A Case Study to Leverage Public and Commercial Resources to Improve in Silico Chemical Safety Assessment


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Motivation
- COSMOS Project (2011-2015): part of SEURAT-1 cluster
- COSMOS DB >3000 registered users (>70% industry)
- Cosmetic Industry, regulatory inventories
- Assessment and in vitro toxicology data
- COSMOS Next Generation (NG) (https://www.cosmosdb.eu/)
- Developed from COSMOS DB as 1st openly sources knowledge hub for chemical safety evaluation leveraging public data systems
- Databases and toxicology
- Gateway for the commercial ChemTunesToxGPS (https://www.chemtunestx.com) to publicly share data and new methods with industry and regulatory agencies
- Assessment and toxicity data by EFSA, ECHA, US FDA converting cosmetic ingredients, food additives, agrochemicals, their metabolites, and impurities
- Chemistry Europe (CE) joined the commercial public resource sharing effort: COSMOS NG exchangees working on CE case studies for TTC and read-across utilizing in silico, bioscaffold, metabolism results, and high throughput and high content read-out and toxicity studies
- We present an ab initio workflow based on case study experiences

Case Study
TARGET:
- HC RE NO. 7
- Systemic toxicity

1. Step 1: Similarity Searching & Selection of Similar Structures
- Select and calculate properties to gain insights and analyze differences between similar structures
- Scaffolds with systemic toxicity: CAS: 4590-04-3, CAS: 72204

2. Step 2: Calculating Properties Within COSMOS NG Table Tabe
- Download Guided Read-Across Workflow Using COSMOS NG (https://cosmosdb.eu/)
- Yang et al. 2021, Comp Tox, Submitted

3. Step 3: Analyzing Similarity and Property-Based Read-Across
- Relevance of similar properties and the best structural matches
- Case study illustrates different value of COSMOS DB and NG as part of the read-across workflow

4. Step 4: Chemical Profiling by Categories & Pathways
- Chemical matching by Chemotaxa Profiles in COSMOS NG

5. Step 5: Attaching Appropriate Toxicology Endpoint Data & Reliability
- Data quality and COSMOS MINIS Grade for analogs in COSMOS NG

6. Step 6: Setting Up an Evidence Table for Read-Across Assessment
- Complete each piece of evidence in Weight of Evidence (WoE) table including quantitative measures to detect final read-across (RA) reliability
- In COSMOS NG – single joint probability between 0.65% based on European distance and Study Reliability Likelihood (SRL) (0.28 documented)
- In commercial system – Desmoplastic Studio (DS) combination available (0.97% WoE with uncertainty of 17%)
- For the case of one analog matching study, single joint probability may be a quick indicator, although 0.30 yields the most conservative evidence
- Rathame et al. 2018, Comp Tox 6, 16-31, (https://doi.org/10.1007/s10567-018-0500-1)

7. Step 7: NOAEL Calculation With Data from COSMOS NG
- Highest No observed adverse effects level (NOAEL) using a dataset of 1658 compounds with qualified MNT/LOEL/LOEL
- Assessed in COSMOS NG following similar structures with amen to the read-across algorithm (see Step 2)
- The NOAEL level is only considered if it is estimated by assuming normal distribution to be 14-33 mg/kg-bw daily

Conclusions
- COSMOS NG: Public web-based searching/analytical system and forum for sharing resources, models and supporting workflow development
- Databases (regulatory inventories, assessment and toxicity data)
- COSMOS MINIS Grade and expert Opinion Score to evaluate the reliability of tox data
- Fingerpointing scheme for structure-based similarity and molecular properties for property-based similarity
- Active tools for computing not only the read-across evidence table
- Case study illustrates different value of COSMOS DB and NG as part of the read-across workflow

Perspectives
- Future data updates: HESS database from Japanese NITE, ESFA, CompToxDB, CompToxDB, Chemistry Safety data from KCS and CE
- Combined collaboration between public and commercial entities - expanding the knowledge domain, increasing reliability, possibility of sharing workflows with an aim of systematic assessment across multiple entities

- Exhibitor Hosted Session “Novel Cheminformatics platforms ChemTunesToxGPS and its public version COSMOS Next Generation”

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ACKNOWLEDGEMENT: This work is funded through the Long Range Science Strategy (LRSS), a program of Cosmetics Europe, with participation of industrial members