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

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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 CONAIE 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 classifications 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 CONAIE (Consortium for in vitro Eye Irritation testing strategy) project funded by the European Chemical Industry Council (CEFIC) and the CE methods evaluation project (CONAIE: 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 (Mp), vapor pressure (VP) 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 vapour pressure) with a Bottom-Up testing strategy using the in vitro test methods RINCE 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) Bottom-Up testing strategy example

This approach combines:
- Reconstructed human cornea epithelium test method (RICE, 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 Light-based Opacimeter (LLBO) device measured the opacity. One outcome of the CONAIE 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.

(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 vapour pressure (>33) were specified to identify No Cat. chemicals.

(C) Initial Defined Approach (DA):
- The outcome of the physico-chemical PCA was integrated with a 'bottom-up' testing strategy:
  - If LogP > 1 and vapour pressure > 3, a No Cat. prediction is made
  - If these criteria are not met, an RICE test is conducted
    o either this RICE test is "−" and by this confirmation the DA concludes with a No Cat. Prediction;
    o or the RICE 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 Defined Approach (IATA SkinEthic™ Human Eye Test, 2-step Bottom-Up Approach):


1Cat. 1 & Cat. 2 combined
2Cat. 1 & Cat. 2
3Cat. 1
4Cat. 2
5No Cat