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Comparison of ToxTree and the Organisation for Economic Co-operation's (OECD's) QSAR Toolbox for Accurate Predictions of Skin Sensitization

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Background and Purpose: Accurately assessing skin sensitization potential of chemicals is important for understanding risks of using consumer products. Many chemicals extracted from products and identified using non-targeted analysis techniques (*e.g.*, liquid chromatography-mass spectrometry [LC-MS]) are data poor, which creates a need for accurate *in silico* predictions of skin sensitization. The Organisation for Economic Co-operation and Development (OECD) Quantitative Structure-Activity Relationship (QSAR) Toolbox and Toxtree are two software programs that predict skin sensitization potential based on chemical structure. These predictions, known as skin sensitization alerts, are categorized by the anticipated reaction mechanism for skin sensitization. Skin sensitization alerts can be used to inform read-across approaches; however, it has been observed that different *in silico* prediction tools often make different skin-sensitization predictions for the same structure.

Methods: This study compared skin sensitization alerts for over 700 compounds with skin sensitization data using the predictions of three tools: (1) the OECD's QSAR Toolbox protein binding alerts for skin sensitization according to the Globally Harmonized System of Classification and Labelling of Chemicals ("GHS"); (2) protein binding alerts for skin sensitization by OASIS ("OASIS"); and (3) the ToxTree Skin Sensitization Reactivity Domain ("ToxTree"). ToxTree can provide one or more of five possible alerts, while GHS and OASIS can provide one or more of 131 or 111 possible alerts, respectively. The potency for chemicals classified as sensitizers was determined based on values proposed by Gould and Taylor (2011). The potency is based on points of departure (PODs) derived either from mouse local lymph node assay (LLNA) data, as represented by an estimated concentration needed to produce a stimulation index of 3 (EC3) value, or from a no effect level from other types of studies (*e.g.,* guinea pig maximization test, human patch testing, Buehler test) that are then converted to equivalent exposure concentrations. Each of the compounds was classified as a non-sensitizer, weak sensitizer, moderate sensitizer, or strong sensitizer.

Results: Overall accuracy was similar for the three prediction methods (74% for GHS, 72% for OASIS, and 75% for ToxTree). GHS, however, was more accurate in predicting chemicals that were non-sensitizers (91% for GHS *vs*. 78% for ToxTree), while ToxTree was more accurate in predicting sensitizers (49% for GHS *vs*. 70% for ToxTree) based on presence and/or absence of alerts. Most of the compounds (73%) with negative predictions using GHS and OASIS but correct positive predictions using ToxTree triggered alerts as Michael acceptors, and most were weak sensitizers.

Conclusions: Of the three methods, ToxTree may be most effective at avoiding false negatives, though combining methods may be useful for finding potential skin sensitization surrogates. The alerts provided by GHS and OASIS are more specific and, therefore, can be used to search for surrogates that are expected to match the skin sensitization reaction mechanism of the target compound more specifically.