflows** using the KNIME technology.



- Mechanism-based profilers** developed and coded as SMARTS patterns, allowing the grouping of similar compounds and searching of data sets.
- Consideration of **toxicokinetics and toxicodynamics** and better understanding of the effect of the test system properties (e.g. sorption) and chemicals (e.g. volatility, stability) for extrapolation from *in vitro* to *in vivo* organ level dose (IVIVE).

Europe and US Perspective and Beyond

- COSMOS has strong links and cooperation with key collaborators in the US.
- This cooperation contributes towards an international scientific and regulatory acceptance of the developed workflows supporting alternative safety assessment of substances.

Conclusions

- Computational modelling, including *in silico* and biokinetic approaches, supports toxicology and risk assessment and contributes to the 3Rs.
- In an international cooperation, COSMOS is developing freely available tools to address the safety assessment needs of the cosmetics industry for repeated dose toxicity and beyond.
- Within the large international cooperation effort of SEURAT-1 to establish an AOP framework, COSMOS contributes mechanistic and chemistry knowledge to support global movements such as Tox 21.

More Information and Contact

- Introduction to the aims and progress of COSMOS:
 - On AltTox.org: <http://alttox.org/ttrc/toxicity-tests/repeated-dose/way-forward/cronin>
 - SEURAT-1 Annual reports: <http://www.seurat-1.eu/pages/library/seurat-1-annual-report.php>
- Website: www.cosmostox.eu
- Contact: info@cosmostox.eu



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