〈**Regular Article**〉

Establishment of a Threshold of Toxicological Concern Concept for Skin Sensitization by *in Vitro/in Silico* Approaches

Takao ASHIKAGA[1,*], Kaori AMBE[2], Masaharu SUZUKI[2],

Masayuki KURIMOTO[1], Takashi YAMADA[1], Masahiro TOHKIN[2]

Abstract

　　Recently, multiple *in vitro* skin sensitization tests have been listed in the Organisation for Economic Co-operation and Development (OECD) guidelines. The threshold of toxicological concern (TTC) is a threshold for human exposure when chemicals do not show any obvious adverse effects at lower doses. In this study, we aimed to develop a quantitative prediction model using an *in vitro/in silico* dataset and to establish a TTC concept for skin sensitization. The EC3 value, the endpoint of the local lymph node assay (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, KeratinoSens™ and h-CLAT) data and physico-chemical properties were used as explanatory variables. A quantitative prediction model for EC3 was developed using support vector regression (SVR), a machine learning approach. Predicted EC3 values were used to establish no expected sensitization induction level (NESIL), and the acceptable exposure level (AEL) for each chemical was calculated by dividing NESIL by the sensitization assessment factor (SAF). Then, by fitting the gamma distribution of AELs using a negative log (10) scale, the 95th and 99th percentile probability were calculated as the dermal sensitization threshold (DST) value. Finally, the conversion of the DST to the threshold concentration of a women's face cream was performed as an example of the application of this concept.

　　This prediction model was validated by a three-fold cross-validation, and the accuracy of prediction of potency class in five categories was 45.8%. Assuming 20% of all chemicals are skin sensitizers, the DST ($\mu g/cm^2$) for women's face cream was 0.129 (99th percentile) and 3.99 (95th percentile). Furthermore, the threshold concentration of this type of products was 0.008% (for DST 99th percentile) and 0.26% (for DST 95th percentile). The TTC concept for skin sensitization can be applied as a non-animal approach in evaluating the safety profile of cosmetic ingredients.

Key words:　TTC, DST, skin sensitization, machine learning.