A Case Study to Leverage Public Resources to Improve *In Silico* Chemical Safety Assessment

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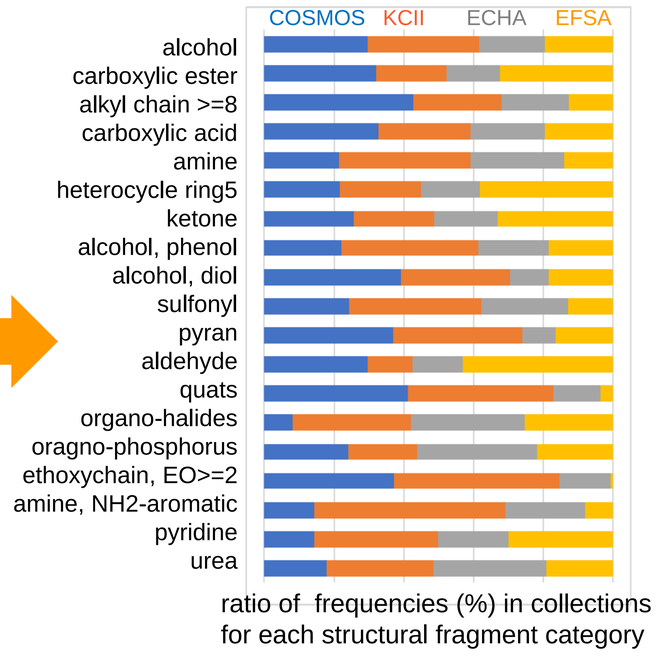
OBJECTIVES

- Non-animal testing-based alternative methods in safety assessment now include the use of formalised methods of QSAR, grouping and read-across for cosmetics ingredients, agrochemicals and their metabolites and impurities.
- Many public databases and *in silico* systems are available from public projects around the world which:
  - Enrich chemical space
  - Enhance reliability with a wider set of tools
- To leverage these public systems more effectively, this study compares the marquee features of some of the well-known systems using a probe molecule of a long alkyl chain (C12-15) benzoic ester.

EXAMPLE: PUBLIC RESOURCES

COSMOS	KCII CSP	ECHA (REACH)	EFSA OpenFoodTox	
17100	2270	1393	1437	COSMOS
	4163	942	594	KCII CSP
		4473	692	ECHA (REACH)
			3805	EFSA OpenFoodTox

Counts of unique compounds investigated within this study, however they do not represent the size of the current content.



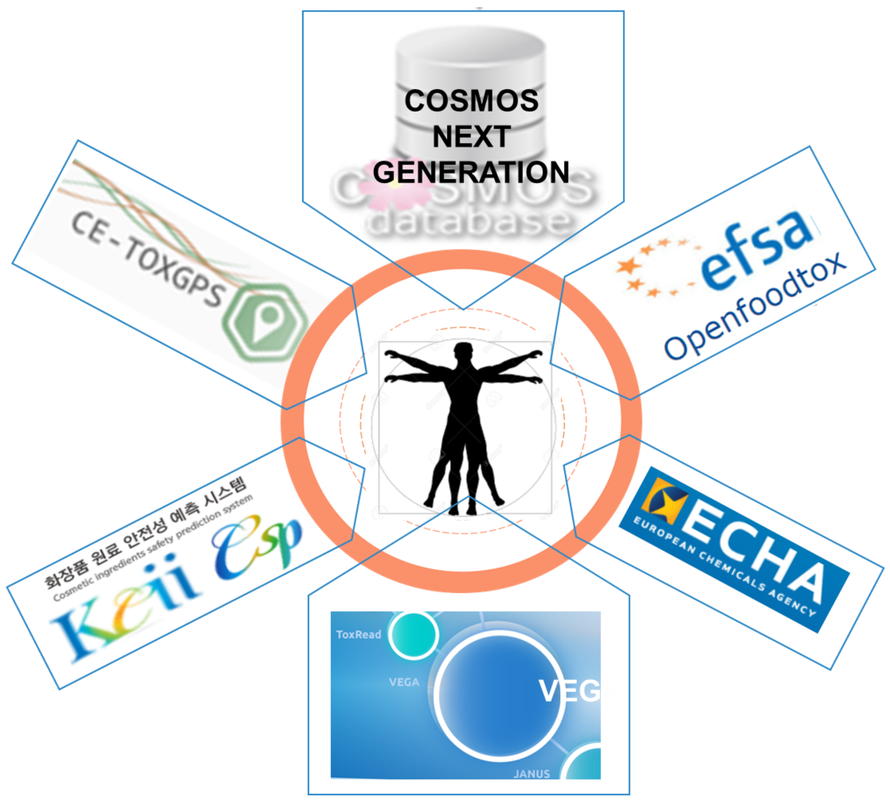
ratio of frequencies (%) in collections for each structural fragment category

COSMOS Database (http://cosmostox.eu)

- Over 20,000 substances used for cosmetics
- Toxicity data, TTC workflow
- Calculation of molecular and physchem properties*NEW*
- *In silico* profilers*NEW*, PK models (from COSMOS)*NEW*

COSMETICS EUROPE - TOXGPS*NEW*

- Cosmetics Europe members' data
- Toxicity data, TTC workflow
- Calculation of molecular and physchem properties
- *In silico* profilers, PK models
- *In silico* prediction models



EFSA OpenFoodTox (https://www.efsa.europa.eu/en/data/chemical-hazards-data)

- Currently over 5,600 substances
- Toxicity data
- Physchem properties data*NEW*
- Toxicokinetic data*NEW*
- Summary of exposure estimates*NEW*
- *in silico* toxicity models*NEW*

KCII CSP (http://csp.kcii.re.kr/)

- Korean cosmetics industry ingredient list provided by KCII for 4323 substances
- Toxicity data, TTC workflow
- Calculation of molecular and physchem properties,
- *in silico* prediction models (QSAR, profilers, rules)
- Read-Across preparation*NEW*

ECHA Registered Substance (https://echa.europa.eu/information-on-chemicals/registered-substances)

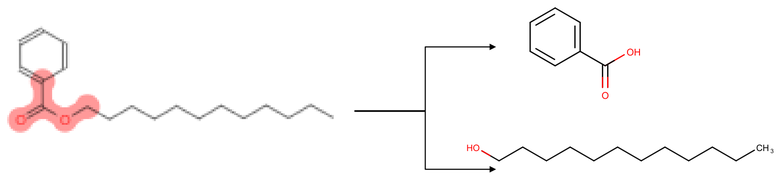
- Over 12,000 compounds for 22 endpoint categories
- Toxicity data (environmental, human health, etc.)
- Toxicokinetics data
- Physchem properties

VEGA System (https://www.vegahub.eu/)

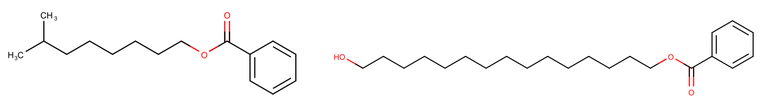
- *In silico* toxicity prediction models (QSAR)
- ToxRead for read-across preparation
- ToxWeight to combine QSAR and read-across

CASE STUDY

- C12-15 alkyl benzoate (CMS-26328) is used as a skin conditioning agent.
- The compound can be readily metabolised by hydrolysis.



- Analogues of parent



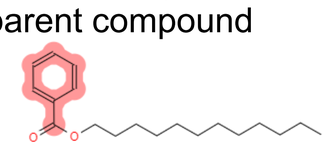
- Although some data are available for analogues and metabolites, no data are found for the parent.
- Example of public data from ECHA

Endpoint	Test Substance Type	Test Substance Name	Result
Ames mutagenicity	Analogue	Finsolv TN	Negative
In vitro chromosome aberration (ictCA)	Analogue	Benzoic acid isononylester	Negative
Micronucleus (MN)	Analogue	Benzoic acid isononylester	Negative
Skin sensitisation	Analogue	Finsolv TN	Human Negative Guinea Pig Negative
DART (Repro & DEV)	Analogue	Benzoic acid isononyl ester	NOAEL = 1000 mkd (HDT)
RDT (13 wk oral rat)	Analogue	Benzoic acid isononylester	NOAEL = 300 mkd (HDT)
Repro (rat oral)	Metabolite	Benzoic acid	NOAEL = 500 mkd (HDT)
Repro (rat oral)	Metabolite	Dodecanol	NOAEL = 1000 mkd (HDT)
DEVTox	Metabolite	Sodium benzoate	NOAEL = 2000 mkd (HDT)

TOXICITY PROFILES

Profilers from COSMOS NG or KCII CSP

- All chemical species (parent, metabolite, analogues) do not match any DNA or protein binders
- No DART rules matched the parent, metabolite, or analogues.
- Liver toxicity profiler rule for "methylated aromatic ring" hits the parent compound



QSAR PREDICTIONS

QSAR results from KCII CSP and VEGA

- All genetic toxicity assays including Ames, ivtCA, MN were negative.
- Both rat and mouse tumorigenicity predicted equivocal results.
- Cleft palate formation was negative.
- No fertility changes were indicated.
- Skin sensitisation – LLNA positive (GHS 1B)
- Human DILI was negative.

In RDT, liver weight changes are associated with Benzoic acid isononylesters. However no relevant pathological changes were observed.

CONCLUSIONS

- The case study was carried out obtaining the data for all chemical species (parent, metabolite, analogues) along with profiler and prediction tools from multiple sources.
- Crossing-over to different regulatory inventories is useful in our effort to expand the chemical space.
- The study demonstrated that systematically leveraging public tools and databases enables more comprehensive analyses.

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