

Occupational contact allergy to monomeric isocyanates

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Summary

Background. The monomeric isocyanates diphenylmethane diisocyanate (MDI), 2,4-toluene diisocyanate (TDI), isophorone diisocyanate (IPDI) and 1,6-hexamethylene diisocyanate (HDI) are used in polyurethane products and sometimes cause contact allergy.

Objectives. To describe patients with isocyanate contact allergy in an occupational dermatology clinic.

Methods. Test files were screened for allergic reactions to isocyanates and 4,4'-diaminodiphenylmethane (MDA). Patients with allergic reactions to some of the allergens were analysed for occupation, exposure, concomitant reactions to other allergens, and diagnosis.

Results. Over a period of almost 13 years, 54 patients reacted to isocyanates (9 to IPDI, 12 to MDI, 6 to TDI, and 1 to HDI) or MDA (44 patients). The motor vehicle, electronics and paint industries, and painting and construction work, were among the most significant occupational fields. An in-house polymeric MDI (PMDI) test substance was superior to commercial MDI preparations. About half of the occupational cases related to MDI products were diagnosed by testing MDA. The most prominent cause of IPDI allergy comprised polyurethane paint hardeners. Some of the IPDI reactions could be explained by cross-allergy to isophoronediamine in epoxy products. Specific exposure to MDA was difficult to trace.

Conclusions. MDA and PMDI test substances were significant in the diagnosis of MDI contact allergy.

Key words: diaminodiphenylmethane; diphenylmethane diisocyanate; hexamethylene diisocyanate; isophorone diamine; isophorone diisocyanate; phenylisocyanate; toluene diisocyanate.

Isocyanates are highly reactive compounds that are used in the production of polyurethane. On a worldwide scale, polyurethane products are most commonly based on two aromatic isocyanates, diphenylmethane diisocyanate

(MDI; containing mostly 4,4'-MDI (CAS 101-68-8; Fig 1) and possibly 2,4'-MDI (CAS 5873-54-1)) and toluene diisocyanate (TDI; Fig. 1, which is usually a mixture of the 2,4-TDI (CAS 584-84-9) and 2,6-TDI (CAS 91-08-7) isomers). MDI and TDI are mainly used in paints and other surface coatings, glues and adhesives, castings, and soft and rigid foams. Aliphatic isocyanates such as isophorone diisocyanate (IPDI; CAS 4098-71-9; Fig. 1) and 1,6-hexamethylene diisocyanate (HDI; CAS 822-06-0; Fig. 1) are used in products requiring light and weather resistance. Isocyanates are a prominent cause of occupational asthma (1). Allergic contact dermatitis caused by isocyanates is less frequently reported (2–6).

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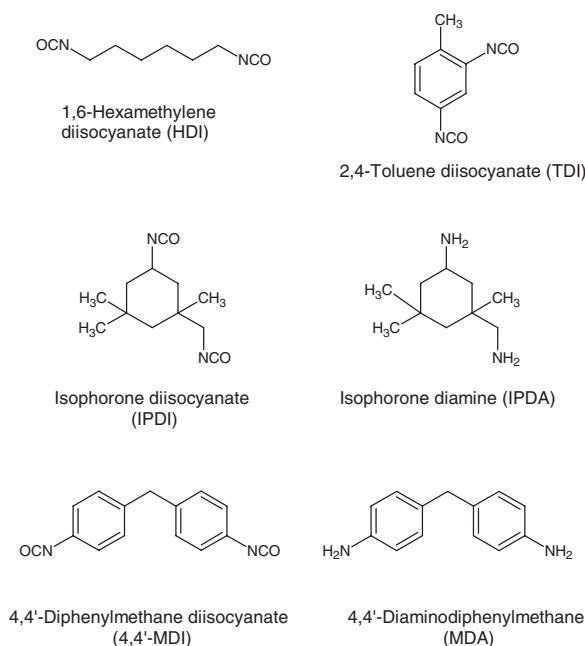


Fig. 1. Chemical structures of monomeric isocyanates and 4,4'-diaminodiphenylmethane.

The objective of the study was to describe sensitization to the monomeric diisocyanates MDI, TDI, IPDI and HDI in patients examined for suspected occupational skin disease at the Finnish Institute of Occupational Health over a period of almost 13 years (1998–2010). As an important marker of MDI hypersensitivity, we studied 4,4'-diaminodiphenylmethane (methylene dianiline; MDA; CAS 101-77-9; Fig. 1) together with the monomeric diisocyanates (7, 8).

Methods

We performed the patch tests with Finn Chambers® (Epitest Ltd Oy, Tuusula, Finland), according to the recommendations of the International Contact Dermatitis Research Group. We read the tests two or three times, on D2, D3, and D4, on D2, D3, and D6, or on D2 and D5, depending on the day of application. We asked patients to inform us of whether they had noticed new reactions after the final reading. All patients at the Finnish Institute of Occupational Health are suspected of having an occupational skin disease. They come from all parts of Finland.

We screened the test files from March 1998 to November 2010 for allergic reactions to MDI, TDI, HDI, IPDI, and phenylisocyanate. These compounds were included in a separate 'isocyanate series'. MDI was concomitantly tested with two preparations, an

in-house substance at 2% concentration and a commercial preparation at 1% concentration. Reactions to MDA were similarly screened. The providers of the test materials varied, and the concentrations and the numbers of tested patients and allergic reactions for each test substance are shown in Table 1. We tested MDA in rubber chemicals, epoxy, and plastic and glues series. The clinical records of all patients with at least one allergic reaction (+/++/+++) to any of the compounds were analysed for occupation, symptoms, material safety data sheets (MSDSs), results of the chemical analyses of the patients' own products, patch test reactions to their own products, and diagnosis.

For chemical analyses, we extracted the test material with acetonitrile to remove the diisocyanates from the test preparations. The extract was added to a solution of acetonitrile containing an excess of 1-(2-methoxyphenyl) piperazine. We analysed the formed urea derivatives by liquid chromatography–mass spectrometry (LC-MS). The LC-MS apparatus was a TSQ Quantum (Thermo Fischer Scientific, San Jose, CA, USA), and the column was a Waters Symmetry C18 (5 µm, 150 cm × 2.1 mm; Waters Corp., Milford, MA, USA). Except for the apparatus, the analytical method was the same as described by Boutin et al. (9).

Results

During the study period, 345 patients were tested with the isocyanate series, and 23 (6.7%) of them reacted positively to at least one isocyanate monomer [12 (3.5%) to MDI, 9 (2.6%) to IPDI, 6 (1.7%) to TDI, and 1 (0.3%) to HDI; 4 tested positive to more than one isocyanate]. Table 1 shows the numbers of positive reactions to different test substances, and Fig. 2 shows the patterns of concomitant reactions to different MDI test substances and MDA. The clinical details of the isocyanate-positive patients are shown in Table 2.

During the study period, MDA was tested in a total of 1277 patients, 44 (3.3%) of whom had an allergic reaction. One patient was not tested with MDA because of previously diagnosed MDA allergy (patient 3 in Table 2). Of these 45 MDA-allergic patients, 25 were tested with isocyanates, and 13 of them reacted positively to at least one isocyanate monomer (patients 1–8 and 10–14 in Table 2). One of the patients (no. 10) has previously been reported on in detail (10). Of the 12 MDI-positive patients, only one was negative for MDA (no. 9). Thirteen MDA-positive patients with no allergic reactions to isocyanates, but with clear or possible exposure to polyurethane products, are shown in Table 3. In the first 9 patients, the MDA reactions were related to occupational exposure to polyurethane products. Nineteen MDA-positive patients

Table 1. Providers and concentrations of test materials, numbers of patients tested with individual test substances, and allergic reactions to each test substance

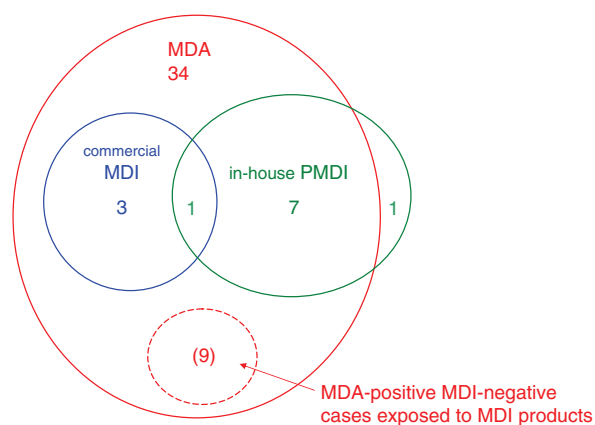
Allergen	Provider	Concentration	Number of patients tested	Number of allergic reactions (%)	Negative reactions when another MDI test substance was positive
4,4'-Diphenylmethane diisocyanate (4,4'-MDI)	Trolab ^a	1% pet.	222	4 (1.8)	1
4,4'-Diphenylmethane diisocyanate (4,4'-MDI)	Brial ^b	1% pet. ^b	124	0	6
Polymeric diphenylmethane diisocyanate (PMDI)	In-house test substance	2% pet.	345	9 (2.6)	3
4,4'-Diaminodiphenyl methane (MDA)	Trolab ^c	0.5% pet.	780	33 (4.2)	—
4,4'-Diaminodiphenyl methane (MDA)	Chemotechnique ^c	0.5% pet.	768	18 (2.3)	—
Hexamethylene diisocyanate (HDI)	Chemotechnique	0.1% pet.	344	1 (0.3)	—
Isophorone diisocyanate (IPDI)	Chemotechnique	1% pet.	344	8 (2.3%)	—
Toluene diisocyanate (TDI)	Trolab ^d	1% pet.	221	3 (1.4)	—
Toluene diisocyanate (TDI)	Brial	1% pet.	124	3 (2.4)	—
Phenyl isocyanate	Brial	0.1% pet.	344	0	—

^aChanged to Brial's test substance in December 2005.

^bThis test substance was analysed twice: in November 2010 it contained 0.3% 4,4'-MDI, and in April 2011 (10 months before the expiry date, February 2012) it contained 0.0035% 4,4'-MDI; no other monomers or oligomers were detected.

^cMDAs from the two providers were used concomitantly in different test series, and a large number of patients were tested with the two preparations.

^dChanged to Brial's test substance in December 2005.

**Fig. 2.** The patterns of concomitant reactions to diphenylmethane diisocyanate (MDI) test substances [commercial 4,4'-MDI and in-house polymeric MDI (PMDI)] and 4,4'-diaminodiphenylmethane (MDA).

with no known exposure to isocyanates are not described in detail. Although 4 of these were diagnosed as having occupational allergic contact dermatitis caused by epoxy compounds, we were not able to show specific exposure to MDA in any of these 19 patients. However, 9 of them had contact allergy to the para-amino compounds *p*-phenylenediamine (PPD), caine mix III, or *N*-isopropyl-*N*-phenyl-4-phenylenediamine. In the whole group of the 45 MDA-positive patients, 13 (29%) had PPD contact allergy.

Discussion

In the present study, we analysed a total of 55 patients with allergic reactions to MDI, MDA, TDI, IPDI, or HDI. The occupational cases of isocyanate allergy comprised several workers in the motor vehicle and electronics industries, and also workers involved in the use or manufacture of polyurethane paints. We had no laboratory technicians, which is the most common occupation in Belgium for workers suffering from isocyanate allergy (4). The most common products causing isocyanate contact allergy were hardeners for glues, foams, paints, coatings, and cast polyurethane. The most common locations of occupational dermatitis were the hands and forearms, but the face was also commonly affected. In a recent report from a general dermatology clinic, facial symptoms were more common among TDI-positive or IPDI-positive cases than among MDA-positive or MDI-positive ones (6). In our study, no difference was noted when MDI-positive patients were compared with IPDI-positive or TDI-positive cases, but facial symptoms were not so common in patients reacting only to MDA.

MDI/MDA

MDI reactions were more common than reactions to other isocyanates, which is in accordance with the fact that MDI represents more than half of the worldwide total production of isocyanates (11). The numbers of MDI/MDA-related cases have also been high

Table 2. Patients with allergic reactions to monomeric isocyanates: their occupation, patch test reactions, location of dermatitis, exposure, and diagnosis

Patient no.	Occupation	Patch test reactions to isocyanates	Patch test reactions to amines corresponding to the positive isocyanates	Exposure data and reactions to patients' own products	Location of dermatitis (in parentheses when no relation to isocyanates or corresponding amines)	Reactions to other allergens	Diagnosis
1	Compositor of printed circuit boards	MDI 1% ++ (T) MDI 2% ++ (O)	MDA ++ IPDA —	Solder paste Heraeus type LP 16939/96 (D3 5% —): 0.03% MDA ^a no MDI ^a , air analysis in work simulation with the paste: 2 µg/m ³ MDA ^a Protective lacquer for circuit board Hysol PC 28 STD/PC28 (5% —, 2% —): urethane prepolymer 35% ^b , TDI < 0.009% ^b , 0.01% MDA ^a , no MDI ^a Urethyl (4% ++, 2% ++, 1% ++): 100% MDI ^b ; used in the production of PU insulation material Epoxy hardener A: MDA 24 ppm ^a PU dust: MDA 5 ppm ^a	Eyelids	Nickel sulfate ++, cocamidopropyl betaine +	OACD from MDA and MDI (previous exposure to MDI could not be excluded)
2	Electronics engineer	MDI 1% ++ (T) MDI 2% — (O)	MDA +++		Forearms	—	OACD from MDI in electronic assembly work
3	Boat builder	MDI 1% + (T) MDI 2% — (O)	MDA NT (previously positive)		No present symptoms Previous face dermatitis when preparing PU insulation foam (One hand)	—	OCA to MDI in the manufacture of PU foam
4	Electrical fitter	MDI 1% + (T) MDI 2% — (O)	MDA ++	PU foam at home No exposure to MDI or MDA found at work	(Hands and axillae)	—	OICD from oils and lubricants CA to MDI and MDA
5	Train carriage fitter Carriage repair	MDI 1% — (T) MDI 2% ++ (O) TDI ?+ (T)	MDA ++	No exposure to MDI or MDA found		PPD ++, IPPD +++, DPPD ++, phenyl cyclohexyl PPD +++, phenyl-β-naphthylamine ++, disperse orange 3 +++, disperse orange 1 +++, aminocazobenzene +++, basic red 46 ++, phenyl-α-naphthylamine ++, Myroxylon pereirae ++, fragrance mix ++	OACD from rubber chemicals CA to MDI
6	Painter	MDI 2% ++ (O) MDI 1% — (B) HDI 7+	MDA ++	No exposure to MDI, MDA or isocyanates found at work Had used PU foam at home, but no symptoms at that time	Hands, forearms, and face	Nickel sulfate ++	OICD from solvents and dusts CA to MDI
7	Carpet installer	MDI 1% — (B) MDI 2% +++ (O)	MDA +++	Hardener for PU glue (2% +++, 1% +++, 0.32% +++, 0.1% ++): 60–70% MDI ^b	Forearms, face, and chest	—	OACD from MDI in a hardener for PU glue
8	Plate maker/aircraft fitter Aircraft workshop	MDI 1% — (B) MDI 2% ++ (O)	MDA ++	Primer (5% ? +, 2% ? +): polymeric MDI 5–15%, MDI monomer <5% ^b	Eyelids and forearms	TGMDA ++	OACD from TGMDA, epoxy resin, and MDI
9	Foreman in a foundry	MDI 1% — (B) MDI 2% + (O)	MDA —	PU hardener (2% ++, 0.64% +, 0.2% —): 100% MDI	Forearms	—	OACD from MDI

Table 2. Continued

Patient no.	Occupation	Patch test reactions to isocyanates	Patch test reactions to amines corresponding to the positive isocyanates	Exposure data and reactions to patients' own products	Location of dermatitis (in parentheses when no relation to isocyanates or corresponding amines)	Reactions to other allergens	Diagnosis
10	Electronics engineer	MDI (O) ++ MDI (T) ?+	MDA ++	Hardener for casting mixture: 98% MDI ^b	Chest, abdomen, feet, face, and wrists	—	OACD from MDI (Ref. 10)
11	Paint factory worker	MDI 1% – (B) MDI 2% ++ (O) TDI (B) ++ IPDI +	MDA ++ IPDA –	Desmodur VL hardener (5% ++, 1.67% ++, 0.5% ++); 99.5% MDI isomers and homologs ^a Desmodur Z 4470 MPA/X: 70% IPDI homopolymer CAS 53880-05-0, IPDI monomer <0.5% ^b Ternafloor 100/200/P300 hardener: IPDA 25–50% Ternafloor 400 hardener: IPDA 25–50%	Face, forearms, neck, and eyelids	Epoxy resin +, nickel sulfate ++	OACD from MDI in paint hardeners (only two episodes of dermatitis after handling MDI-based product) OCA to IPDI, TDI, and epoxy resin (TDI allergy resulting from cross-allergy to MDI or separate exposure)
12	Painter in the manufacture of windows and doors	IPDI: I, D4 +, D18 ++; II, D4 +++ MDI 2% (O): I, D4 –; II, D4 –, D18 ?+, D21 + MDI 1% (B) –	MDA: I, D4 –; II, D4 ?+, D11 ++, D18 + IPDA –	Exposure to HDI and TDI but not to IPDI or MDA ^a A PU hardener possibly contained MDI, but a high HDI content interfered with the analysis	Hands, wrists, and forearms	PPD: I, D4 –; II, D4 –, D11 +, D18 +	OICD from paint dust OCA to IPDI, MDA, MDI
13	Set painter in a theatre	IPDI ++ HDI ?+	MDA ++ IPDA –	Paint hardener (5% ++, 1.67% ++, 0.5% ++, 0.167% ?+, 0.05% ?+); about 100% IPDI ^a , MDI <5 ppm ^a , MDA < 30 ppm ^a PU foams (no symptoms)	Forearms	—	OACD from IPDI in a paint hardener OCA to MDA
14	Floor coating worker	IPDI +	IPDA ++ MDA ++	Mastertop FC 307 epoxy hardener: 25–50% IPDA ^b Nanten hardener for PU floor coating: 4,4'-MDI 30–60%, 2,4'-MDI 7–13% ^b No present exposure to IPDI or MDA ^b	Face and hands	Epoxy resin ++, Novolac epoxy resin +, xylylenediamine ++, PPD +	OACD from epoxy resin, IPDA and xylylenediamine OCA to IPDI and MDA (IPDI allergy either cross-allergy to IPDA or resulting from past specific exposure)
15	Machine assistant on icebreaker	IPDI: I, ?+; II, ++	IPDA: I, –; II, NT MDA –	No present exposure to IPDA, IPDI or other isocyanates found Past exposure to IPDA in a hardener for epoxy filler ^b Exposure to a PU paint hardener based on HDI ^b (2% –)	Hands	Epoxy resin – (previously ++)	OICD from solvents and oils OCA to IPDI
16	Instrument fitter in aircraft workshop	IPDI +	IPDA – MDA –	No present exposure to IPDI ^b	Eyelids, face, and forearms	Epoxy resin NT (previously ++)	OACD from epoxy resin Possible OCA to IPDI

Table 2. Continued

Patient no.	Occupation	Patch test reactions to isocyanates	Patch test reactions to amines corresponding to the positive isocyanates	Exposure data and reactions to patients' own products	Location of dermatitis (in parentheses when no relation to isocyanates or corresponding amines)	Reactions to other allergens	Diagnosis
17	Painter of buildings	IPDI ++ HDI ?+	IPDA +++ MDA —	Teknofloor 2K paint (2% ++, 1% ++): 1–2.5% IPDA ^b No exposure to isocyanates ^b	Hands, forearms, and arms	Epoxy resin +, TMD ++, Tris-dimethylaminomethylphenol ++, formaldehyde ++ and several liberators positive, fragrance mix I ++	Prurigo nodularis; past OACD from epoxy resin and IPDA (IPDI) reaction represents cross-allergy to IPDA)
18	Worker in flame cutting of scrap iron	IPDI +++ TDI (B) ++	IPDA NT MDA NT Previously —	Had studied prepress production (imaging technology); no skin symptoms at that time	(Hands)	Formaldehyde ++, quaternium — 15 +, imidazolidinyl urea +	Atopic dermatitis CA to IPDI and TDI
19	Plastics worker in manufacture of acrylonitrile-butadiene-styrene plastics	IPDI + TDI (T) +	IPDA — MDA —	No exposure to IPDI, TDI or other isocyanates found ^{a,b,c}	(Face, forearms, arms, axillae, abdomen, and lower extremities)	PPD ++, methylidibromo glutaronitrile ++	OACD from plastic fumes CA to IPDI and TDI
20	Wood industry worker in manufacture of windows, doors, and frames	TDI (T) +	MDA —	Paint hardener TV300 (NT): isocyanate prepolymer 40–50%, TDI monomer <0.2% ^b , HMDI monomer <0.2% ^b Hardener D-Dur (5% pet. —): 0.5–2% HDI ^b	Arms, hands, face, neck, legs, and sides of the trunk	—	OACD from TDI in a hardener for wood paint
21	Warehouse worker in supermarket	TDI (T) +++	MDA —	No present exposure to TDI or other isocyanates found	(Hands)	Nickel sulfate +	Pompholyx CA to TDI
22	Lamp assembler	TDI (B) +	MDA ?+	No exposure to TDI or other isocyanates found ^a	(Hands, face, axillae, and feet)	Colophonium +, abietic acid +, epoxy resin NT (previously ++), resorcinol monobenzoate +++, thiuram mix NT (previously +)	OACD from thiurams CA to TDI
23	Salesperson in a plastic and rubber product store	HDI + TDI (T) ?+	MDA —	Sample of foamed plastic: 2 ppm 2,4-TDI ^a Sample of foamed polyester plastic: 3.5 ppm 2,4-TDI ^a ; no HDI	Hands (especially after cutting foamed plastic)	Neomycin sulfate ++	OACD from plastic dust Possible OACD from TDI in foamed plastics

B, Brial; CA, contact allergy; DPPD, diphenyl *p*-phenylenediamine; HDI, hexamethylene diisocyanate; I, the first test session; II, the second test session; IPDA, isophorone diamine; IPDI, isophorone diisocyanate; IPPD, isopropyl aminodiphenyl; MDA, 4,4'-diaminodiphenylmethane; MDI, diphenylmethane diisocyanate; NT, not tested; O, in-house test substance; OACD, occupational allergic contact dermatitis; OCA, occupational contact allergy; OIAC, occupational irritant contact dermatitis; PPD, *p*-phenylenediamine; PU, polyurethane; T, Trolab; TDI, toluene diisocyanate; TMD, trimethylhexamethylenediamine; TCMDA, *N,N*-tetraglycidyl-4,4'-methylene dianiline.

^aChemical analysis.

^bMaterial safety data sheet.

^cInquiries from the manufacturers.

Table 3. Isocyanate-negative patients with allergic reactions to 4,4'-diaminodiphenylmethane (MDA) and exposure to polyurethane products

Patient no.	Occupation	Patch test results for MDA and MDI	Exposure	Location of dermatitis	Other contact allergies	Diagnosis
1	Painter, coater	MDA + MDI (T/O) –	Epoxy coating part A: epoxy resin >50% Epoxy coating part B: xylene diamine < 20% PU glue and filler: probably MDI ^a Hardener for PU coating: MDI 75–100% ^b Normafloor 105 hardener (2% ++ 0.5% +): 0–2.5% xylene diamine ^b	Hands	Epoxy resin +, xylylenediamine +++, IPDA +++, IPDI –	OACD from epoxy resin, xylylenediamine, and MDA
2	Managing director (floor coatings)	MDA + MDI (T/O) –	Hardener for PU coating: MDI 75–100% ^b Normafloor 105 hardener (2% ++ 0.5% +): 0–2.5% xylene diamine ^b	Eyelids, face, forearms, and hands	PPD ++, epoxy resin ?+, xylene diamine ++	OACD from MDA and xylylenediamine
3	Motor vehicle mechanic	MDA ++ MDI (T/O) –	Hardener for PU glue A (2% ++, 1% ++, 0.5% ++): MDI ^b Filler: MDI < 0.5%, TDI < 0.5% ^b Pistol foam: MDI ^b Hardener for PU glue B: MDI ^b Past exposure to PU glue and filler: probably MDI ^a	Hands	TDI –	OACD from MDA
4	Glazier in the manufacture of buses	MDA + MDI (T/O) –	Hardener for PU glue B: MDI ^b Past exposure to PU glue and filler: probably MDI ^a	Hands	Formaldehyde ++, imidazolidinyl urea ++, diazolidinyl urea ++, melamine formaldehyde resin ++	Past OACD from MDA OACD from formaldehyde
5	Tank truck mechanic	MDA ++ MDI NT	Past exposure to uncured PU insulating material and present exposure to PU dust	Hands	Potassium dichromate ++, cobalt chloride ++, nickel sulfate ++	OACD from chromium, nickel, cobalt, and MDA
6	Reinforced plastic worker in the manufacture of motor vehicles	MDA ++ MDI (T/O) –	Hardener for PU glue: 100% MDI isomers and homologues ^b	Hands, forearms, and ankles	Epoxy resin –	OACD from MDA OICD from fibreglass dust
7	Boat builder (injection of fibreglass)	MDA +++ MDI (T/O) –	Casted PU	Hands, neck, forearms, trunk, and thighs	Preventol™ D2 ++, TMTM +++, TETD +++, PTD +, cobalt chloride +++, cyclohexylthiophthalimide ++, zinc diethyldithiocarbamate +++, melamine formaldehyde resin +++, formaldehyde ++	OACD from rubber chemicals, cobalt, formaldehyde, and MDA
8	Plumber	MDA +++ MDI NT	Past exposure to PU foam	Hands	MDBGN +++	OACD from MDBGN OCA to MDA
9	Painter	MDA + MDI (T/O) –	Hardener for PU floor coating: 98% MDI isomers/homologues ^b Epoxy hardeners: xylene diamine ^b	Hands, face, forearms, feet, and legs	Xylene diamine ++	OACD from xylylenediamine OCA to MDA (no clear symptoms from PU products)

Table 3. *Continued*

Patient no.	Occupation	Patch test results for MDA and MDI	Exposure	Location of dermatitis	Other contact allergies	Diagnosis
10	Grinder in boat building	MDA ++ MDI (T/O) —	Hardener for PU lacquer (5% —): isocyanate prepolymer 20–30%, TDI <0.5% ^b Hardener for epoxy filler (1% +++); MDA 5 ppm ^c , 1,3-dibenzene diamine 0.6% ^c	Hands, forearms, arms, neck, and eyelids	Epoxy resin ++, Novolac epoxy resin +, phenyl glycidylether +, bromo epoxy resin ++, butanediol diglycidylether ++, nickel sulfate +, TDI —	OACD from epoxy compounds MDA sensitivity possibly represents cross-reactivity to other amines in the epoxy hardener
11	Assembler of door fittings (ex-painter)	MDA ++ MDI NT	Airborne exposure to MDI possible, but no airborne symptoms; previous painting work	—	Caine mix III ++++, PPD +	Chronic leg dermatitis CA to MDA
12	Tiler	MDA ++ MDI NT	Past exposure to PU foam (no skin symptoms) Epoxy sealing material	Hands and face	PPD ++, epoxy resin NT, Novolac epoxy resin ++, bromo epoxy resin ++	OACD from epoxy resin
13	Assembler of electric devices	MDA ++ MDI (T/O) —	Handled freshly powder-painted items	Hands and feet	Osmaron B ++, clioquinol ++	CA to MDA

CA, contact allergy; IPDA, isophorone isophoronediamine; IPDI, isophorone diisocyanate; MDBGN, methyl/dibromo glutaronitrile; MDI, diphenylmethane diisocyanate; NT, not tested; O, in-house test substance; OACD, occupational allergic contact dermatitis; OCA, occupational contact allergy; OICD, occupational irritant contact dermatitis; PPD, *p*-phenylenediamine; PTD, dipentamethylenethiuram disulfide; PU, polyurethane; T, Trolab; TDI, toluene diisocyanate; TETD, tetraethylthiuram disulfide; TMTM, tetramethylthiuram monosulfide.

^aOther information.

^bMaterial safety data sheet.

^cChemical analysis.

in previous, larger studies (4, 6). The main problem in the diagnosis of isocyanate contact allergy is the instability of commercially available 4,4'-MDI test substances, owing to polymerization. When test preparations from 12 different dermatology clinics were analysed in Malmö, none of them contained more than 12% of the labelled concentration (8). Patch test preparations made of polymeric MDI (PMDI) are more stable and more homogeneous than 4,4'-MDI preparations, and the Malmö group has recommended that a PMDI product with a monomer content of at least 35% should be used at a concentration of 2% in petrolatum in the patch test (7). Since 1998, our isocyanate series has included an in-house test substance prepared from a product containing 39% 4,4'-MDI, 15% MDI triisocyanate, and ~5% 2,4'-MDI (Merck KGaA, Darmstadt, Germany). In line with the Swedish results, this test material was superior to commercial preparations: 8 of 12 MDI-positive cases were found with this in-house preparation. However, 3 of our patients reacted positively to the commercial Trolab® preparation, but negatively to the in-house preparation. We stored the diluted test preparations in a refrigerator rather than in a freezer, for practical reasons. According to the Swedish studies, MDI preparations are stable only when kept frozen (12); they also recommend reading the tests on D7 (7). Our study possibly contained false-negative results, owing to the problems of MDI testing and the inability to perform routine readings on D7 or later. One of the patients (no. 12 in Table 2) reported late reactions to MDI.

Many previous reports have implied that MDA is a good marker for MDI sensitivity (2, 4, 7). The present results support this concept: we had 17 cases of occupational sensitization related to MDI products, but only 8 of them reacted positively to MDI, and, in 9 cases, the diagnosis of occupational contact allergy was based on positive MDA reactions [in 1 case, also on positive reactions to an MDI-containing product (No. 3 in Table 3)].

According to the national Product Register of Chemicals, MDA is declared in the MSDSs of only a few products sold on the Finnish market, all of which are hardeners for epoxy products, mainly paints and coatings. We did not find such products in the exposure assessment of our patients, but our chemical analyses detected minute amounts of MDA in epoxy hardeners used by 2 patients (no. 3 in Table 2, no. 10 in Table 3), and 1 patient (no. 1 in Table 2) had used a solder paste and a protective lacquer for circuit boards with MDA contents of 0.03% and 0.01%, respectively. In addition, 10 other MDA-allergic patients were diagnosed as having contracted occupational allergic dermatitis from epoxy compounds; specific exposure to MDA cannot be excluded in these

cases. The relative number of concomitant reactions to PPD (29%) was about the same as in three recent reports from Italy, Germany, and Finland (32%, 32%, and 35%, respectively) (6, 13, 14). Thus, specific exposure to MDA was difficult to trace, and reactions to MDA could most often be explained by exposure to MDI or cross-allergy to other para-amino compounds.

TDI

The quantitatively second most used isocyanate after MDI is TDI. This is used in paints, varnishes, glues, soft foams, and sealing compounds. According to the national Product Register of Chemicals, TDI is declared in the MSDSs of products such as paints, glues for construction work, materials for the manufacture of shoes, and raw materials for plastic products. The literature contains reports of positive patch test reactions to TDI (4, 6, 15–18), but only a few of the cases have shown specific exposure to TDI (4, 15). In the present study, allergic reactions to TDI were seen in 6 patients, but we traced specific exposure to TDI for only 1 of the patients (to a hardener of a wood paint; no. 20). In addition, 1 patient had a doubtful reaction to TDI, and was exposed to minimal amounts of TDI in foamed plastics (no. 23). One of the TDI-allergic patients was exposed to MDI-based and IPDI-based products, but TDI was not mentioned in the MSDSs (no. 11), and another patient had previously studied prepress production in the imaging industry, where isocyanates may be used (no. 18). We could find no other possible source of sensitization. Animal tests have shown cross-reactions between TDI and MDI (19), but simultaneous reactions were seen in only 1 of our 6 TDI-positive patients. This finding was in line with the results from general dermatology patients in the Turku region of Finland (6).

IPDI

IPDI belongs to the aliphatic diisocyanates, which are used in the formulation of light-stable polyurethane coatings (11). Positive patch test reactions to IPDI without data on specific exposure to IPDI have previously been reported (3, 6, 16, 17). Some of the patients had reacted positively to isophorone diamine (IPDA) (6), and in these cases a possible explanation for the simultaneous reactions is cross-allergy between IPDI and the corresponding amine IPDA (20). Although the consumption of aliphatic isocyanates (including IPDI) is only a small fraction of the consumption of aromatic isocyanates, MDI and TDI (11), in the present study IPDI reactions formed the second largest group after MDI/MDA reactions. IPDI reactions were also quite common in the Turku study (6). We found specific exposure to IPDI in 2

of the 9 IPDI-allergic patients. The first patient (no. 13 in Table 2) was a set painter in a theatre, and developed occupational allergic contact dermatitis after handling a polyurethane paint. The MSDS of the hardener of the paint declared only MDI prepolymer, but our chemical analysis detected about 100% IPDI in the product, and no MDI. The second patient (no. 11 in Table 2) worked in a paint factory, and had handled an IPDI-based paint hardener, but had not had symptoms while handling this product. In 2 other IPDI-allergic cases, the cause of the dermatitis was epoxy resin and its hardener, IPDA (nos. 14 and 17 in Table 2). In these cases, we considered that the reactions to IPDI represented cross-allergy to IPDA, but specific past exposure to IPDI could not be excluded. Two other patients (nos. 12 and 16 in Table 2) were currently exposed to polyurethane paint hardeners, which, according to the MSDSs and chemical analyses, did not contain IPDI, although they did contain other isocyanates. In conclusion, allergic reactions to IPDI mostly derived from handling hardeners for polyurethane paints. Some IPDI reactions could be explained by cross-allergy to IPDA in epoxy hardeners.

HDI

HDI-based products are commonly used in lacquers, coatings, and spray paints. Although HDI is a strong allergen according to animal studies, stronger than MDI or TDI (21), not many reports of allergic contact dermatitis exist (4, 22, 23). Our results were in line with other recent series (4, 6): only one patient reacted to HDI, but in this case we were not able to show any specific exposure to the chemical. The reason for the low sensitivity rates is possibly minor exposure to monomeric HDI. HDI-based products are not used in as high amounts as MDI-based products, and the monomer content of modern HDI oligomer-based products is usually very low (<1%). In our experience, HDI trimers are much more prominent allergens than the monomer itself: since 2000, we have seen a total of 6 patients with contact allergy to HDI trimers, 4 of whom were presented in our recent report (24).

References

- 1 Tarlo S M, Balmes J, Balkissoon R et al. Diagnosis and management of work-related asthma: American College of Chest Physicians Consensus Statement. *Chest* 2008; **134**: 1S–41S.
- 2 Estlander T, Kanerva L, Jolanki R. Polyurethane resin. In: *Handbook of Occupational Dermatology*, 1st edition, Kanerva L, Elsnar P, Wahlberg J E, Maibach H I (eds): Berlin, Springer-Verlag, 2000: pp. 597–601.
- 3 Frick M, Björkner B, Hamnerius N, Zimerson E. Allergic contact dermatitis from dicyclohexylmethane-4, 4'-diisocyanate. *Contact Dermatitis* 2003; **48**: 305–309.
- 4 Goossens A, Detienne T, Bruze M. Occupational allergic contact dermatitis caused by isocyanates. *Contact Dermatitis* 2002; **47**: 304–308.
- 5 Frick M, Isaksson M, Björkner B, Hindsén M, Pontén A, Bruze M. Occupational allergic contact dermatitis in a company manufacturing boards coated with

Phenylisocyanate

Phenylisocyanate (CAS 103-71-9) is an aromatic monoisocyanate that is a trace constituent in commercial MDI products. In the mouse ear-swelling test, it was found to be a potent contact sensitizer (25). A commercial preparation was included in our isocyanate series, and a total of 344 patients tested negative. Phenylisocyanate does not seem to be a significant occupational contact allergen, but it is noteworthy that we have not controlled the stability of the patch test substance.

Conclusions

The motor vehicle and electronic industries, and polyurethane paint manufacture, were significant occupational fields for isocyanate contact allergy. The use of paints and other coatings in construction work was also a prominent area. The most common products causing isocyanate allergy were hardeners for glues, foams, paints, coatings, and cast polyurethane. MDI was the most commonly positive isocyanate. An in-house PMDI test substance prepared from a product containing 39% 4,4'-MDI, 15% MDI triisocyanate and 5% 2,4'-MDI was superior to commercial preparations: 8 of 12 MDI-positive cases were found with this in-house preparation. This test substance is now included in the national recommendation of plastic and glue allergens, and Finnish dermatologists can obtain this substance from Chemotechnique Diagnostics®, Vellinge, Sweden. MDA was significant in diagnosing MDI-related contact allergy: only 1 of the 12 MDI-positive cases was negative for MDA, and in about half of the occupational cases related to MDI products, the contact allergy diagnosis was based on a positive MDA reaction. Specific exposure to MDA was difficult to show, and reactions to MDA could most often be explained by exposure to MDI or cross-allergy to other para-amino compounds. Contact allergy to IPDI was relatively common. IPDI reactions mostly resulted from handling hardeners for polyurethane paints, and some of them could be explained by cross-allergy to IPDA in epoxy hardeners. In our study, HDI monomer allergy had no clinical importance.

- isocyanate lacquer. *Contact Dermatitis* 2003; **48**: 255–260.
- 6 Liippo J, Lammintausta K. Contact sensitization to 4,4'-diaminodiphenyl methane and to isocyanates among general dermatology patients. *Contact Dermatitis* 2008; **59**: 109–114.
 - 7 Frick-Engfeldt M, Isaksson M, Zimerson E, Bruze M. How to optimize patch testing with diphenylmethane diisocyanate. *Contact Dermatitis* 2007; **57**: 138–151.
 - 8 Frick M, Zimerson E, Karlsson D, Marand Å, Skarping G, Isaksson M, Bruze M. Poor correlation between stated and found concentrations of diphenylmethane-4,4'-diisocyanate (4,4'-MDI) in petrolatum patch-test preparations. *Contact Dermatitis* 2004; **51**: 73–78.
 - 9 Boutin M, Lesage J, Ostigy C, Pauluhn J, Bertrand M J. Identification of the isocyanates generated during the thermal degradation of a polyurethane car paint. *J Anal Appl Pyrolysis* 2004; **71**: 791–802.
 - 10 Hannu T, Estlander T, Jolanki R. Allergic contact dermatitis due to MDI and MDA from accidental occupational exposure. *Contact Dermatitis* 2005; **52**: 108–109.
 - 11 Six C, Richter F. Isocyanates, organic. *Ullmann's Encyclopedia of Industrial Chemistry (Release 2011)*; Weinheim, Wiley Online Library, 2005; pp. 63–82.
 - 12 Frick-Engfeldt M, Zimerson E, Karlsson D, Skarping G, Isaksson M, Bruze M. Is it possible to improve the patch-test diagnostics for isocyanates? A stability study of petrolatum preparations of diphenylmethane-4,4'-diisocyanate and polymeric diphenylmethane diisocyanate. *Contact Dermatitis* 2007; **56**: 27–34.
 - 13 Uter W, Lessmann H, Geier J, Becker D, Fuchs T, Richter G. The spectrum of allergic (cross-) sensitivity in clinical patch testing with 'para amino' compounds. *Allergy* 2002; **57**: 319–322.
 - 14 Fortina A, Piaserico S, Larese F, Recchia G P, Corradin M T, Gennaro F, Carrabba E, Peserico A. Diaminodiphenylmethane (DDM): frequency of sensitization, clinical relevance and concomitant positive reactions. *Contact Dermatitis* 2001; **44**: 283–288.
 - 15 Huang J, Wang X P, Chen B M, Ueda A, Aoyama K, Matsushita T. Immunological effects of toluene diisocyanate exposure on painters. *Arch Environ Contam Toxicol* 1991; **21**: 607–611.
 - 16 Militello G, Sasseville D, Ditre C, Brod B A. Allergic contact dermatitis from isocyanates among sculptors. *Dermatitis* 2004; **15**: 150–153.
 - 17 Estlander T, Keskinen H, Jolanki R, Kanerva L. Occupational dermatitis from exposure to polyurethane chemicals. *Contact Dermatitis* 1992; **27**: 161–165.
 - 18 Le Coz C J, El Aboubi S, Ball C. Active sensitization to toluene di-isocyanate. *Contact Dermatitis* 1999; **41**: 104–105.
 - 19 Tanaka K, Takeoka A, Nishimura F, Hanada S. Contact sensitivity induced in mice by methylene bisphenyl diisocyanate. *Contact Dermatitis* 1987; **17**: 199–204.
 - 20 Lachapelle J M, Lachapelle-Ketelaer M J. Cross-sensitivity between isophorone diamine (IPD) and isophorone diisocyanate (IPDI). *Contact Dermatitis* 1979; **5**: 55.
 - 21 Thorne P S, Hillebrand J A, Lewis G R, Karol M H. Contact sensitivity by diisocyanates: potencies and cross-reactivities. *Toxicol Appl Pharmacol* 1987; **87**: 155–165.
 - 22 Morgan C J, Haworth A E. Allergic contact dermatitis from 1,6-hexamethylene diisocyanate in a domestic setting. *Contact Dermatitis* 2003; **48**: 224.
 - 23 Wilkinson S M, Cartwright P H, Armitage J, English J S. Allergic contact dermatitis from 1,6-diisocyanatohexane in an anti-pill finish. *Contact Dermatitis* 1991; **25**: 94–96.
 - 24 Aalto-Korte K, Pesonen M, Kuuliala O, Alanko K, Jolanki R. Contact allergy to aliphatic polyisocyanates based on hexamethylene-1,6-diisocyanate (HDI). *Contact Dermatitis* **63**: 357–363.
 - 25 Karol M H, Kramarik J A. Phenyl isocyanate is a potent chemical sensitizer. *Toxicol Lett* 1996; **89**: 139–146.