

Allergic contact dermatitis from dicyclohexylmethane-4,4'-diisocyanate

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From August 1999 to April 2001, there was an outbreak of severe eczema at a factory manufacturing medical equipment. A glue, mainly based on the isocyanate dicyclohexylmethane-4,4'-diisocyanate (DMDI), was suspected as being the cause of the problem. 16 workers with recent episodes of eczema were patch tested with a standard series, an isocyanate series and work material. The latter consisted of, among other things, the glue, DMDI, and an amine, dicyclohexylmethane-4,4'-diamine (DMDA), which is formed when DMDI reacts with water. 13 patients reacted to DMDI, 9 to 1,6-hexamethylenediisocyanate (HDI) and 4 to isophoronediiisocyanate (IPDI), all of which are aliphatic isocyanates. None reacted to the aromatic isocyanates, diphenylmethane-4,4'-diisocyanate (MDI) or toluenediisocyanate (TDI). One explanation for this pattern could be that aromatic diisocyanates are more reactive than the aliphatic ones and that, therefore, they are inactivated before penetrating the skin. 5 patients reacted to DMDA and 5 to 4,4'-diaminodiphenylmethane (MDA). Concurrent reactions to DMDA and or MDA with DMDI could be due to cross-reactivity. The positive reactions to MDA could also be a marker of MDI exposure. Yet another patient, investigated in 1997 with suspected work-related contact dermatitis from the glue, is described. She, however, showed no positive reactions to any isocyanates.

Key words: dicyclohexylmethane-4, 4' diisocyanate; allergic contact dermatitis; CAS 1761-71-3; CAS 5124-30-1; contact allergy; DMDI; methylenebis(4-cyclohexylisocyanate); occupational; polyurethane. © Blackwell Munksgaard, 2003.

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Isocyanates, chemicals with the general formula $R-(N=C=O)_n$, are widely used in the plastics industry due to their ability to form polyurethane (PUR) upon addition reaction with multifunctional alcohols (polyols). Generally, the polyols are polyesters or polyethers with terminal OH groups, or castor oil or tall oil with secondary OH-groups (1). There is a wide range of PUR products, ranging from rigid and flexible foams to elastomers (rubber), lacquers and adhesives. The properties of PUR products vary depending upon the raw materials, such as isocyanates, polyols, catalysts, ultraviolet stabilizers, antioxidants, blowing agents, cross-linkers, etc., used. Depending on the molecular structure, isocyanates can be divided into 2 groups, aromatic and aliphatic. Aliphatic isocyanates are considerably more expensive than aromatic, and they account for less than 5% of the isocyanate market. They, however, are used in the manufacture of colour-stable PUR for coatings and elastomer applications, because the aromatic isocyanates undergo

oxidative discoloration upon exposure to light and moisture (2).

In a company manufacturing medical equipment, there was an outbreak of dermatitis among the workers. A glue mainly based on the aliphatic isocyanate dicyclohexylmethane-4,4'-diisocyanate (DMDI), synonymous with hydrogenated methylene-4,4'-diphenyldiisocyanate (HMDI) (Fig. 1), was suspected as being the cause of the problem. About 100 persons worked in the department where the glue was handled, and from August 1999 to April 2001, 16 workers were referred to us because they had developed work-related skin lesions that were suspected to be caused by the glue. The glue and the polyol were stored in barrels connected to hoses in a

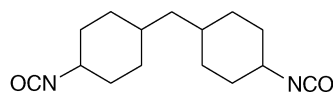


Fig. 1. Dicyclohexylmethane-4,4'-diisocyanate (DMDI).

separate room. They were mixed and transferred into the production area, where about 100 g was used for each produced unit. The polyol and glue mixture was evenly distributed by centripetal forces by rotating the product in a centrifuge. Thereafter, it was cured by heating the product to 55°C for 25 min. There was potential skin exposure both when connecting the hoses to new barrels of raw material and at the stage in the process where the polyol and isocyanate glue were dispensed into the product. The area around this part of the process was contaminated. Of the 16 workers investigated, 3 patients (nos. 1, 3 and 10; Table 1) are discussed in more detail: patient no. 1, because her problems were the origin of the investigation; patient nos. 3 and 10, because their histories are good descriptions of the contact allergic potency of DMDI.

Patients

Case no. 1

In August 1999, the company experienced an accident in a centrifuge. The breakdown occurred because someone had probably forgotten to add hardening polyol to the isocyanate glue, which resulted in a massive contamination of the centrifuge. 4 employees participated in the cleaning of the centrifuge. A few days after cleaning the centrifuge, a 41-year-old woman developed eczematous dermatitis on the hands, arms and face, and her ears became swollen. She was referred to the Karlskrona

branch Department of the Department of Occupational and Environmental Dermatology in Malmö for clinical investigation and patch testing. About a month after the breakdown, she was tested with a standard series and an isocyanates series.

In connection with the investigation, she called attention to the fact that several employees at the factory complained about skin problems mainly located on the face and on the arms and trunk. Therefore, in late September 1999, a physician and chemists from our department conducted a site visit to the factory. Samples of work material, such as gloves, soaps, protection coats, isocyanate glue and polyol, were collected, as well as material safety data sheets (MSDSs) for each product. The MSDS for the isocyanate glue stated that it contained about 5% toluenediisocyanate (TDI), which can be found in the isocyanates series mentioned above, and about 70% DMDI, which is not included in this series.

Case no. 3

A 30-year-old man worked nearby the centrifuge at the time of the breakdown but did not participate in the cleaning. Nevertheless, a few days after the accident, he developed an itchy rash on the forehead and on the arms. He was patch tested, and when he removed the patch with DMDI, he accidentally got some of the test substance on his fingers. He then scratched himself under the right eye and on his nose, which resulted in well-defined dermatitis at these locations.

Table 1. Patients examined as well as positive reactions, employment time before elicitation and site of lesion

Patient	Sex	Contact allergy	Employment duration before elicitation	Site of lesions
1	Female	MDA, IPDI, HDI, DMDI and isocyanate glue	3 weeks	Neck, ears, face, upper arms and wrists
2	Male	MDA, HDI, DMDI, DMDA and isocyanate glue	4 weeks	Arms, ears and left thigh
3	Male	MDA, HDI, DMDI and isocyanate glue	2 weeks	Arms and face
4	Male	Balsam of Peru, MDA, IPDI, HDI, DMDI, isocyanate glue, protection coat and gloves	4 weeks	Arms, face, ears and the dorsal left hand
5	Male	Epoxy resin, IPDI, HDI and DMDI	6 weeks	Arms and face
6	Male	—	?	Nummular eczema on arms and legs
7	Female	Nickel, DMDI and isocyanate glue	2.5 years	Face and neck
8	Female	DMDI and isocyanate glue	5 weeks	Face, ears and neck
9	Male	DMDI and isocyanate glue	3 weeks	Face, ears and forearms
10	Female	MDA, IPDI, IPDA, HDI, DMDI, DMDA isocyanate glue	11 months	Face, ears and forearms
11	Male	HDI, DMDI and isocyanate glue	5 weeks	Forearms and thighs
12	Male	—	?	Dry skin
13	Male	DMDI, DMDA and isocyanate glue	4.5 years	Face and trunk
14	Male	HDI, DMDI, DMDA and isocyanate glue	8 months	Arms and sides of trunk
15	Female	HDI, DMDI, DMDA and isocyanate glue	4 years	Neck, face and ears
16	Male	—	4 years	Trunk and arms
17	Female	Potassium dichromate, nickel and Euxyl K400	1 year	Face, forearms and knee

DMDA = dicyclohexylmethane-4,4'-diamine; DMDI = dicyclohexylmethane-4,4'-diisocyanate; HDI = 1,6-hexamethylenediisocyanate; IPDA = isophorone diamine; IPDI = isophoronediiisocyanate; MDA = 4,4'-diaminodiphenylmethane.

Case no. 10

A 33-year-old woman worked as an analytical chemist, mostly involved in method development. In connection with the cases of contact allergy from the isocyanate glue, she was, in January 2000, designated to analyse this particular glue. About a month later, she developed dermatitis, mainly situated on the ears, cheeks and chin.

Materials and Methods

During the period from August 1999 to April 2001, 16 of about 100 employees working in the department that used the DMDI-based glue sought medical assistance for skin problems and were consequently referred to the Karlskrona branch department and patch tested with the department's standard series and isocyanates series, as well as with a series of work materials. The standard series used at the time comprised of the European standard series excluding clioquinol, *N*-isopropyl-*N'*-phenyl-4-phenylenediamine and lanolin alcohol, supplemented with black rubber mix, Germall II, Amerchol L-101, caine mix II, lichen acid mix and tosylamide/formaldehyde resin, ethylenediamine dihydrochloride and carba mix. The isocyanates series used comprised the isocyanates series from Chemotechnique Diagnostics (Malmö, Sweden), supplemented with DMDI (Aldrich Chemical Company Inc., Milwaukee, WI, USA) and its corresponding amine, dicyclohexylmethane-4,4'-diamine (DMDA) (Fluka Chemie GmbH, Buchs, Switzerland), synonymous with hydrogenated methylene-4,4'-diphenyldiamine (HMDA). Consecutive dermatitis patients at the Department of Occupational and Environmental Dermatology in Malmö served as controls and were patch tested with DMDI 1% w/w petrolatum (pet.) and DMDA 0.1% pet. and 0.5% pet. Patch testing was performed using the Finn Chamber (Epitest Ltd. Oy, Tuusula, Finland) on Scanpor (Norgesplaster A/S, Vennesla, Norway) tape technique fixed with Scanpor or Medipore™ (Healthcare 3M, Borken, Germany) tape. Patch tests were removed after 2 days by the patient and read after 1 day, according to International Contact Dermatitis Research Group criteria (3). In 7 cases, a 2nd reading was done 7 days after the initial application of patches.

Patient no. 17 (Table 1) had been referred to the Karlskrona branch department 2 years earlier in April 1997, with skin lesions on locations similar to those described by the workers investigated during the period from August 1999 to April 2001. She was tested with the standard series previously described, a plastics and glues series

(Chemotechnique Diagnostics) and an isocyanate series (Chemotechnique Diagnostics), as well as with preparations of DMDI and DMDA. She, however, was not tested with any work material.

Results

Contact allergy from the isocyanate glue was demonstrated in 13 patients. Additionally, they all reacted to the main constituent of the glue, that is DMDI, while none reacted to the other constituent, TDI. In 4 patients no work- or isocyanate-related allergy could be demonstrated. 5 patients showed simultaneous reactions to DMDI and DMDA. In several cases, the patients also showed multiple reactions to 1 or more preparations of the isocyanate series. 9 patients also reacted to 1,6-hexamethylenediisocyanate (HDI), 4 to isophoronediiisocyanate (IPDI), 1 to isophorone diamine (IPDA) and 5 to MDA. Table 1 lists the positive reactions to each of the tested patients as well as sites of lesions and the duration of employment before elicitation. In Table 2, the number of positive reactions to each preparation of the isocyanate series is listed.

Discussion

It has been suggested by Emmet (4) that aromatic diisocyanates are strong respiratory sensitizers but weak cutaneous sensitizers. In Fisher's Contact Dermatitis 5th edition (5), this view is expanded to suggest that the opposite might be true for the aliphatic diisocyanates. This is in accordance to our observations. None of the 17 patients tested showed positive patch-test reactions to the aromatic diisocyanates MDI and TDI and neither did they show any respiratory symptoms. 4 patients, however, showed positive patch-test reactions to IPDI, 9 to HDI and 13 to DMDI, all of which are aliphatic diisocyanates. We believe that one explanation for this pattern could be that aromatic diisocyanates are chemically more reactive than aliphatic. Therefore, they might react before penetrating the skin and thereby their allergic potential diminishes.

In a recent report by Frick et al. (6), it is proposed that positive reactions to isocyanates appear late and that a 2nd reading on day 7 (D7) is preferable. In this investigation, 7 patients (nos. 3, 4, 5, 6, 9, 12 and 16) were read on both D3 and D7, while the others were read only on D3. In the 7 patients read twice, 1 case of contact allergy to MDA (patient no. 4), 1 case of contact allergy to IPDI (patient no. 5) and 1 case of contact allergy to DMDI and isocyanate glue (patient no. 9) would have been missed if there had been only 1 reading.

Table 2. Number of positive reactions to each preparation

Chemical/product	Concentration (w/w percentage pet.)	No. positive (total no. of tested)
Toluenediisocyanate	2	0 (17)
Diphenylmethane-4,4'-diisocyanate	2	0 (17)
4,4'-Diaminodiphenylmethane	0.5	5 (17)
Isophoronediiisocyanate	1	4 (17)
Isophorone diamine	0.1	1 (17)
1,6-Hexamethylenediisocyanate	0.1	9 (17)
Dicyclohexylmethane-4,4'-diisocyanate	1	13 (17)
Dicyclohexylmethane-4,4'-diisocyanate	0.1	13 (17)
Dicyclohexylmethane-4,4'-diisocyanate	0.01	5 (12)
Dicyclohexylmethane-4,4'-diamine	0.5	4 (5)
Dicyclohexylmethane-4,4'-diamine	0.1	5 (17)
Dicyclohexylmethane-4,4'-diamine	0.01	1 (12)
Isocyanate glue	2	13 (17)
Isocyanate glue	0.2	13 (17)

In many reports on contact allergy to isocyanates, simultaneous patch-test reactions to MDI and MDA have been described. The suggested explanation is either cross-reactivity or an exclusive sensitization to MDA that results in a positive patch-test reaction to MDI that is not directed to MDI itself but to MDA formed when MDI reacts with water, i.e. on or in moist skin (1, 7–10). To test whether DMDI relates to its corresponding amine, DMDA, in a similar way, we also performed patch testing with DMDA. Up until December 2000, 10 DMDI-sensitive patients had been patch tested with DMDA 0.1% pet. 1 showed a positive reaction. It was suspected that the concentration was too low, leading to false-negative test reactions, and hence the concentration was raised to 0.5% pet. Thereafter, another 5 patients were tested, and 4 of these were positive to DMDA as well as to DMDI. Although all these 4 also reacted to DMDA 0.1% pet., we still recommend that 0.5% pet. is used to prevent false-negative test reactions.

5 patients showed simultaneous reactions to DMDI and MDA. 2 of these also had concurrent reactions to DMDA. To our knowledge, none had had prior contact with MDA. The pattern of simultaneous reactions to DMDI and MDA has been reported before by Emmet (4) and also by Malten (11). Emmet tested 2 employees who worked at a PUR moulding plant and who had eczema on the forearms and face. They showed positive reactions to both DMDI and MDA. MDA was used as a catalyst in the process. In Malten's article, however, the chemical engineer, with dermatitis on the face and forearms and who showed the same pattern of reaction, had had no prior contact with MDA. It was suggested that the concurrent reactions could be due to an immunochemical relation between the 2 substances

in the same way that MDI and MDA are thought to relate. Frick et al. (6) described yet another case of concurrent reactions to DMDI and MDA, where a man working as an operator by a machine spraying MDI-based lacquer upon boards for flooring showed positive reactions to the lacquer as well as to MDA and DMDI. The operator had had no known prior contact with DMDI. Goossens et al. (12) reported 22 cases diagnosed as occupation-related contact dermatitis from isocyanates and PUR products, where 10 patients with allergic contact dermatitis from isocyanates showed concurrent reactions to MDA. 9 patients reacted only to MDA and not to the isocyanate to which they were exposed. These authors suggest that MDA may be an important marker of isocyanate sensitivity. Estlander et al. (1), as well as Frick et al. (6), support this suggestion, at least for MDI sensitivity. In fact, it is possible that the positive reactions to MDA seen among our 5 patients are markers of MDI sensitivity, as there was potential exposure to MDI at the company but not to MDA.

3 of the patients also reacted to IPDI and 1 reacted to both IPDI and IPDA. As far as we know, none had had contact with these substances before. Cross-reactivity between IPDA and IPDI has been described previously by Lachapelle (13), who reported 4 patients with known contact allergy to IPDA who also reacted to IPDI upon patch testing.

9 of our patients reacted to HDI. Animal experiments on the basis of mouse-ear swelling tests showed that HDI was the most potent sensitizer, followed by DMDI, MDI and TDI in declining order of potency (14). To our knowledge, however, none of our patients had had any prior contact with HDI.

8 of the employees at the company who developed contact dermatitis from DMDI had all been

recently employed. When they were educated about isocyanates, the emphasis was upon the respiratory health effects rather than the potential cutaneous health effect. The company had also done air measurements of various isocyanates but had neglected to measure DMDI. Air measurements of this isocyanate, however, could give a false feeling of security, because it has a rather low vapour pressure compared with many other common isocyanates such as TDI and HDI and therefore only small amounts can be expected in the air. When measurements of DMDI were done later, no DMDI could be detected in the air. Hence, although precautions were taken to avoid inhaling isocyanates, very few were taken to avoid contamination of the skin while handling the isocyanate mixture. At the site visit, we observed that several machines and tools were contaminated. The workers, who wore gloves, often touched themselves on the face when adjusting the compulsory hairnet. This could probably explain why almost everyone who was examined showed eczema located on the face and swelling of the ears. Furthermore, their safety coats were contaminated with the glue and there were not enough coats for everyone, so they were shared among the workers.

DMDI seem to be a very potent skin sensitizer, and besides the above-mentioned reports, King (15) and White et al. (16) have also reported cases of contact allergy to it. King (15) described the case of a 23-year-old student who, just a few days after starting a project on PUR foam, developed rashes on her forehead, neck and ears. He suggested the reaction to be due to an initial irritant contact dermatitis, followed by secondary development of allergic contact dermatitis. White et al. (16) patch tested 7 female workers at a factory that made car badges. Within 6 months of a new process being introduced, they had all experienced rashes on their arms and faces. 2 showed positive reactions to DMDI. It was also believed that irritant contact dermatitis from DMDI was the cause of 3 workers' skin problems. Furthermore, Israeli et al. (17) have reported on a factory where DMDI was used to coat glass bottles and where 11 of 15 workers developed rashes 4–7 days after being exposed. They were not patch tested.

DMDI has been reported as a strong sensitizer in several reports, and it is evident that extreme

caution is necessary when working with products containing this substance.

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