An exposure-led safety assessment framework for systemic toxicity: initial case studies from Cosmetics Europe

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Abstract

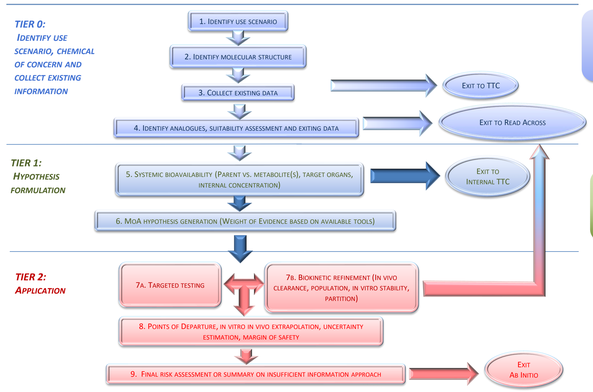
Cosmetics Europe is currently developing a **strategy on repeated dose systemic toxicity** within its research programme, namely the Long Range Science Strategy (LRSS). This strategy aims at developing safety assessment approaches for cosmetics **based on the use of non-animal approaches only.**

Case studies have a central place in this strategy. They **help evaluate a safety assessment workflow** that integrates **existing data and/or novel data types** using both **kinetics** and **toxicodynamic** tools, building on a framework developed within SEURAT1.

This framework features **3 tiers** that offer the opportunity to explore different approaches of differing levels of complexity such as the **threshold of toxicological concern (TTC), read-across,** and fully **quantitative in vitro to in vivo extrapolation (QIVIVE)** based on the mode of action of the chemical. Each tier can lead to a conclusion on safety assessment, and if not, the next tier is implemented.

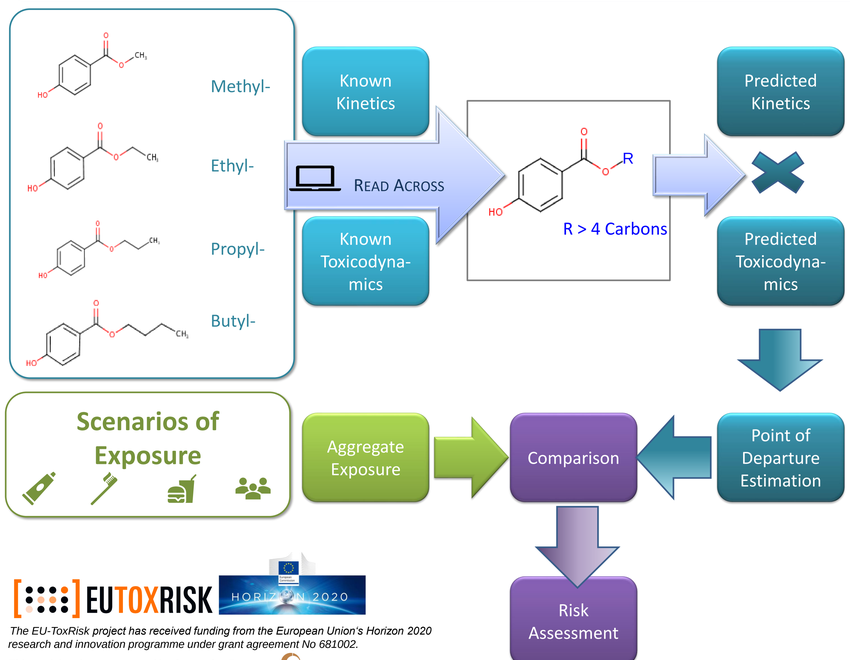
- The **first tier** considers existing **exposure data** and **chemical similarity** and **conclusion can be based on approaches such as TTC or read across.**
- The **second tier** targets syst**emic bioavailability (PBPK modelling)** and hypothesis generation on mode of action, and conclusion can be further based on approaches such as biological read across or internal TTC.
- Tier 3 encompasses targeted testing (taking account of both kinetics and modes of action) and quantitative in vitro to in vivo extrapolation to allow having the same dose metric at the level of exposure assessment and the reference dose that is derived from the point of departure.

The overall process is iterative and just enough data is generated to support decision making. We present here the initial outcomes and results of a case study on parabens, implementing this workflow. This work is conducted in **cooperation between EU-ToxRisk and Cosmetics Europe.**



TIER 0: IDENTIFY USE SCENARIO, CHEMICAL OF CONCERN AND COLLECT EXISTING INFORMATION — Done + under Re-evaluation

TIER 1: HYPOTHESIS FORMULATION — Ongoing!



Chemistry								In Vivo Data Available
Paraben	Proper.	Alerts	Acute	Short t.	Sub-chro.	Chro.	Repro.	Develop.
Me-	X	X	X	X	X	X	X	X
Et-	X	X				X	X	
Pro-	X	X	X	X		X	X	X
But-	X	X	X	X	X		X	X

In Vitro Data Avaialble					ADME/PK		
Acute tox. (IC50)	Genotox.	Skin sens.	Tox-Cast	ERBA	Skin abs.	PK (oral & dermal rats)	Metab.
X	X	X	X	X	X	X	
	X	X	X	X			
X	X	X	X	X	X	X	X
	X		X	X	X	X	

Chemical Properties		
Parameter	Experimental	Predicted
Melting Point	X	X
Density	X	X
Log P	X	X
pKa	X	X
Water solubility	X	X
Molecular weight		X
Oxidation		X

Metabolism						
Parent Com	Primary Metabolism		Secondary Metabolism		Tertiary Metabolism	
Paraben	*Enzymatic Hydrolysis:*	4-Hydroxybenzoic acid Alcohol	*Glycine:*	4-Hydroxyhippuric acid	*Enzymatic Hydrolysis:*	4-Hydroxybenzoic acid
			UGT:	Ester-glucuronide		
			UGT:	Ether-glucuronide		
	UGT:	Ether-glucuronide	*Enzymatic Hydrolysis*	Stable		
	Sulfuric acid:	4-Carboxyphenyl sulfate				

PharmacoKinetics							
Paraben	Species	Strain	Sex	Route	C_{max} (ng eq/mL)	t_{max} (h)	AUC_{0-t} (ng eq/mL)
Me-	Rat	Sprague-Dawley	M	Oral	26592	1	82153
	Rat	Sprague-Dawley	F	Oral	38664	0.5	143630
	Rat	Sprague-Dawley	M	Dermal	3146	1	20452
	Rat	Sprague-Dawley	F	Dermal	1707	8	20791
Pro-	Rat	Sprague-Dawley	M	Oral	11432	0.5	58344
	Rat	Sprague-Dawley	F	Oral	42280	0.5	118154
	Rat	Sprague-Dawley	M	Dermal	693	8	5421
	Rat	Sprague-Dawley	F	Dermal	1033	8	6390
Bu-	Rat	Sprague-Dawley	M	Oral	15229	0.5	73585
	Rat	Sprague-Dawley	F	Oral	21040	0.5	99336
	Rat	Sprague-Dawley	M	Dermal	986	1	12216
	Rat	Sprague-Dawley	F	Dermal	614	8	9760
	Rat	Sprague-Dawley	M	Subcut	6501	2	52033
	Rat	Sprague-Dawley	F	Subcut	12190	4	88917

Skin Penetration (figures not shown)					
Membrane		Concentration (mg/cm³)	Lag Time (h)	Steady State Flux (Jss) (µg/cm² /h)	Permeability Coefficient (Kp) (cm/s)
	Hairless mouse full thickness skin				
	Intact full thickness pig ear skin				
	Silicone				
	Human skin				

ToxCast Data (figures not shown)										
cell cycle	cell morphology	background measure-ment	cell adhesion molecules	gcpr	protease	protease inhibitor	esterase	hydro-lase	ion channel	steroid hormone

EUTOXRISK HORIZON 2020

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