The importance of understanding physico-chemical properties of chemicals in the evaluation of serious eye damage/eye irritation: Cosmetic Europe analysis.

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

[1]Cosmetics Europe, Brussels, Belgium, [2]Adriaens Consulting, Aalter, Belgium, [3]L'Oréal R&I, Aulnay France ,, [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

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Introduction

An important part of Cosmetics Europe (CE) eye programme is understanding physico-chemical properties of chemicals and integrating these with *in vitro* test methods to refine / improve performance of testing strategies / approaches to identify serious eye damage / eye irritation. This is in accordance with the OECD guidance document on an Integrated Approach on Testing and Assessment (IATA) for serious eye damage and eye irritation which has recently been adopted and published (OECD 2017). According to this document physico-chemical properties may be used to help orient chemicals to a Top-Down or Bottom-Up approach (Scott et al., 2010). A principal component analysis (PCA) was performed for 130 chemicals to explore the relationship between physico-chemical properties and UN GHS classification of chemicals.

Materials and methods

The 130 chemicals used for this analysis were taken from the CON4EI (Consortium for *in vitro* Eye Irritation testing strategy; 80 chemicals) project funded by the European Chemical Industry Council (CEFIC) and the CE methods evaluation project (50 chemicals). For all chemicals reliable *in vivo* data were available from the CE Draize eye test Reference Database (DRD, Barroso *et al*., 2017) with UN GHS classifications and known drivers of classification.

The selected physico-chemicals properties were molecular weight (MW), molar volume (MolarV) octanol-water partition coefficient (LogP), melting point (Melt), vapor pressure (VapPress), water/lipid solubility (WatSol), surface tension (SurfT), polar surface (PolarS), and number of H bond donors/acceptors (H donors/H acc). Physico-chemical data were retrieved from the following sources: ECHA website for information on chemicals (highest priority); EPA Chemistry Dashboard website; PubChem website; ChemSpider website and other sources such as e.g. Scientific Committee on Consumer Safety (SCCS) opinion publications.

PCA was performed on the following subgroups of chemicals: neat chemicals, neat liquids, neat solids, diluted chemicals (surfactants), subgroups representing different organic functional groups (OFG). For each group, biplots of the first two components for the physico-chemical (max 10) properties are presented.

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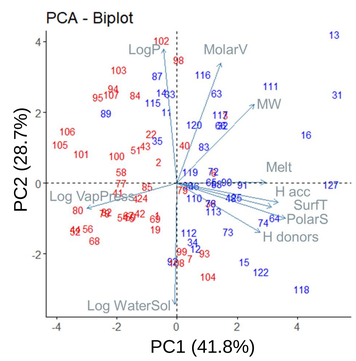
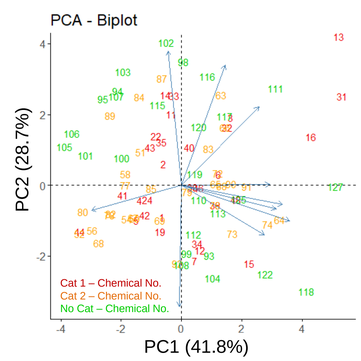
Results & Discussion

PCA – Neat chemicals (n=88)



PC1 separates Liquids (higher Log Vapor pressure) from Solids (higher Melting point).



PC1 & PC2 do not separate GHS categories → separate PCA analysis on subgroups

Interpretation

The first component (PC1), explains about 42% and the second component (PC2) about 29% of the total variation among the chemicals.

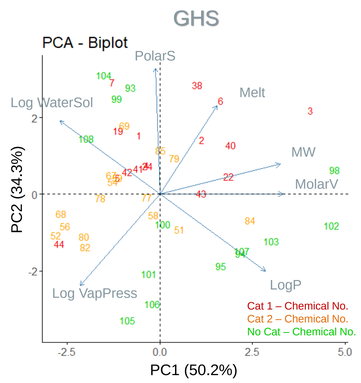
PC1 contrasts melting point, surface tension, polar surface area, number of H bond acceptors and donors of the chemicals (positively correlated with PC1) with log vapor pressure (negatively correlated with PC1).

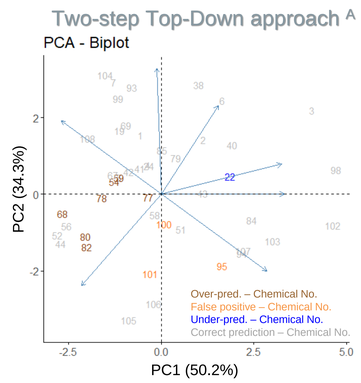
PC2 contrasts LogP, molar volume and molecular weight with log water solubility (e.g. water solubility of chemical #98 is much less then for #99).

Further results from PCA not shown

- Subgroup **solids** (n=57): the physico-chemical properties could not separate UN GHS categories for the subgroup of solid chemicals.
- Subgroup OFG – **carboxylic** (n=22): PC1: water solubility contrasts with LogP, molar volume and molecular weight with a tendency to separate Cat 1/Cat 2 chemicals from No Cat chemicals.
- Subgroup **surfactants** (n=13): molecular weight, water solubility, melting point and polar surface are important physico-chemical properties that can separate chemicals inducing serious eye damage (Cat 1) vs not Cat 1. It is recognized that the dataset is small and more data are needed to confirm these findings.

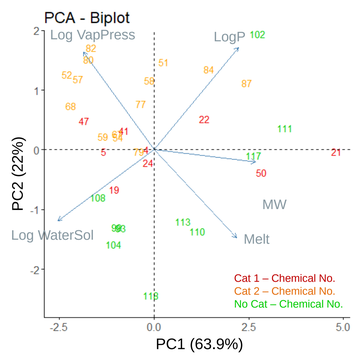
PCA – Neat liquids (n=46)





- Water solubility contrasts with LogP and roughly separates Cat 1 / Cat 2 liquids from No Cat liquids.
- No Cat liquids #93, #99, #104, and #108 are alcohols.
- Cat 1 liquids tend to have a higher melting point whereas Cat 2 liquids tend to have higher vapor pressure.
- [A] Predictions based on a two-step testing strategy, BCOP LLBO / RhCE OECD TG 492 (see poster abstract #307), over-predictions are more frequently observed for liquids with higher vapor pressure.

PCA – Aldehyde, alcohol, ketone & ether w/o carboxylic function OFG (n=33)



- PC1: Molecular weight contrasts with water solubility and is not associated with a separation between UN GHS categories.
- PC2: Vapor pressure and LogP contrasts with melting point and water solubility, chemicals with higher vapor pressure and LogP tending to correspond with Cat 1/Cat 2.
- No. 21: Quinacrine, a solid, is under-predicted by several *in vitro* test methods.

Conclusion

Based on the first two components, it was possible to discriminate: (1) between chemicals requiring and those not requiring classification for serious eye damage/eye irritation or (2) between chemicals inducing serious eye damage (Cat 1) vs not Cat 1. Furthermore, the importance of the physico-chemical properties and discriminative ability differed between subgroups of chemicals.

References

Barroso *et al*., 2017. *Arch. Toxicol*. 91, 521-547. doi: 10.1007/s00204-016-1679-x.

OECD (2017). Guidance Document on an Integrated Approach on Testing and Assessment for Serious Eye Damage and Eye Irritation. Series on Testing and Assessment No. 263. ENV Publications, Organisation for Economic Cooperation and Development, Paris.

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