

Analytical Methodologies for Common Skin Allergens – Organic Thioureas, Isothiocyanates and Fragrance Hydroperoxides in Everyday Life Products

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On 22 March 2018 Ahmed Gamal Ramzi defended his thesis "Analytical methodologies for common skin allergens – Organic thioureas, isothiocyanates and fragrance hydroperoxides in everyday life products" at the Department of Environmental Science and Analytical Chemistry, Stockholm University. Professor Anneli Julander from Karolinska Institute was opponent, Professor Ulrika Nilsson, Stockholm University, was main supervisor and Professor Lina Hagvall, Sahlgrenska Academy at University of Gothenburg, acted as co-supervisor.

The thesis describes analytical methodologies for the determination of important skin-sensitizing chemicals in two types of commercial items: chloroprene rubber and fragrance products, which are both well-known to be associated with contact allergy.

Chloroprene rubber (neoprene®) is widely used in different applications and products, such as bags, gloves, wetsuits, braces, mouse pads etc. Exposure to chloroprene rubber materials has resulted in numerous cases of allergic contact dermatitis. Organic thioureas have been considered the main culprits, even though they at the same time have been classified as weak or non-sensitizers in the murine local lymph node assay (LLNA). Previous findings indicate that a possible reason for sensitization is that organic thioureas are being metabolized in the skin to strong haptens, such as isothiocyanates and isocyanates, after skin exposure. In this thesis, chemical analyses of a number of chloroprene products from the Swedish open market showed the presence of diethylthiourea in all analyzed items, while other organic thioureas could not be detected. The levels of diethylthiourea varied, with the highest at 158 µg/cm in a used back support that had previously caused allergic contact dermatitis in a patient. Furthermore, it was discovered that all the examined items emitted ethyl isothiocyanate. LLNA showed that ethyl isothiocyanate is a strong skin sensitizer, as has been shown earlier for other tested isothiocyanates. Isothiocyanates were shown to be thermally formed from diethyl-, diphenyl- and dibutylthiourea at a temperature as low as 35°C, i. e. around skin temperature. Altogether, the results from these experiments, patch tests and chemical analyses reveal that isothiocyanates are important haptens in contact allergy to chloroprene rubber.

Fragrances constitute one of the main causes of contact allergy, next to nickel and preservatives. The most widespread fragrances in cosmetics and perfumes on the market are monoterpenoid compounds, such as linalool and limonene, which at air exposure easily oxidize to hydroperoxides, that are strongly skin-sensitizing and the main haptens. Despite this, there is so far no EU regulation concerning fragrance hydroperoxides in products, which probably is due to lack of reliable analytical methods. Presented in this thesis is a toolbox of different analytical methods, applied on essential oils, shampoo, patch test preparations and different types of perfumes. Furthermore,



Ahmed Ramzi with the Supervisor Ulrika Nilsson.

one of the studies elucidated the first case (to my knowledge) of allergic contact dermatitis as being associated with fragrance hydroperoxides in a commercial product. The product investigated was a shampoo, heavily fragranced with linalool and shown to contain linalool hydroperoxides.

Taken together, the thesis shows the importance of developing analytical methods to be able to identify, measure and detect important haptens in contact allergy.

LIST OF ORIGINAL PUBLICATIONS

1. Ramzy AG, Hagvall L, Pei MN, Samuelsson K, Nilsson U. Investigation of diethylthiourea and ethyl isothiocyanate as potent skin allergens in chloroprene rubber. *Contact Dermatitis* 2015; 72: 139–146.
2. Ramzy AG, Lammintausta K, Matura M, Bråred Christensson J, Nilsson U, Hagvall L. Isothiocyanates are important as haptens in contact allergy to chloroprene rubber. *Br J Dermatol* 2017; 177: 522–530.
3. Rudbäck J, Ramzy A, Karlberg A-T, Nilsson U. Determination of allergenic hydroperoxides in essential oils using gas chromatography with electron ionization mass spectrometry. *J Sep Sci* 2014; 37: 982–989.
4. Elliot JF, Ramzy A, Nilsson U, Moffat W, Suzuki K. Severe intractable eyelid dermatitis probably caused by exposure to hydroperoxides of linalool in a heavily fragranced shampoo. *Contact Dermatitis* 2017; 76: 114–115.
5. Ramzi A, Ahmadi H, Sadiktsis I, Nilsson U. A two-dimensional non-comprehensive reversed/normal phase high-performance liquid chromatography/tandem mass spectrometry system for determination of limonene and linalool hydroperoxides. *J Chromatography A* 2018; 1566: 102–110.