Comparative Case Studies to Establish a Standardized Process for Read-Across within a Daily Safety Assessment Workflow

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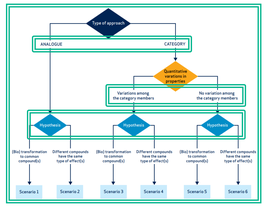
Background

- ✓ Our previous study summarized available tools for read-across and proposed a **combined approach** [1].
- ✓ Basic principles for read-across were based on ECHA-RAAF[2].

1. Analogue or category
2. Variation between category
3. Hypothesis
   a) metabolic similarity and/or
   b) biological similarity



- ✓Process still requires "expert judgement" and remains challenging due to
  1) Wide variety of diverse tools to choose from
  2) Complex read-across scenarios
  3) New approach methodology (NAMs) are still not common to evaluate biological similarity
- ✓ **Metabolic assessment** based on in silico approaches may be a preliminary option.

Objective

Establish standardized process on read-across by comparison of two case studies using ChemTunes·ToxGPS and AMBIT.

Methods

Searching for analogue candidate

Used tools	Available descriptor				Physchem. similarity	Toxicity databases
	MACCS	RDKit	CDKit	ToxPrint		
TOX GPS	X	X		X	X	COSMOS, EFSA, ECHA, FDA
ambit			X			ECHA

Structural similarity

- ✓ Chemical descriptor : Tanimoto coefficient
- ✓ Physicochemical properties: Pearson's correlation / Euclidean distance

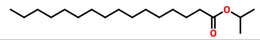
Metabolic similarity

- ✓ Skin metabolism: OASIS (TIMES-SS)
- ✓ Liver metabolism: Liver Biopath (ChemTunes)

Selection criteria of analogue candidates

- ✓ Based on 1) structural similarity, and 2) Point-of-Departure (PoD) data

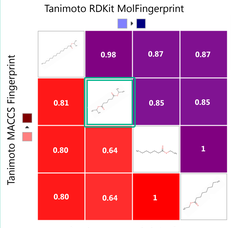
Case Study 1

Structure	
INCI	Isopropyl palmitate
CAS	142-91-6

This chemical is used as a skin conditioner, emulsifier and binder, and also in fragrances[3].

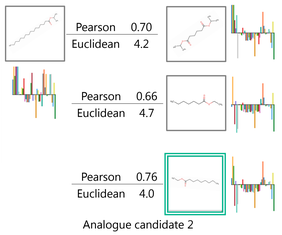
1. Search for analogue candidate (ChemTunes · TOX GPS)

Fingerprint



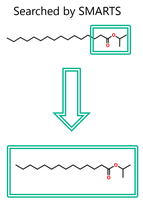
Analogue candidate 1

Physicochemical properties



Analogue candidate 2

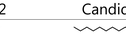
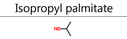
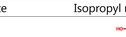
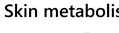
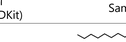
Search for substructure



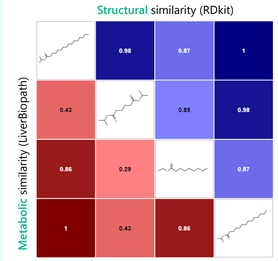
Analogue candidate 3

2. Evaluation on metabolic similarity

Skin metabolism (TIMES-SS)

	Target	Candidate 1	Candidate 2	Candidate 3
Parent				
	Isopropyl palmitate	Diisopropyl adipate	Ethyl nonanoate	Isopropyl myristate
Metabolite 1				
Difference	---	Same	Ethyl or propyl Similarity = 0.6 (RDKit)	Same
Metabolite 2				
Difference	---	Carboxyl ester Similarity = 0.51	C- chain length Similarity = 1 (RDKit)	C- chain length Similarity = 1 (RDKit)

Liver metabolism (ChemTunes · TOX GPS)



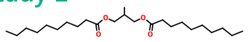
Possible Reasoning

Candidate 1: Metabolite 2 is not sufficiently similar to be used in read-across.

Candidate 2: Branched alcohol (metabolite 1) can be more toxic [4,5], but the variation of PoD between carboxyl ester will be within 4.5[6].

Candidate 3: The structural and metabolic differences between target and analogue are very small.

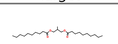
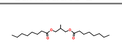
Case Study 2

Structure	
INCI	Neopentyl glycol dicaprate
CAS	27841-06-1

This chemical is used in various products, including face powders which may be inhaled [7].

1. Search for analogue candidates ambit

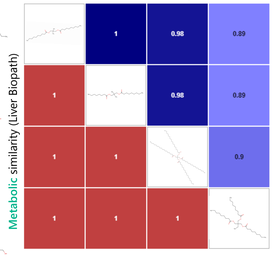
Three candidates with PoD: similarity > 0.8 (no candidates with the similarity over 0.9)

		Target	Candidate 1	Candidate 2	Candidate 3
Structure					
Name		Neopentyl Glycol Dicaprate	Neopentyl Glycol Dicaprylate	Trimethylolpropane Trinonanoate	Pentaerythrityl Tetrastearate
CAS		27841-06-1	31335-74-7	126-57-8	115-83-3
Genotoxicity	Mutagenicity	Negative	Negative	Negative	Negative
	CA/MN	n.t.	Negative	Negative	Negative
Sensitization	GPMT	Negative	n.t.	Negative	Negative
	TIMES-SS	Negative	Negative	Negative	Negative
PoD	Oral	n.t.	n.t.	OECD422 NOAEL:1000 mg/kg	28-days NOAEL: 1000 mg/kg
	Inhalation	n.t.	90-days NOAEC: 500 mg/m^3 (unspecified mixture)	n.t.	n.t.

2. Evaluation on metabolic similarity

Skin metabolism (TIMES-SS)

Liver metabolism (ChemTunes · TOX GPS)



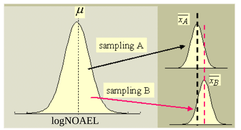
Possible Reasoning

Both structural/metabolic differences are quite small and toxicological profiles are close. Therefore category approach is applicable to target chemical.

NOAEL Distribution Confidence Interval

(ChemTunes · TOX GPS)

- ✓ Can a range of possible NOAEL for the target be estimated from NOAEL distributions of similar analogues?
- ✓ Is uncertainty of the estimated NOAEL less when the analogues are more highly similar?



Yang et al. Manuscript in preparation, 2019.

- ✓ Analyze NOAEL distributions for subsets (e.g. A and B) of compounds having similarities to the target within a specified range (e.g., 0.7 - 0.8 or 0.8 - 0.9).
- ✓ Estimate NOAEL confidence interval for target.

Discussion

- ✓ Combined use of ChemTunes·ToxGPS/AMBIT as well as metabolic models is complementary and helpful for hypothesis-driven read-across.
- ✓ Other study reported reasonable similarity score of 0.6[8].
- ✓ Several structural categories have higher variability of PoD between 3.2 to 5[6].
  (ex. Aromatic nitros, aromatic phenols, nitrophenols/anilines, carboxylethers, glycoethers)
  ⇒ These exceptional classes may require additional extrapolation factors.

Summary

Proposed standardized process

i) Collect available analogue candidates based on structure- and property-based similarities
ii) Select appropriate candidate by metabolic similarity
iii) Consider extrapolation factor on read-across.

References

1: A. Granitzny et al., 2018, EUROTOX, 2: ECHA, 2017, 3: IJT 34(Suppl.2):5-69, 2015, 4-5: T. W.Schultz et al., 2017, 6: M. Batke et al., 2016, 7: CIR, 2017, 8: Y. K. Koleva et al., 2008