

Development of a New TTC (Threshold of Toxicological Concern) Database for Cosmetics Ingredients



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Introduction and Aims

The Threshold of Toxicological Concern (TTC) approach is being considered as one of the alternatives for the safety assessment of cosmetics ingredients. The aim of this work package 2 is to develop TTC methods suitable for the assessment of cosmetics ingredients by:

- 1) *establishing a framework for cosmetics ingredients*
 - develop a new non-cancer COSMOS TTC database and evaluate/modify decision trees (build on Blackburn 2005 approach)
- 2) *addressing the oral-to-dermal extrapolation*
 - bioavailability and metabolism (build on Kroes 2007 approach)

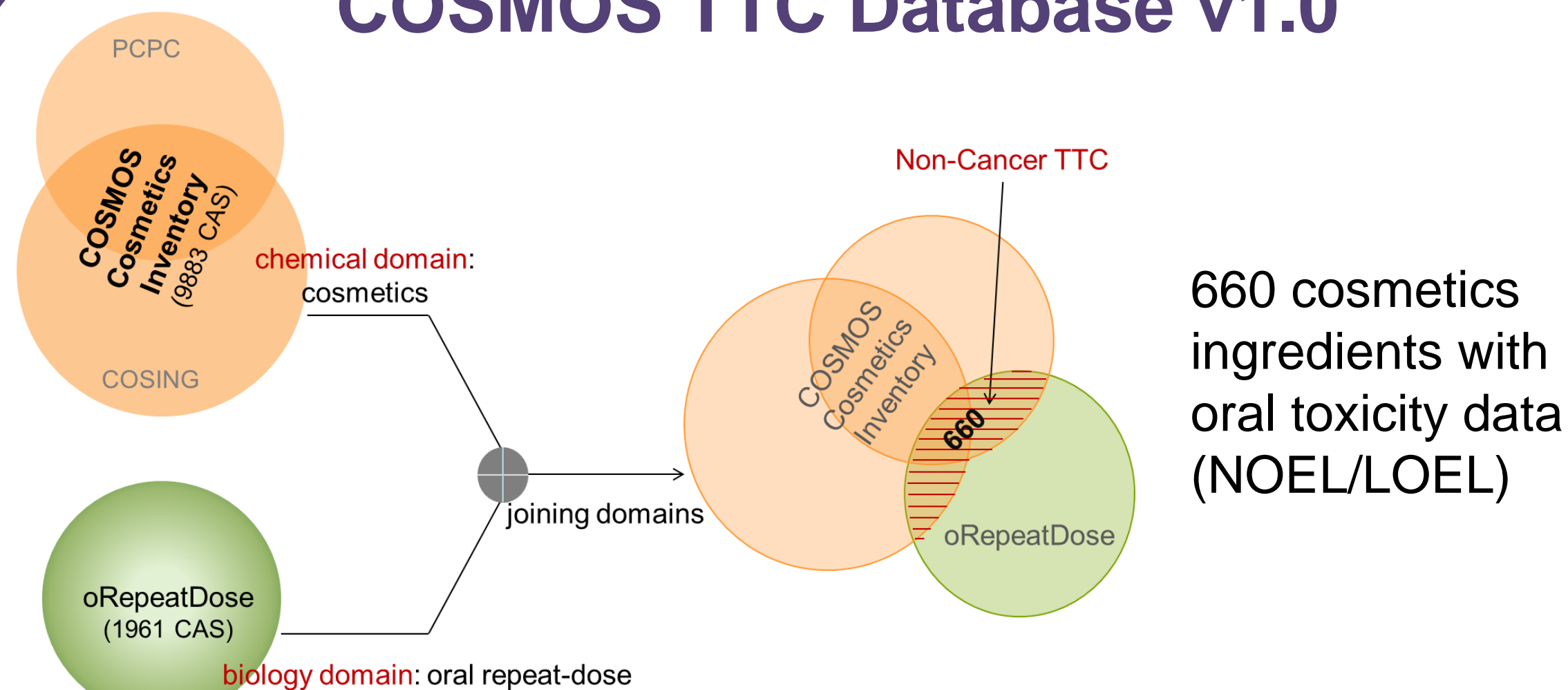
Oral Toxicity Data Sources of COSMOS TTC v1.0

	Munro	RepDose	EPA	FDA
Munro	178	49	10	105
RepDose		129	6	52
EPA			32	3
FDA				508

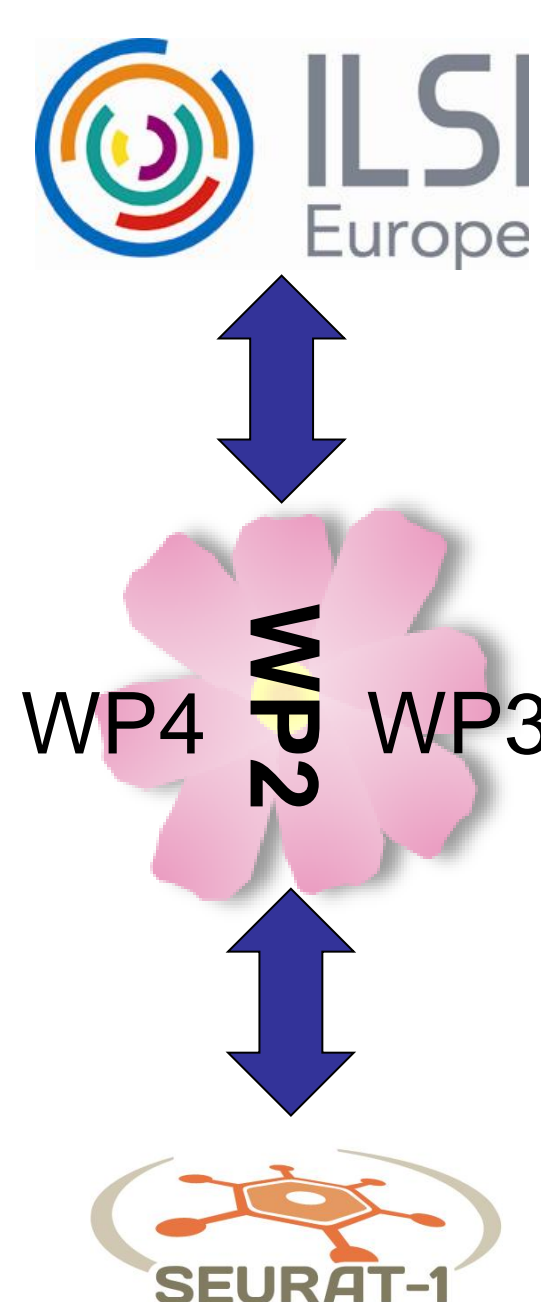
- Current data version - v.1.4
 - ~750 compounds
 - EPA (ToxRef) count - up to 153
 - Toxicity data evaluation on-going by ILSI expert working group

- V1.0 was used in TTC analysis
- Munro dataset 1986
- Fraunhofer Repdose
- US EPA: ToxRefDB and IRIS data containing regulatory or risk assessment NOEL/LOEL values
- US FDA: Direct and indirect food additives from CERES database

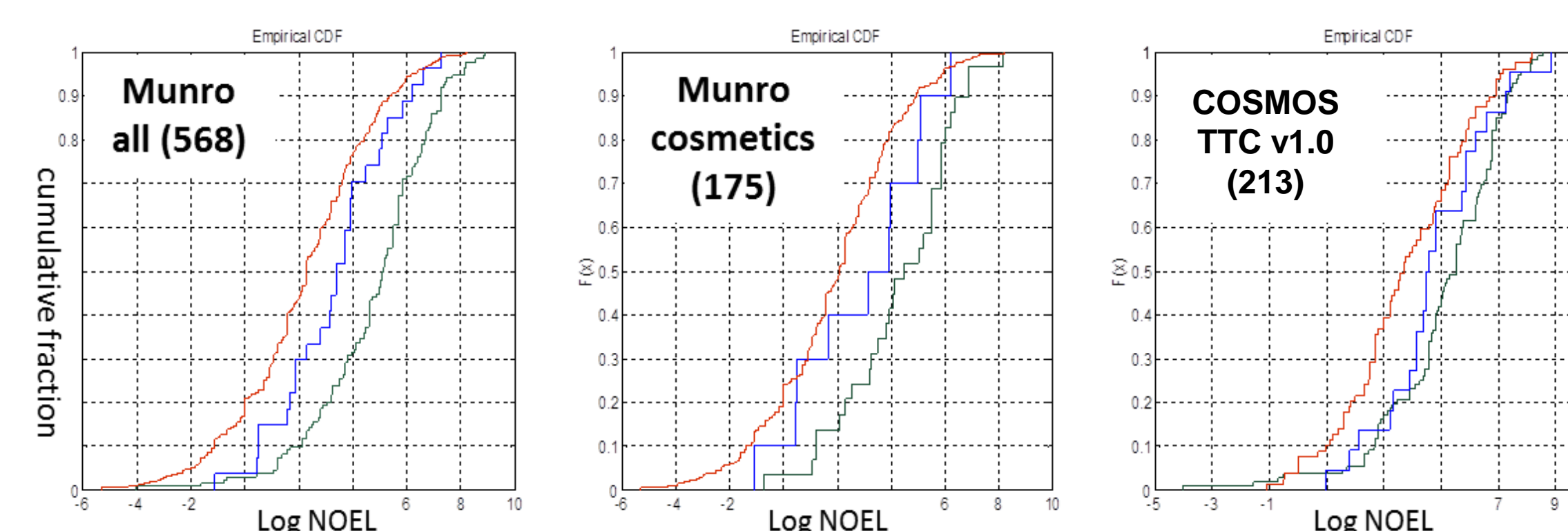
COSMOS TTC Database v1.0



- **COSMOS inventory** – combination of CosIng and PCPC cosmetics ingredients list (for more details see the work package 3 poster by M Pavan et al)
- **oRepeatDose database** – *in vivo* toxicity data from US FDA, US EPA, Fraunhofer, Munro dataset



Cumulative Distribution of NOELs

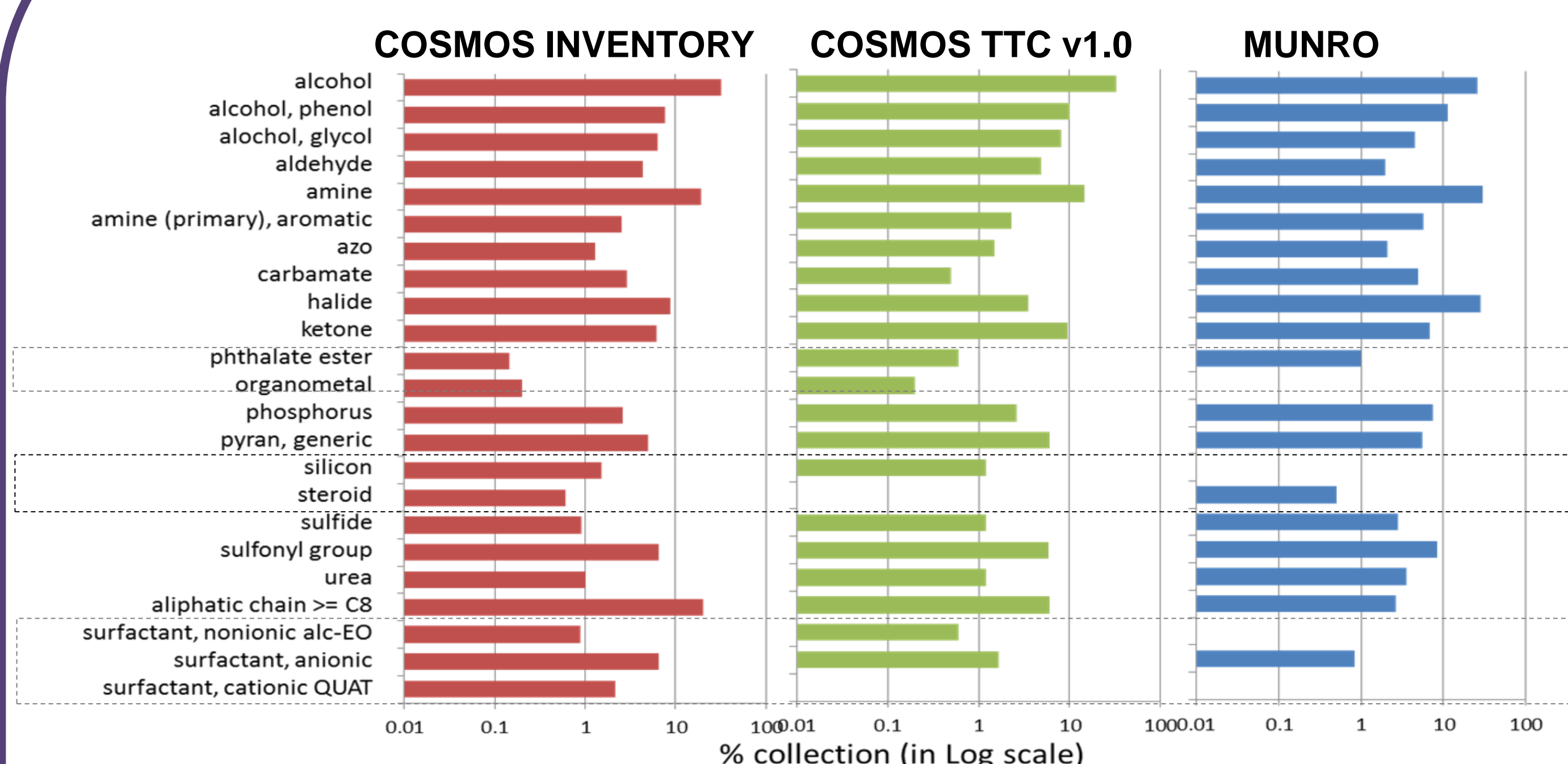


Cramer Class III (red); Cramer Class II (blue); Cramer Class I (green)

Cramer class	5th percentile NOEL (µg/kg/day)		
	Munro all (568)	Munro cosmetics (175)	COSMOS TTC v1.0 (213)
Class I	3,000 (134)	3,330 (105)	5,950 (112)
Class II	1,410 (27)	2,830 (17)	4,680 (22)
Class III	150 (407)	4,290 (53)	1,000 (79)

Numbers in () represent the counts; Organophosphates are not included.

Comparison of Structure Categories



- Cosmetics ingredients cover the use categories including: skin care, moisturiser, humectant, hair dye, perfume/fragrance, antimicrobials, emulsifiers, surfactants, and plasticisers,
- COSMOS TTC covers most of the cosmetics inventory chemical space, except steroid (which is covered by Munro) and quat surfactants.

Comparisons of physicochemical properties are discussed in the WP3 poster

Conclusions and Next Steps

- Current TTC approach may be applicable to cosmetics ingredients.
- Cramer Classes may need to be revisited for certain types of cosmetics ingredients.
- Expand toxicity data compilation in the second year
 - COSMOS TTC database: include more data sources, e.g., EU SCCS, US PCPC along with US FDA and US EPA.
- Oral-to-dermal extrapolation
 - Build skin penetration database including skin metabolism
 - Apply bioavailability modelling including PBPK approach.

References

- Blackburn K et al (2005) *Reg. Toxicol. and Pharmacol.* 43: 249–259
- Kroes R et al (2007) *Food and Chem. Toxicol.* 45: 2533–2562
- Munro I et al (1996) *Food and Chem Toxicol.* 34: 829 – 867
- Worth A et al (2012) JRC report EUR 25162 EN
- Jacobs K et al (2012) 51st Society of Toxicology Annual Meeting, 244 Poster Board331, March 2012

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