Evaluating a Skin Sensitization Model and Examining Common Assumptions of Skin Sensitizers

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Skin sensitization is an adverse outcome that has been well studied over many decades. It was summarized using the adverse outcome pathway (AOP) framework as part of the OECD work programme (OECD, 2012). Currently there is a strong focus on how AOPs can be applied for different regulatory purposes including the development and application of Integrated Approaches to Testing and Assessment (IATA). One example is an Integrated Testing Strategy developed by Jaworska et al (2013) known as ITS-2 which was derived using a Bayesian network and which relied upon information generated from different *in vitro* and *in chemico* assays that characterized the key events within the AOP. Here we evaluated the performance of the ITS-2 model on a separate set of 50 compounds containing sensitizers and non-sensitizers. We explored replacing TIMES-SS, a commercial expert system with the freely available OECD Toolbox Protein binding alerts and re-deriving the model resulted in comparable predictive performance. We also examined whether penetration, expressed as a percentage of the total amount, is a relevant predictor of skin sensitization potential and potency. General dogma supposes size and hydrophobicity as modelled by MW and LogKow are important parameters for evaluating penetration, with a MW>500 often being cited as a threshold for skin sensitization. Roberts et al (2013) examined the training set within TIMES-SS and the extent to which substances with a MW > 500 were sensitizing. Their dataset was limited with 13 compounds above a MW of 500 and of those only 5 were sensitizers. Here we present preliminary findings using the ECHA REACH dissemination dataset which identified 176 compounds with a MW greater than 500 and of those 31 were sensitizers. The findings confirm those of Roberts et al. (2013) and provide greater confidence that penetration is not a relevant predictor for skin sensitization.

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