GÖTEBORGS UNIVERSITET

Epoxides as Contact Allergens

Formation, Sensitising Potency and Structure-Activity Relationships

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ABSTRACT

Chemicals in our environment with which we have repeated skin contact can cause skin sensitisation (contact allergy). To trigger an immune response a compound (hapten) must be able to penetrate the skin, where it needs to be reactive enough to bind to proteins and form immunogenic complexes that are recognised as foreign. Electrophilicity has been identified as an important characteristic, which enables haptens to react with nucleophilic amino acids in proteins. In this thesis, a specific type of electrophiles, epoxides, have been investigated. Skin sensitising potencies related to physicochemical parameters have been investigated using structure-activity relationship (SAR) data. Studies on the formation of epoxides by abiotic (air oxidation) and biotic (metabolically in skin) activation from unsaturated compounds and the impact on the sensitising potency of such compounds were also performed.

Cinnamic alcohol, a fragrance and flavouring compound, is a well-known contact allergen. However, it lacks the necessary structural alerts to function as a hapten and must be activated to be able to act as a sensitiser. In this thesis, cinnamic alcohol was used to study the formation of allergenic oxidation products (i.e. epoxides) by air exposure and metabolically. The autoxidation study was performed to gain knowledge regarding stability of cinnamic alcohol upon air exposure, oxidation products and sensitising potencies. The sensitising potency (as examined by the murine local lymph node assay) of cinnamic alcohol after two weeks of air exposure was enhanced about four-fold. Two strongly sensitising compounds, epoxy cinnamic alcohol and cinnamic aldehyde, were detected in the formed oxidation mixture. Thus, for the first time, it was shown that cinnamic alcohol acts as a prehapten. The bioactivation of cinnamic alcohol, using human liver microsomes, resulted in the same oxidation products although the mechanism for their formation is completely different. In addition, epoxy cinnamic aldehyde was detected. Most likely, the two epoxides and cinnamic aldehyde are all contributing to the sensitising potency of cinnamic alcohol whether they are formed outside the skin or in the skin. Up to now, the contact allergenic effect seen from cinnamic alcohol has only been associated with cinnamic aldehyde formed as a metabolite from cinnamic alcohol. The present findings shed new light on the mechanism behind the allergenic effect of cinnamic alcohol and offer explanations to the many clinical cases of contact allergy to cinnamic alcohol not reacting to the aldehyde.

Terminal epoxides are known contact sensitisers present in compounds used in epoxy resin systems (ERS). The most commonly used epoxy resin monomer (ERM), diglycidyl ether of bisphenol A (DGEBA), is causing high rates of occupational contact allergy. Thus, it would be highly advantageous to replace this strongly sensitising compound with less hazardous alternatives, since even a single accidental exposure may induce primary sensitisation to ERM. In this thesis, specially-designed analogues of phenyl glycidyl ether (PGE) and DGEBA, with terminal epoxides intact, were investigated. The results reveal that the design of series of well-defined compounds can give important insights into the SARs thereof and increased knowledge about the structural basis for sensitisation potential. It has been demonstrated, for the first time, how the chemical reactivity and the sensitising potency of terminal epoxides vary with the overall structure of the compound. Using this knowledge regarding SARs of terminal epoxides novel epoxy resin monomers with reduced sensitising potency were achieved for the first time without compromising the technical properties. By modifying the intrinsic reactivity of ERMs, the fundamental and underlying causes of contact allergy to ERS have been addressed. Using these modified analogues with reduced sensitising potency, in addition to regulations and protective clothing, would reduce occupational contact allergy in the future.

Keywords: Allergic contact dermatitis, Autoxidation, Bioactivation, Cinnamic alcohol, Diglycidyl ether of bisphenol A (DGEBA), Epoxide, Epoxy resin, Local lymph node assay, Polymerisation, Peptide reactivity, Prehapten, Prohapten, Sensitisation, Skin, Structure-Activity Relationship, Thermogravimetric Analysis