Defining physicochemical exclusion rules to identify chemicals that do not require classification of serious eye damage/eye irritation: a Cosmetic Europe analysis

Abstract # 383

Nathalie Alépée[1], Takayuki Abo[2], Els Adriaens[3], Dan Bagley[4], Jalila Hibatallah[5], Karsten R Mewes[6], Arianna Giusti[7]

[1] L'Oréal Research & Innovation, [2] Kao Corporation, [3] Adriaens Consulting bvba, [2] Kao Corporation, [4] Colgate-Palmolive, [5] Chanel Parfums Beauté, [6] Henkel AG & Co. KGaA, [7] Cosmetics Europe - The Personal Care Association

Introduction

Cosmetics Europe's (CE) ocular toxicity programme focuses on the development of defined approaches (DA) to identify ocular effects of chemicals. One key outcome of this programme was that combining the results of two OECD adopted *in vitro* test methods (OECD TG 492 and OECD TG 437) with physicochemical properties in a stepwise strategy resulted in an improvement of the specificity, without reducing the sensitivity, when compared to the combination of the *in vitro* methods alone (Alépée et al., 2019).

The selection of the physicochemical properties was based on principal component analysis (PCA). The outcome of this analysis showed that four out of the six investigated physicochemical properties were important for the development of physicochemical property exclusion rules. In a next step, decision trees were used to identify limit values for the physicochemical properties of interest. Table 1 shows for each physicochemical property and for the combination of properties, the proportion of liquids that have this characteristic within each UN GHS category. None of the *in vivo* Cat. 1 and Cat. 2 liquids have the combined properties of LogP > 1 and VP > 3 and ST < 30. As such, the combination of these physicochemical property limits can be used as an exclusion rule to identify chemicals with no serious eye damage or eye irritation potential.

The performance of DAL-1 to distinguish between the three UN GHS categories (Cat. 1: serious eye damage, Cat. 2: eye irritation, and No Cat.) is presented in Abstract #1043. The current poster focuses on the **robustness** of the PCP exclusion rules, in terms of borderline cases that can potentially affect the sensitivity of the DA. Furthermore, the **data sources** (experimental vs predicted values) in terms of agreement of the PCP values and the consequence this has on the decision made was investigated in more detail.

Physicochemical properties for the reference chemicals were extracted from the following sources (listed in order of priority): the European Chemicals Agency (ECHA), the EPA Chemistry Dashboard website, the PubChem website), the ChemSpider website and other sources like e.g. Scientific Committee on Consumer Safety (SCCS) opinions publications. Furthermore, highest priority was given to experimentally derived measurements followed by computational methods (e.g. Quantitative Structure-Activity Relationships (Q)SAR) used to determine physicochemical properties.

Table 1. *Proportion of liquids among the UN GHS categories that have values below (WS and ST) or above (LogP and VP) the physicochemical property limit*

UN GHS	LogP > 1	VP > 3 (mm Hg)	ST < 30 (dyne/cm)	LogP > 1 & VP > 3	LogP > 1 & VP > 3 & ST < 30	WS < 0.02 (mg/mL)
Cat. 1 (N=26)	50%	8%	27%	4%	0%	0%
Cat. 2 (N=34)	50%	21%	41%	3%	0%	6%
No Cat. (N=134)	75%	34%	46%	25%	23%	30%

VP: Vapor Pressure in mm Hg
ST: Surface Tension in Dyne/cm
WS: Water Solubility in mg/mL

Results and discussion

Robustness of the exclusion criteria

The robustness of the exclusion criteria is evaluated for each physicochemical property (PCP) separately. The results are shown in violin plots (Fig. 1 - 4). For VP and WS log-transformed values are shown in the violin plots since the distribution of the original data was very skewed.

- dotted line = cut-off value for the corresponding physicochemical property
- (●) chemicals for which the combination of the 3 PCPs are met (LogP > 1 & VP > 3 & ST < 30)
- (●) chemicals for which 2 out of 3 exclusion criteria are met (LogP, VP, ST)

Interpretation: The red dots (●) visualize the robustness of each PCP. It is not desirable that *in vivo* Cat. 2 or Cat. 1 liquids have values close to the cut-off value since a slightly different value can result in a false negative prediction.

For example (Fig. 1), the dataset contains an *in vivo* Cat. 1 liquid for which the exclusion rules for VP (=127) and ST (=26.4) are met but the LogP = 0.45 (experimentally derived), this is not considered as a borderline case for LogP (cut-off value = 1). The predicted value = 0.55 (OPERA) so clearly < 1.

Fig. 1: Distribution LogP – One *in vivo* Cat. 1 and 6 *in vivo* Cat. 2 liquids have a VP > 3 and ST < 30 with **LogP ≤ 1** (max = 0.77).

Fig. 2: Distribution VP (log-transformed) – Three *in vivo* Cat. 1 and 4 *in vivo* Cat. 2 liquids have a LogP > 1 and ST < 30 with a **VP ≤ 3** (max = 1.92).

Fig. 3: Distribution ST – One *in vivo* Cat. 1 and one *in vivo* Cat. 2 liquid have a LogP > 1 and VP > 3 with a **ST ≥ 30** (min = 42).

Fig. 4: Distribution WS (log-transformed) – The majority of the *in vivo* Cat. 1 and *in vivo* Cat. 2 liquids have WS > 0.02 (log(0.02)= -1.7). None of the *in vivo* Cat. 1 liquids have WS < 0.02, two *in vivo* Cat. 2 lids have a WS < 0.02 (see also Table 1, 2/34 = 6%)

Figs 1 to 4: (●) LogP > 1 & VP > 3 & ST < 30 = exclusion criteria met

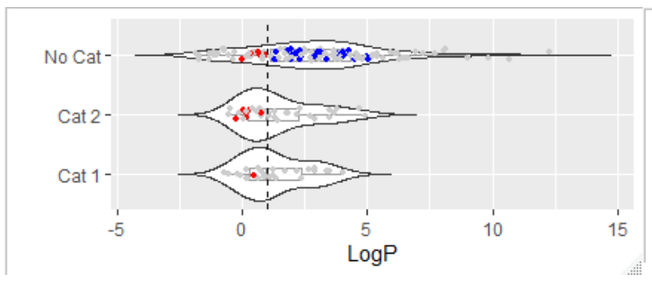

Fig 1 – LogP *(●) LogP ≤ 1 and VP > 3 and ST < 30 and (●) remaining liquids*

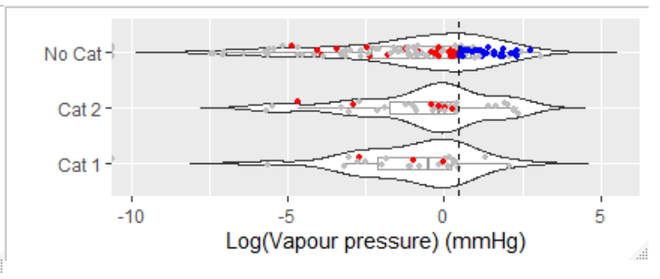

Fig. 2 – Vapor Pressure: *(●) VP ≤ 3 and a LogP > 1 and ST < 30 and (●) remaining liquids*

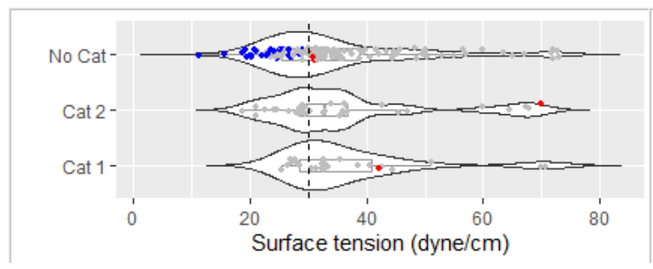

Fig. 3 – Surface Tension *(●) ST ≥ 30 and LogP > 1 and VP > 3 and (●) remaining liquids*

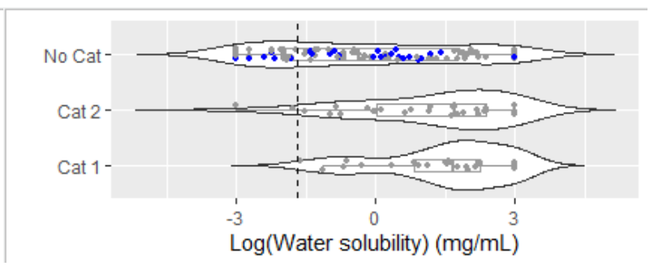

Fig. 4 - Water Solubility*: (●) all other combinations for LogP, VP, and ST*

Impact of the data source – measured or predicted

Fig. 5 shows the relationship between experimentally derived measures values (x-axis) and predicted values (y-axis) for LogP.

- Grey line = line of agreement
- Black line = LOESS line or locally weighted fit; shows the relationship between experimental and predicted values
- Black dotted lines: threshold value used for the exclusion rules (LogP = 1)
- Grey area in the plot: experimental and predicted LogP value are both > 1 or < 1 (agree)
- Red area in the plot: disagreement between the experimental and predicted LogP value

Interpretation:

Background information QSAR OPERA model: the goodness of fit between the observed & predicted LogP values for the OPERA model is 86% (R^2 = 0.86, Training set = 10531 chemicals). Indeed, several dots are close to or on the line of agreement.

For this dataset, experimental values tend to correspond with lower predicted values, especially for higher experimental LogP (> 2.5), LOESS curves under line of agreement. Note that for only 4 liquids the experimental value is > 1 with a predicted value < 1. Since none of the other exclusion criteria were met this had no impact on the specificity of the DA.

The difference between experimental and predicted values can only have an impact for the liquids that fall in the red area of the plot. For LogP, disagreement was observed for 6/98 (6%) liquids. For VP and WS disagreement was observed for 8/118 (7%) and 8/99 (8%), respectively (scatter plots not shown). The analysis was not performed for ST since most of the values (~80%) are predicted values.

When only predicted values for the PCPs were used, none of the *in vivo* Cat. 1 or Cat. 2 liquids did meet the exclusion criteria therefore having no impact on the sensitivity of the DA.

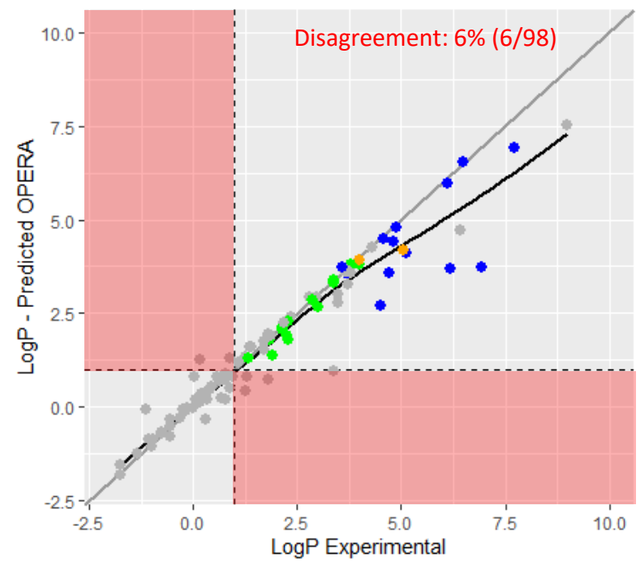

Fig 5. *Experimental vs predicted values for LogP. ● Exclusion rules not met, ● Exclusion rules for LogP, VP and ST met, ● Exclusion rules for WS met ● All exclusion rules met (LogP, VP, ST and WS)*

Conclusion

OECD TG 492	N	% of correctly identified *in vivo* No Cat. liquids	
		in vitro methods only	DAL-1: (PCP & *in vitro*)
SkinEthic™ HCE EIT	46	63%	80%
EpiOcular™ EIT	56	58%	72%

- The combination of physicochemical properties with *in vitro* test methods (OECD TG 492, see left Table) resulted in an increase of the specificity (% of correctly identified *in vivo* No Cat. liquids) of on average 15%.
- Physicochemical exclusion rules are valuable tools to support the identification of UN GHS No Cat. without decreasing the sensitivity of the DA.
- The sensitivity of the DA was not affected when the decision was based on the predicted physicochemical properties only.

Alépée et al., 2019. Toxicol In Vitro; 59:100-114. doi: 10.1016/j.tiv.2019.04.011.

Cosmetics Europe
the personal care association