Cosmetics Europe Analysis: Towards development of an ocular toxicity Defined Approach using *in vitro* test methods and physico-chemical properties as components within an IATA

Abstract No.: 1497
Poster board No.: P711

Desprez B[1], Alépée N[2], Adriaens E[3], Bagley D[4], Hibatallah J[5], Mewes K.R[6], Pfannenbecker U[7], Sala À[8], McNamee P[9]

[1]Cosmetics Europe - The Personal Care Association, Brussels, Belgium, [2]L'Oréal Research & Innovation, Aulnay Sous Bois, France, [3]Adriaens Consulting, Aalter, Belgium, [4]Colgate-Palmolive, Piscataway, New Jersey, United States, [5]Chanel Parfums Beauté, Neuilly sur Seine, France, [6]Henkel AG & Co. KGaA, Düsseldorf, Germany, [7]Beiersdorf AG, Hamburg, Germany; [8]Kao Corporation, S.A., Barcelona, Spain, [9]The Procter & Gamble Company, Egham, United Kingdom

Introduction

- **In 2017, OECD published Guidance Document no. 263 on an Integrated Approach on Testing and Assessment (IATA)** for serious eye damage and eye irritation. This provides guidance on how to integrate existing and/or newly generated information for decision making, including decisions on the need for further testing or on classification & labelling for potential eye hazard of chemicals.
- In this context, **physico-chemical properties may be used** to identify e.g. chemicals not likely to cause serious eye damage/eye irritation **and to help orient chemicals towards a Top-Down or Bottom-Up approach**. **Cosmetics Europe (CE) has therefore created a comprehensive database** of chemicals for which *in vitro* data are available with corresponding historical *in vivo* data, including physico-chemical properties.
- This database was used to build on initial testing strategies developed within the CEFIC CON4EI project to evaluate their robustness and to identify areas for refinement.
- One such area identified is the **incorporation of physico-chemical properties**. To better understanding the importance of physico-chemical properties, a **principal component analysis (PCA)** was performed to explore the relationship between physico-chemical properties and UN GHS classification of chemicals.
- Based on this initial analysis, it was concluded that for neat liquids, separation between Cat. 1 and Cat. 2 versus No Cat. was, to a certain extent, possible based on **LogP and vapour pressure**. This information was then **combined** with **a testing strategy to develop a Defined Approach for neat liquids**.

Materials and Methods

- We used **62 neat liquids** for this analysis from two projects, the **CON4EI** (Consortium for *in vitro* Eye Irritation testing strategy) project funded by the European Chemical Industry Council (CEFIC) and the **CE methods evaluation project (CON4EI: 38 chemicals, CE: 24 chemicals)**.
- For **all chemicals, reliable *in vivo* data were available from CE Draize eye test Reference Database** (DRD, Barroso et al., Arch. Toxicol., 2017) with UN GHS classifications and known drivers of classification.
- The **physico-chemical properties investigated** were **molecular weight** (MW), **octanol-water partition coefficient** (LogP), **melting point** (Melt), **vapor pressure** (LogVP), and **water/lipid solubility** (LogWS).
- Physico-chemical properties data were retrieved from following sources: ECHA website for information on chemicals (highest priority), EPA Chemistry Dashboard website, PubChem website, ChemSpider website along with other sources like e.g. SCCS opinion publications.

Conclusions & Next Steps

Initial Defined Approach (DA) for neat liquids

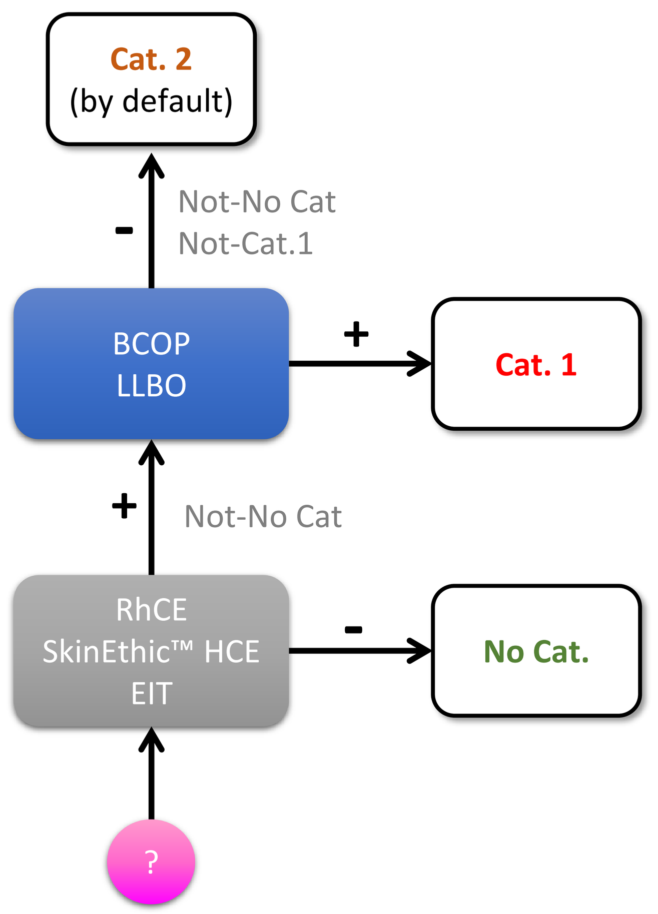
- In the example provided here, **combining the physico-chemical properties (LogP and vapor pressure) with a Bottom-Up** testing strategy using the *in vitro* test methods RhCE SkinEthic™ HCE EIT and BCOP LLBO results in **a higher specificity without majorly affecting the sensitivity**
- It is **important to increase specificity in DAs** to prevent over-predictions in the long term as over-sensitive and less specific testing strategies will change the prevalence of the chemicals in the real world.

Next steps

- An initial DA is presented here. This work is **continuing** in the CE Eye Programme to understand how initial **DAs can be refined and applicability extended beyond neat liquids**.
- This is through integration of additional physico-chemical properties and how these can be further combined with testing strategies based on *in vitro* test methods.

Testing Strategy and Defined Approach (DA) for neat liquids

(A)



(A) Bottom-Up testing strategy example

This approach combines:

- Reconstructed human cornea epithelium test method (RhCE, OECD test guideline (TG) No. 492), at the Bottom;
- The Bovine Corneal Opacity test method (BCOP OECD TG No. 437) at the Top

In the BCOP, the Laser Light-based Opacitometer (LLBO) device measured the opacity. One outcome of the CON4EI project showed that the sensitivity of the BCOP LLBO is higher than the OECD adopted BCOP OP-KIT with respect to the correct identification of Cat. 1.

Performance of the Bottom-Up Example:

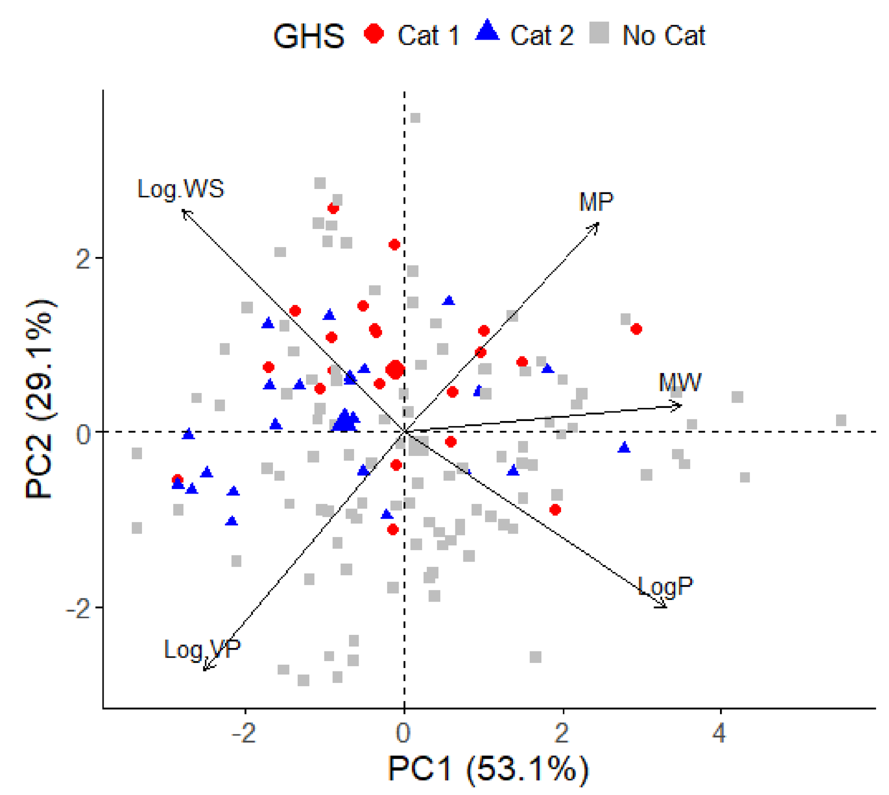
	2-Step Bottom-Up Approach		
UN GHS (N=62)	**Cat. 1**	**Cat. 2**	**No Cat**
Cat 1 (N = 16)	**81.3%**	18.7%	0%
Cat 2 (N = 14)	28.6%	**71.4%**	0%
No Cat (N = 32)	25.0%		**75.0%**

(B)

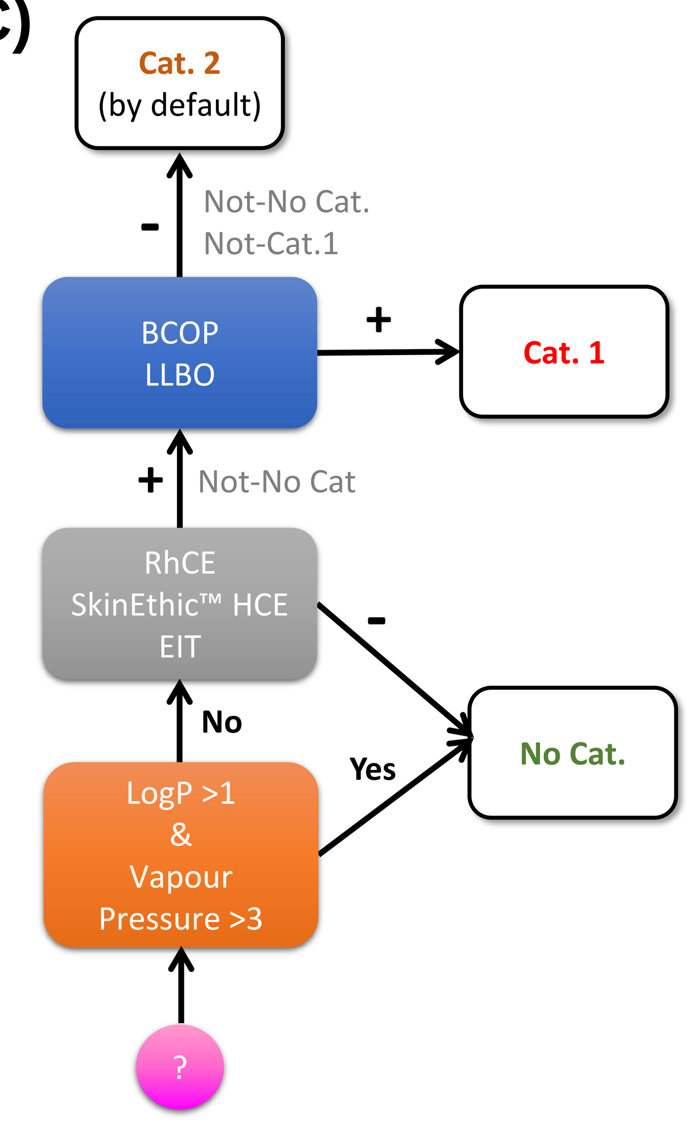
(B) Physico-chemical properties:

- We used Principal Component Analysis (PCA) on a selected number of physico-chemical properties;
- From this PCA, it was identified that higher values for LogP and vapour pressure are related to UN GHS No Cat. Chemicals;
- Based on this analysis cut-off values for LogP (>1) and vapor pressure (>3) were specified to identify No Cat. chemicals.

PCA - Biplot



(C)



(C) Initial Defined Approach (DA):

The outcome of the physico-chemical PCA was integrated with a 'bottom-up' testing strategy.

- If LogP is >1 and vapour pressure >3, a No Cat. prediction is made
- If these criteria are not met, an RhCE test is conducted
  - either this RhCE test is "-" and by this confirmation the DA concludes with a No Cat. Prediction ;
  - or the RhCE test is "+", the test chemical is not-No Cat, and no final prediction can yet be made. In this case, the BCOP LLBO allows the final conclusion:
    - if the BCOP LLBO test is "+" a final Cat. 1 prediction is made
    - If the BCOP LLBP test is "-", the test chemical is not-No Cat. and not-Cat. 1, thus a final (by default) Cat.2 prediction is made

Performance of the Initial Defined Approach:

	Initial Defined Approach (Combination Phys-chem. Properties & 2-step Bottom-Up Approach)		
UN GHS (N=62)	**Cat. 1**	**Cat. 2**	**No Cat**
Cat 1 (N = 16)	**81.3%**	18.7%	0%
Cat 2 (N = 14)	28.6%	**64.3%**	7.1%
No Cat (N = 32)	3.1%		**96.9%**