

Formation of Skin Sensitizers from Fragrance Terpenes via Oxidative Activation Routes

Chemical Analysis, Structure Elucidation and
Experimental Sensitization Studies

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AKADEMISK AVHANDLING

för avläggande av filosofie doktorsexamen i kemi som, med medgivande av Institutionen för kemi, Göteborgs universitet, kommer att försvaras offentligt fredagen den 30 januari 2009 kl. 10.00 i sal KB, Kemigården 4, Göteborgs universitet och Chalmers tekniska högskola. Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent är Dr Andreas Luch, Depts. of Product Safety & Scientific Services, Federal Institute for Risk Assessment, Berlin, Germany

ABSTRACT

The work presented in this thesis emphasizes the importance of considering oxidative activation in the toxicity assessment of fragrance chemicals. Compounds without contact allergenic properties can be activated either via autoxidation in contact with air or via cutaneous metabolism to reactive products which can cause contact allergy. It is important to prevent sensitization as the immunological memory formed in the development of contact allergy persists throughout life. The investigation of compounds susceptible to oxidative activation, thereby forming sensitizing compounds is important in the work of prevention of contact allergy. The overall aim of this thesis was to investigate mechanisms of activation via autoxidation and metabolism of single fragrance compounds and essential oils, and to study the impact of this activation on the contact allergenic activity.

The oxidative activation via autoxidation and cutaneous metabolism of the fragrance compounds geraniol and geranial was studied. It was shown that both compounds were susceptible to autoxidation, forming oxidation products with increased sensitizing capacity compared to the original compound. The oxidation products of geraniol were formed by two separate pathways, corresponding to autoxidation of each of the two double bonds in geraniol, respectively. Hydroperoxides, which previously have been identified as the most important sensitizers in the oxidation mixtures of air-exposed fragrance compounds could not be detected in air-exposed geranial. Instead, a sensitizing epoxide was detected. Geraniol and geranial were also activated metabolically. Many of the metabolites identified were also present in the autoxidation mixtures.

The autoxidation of lavender oil was studied in order to investigate if essential oils possess a natural protection against autoxidation. The results were compared to the results from the autoxidation studies of linalyl acetate and linalool, the main components of lavender oil. It was found that the autoxidation proceeded in the same way in both the pure samples and the lavender oil, and that sensitizing oxidation products were formed in both cases. The most important sensitizers formed were hydroperoxides of linalool and linalyl acetate.

This thesis adds important information on routes of autoxidation as well as on the relationship between metabolic and air induced activation of non- or weakly sensitizing compounds to sensitizers. The results presented here indicate that other fragrance terpenes could be susceptible to oxidative activation via autoxidation or cutaneous metabolism. This should be considered in the risk assessment of fragrance chemicals.

Keywords: autoxidation, contact allergy, cytochrome P450, essential oil, fragrance, hydroperoxide, local lymph node assay, metabolism, predictive testing, sensitization, skin, terpene

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