

Experimental and Clinical Studies on Contact Allergy to Diphenylmethane-4,4'-diisocyanate and Related Substances

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The exposure to isocyanates is more of an occupational problem than a consumer problem. The main route of exposure is assumed to be through inhalation. Isocyanates that have high vapor pressure, such as toluene diisocyanate (TDI), can be airborne at room temperature. Other isocyanates such as diphenylmethane diisocyanate (MDI) are volatile only when heated. Industrial processes that can cause exposure to isocyanates are, for example, spraying or heating. Inhalation of isocyanates can cause disorders of the respiratory tract. Isocyanates are well known to cause direct toxic and irritant effects, such as irritation of the nose, throat, and upper airways and also eye and skin irritation. In animal and human studies, it has been found that isocyanates cause skin sensitization and sensitization of the lung. The sensitization mechanism and metabolism of isocyanates is not fully understood. Concurrent reactions are often seen between different isocyanates and their different corresponding amines. It is not always evident whether the concurrent reactions are due to co-exposure or possible cross-reactivity. Patch test preparations of 4,4'-MDI have been shown to contain only fractions of what is stated. Concentrations of 4,4'-MDI in test preparations decrease rapidly.

The aims of this thesis were: (i) to study the dermal uptake and metabolism of isocyanates by dermal provocation of volunteers with different doses of 4,4'-MDI; (ii) to investigate the sensitizing capacities and cross-reactivity patterns of some common isocyanates and the corresponding amines in order to provide a better understanding of isocyanate contact allergy; and (iii) to investigate the cause behind the rapid decrease in 4,4'-MDI in patch-test preparations.

The main findings were as follows: (i) The distribution after dermal uptake of diphenylmethane-4,4'-diisocyanate (4,4'-MDI) appears to be a slower process than what is seen for airway uptake. Instead, our results indicated that the distribution of 4,4'-MDI in the skin and the subsequent elimination is a slow process, and the proportion absorbed into the skin was approximately half of the amount applied. The main amount absorbed reacts with cell components or forms polyurea and



Haneen Hamada with Associate Professor Erik Zimerson (Main Supervisor), Department of Occupational and Environmental Dermatology, Lund University, Malmö to the left and Associate Professor Lina Hagvall (Opponent), Department of Dermatology, Gothenburg University, Gothenburg, to the right.

is probably released as diphenylmethane-4,4'-diamine (4,4'-MDA) by spontaneous or enzymatic hydrolysis over weeks or months, distributed systemically, and finally eliminated. A proportion of reacted 4,4'-MDI is probably eliminated from the skin upon cellular renewal. Patch testing with freshly made preparations of 2% 4,4'-MDI might lead to active sensitization. Thus, a concentration of 0.5% in pet., which has been recommended by the European Society for Contact Dermatitis (ESCD) based on our results, should be used (Papers I and II). (ii) 4,4'-MDI, 4,4'-MDA, dicyclohexylmethane-4,4'-diisocyanate (4,4'-DMDI), dicyclohexylmethane-4,4'-diamine (4,4'-DMDA), and p-phenylene diamine (PPD) are strong sensitizers among our group of sensitizers. 4,4'-MDI sensitized animals cross-react to 4,4'-MDA and to 4,4'-DMDI and animals sensitized to 4,4'-MDA cross-reacted to 4,4'-DMDA. PPD-sensitized animals showed cross-reactivity to 4,4'-MDA and there was an indication of cross-reactivity to 4,4'-DMDA. 4,4'-MDI-sensitized animals did not show cross-reactivity to PPD, so PPD cannot be used as a marker of 4,4'-MDI allergy. (iii) 4,4'-MDI reacts with water, protein, or other components

found in Freund's complete adjuvant used in the Guinea Pig Maximization Test (GPMT). Aged, pure 4,4'-MDI is instable, even when stored in the freezer. The outcome of 4,4'-MDI sensitization in the GPMT might be affected by the instability of the pure substance and also its reaction with Freund's complete adjuvant. Induction substances should be prepared in close connection with the intradermal injection (Papers III, IV, and V). (iv) Evaporation and reaction with water can be excluded as significant factors for the instability of the 4,4'-MDI patch test preparations. Most data indicate that trimerization and perhaps also dimerization is the main factor influencing this instability. The 4,4'-MDI trimer might be a weak allergen due to the higher molecular weight making it more difficult to penetrate through the skin. Since many patients have been patch tested with aged 4,4'-MDI patch test preparations (where the patients do not react), we can conclude that if the trimer is present, it does not cross-react with 4,4'-MDI (Paper VI).

List of publications

1. Hamada H, Isaksson M, Bruze M, Engfeldt M, Liljelind I, Axelsson S, et al. Dermal uptake study with 4,4'-diphenylmethane diisocyanate led to active sensitization. *Contact Dermatitis* 2013; 66: 101–105
2. Hamada H, Liljelind I, Bruze M, Engfeldt M, Isaksson M, Jönsson B, et al. Assessment of dermal uptake of diphenylmethane-4,4'-diisocyanate using tape stripping and biological monitoring. *Eur J Dermatol* (in print).
3. Hamada H, Bruze M, Zimerson E, Isaksson M, Engfeldt M. Sensitization and cross-reactivity patterns of contact allergy to diisocyanates and corresponding amines. Investigation of diphenylmethane-4,4'-diisocyanate, diphenylmethane-4,4'-diamine, dicyclohexylmethane-4,4'-diisocyanate, and dicyclohexylmethane-4,4'-diamine. *Contact Dermatitis*. 2017 May 29. doi: 10.1111/cod.12809. [Epub ahead of print] PMID: 28555927
4. Hamada H, Bruze M, Zimerson E, Isaksson M, Engfeldt M. Sensitizing capacities and cross-reactivity patterns of some diisocyanates and amines using the guinea pig maximization test. Can p-phenylenediamine be used as a marker for diisocyanate contact allergy? Submitted
5. Hamada H, Bruze M, Zimerson E, Isaksson M, Engfeldt M. Factors affecting the concentration of diphenylmethane-4,4'- diisocyanate in Freund's complete adjuvant. Can they affect the outcome of the guinea pig maximization test? *J Clin Exp Dermatol Res* 2017; 8: 402.
6. Hamada H, Engfeldt M, Bruze M, Isaksson M, Zimerson E. The mystical instability of diphenylmethane-4,4'-diisocyanate (4,4'-MDI) in petrolatum patch test preparations used for diagnoses of contact allergy. In manuscript