G Ouedrago,[1] M Cronin,[2] M Dent,[3] A Detroyer,[1] S Gutsell,[3] N Hewitt,[4] G Kenna,[4] P Kern,[5] C-T Krueger,[6] C Mahony,[7] A Najjar,[6] K Przybylak,[3] J Rathman,[7] M Varçin,[4] C Yang[7]

P714

Role of a Molecular Informatics Platform to Connect Risk Assessments within Cosmetics Industry

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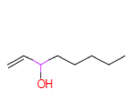
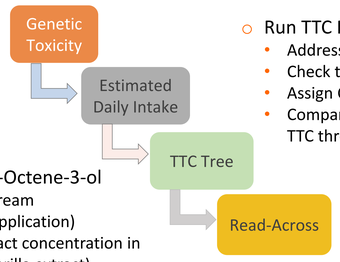
1 OBJECTIVES

- A key objective of the Systemic Toxicity Task Force in Cosmetic Europe's Long-Range Science Strategy (LRSS) program is to explore new approach methodologies (NAM) for the safety assessment of cosmetic ingredients.
- Task force has adopted the ChemTunes.ToxGPS® chemoinformatics platform, allowing CE members to expand functionalities and integrate data and knowledge. This poster is focused on the Tier 0 process.
- Case study approach is being used to guide design and development. A detailed example is presented here for 1-Octene-3-ol (amylvinyl carbinol) applying TTC and read-across in the assessment of genetic toxicity.

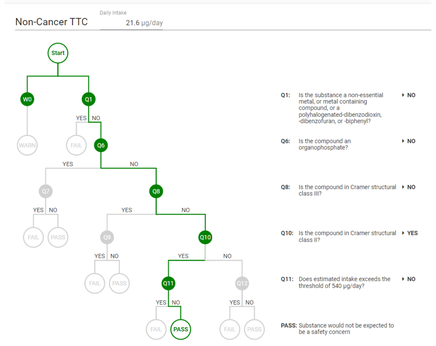
2 USE CASE ILLUSTRATION





- Exposure scenario for 1-Octene-3-ol
  - Hypothetical leave-on cream (32.7 mg product/day application)
  - Assumed botanical extract concentration in formula: 0.01 % (e.g., perilla extract)
  - 1-Octene-3-ol level in the extract: 0.11 %
  - Estimated daily intake (EDI): 0.216 µg/day
- Run TTC Process
  - Address genotoxicity
  - Check the COC
  - Assign Cramer Classes
  - Compare with EDI and TTC thresholds
- Run Read-Across for more compound-specific safety

3 THRESHOLD OF TOXICOLOGICAL CONCERN



TTC Process Tree

- 1-Octene-3-ol is not one of the COC structures.
- 1-Octene-3-ol is not genotoxic (confirmed through RAX)
- Cramer Class II (Toxtree v3.1.0 build 1851, implemented in ChemTunes.ToxGPS)
- Expected daily intake (EDI) of 1-Octene-3-ol (0.216 µg/day) is much lower than the 540 µg/day threshold.
- The tree indicates a safe exit even when 21.6 µg/day (100x EDI) is entered.

Q1. COC structure classes include polyhalogenated-dibenzodioxins, -dibenzofurans, -biphenyls, nitroso, azoxy, and aflatoxin-like substances are not evaluated in TTC.

5 EVIDENCE USED IN READ-ACROSS (RAX)

- ***Analogue Quality (AQ)***

$$AQ = \left(Structure_{sim} \times Property_{sim} \times Assay_{sim}\right)^{1/3}$$

  - Structure fingerprints
  - Mechanistically-relevant structure categories
  - Property-based similarity
  - Assay vector-based similarity
- ***Study Data Quality (SQ)***

  Based on concept similar to Klimisch score

  SQ values range from 0 (poor) to 1 (high)

READ-ACROSS (RAX) RELIABILITY

$$RR = AQ \times SQ$$

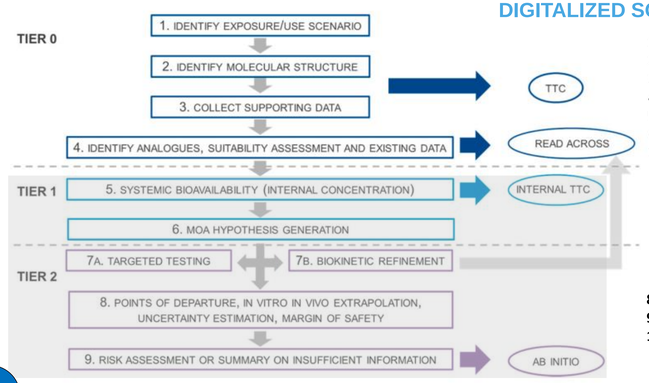
RR uncertainty

RAX OUTCOME & UNCERTAINTY

- Classification Endpoints
- Numeric endpoints (NOAEL or EC3): 95% Confidence Interval

SEURAT-1 WORKFLOW

DIGITALIZED SOFTWARE WORKFLOW



1. **Exposure/Use Scenarios:**
2. **Searching: Target Structure**
3. **Searching: Target Data Collection**
4. **Run TTC Tree**
5. **Searching: Analogue Structures**
6. **Searching: Analogue Data Collection**
7. **Analysis: Analogue Qualification**

8. **Run RAX**
9. **Run POD Service: Derive POD**
10. **Assess Confidence**

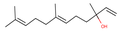
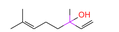
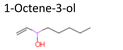
6 READ-ACROSS

For simplicity, genetic toxicity is presented as an example. Listed are the various sources of evidence used in the Dempster-Shafer Decision Theory (DST) combination.

Compound Summary	CMS-7321 Target	CMS-4400 Analog-2.1	CMS-2195 Analog-2.2	CMS-6748 Analog-2.3
CMS ID				
Fingerprints				
RDKit Morgan Fingerprint				
Tanimoto	1	0.47	0.43	0.31
ToxPrint Fingerprint				
Tanimoto	1	0.53	0.47	0.44
ChemotypeProfiles				
DNA binders		No Hits	No Hits	No Hits
Skyline Profiles				
Properties				
Skyline				
Pearson similarity	1	0.93	0.92	0.90
Tox21/Cast Assays				
Skyline				
Euclidean similarity	1	0.81	0.71	0.69
Analogue Quality		0.74	0.67	0.65
Exp. Genetic Toxicity Data				
Study Type		Bacteria Rev. Mutagenesis	Bacteria Rev. Mutagenesis	Bacteria Rev. Mutagenesis
Study Description		6 strains w, w/o S9; control	5 strains w, w/o S9; control	5 strains w, w/o S9; control
Study Quality (SQ)		HIGH (0.95)	MED-HIGH (0.90)	MED-HIGH (0.85)
Study Result		NEGATIVE (NTP)	NEGATIVE	NEGATIVE
Exp. Genetic Toxicity Data				
Study Type		In Vivo Micronucleus	In Vivo Micronucleus	In Vitro Chromosome Ab.
Study Description		Mouse Bone Marrow	Mouse Bone Marrow	Human Lymphocytes
Study Quality (SQ)		HIGH (0.90)	HIGH (0.90)	MED (0.80)
Study Result		NEGATIVE (NTP)	NEGATIVE (NTP)	NEGATIVE
Prediction Uncertaint:	0.221	0.223	0.223	0.222
Study Result	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE
RAX Reliability WOE: RDT (Per Analogue)		0.901	0.842	0.785
RAX Reliability WOE: RDT (All)		0.997	Overal read-across reliability is improved (99% confidence) by combining all evidence.	
RAX Outcome				
Experiment only	NEGATIVE [pNEG=0.997, unc=0.003]		Based on assay data only, the target is deemed non-genotoxic with low (<1%) uncertainty.	
Experiment + In Silico	NEG [pNEG=0.982, unc=0.017]		Based on assay data and in silico data, the target is deemed non-genotoxic with low (<1%)	

- Structure-based similarity
  - Many fingerprint similarities are compared including Morgan and ToxPrint. The latter was used to calculate AQ.
- Properties-based similarity (13)
  - Size, interfacial, shape,
  - Quantum mechanical to capture chemical reactivity
- Genetic toxicity – Experimental data
  - Ames assay, in vitro chromosome aberration, and micronucleus data are combined by DST.
- Genetic toxicity - In silico data
  - ToxGPS Ames results are shown as an example
  - QSAR and Rule-base outcomes are combined.
- The genetic toxicity outcome of 1-Octene-3-ol (amylvinyl carbinol) can be read across from three analogues. The combined Read-Across Reliability was very high (>99%). The RAX outcome indicates the target is expected to be NEGATIVE for genetic toxicity.

4 DATA USED IN THIS STUDY*

	Ames Mutagenicity	Ivt chromo. aberration	In vivo micronucleus	Other genetox	Repeated Dose	Reproductive-Developmental	Endocrine Disruption Screening Assays[1]	Skin Sensitization
CMS-2195 Nerolidol 	Call: NEG (OECD 471, 4 TA & 1 WP2 strains, +-S9, control) SQ: 0.85 Source: ECHA	No data found	Call: NEG (OECD 474 mouse M, bone marrow) SQ: 0.90 Source: ECHA	• ToxCast DNA binding, damage/repair assays (aggregated to 46 assays from 98)[1]	• 57-day rat (OECD 422) oral-dietary - NOAEL (F)=105 mkd - Systemic, Clin Path, Hepatotoxicity - Source: RIFM, ECHA - SQ: 0.9 (Klimisch=1)	• Rat (OECD 422) oral-dietary - Developmental NOAEL=226 (M), 340–468 (F, GD-LD) - Reproductive NOAEL= 705 (F/P0), 758 (M/P0)) - Source: RIFM, ECHA - SQ:	CMS-2195	• LLNA: GHS 1B; EC3=4.9 % (w/v) [CT; ECHA]
CMS-4400 Linalool 	Call: NEG SQ: 0.95 (OECD 471) Source: CT (NTP, PAFA)	Call: NEG (CHL) SQ: 0.80 Source: PAFA	Call: NEG (OECD 474) mouse M/F, bone marrow SQ: 0.90 Source: ECHA	• ivtMM (MLA): NEG - SQ: 0.85 (OECD 476) - Source: ECHA • ToxCast DNA binding, damage/repair assays[1]	• 28-day rat oral study - LOEL=160 mkd - kidney, liver, stomach - Source: CT-RepDose - SQ:	• Rat oral-gavage developmental study - NOEL=1000 mkd - No effects - Source: INT J Toxicol 27:183-188, 2008 - SQ: 0.8	CMS-4400	• LLNA: weak sensitizer [Master Table] • RIPT : negative [BASF] • Human maximation: negative [BASF, RIFM] • Human: Positive [BASF]
CMS-7321 1-Octene-3-ol 	No experimental data QSAR from OECD Toolbox Source: ECHA	No data found	No data found	• ivtMN of 1-pentene-3-ol: NEG (Read-Across) - Source: RIFM • ToxCast DNA binding, damage/repair assays[1]	• 90-day rat oral-dietary - NOEL=14.5 mkd - No effects - Source: RIFM, PAFA. Fd.Cosm.Tox. 7, 405, 1969 - SQ: 0.8	Insufficient data [RIFM 2019]	CMS-7321	• In vitro: GHS 1B by DPRA, KeratinoSense [ECHA] • In vitro: Category 1B by ARE-Nrf2 Luciferase Test [ECHA]
CMS-6748 Farnesol	Call: NEG SQ: 0.9 (OECD 471) Source: ECHA	Call: NEG (Human lymphocytes) SQ: 0.8 (OECD 473) Source: ECHA	No data found	• ivtMM (MLA): NEG - SQ: 0.85 (OECD 476) - Source: ECHA • ToxCast DNA binding, damage/repair assays[1]	• Rat 28-day oral-gavage study; - LOEL= 500 (PAFA); NOAEL=1000 mkd [RIFM] - Organ wT, Clin Chem [PAFA]; No effects [RIFM] - Source: PAFA; RIFM - SQ: 0.8 (PAFA); 0.7 (RIFM)	RAX based on nerolidol [ECHA]	CMS-6748	• LLNA GHS 1B; EC3 pf 6.3% (w/v) [BASF] • Human HRIPT NEG; Human POS [BASF]

[1]The bar charts show standardized assay profiles. Each bar represents a closely related assay group.

*The selection of analogues was limited to the constituents found in the perilla extract.

MN-AM: B Bienfait, B Hobocienski, J Marusczyk, T Magdziara, A Mostrag, J Park, V Ribeiro, C Schwab, O Sacher
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