Improving In Silico Assessment of Cosmetic Ingredients by Leveraging In Vivo Data from Public Systems

Aleksandra Mostrag[1], Jonghyn Kim[2], JungSoo Kim[3], SiJun Park[3], Woo-Hyuck Choi[4], Yooree Lim[2], Sungmin Yang[2], Jongjin Park[1], Jörg Maruszyck[1], Christof Schwab[1], James F Rathman[1,5], Chihae Yang[1,5], Mark Cronin[6], Andrew Worth[7], Andrea Richarz[7]

[1]MN-AM, Nürnberg, Germany & Columbus OH USA; [2]Korean Cosmetics Institute of Industries, Osan Korea; [3]Advanced Cosmeceutical Technology, Su Won, Korea; [4]LG Household & Health Care, Seoul, Korea; [5]The Ohio State University, Columbus OH USA; [6] Liverpool John Moores University, Liverpool, UK; [7]EC Joint Research Center, Ispra, Italy

MOTIVATION

- COSMOS Database (www.cosmosdb.eu) is a public resource for cosmetics ingredients of toxicity data and safety evaluation results.
  - One of seven projects in the SEURAT-1 cluster (2011-2015)
  - Over 2000 registered users (> 70% industry)
- KCII CSP (Chemical Safety Prediction) is an in silico system constructed for the members of the Korean Cosmetics Institute of Industries (KCII).
  - Over 1800 companies with approximately 4000 users
- COSMOS and KCII CSP exchange data and tools that are essential to enhance the applicability and utilities of the in silico system.

COSMOS DATA IN KCII CSP

- Cosmos TTC Dataset
- SCCS assessment results (e.g., MoS)
- Toxicity data - oREPEATOX DB (218 organic chemicals with toxicity data)
- US FDA PAFA database (1496 substances with toxicity data)
- Profiling tools
  - DNA and Protein Binders

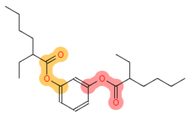
IN SILICO TOOLS IN KCII CSP

Database on Toxicity, Safety

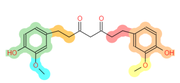
Analogs & Profiles

ToxGPS® In Silico Prediction, Workflows, Assessment

- Database
  - KCII Cosmetic Safety Evaluation Data (Korean cosmetics ingredients, ~4500)
- Profilers: DART rules and DNA-/Protein binders from COSMOS
- Other tools
  - Threshold of Toxicological Concern (TTC) Workflow
  - Calculation of molecular and physicochemical properties
  - Predictions (QSAR and Structural Rules)
    - Genetic toxicity (Bacterial reverse mutagenesis, Chromosome aberration, Micronucleus)
    - Tumorigenicity (rat, mouse)
    - Reproductive/Developmental toxicity (DART rules and models)
    - Human Drug-Induced Liver Injury
    - Acute toxicity
    - Skin sensitization



DNA Binders (COSMOS)[1-3]



- Alkyl-phenols 9 atoms
- Alkyl-phenols 9 atoms
- Hydroquinones 9 atoms
- Hydroquinones 9 atoms

Protein Binders (COSMOS)[4-11]

- Alkyl-phenols 9 atoms
- Alkyl-phenols 9 atoms
- Hydroquinones 9 atoms
- Hydroquinones 9 atoms
- 1,3 Dicarbonyl 7 atoms

ACKNOWLEDGEMENT

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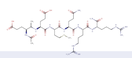
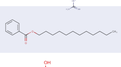
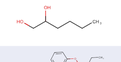
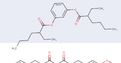
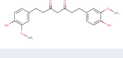
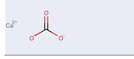
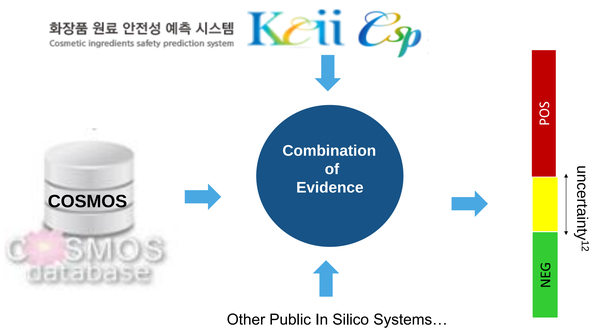
CASE STUDY SUBSTANCES

- To demonstrate the applicability of the in silico methods based on COSMOS DB and KCII CSP, a variety of substances possibly used in cosmetic formulations were selected

Structure	Name	CMS CAS	USE	Estimated Daily Intake (mg/day)
	Acetyl Hexapeptide-8	CMS-56823 616204-22-9	Skin-conditioning	0.0001
	C12-15 Alkyl Benzoate	CMS-26328 68411-27-8	Skin-conditioning	44.0
	1,2-Hexanediol	CMS-21952 6920-22-5	Solvent, Skin-conditioning	30.8
	Resorcinol Bis-Ethylhexanoate	No CMS 153195-60-9	Whitening	No info
	Tetrahydro-curcumin	CMS-51704 36062-04-1	Antioxidant, Skin Bleaching, Skin Protectant, Sunscreen	No info
	Calcium Carbonate	CMS-7424 471-34-1	Abrasive, Buffering, Bulking, Opacifying, Oral care, Cosmetics colorant	No info

- Hexapeptide can be assessed by applying TTC due to low exposure.
- C12-15 Alkyl Benzoate was approached by read-across using analog data from COSMOS DB and ECHA.
- Calcium carbonate was a data-rich compound in COSMOS DB and CIR.



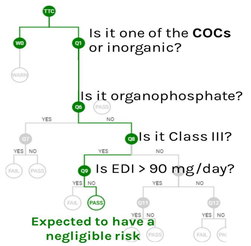
RESULTS – TTC WORKFLOW

- Data-rich and data-poor cases

Endpoints	$CaCO_3$	Acetyl Hexapeptide-8
Genetic Toxicity • Ames Test • Ivt CA	 • Negative • Negative	NO DATA
Carcinogenicity	• No chronic or 2-year data • Not likely to be carcinogenic by EFSA panel (2011)	NO DATA
DART	• Repro NOEL=1000 mkd • DevTox NOAEL= 1563 mkd • High maternal Ca levels can be fetotoxic	NO DATA
Dermal Toxicity	• Not a skin irritant • Non-sensitizer	NO DATA

Data sources include COSMOS (US FDA PAFA), EFSA, and CIR.

- Threshold of Toxicological Concern
  - Acetyl hexapeptide-8 is a data-poor compound with low exposure in use
  - Cramer Class III
  - Estimated daily exposure: 0.105 μg/day



RESULTS – IN SILICO PREDICTION

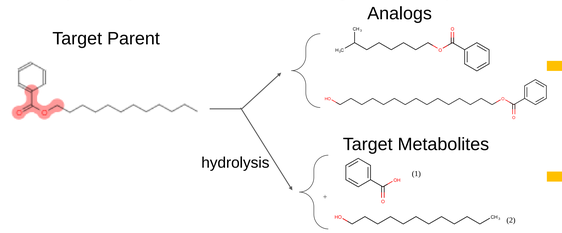
- QSAR and Structural Rules
  - In general, genetic toxicity (especially Ames mutagenicity) and skin sensitization predictions have acceptable reliability due to strong interactions between small molecules and DNA or protein molecules

Structure	Genetic Toxicity			Tumorigenicity		Skin Sensitization
	Ames Test	Ivt CA	In vivo MN	Rat	Mouse	LLNA hazard
C12-15 Alkyl Benzoate*	NEGATIVE Uncertainty=0.22	NEGATIVE Uncertainty=0.37	NEGATIVE Uncertainty=0.04	EQUIVOCAL Uncertainty=0.39	EQUIVOCAL Uncertainty=0.38	POSITIVE Uncertainty=0.12
1,2-Hexanediol	NEGATIVE Uncertainty=0.22	NEGATIVE Uncertainty=0.37	NEGATIVE Uncertainty=0.07	EQUIVOCAL Uncertainty=0.36	EQUIVOCAL Uncertainty=0.38	NEGATIVE Uncertainty=0.01
Resorcinol Bis-Ethylhexanoate	NEGATIVE Uncertainty=0.22	NEGATIVE Uncertainty=0.37	NEGATIVE Uncertainty=0.08	EQUIVOCAL Uncertainty=0.37	NEGATIVE Uncertainty=0.08	NEGATIVE Uncertainty=0.12
Tetrahydro-curcumin	NEGATIVE Uncertainty=0.22	NEGATIVE Uncertainty=0.13	NEGATIVE Uncertainty=0.04	NEGATIVE Uncertainty=0.18	NEGATIVE Uncertainty=0.04	POSITIVE Uncertainty=0.01

* ECHA provides experimental data based on read-across for this substance
* CIR reports negative LLNA results for this substance; however, the experimental results were for formulations, not neat chemical

RESULTS – READ-ACROSS

- CASE: C12-15 Alkyl Benzoate for DART Effects
  - Read-across analysis showed that DART effects can be read from its metabolites
  - Assuming comparable study reliabilities for benzoic acid, dodecanol, and octadecanol, the NOAEL of the target compound would be expected to be higher than 1200 mg/kg-bw/day (after adjustment for molecular weight difference)

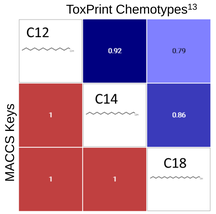


No DART Data for analogs

DART Data
- Benzoic acid
- Analogs of C12-15 alcohol
  - C14, C18, C22-alcohols
  - Similarities are high

Name	Benzoic Acid	Myristyl Alcohol	Other Similar Alcohols
Repro	• Rat oral 4-GEN study: 0, 250, 500 mg/kg-bw/day • NOAEL=500 mg/kg bw/day • No effects	NO DATA	• Data from **Dodecanol** • Rat oral 1-GEN study: 100, 500, 2000 mg/kg-bw/day; • NOAEL >=2000 • No effects
DevTox	Sodium benzoate data	NO DATA	• Data from **Octadecan-1-ol** • Rat oral 100, 500, 2000 mg/kg bw/day • NOAEL=2000

ToxPrint Chemotypes[13]



CONCLUSION

- Case studies for collaborative use of COSMOS DB and KCII CSP prediction system were demonstrated to address data-poor, low exposure at use, or polydispersed substances.
- Based on all available information, appropriate methods (TTC, QSAR/Alerts, or Read-Across) can be recommended.

REFERENCES

(1) Enoch SJ, Cronin MTD. CRT, 2010, 40, 728-748; (2) Enoch SJ et al. ATLA 2011, 39, 131-145; (3) Enoch SJ, Cronin MTD. Mutat. Res., 2012, 743(1-2), 10-19; (4) Enoch SJ et al. CRT, 2011, 41, 783-802; (5) Bajot F et al. SAR and QSAR in Env Res, 2011, 22, 51-65; (6) Enoch SJ et al. SAR and QSAR in Env Res, 2012, 23, 649-663; (7) Nelms MD et al. 2013. SAR and QSAR in Env Res, 2013, 24, 695-709; (8) Rodriguez-Sanchez N et al. SAR and QSAR in Env Res, 2013, 24, 963-977; (9) Enoch SJ et al. SAR and QSAR in Env Res, 2013, 24, 385-392; (10) Richarz AN et al. SAR and QSAR in Environmental Research, 2014, 25, 325-341; (11) Ebrell DJ et al. CRT, 2016, 29, 1073-1081; (12) Rathman JF et al. Computational Toxicology, 2018, 6, 16-31; (13) www.toxprint.org

Contact: chihae.yang@mn-am.com