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Comparing the Skin Sensitization Potency of Acrylate and Methacrylate Analogs

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Background and Purpose: (Meth)acrylates are chemicals that are present in a wide range of consumer products including adhesives, electronics, paints and coatings, bandages, and cosmetics. Many of these chemicals are skin sensitizers and have the potential to present a biocompatibility concern to the average consumer. While there are many (meth)acrylates used in various products, not all have publicly available experimental sensitization data which can make assessing the sensitization risk of these chemicals difficult. Normally, chemicals lacking toxicity data can be addressed using read-across to analogs but this must be done cautiously. Methacrylates, chemicals with a methyl group adjacent to the acrylate carbon-carbon double bond, are generally thought to be less potent sensitizers than the non-methylated acrylate analog but support for this is not well documented. The objective of our research was to investigate the skin sensitization point of departure (POD) of pairings of acrylates and methacrylates to determine if experimental data support the idea that acrylates are generally more potent sensitizers than the corresponding methacrylate. We also investigated whether predictive toxicity programs account for this difference and lead to accurate predictions of sensitization potency.

Methods: We conducted a search to identify acrylate and methacrylate pairs that have publicly available skin sensitization data. In this search, we focused on identifying pairs that had data from the same type of *in vivo* study with an emphasis on mouse local lymph node assay (LLNA) data. The POD for each type of study was identified and expressed in terms of μg/cm^2, recognized as the relevant dose metric for skin sensitization. PODs were also derived from predictive quantitative structure-activity relationship (QSAR) programs (*e.g.*, Derek Nexus, Organisation for Economic Co-operation and Development [OECD] QSAR Toolbox) to compare to those from the available study data.

Results: Based on the chemical pairings identified, the methacrylate was consistently found to be less potent when compared to the analogous acrylate. This was true for comparisons based on LLNA data as well as for comparisons based on other test types (*e.g.*, human repeat insult patch tests). However, the difference of potency ranged from less than one to two orders of magnitude, suggesting that read across suitability is limited in terms of quantitative potency. There was no apparent difference in chemical properties (*e.g.*, molecular weight) which clearly explained the variability in potency. QSAR-derived PODs demonstrated a similar pattern with methacrylates being less potent than the corresponding acrylates. In some cases, the derived PODs from *in silico* modeling were more potent than those obtained from *in vivo* study data.

Conclusions: The available data lend support to the concept that acrylates are more potent than their methacrylate analogs, although the magnitude of difference cannot be predicted. We also observed a difference between the QSAR-derived PODs and PODs that are based on animal study data. This is due, at least in part, to QSAR models using both acrylate and methacrylate data to derive a predicted EC3 (estimated concentration needed to produce a stimulation index of 3). Scientists evaluating the skin sensitization potential of products containing novel (meth)acrylates should consider these factors when trying to predict skin sensitization risk.