Synopsis of Original Research Paper

Establishment of a threshold of toxicological concern (TTC) concept for skin sensitization by in vitro/in silico approaches

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Recently, several in *vitro* skin sensitization tests have been listed in the OECD guidelines. The threshold of toxicological concern (TTC) is a threshold value for human exposure that does not show any obvious adverse effects at the lower doses for all chemicals. In this study, we aimed to develop a quantitative prediction model using *in vitro/in silico* dataset and establish a TTC concept for skin sensitization.

The EC3 value, which is the endpoint of the LLNA, was used as the objective variable, and data on 120 substances were extracted from the dataset published by Cosmetics Europe. *In vitro* tests (DPRA, KeratinoSensTM and h-CLAT) data and physico-chemical properties were used as the explanatory variables. A quantitative prediction model for EC3 was developed using support vector regression (SVR), which is a machine learning approach. Predicted EC3 values were used to establish a no expected sensitization induction level (NESIL), and acceptable exposure level (AEL) for each chemical was calculated by dividing NESIL by sensitization assessment factor (SAF). Then by fitting gamma distribution of the AELs using a negative log (10) scale, 95 and 99 percentile probability were calculated as the Dermal Sensitization Threshold (DST) value. Finally, conversion of the DST to the threshold concentration of a women's face cream was done as an example of the application of this concept.

This prediction model was validated by 3-hold cross validation, and the accuracy of prediction of potency class in five categories was 45.8%. Assuming 20% of all chemicals to be skin sensitizers, the DST (μg/cm2) for women's face cream was calculated as 0.129 (99 percentile) and 3.99 (95 percentile), respectively. Furthermore, the threshold concentration of this type of products was calculated as 0.008 % (for DST 99 percentile) and 0.26% (for DST 95percentile). This TTC concept will be useful for the safety evaluation of, for example, impurities in cosmetic ingredients as a non-animal approach.