

Isocyanates

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Owing to the widespread use of isocyanate-derived products across multiple industries, it is important for physicians to be aware of their sensitizing potential. We first provide a general overview of isocyanates and the industries that may be associated with exposure to these compounds. This is followed by a description of the most commonly used isocyanate products in commercial patch test preparations. Finally, we discuss appropriate isocyanate patch testing methodology and optimal isocyanate patch test concentrations.

ISOCYANATES ARE low-molecular-weight compounds containing one or more reactive $\text{N}=\text{C}=\text{O}$ groups.

The most important application of isocyanates is in the production of polyurethanes, which are formed when diisocyanates react with hydroxyl groups from other compounds (such as polyacrylates, polyethers, and polyesters) to form long polymer chains. Polyurethanes are used in a wide variety of consumer products, including adhesives, coatings, foams, and synthetic rubber. In 2002, the estimated worldwide production of polyurethanes reached 10 million metric tons (6 million metric tons of isocyanates).¹ With the increasingly widespread use of isocyanates, it is important for providers to be aware of their sensitizing potential. Table 1 shows several examples of industries and activities that may be associated with isocyanate exposure.¹

Isocyanates are considered an important cause of occupational asthma worldwide, although inhalational exposure to these compounds has been reduced in recent years through the use of less volatile compounds and through improved regulatory control mechanisms by manufacturing facilities.² Less commonly, isocyanates have been reported to cause allergic contact dermatitis in both domestic and occupational settings. One study described 5 cases of isocyanate contact allergy in a company manufacturing flooring boards coated with a polyurethane lacquer containing diphenylmethane diisocyanate monomers.³ Others have reported individual cases of allergic contact dermatitis secondary to iso-

cyanates within tile coatings, spectacle frames, and an office-label cartridge gun.⁴⁻⁶ Patients most commonly present with hand and/or forearm involvement, occasionally associated with a facial dermatitis that may reflect an airborne component. Isocyanate allergic contact dermatitis is rarely reported in individuals with isocyanate-induced asthma.²

As of this writing, the Chemotechnique Diagnostic isocyanate series includes the following isocyanates: toluene-2,4-diisocyanate (TDI), isophorone diisocyanate (IPDI), hexamethylene diisocyanate (HDI), diphenylmethane-4,4'-diisocyanate (4,4'-MDI). In addition, it includes isophorone diamine and diaminodiphenylmethane (MDA), which may both serve as markers of isocyanate allergy. Trolab and SmartPractice do not have a dedicated isocyanate series, but instead have several of these substances incorporated into their epoxy or plastics and glues series. Both 4,4'-MDI and TDI are the most commonly used diisocyanates in industry, accounting for more than 95% of global isocyanate production.⁷ Recently, consumption of 4,4'-MDI has exceeded that of TDI owing to the latter's volatile properties and the potential for respiratory health risks.⁸ Diaminodiphenylmethane is an aromatic diamine that may be formed from 4,4'-MDI through a hydrolysis reaction after contact with water in or on the skin. It is frequently used as a catalyst in polyurethane systems, hardener in epoxy resins, and antioxidant in the manufacturing and production of rubber. Although not included in most patch test series, dicyclohexylmethane-4,4'-diisocyanate has also been reported as a strong sensitizer.⁹

Several reports have noted that patients may have simultaneous positive reactions to MDA and 4,4'-MDI, or test positive to MDA without reacting to 4,4'-MDI, despite no previous known exposure to MDA.^{3,8,10} It is thought that these discrepancies may reflect either cross-reactivity or, in the latter case, an exclusive sensitization to 4,4'-MDI-derived MDA after water contact. However, others have proposed that concomitant reactions to 4,4'-MDI and MDA may arise through a more complex pathway where 4,4'-MDI either polymerizes into ureas and/or forms 4,4'-MDI conjugates with skin constituents.¹¹ These compounds can subsequently be hydrolyzed to MDA, which is then metabolized into one or more haptens. This multistep process may explain why positive 4,4'-MDI patch test reactions often appear late, and it is recommended that additional readings of MDI products are performed at least 7 days after patch test placement.¹¹ Patients should be instructed to contact their provider should any reactions appear after the final clinic reading.

Complicating matters further, significant differences between the stated and actual concentration of 4,4'-MDI within patch

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TABLE 1. Examples of Industries That May Be Associated With Isocyanate Exposure*

Industry	Activity/Product
Automotive, ship, aircraft, train	Painting, sealing, roof liner, acoustic panels, truck bed liners, cutting, welding, grinding
Building/construction	Sealing, painting, caulking, insulation, paint removal, floor and wall coverings
Clothing and leisure	Manufacture of textiles, shoes, sports equipment
Paints	Manufacture of paints, automotive and industrial painting, removal of paints and varnishes with heat
Graphics	Manufacture of printing inks, lamination, curing
Food	Can varnishing, insulation of refrigerators and freezers
Plastics	Foams, automotive fittings
Tunneling/mining	Rock consolidation, sealing
Wood and furniture	Adhesives, varnishes, upholstery padding, painting
Engineering	Gluing, manufacture of elastomers, painting, insulation
Medical care	Bandaging, casting

*Modified from Redlich et al.¹

testing material have been found by Frick et al.⁷ This finding emphasizes the importance of testing with the patient's own work material and suggests that there may be a high rate of false-negative reactions to 4,4'-MDI.⁷ When work material is not available, it is recommended that patients be tested with polymeric MDI (PMDI), a general term for a complex mixture of isocyanates consisting predominantly of 4,4'-MDI and varying lower concentrations of 2,2'-MDI, 2,4'-MDI, and oligomers of 4,4'-MDI.¹² Polymeric MDI products have been shown to be more stable and homogeneous than pure 4,4'-MDI used in commercial patch test preparations, and patch testing with PMDIs generally detects more patients with MDI sensitization than 4,4'-MDI alone.^{11,12} Furthermore, testing with PMDI products may better reflect the allergens that patients are exposed to because most MDI-containing isocyanate products are actually PMDI.¹² In contrast with 4,4'-MDI, patch test preparations of TDI, HDI, and IPDI have been found to be relatively stable.¹³

Although commercial patch tests of PMDI are not available, PMDI products can be obtained from several companies for patch test preparation.¹¹ Alternatively, several patch test suppliers confirmed that they would be able to prepare a customized PMDI patch test upon request. It has been suggested that PMDI have a monomer content of at least 35% tested at 2.0% petrolatum, which corresponds to a monomer patch test concentration of approximately 0.7%.¹¹ If MDA is instead used as a marker of 4,4'-MDI or other isocyanate contact allergy, it may be tested in either 0.25% or 0.5% petrolatum, although the higher concentration has occasionally been reported to induce active sensitization.¹¹

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