

Occupational contact dermatitis caused by 1,3-benzenedimethanamine, *N*-(2-phenylethyl) derivatives in hardeners for epoxy paints and coatings

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Summary

Background. Amines in epoxy hardeners are significant causes of occupational allergic contact dermatitis among workers who use epoxy resin systems.

Objectives. To describe a novel group of contact allergens: *N*-(2-phenylethyl) derivatives of the reactive amine 1,3-benzenedimethanamine (1,3-BDMA).

Methods. We describe the clinical examinations and exposure of 6 patients with occupational contact allergy to derivatives of 1,3-BDMA.

Results. Of the 6 patients, 4 were spray painters who used epoxy paints, 1 was a floor layer who handled a variety of epoxy coatings, and 1 was a worker in epoxy hardener manufacture. We were able to confirm exposure to epoxy hardeners that contained derivatives of 1,3-BDMA in 5 of the 6 sensitized patients. Despite the close structural resemblance between derivatives of 1,3-BDMA and *m*-xylylenediamine (MXDA), only 3 patients reacted positively to MXDA. Concomitant contact allergy to diglycidyl ether of bisphenol A resin was seen in 2 of the 6 patients.

Conclusions. Because of the lack of a commercially available patch test substance, the diagnosis of contact allergy to derivatives of 1,3-BDMA requires patch testing with either the epoxy hardener product or a hardener ingredient that contains the derivatives of 1,3-BDMA.

Key words: CAS no. 1477-55-0; CAS no. 404362-22-7; contact allergy; curing agent; epoxy hardener; *m*-xylylenediamine; painters.

Epoxy resin systems are extensively used in industrial applications (1). They are among the most common causes of occupational contact dermatitis (2). Of the components of the epoxy resin systems, diglycidyl ether of bisphenol A resin (DGEBA-R) is the most frequent sensitizer, followed by reactive diluents and amine hardeners (3, 4). Concomitant sensitization to epoxy

hardeners and epoxy resins is common, but isolated cases of contact allergy to hardeners also occur (3, 5). A wide variety of epoxy hardeners for different applications and curing conditions are commercially available. *m*-Xylylenediamine (MXDA) (CAS no. 1477-55-0) is a commonly used epoxy curing agent (1), and is currently the most significant sensitizer in epoxy hardeners (6, 7). MXDA is also known by its synonym name, 1,3-benzenedimethanamine (1,3-BDMA). We report 6 patients with occupational contact allergy to an epoxy hardener containing derivatives of 1,3-BDMA [1,3-benzenedimethanamine, *N*-(2-phenylethyl) derivatives, CAS no. 404362-22-7], a compound that closely resembles MXDA and is used as a curing agent in epoxy paints and coatings. To our knowledge, contact allergy

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to derivatives of 1,3-BDMA has not been previously reported.

Patients and Methods

Patient assessments

The 6 patients were examined at the Finnish Institute of Occupational Health because of suspected occupational skin disease during 2013–2015. We derived the data on their occupational exposure, clinical history and patch test results from the medical records. We performed patch tests on all of the patients with Finn Chambers® (Smart Practice, Phoenix, AZ, USA), in accordance with the recommendations of the ICDRG and the ESCD (8). We read the tests two or three times [on day (D) 2, D3, and D4, or on D2, D3, and D6, or on D2 and D5], depending on the day of the week on which the test patches were applied. Patch tests were performed on all of the patients with modified European baseline, antimicrobial, epoxy chemicals and glues and plastics series, as well as with the patients' own workplace materials, including the epoxy hardeners if available (see below).

Test preparations

Serial dilution preparations for patch testing were prepared in-house. First, we prepared a 5% stock solution by mixing 0.5 g of the substance with 10 g of petrolatum (pet.). The desired concentrations for the dilution series were then prepared by further diluting the 5% stock solution with pet. Hardener A was tested in patient 1 as a dilution series from 1% to 0.0001% pet. Table 1 shows the concentrations that yielded reactions in the patch test. Hardener B was tested in patient 2 as a similar dilution series (1% to 0.0001% pet.), and in patients 3 and 6 at 0.5%, 0.16% and 0.05% pet. The hardener ingredient Aradur® 3277 BD (Huntsman Advanced Materials Europe, Everberg, Belgium), once identified as the possible source of sensitization, was patch tested in patient 1 as a dilution series from 0.16% to as low as 0.000016% pet. In patient 2, a strong allergy was suspected, and the two highest concentrations of Aradur® 3277 BD were therefore omitted (Table 1). It was tested at 0.16%, 0.05% and 0.016% pet. in patients 3 and 4, and at 1% and 0.1% pet. in patient 5. In patient 6, who had a known exposure to the hardener ingredient itself, we used a dilution series from 0.16% to 0.0005%. MXDA (Sigma-Aldrich, Saint Louis, MO, USA) was patch tested in all of the patients as a 0.32% pet. in-house preparation.

Patch testing in control patients

Hardener A was patch tested in 20 unexposed control patients 0.032% and 0.01% pet., and gave negative results. Aradur® 3277 BD was patch tested in 20 control patients 0.05% pet., and gave negative results.

Results

The patient characteristics and patch test reactions are summarized in Table 1. Patient 1 presented in 2013. He was a painter who handled a wide variety of two-component epoxy paints and coatings in his work. After a few days of work with a novel epoxy hardener product (hardener A), he developed eczema on the forearms and wrists, and later on the face, eyelids, and knees, where contact with uncured epoxy floor coating had occurred. His eczema relapsed when he was at work, and healed during sick-leave. As the only positive patch test reaction, the patient had an extremely strong positive reaction to hardener A. A sample of a hardener ingredient mixture (Aradur® 3277 BD) used in hardener A was kindly provided by the manufacturer of hardener A, and patch tested in patient 1; it elicited strong to extreme positive reactions (Table 1). Later, it turned out that the patient had also used another epoxy paint hardener (hardener B, produced by the same manufacturer as hardener A), which contained the same ingredient mixture, Aradur® 3277 BD (Table 2). Patient 1 was not patch tested with hardener B.

The hardener ingredient mixture Aradur® 3277 BD contains derivatives of 1,3-BDMA as the major component, and 1,3,5-tris(3-dimethylamino)propyl-s-hexahydro-1,3,5-triazine (CAS no. 15875-13-5) as a minor component (Table 2). The components of the ingredient mixture were not available as separate substances. Our attempts to separate the derivatives of 1,3-BDMA and 1,3,5-tris(3-dimethylamino)propyl-s-hexahydro-1,3,5-triazine by thin-layer chromatography of Aradur® 3277 BD were unsuccessful. Therefore, we had to rely on patch testing with Aradur® 3277 BD itself.

After assessment of patient 1, we screened consecutive patients with known exposure to epoxy hardeners by patch testing them with Aradur® 3277 BD as a dilution series of 0.16%, 0.05% and 0.016% pet. In 1 case (patient 2, Table 2), the two highest concentrations (0.16% and 0.05%) were omitted, owing to a history suggestive of strong allergy to the epoxy hardener. So far, we have screened a total of 12 patients, and thereby identified another 5 patients with positive reactions to Aradur® 3277 BD (patients 2–6).

Patients 2–4 were painters who were mainly involved in spray painting with two-component epoxy and

Table 1. Patient characteristics and patch test reactions [final reading on day (D) 4, D5 or D6]

Patient number, age (years), sex, occupation	Exposure to derivatives of 1,3-BDMA	Symptoms	Patch test results on final reading (day 4, 5 or 6)				
			Hardener A	Hardener B	Aradur® 3277 BD *	MXDA 0.32% pet.	Other patch test reactions
1, 38, M, painter	Hardener A and hardener B in floor coating and spray painting	Eczema on forearms, wrists, face, eyelids, and knees	1%, +++ 0.32%, +++ 0.1%, +++ 0.032%, ++ 0.01%, + 0.0032%, ?+	NT	0.16%, +++ 0.05%, ++ 0.016%, + 0.005%, ?+	Negative	None
2, 40, M, painter	Hardener B in spray painting	Eczema on forearms, face, eyelids, front of legs, and knees	NT	1%, +++ 0.32%, +++ 0.1%, +++ 0.01%, ++ 0.0032%, + 0.001%, ?+	0.016%, +++ 0.005%, ++ 0.0016%, + 0.0005%, ?+	+	DGEBA-R 1%, +
3, 53, M, painter	Hardener B in spray painting	Eczema on face, eyelids, and neck	NT	0.5%, ++ 0.16%, ?+	0.16%, ++ 0.05%, ?+	Negative	DGEBA-R 1%, +++
4, 36, F, painter	Hardener B in spray painting	Eczema on forearms, wrists, face, and eyelids	NT	NT	0.016%, ? 0.16%, +++ 0.05%, ++	Negative	Nickel sulfate 5%, +++
5, 49, M, floor layer	Undefined	Eczema on forearms	NT	NT	0.016%, ?+	++	Tris-DMP 0.32%, + MDA 0.5%, +++ PPD 1%, ++
6, 29, M, worker in paint factory	Ingredients for hardener B in manufacture of epoxy hardeners	Eczema on forearms, upper arms, and front of legs	NT	0.5%, +++ 0.16%, +++ 0.05%, ++	0.1%, ?+ 0.16%, +++ 0.05%, +++ 0.016%, +++ 0.005%, +++ 0.0016%, ++ 0.0005%, ++	++	

The vehicle used for all test substances was pet.

1,3-BDMA, 1,3-benzenedimethanamine; DGEBA-R, diglycidyl ether of bisphenol A resin; F, female; M, male; MDA, 4,4'-diaminodiphenylmethane; MXDA, *m*-xylylenediamine; NT, not tested; PPD, *p*-phenylenediamine; Tris-DMP, 2,4,6-tris-(dimethylamino)phenol.

*Huntsman Advanced Materials Europe, Everberg, Belgium. Mixture of 30–60% 1,3-BDMA, *N*-(2-phenylethyl) derivatives (derivatives of 1,3-BDMA, CAS no. 404362-22-7) and 3–7% 1,3,5-tris-(3-dimethylamino)propyl-*s*-hexahydro-1,3,5-triazine (CAS no. 15875-13-5); present in hardeners A and B.

Table 2. Concentrations of derivatives of 1,3-benzenedimethanamine (derivatives of 1,3-BDMA) and 1,3,5-tris(3-dimethylamino)propyl-s-hexahydro-1,3,5-triazine in hardeners A and B and the hardener ingredient mixture Aradur® 3277 BD common to hardeners A and B according to safety data sheets

	Derivatives of 1,3-BDMA (%)	1,3,5-Tris(3-dimethylamino) propyl-s-hexahydro-1, 3,5-triazine (%)
Hardener A	50–75	1–5
Hardener B	25–35	1–5
Aradur® 3277 BD*	30–60	3–7

*Huntsman Advanced Materials Europe, Everberg, Belgium.

polyurethane paints and coatings. All 4 presented with facial and eyelid eczema. One of them (patient 3) had only facial and neck eczema, whereas the others also had eczema on the forearms, wrists, and anterior side of the legs and knees (Table 1). In all of the patients, the eczema healed during sick-leave and relapsed when they were at work. The eczema had occurred rapidly (weeks to a few months) in all of the patients after a novel epoxy hardener, hardener B, had been introduced in their spray painting work.

Patient 5 was a floor layer who had used a wide variety of two-component epoxy, acrylate and polyurethane coatings in his work. He presented with recurring dermatitis on the forearms, which healed during sick-leave. He had recently used several epoxy products from the manufacturer of hardeners A and B, as well as from other manufacturers, but exposure to a hardener containing derivatives of 1,3-BDMA could not be confirmed. He reacted positively to Aradur® 3277 BD and also to MXDA, 2,4,6-tris-(dimethylamino)phenol (tris-DMP) (CAS no. 21454-20-6), and 4,4'-diaminodiphenylmethane (CAS no. 101-77-9) (Table 1), the last of these reactions probably indicating contact allergy to 4,4'-diphenylmethane diisocyanate (MDI) (CAS no. 101-68-8) (9). On the basis of the material safety data sheets of the recently used products, exposure and contact allergies to MXDA, tris-DMP and MDI were considered to have current relevance to his forearm dermatitis.

Patient 6 was a worker in a paint factory. He was involved in the manufacture of epoxy hardener products, and mixed the ingredients of hardener B. He developed eczema on the legs, forearms, and upper arms, which healed after he was relocated within the factory and no longer handled ingredients for epoxy hardeners.

Discussion

We describe 6 patients with occupational contact allergy to *N*-(2-phenylethyl) derivatives of 1,3-BDMA, a reactive

amine that is used in hardeners for epoxy paints and coatings. Four of our 6 patients were spray painters who had used the hardeners with derivatives of 1,3-BDMA in their work. One of our patients was involved in the manufacture of epoxy hardeners, and had been handling hardener ingredients, including one which contained derivatives of 1,3-BDMA. In 1 patient, exposure to derivatives of 1,3-BDMA could not be confirmed, and so the source of his contact allergy to derivatives of 1,3-BDMA could not be defined, although it was considered to be occupational. As a floor layer, over the years, he had used a variety of epoxy paints and coatings in his work, and was unable to recall them all.

All 4 patients involved in spray painting suffered from eyelid and facial eczema, which may represent airborne contact dermatitis. This is common among patients with contact allergy to components of epoxy resin systems, especially among those with allergy to amine hardeners (3, 10–12). All 4 spray painters developed allergic contact dermatitis rapidly, in weeks to a few months, after they had started to use a novel epoxy hardener that contained derivatives of 1,3-BDMA.

No patch test substance for derivatives of 1,3-BDMA is commercially available. Our patients' diagnosis of contact allergy to derivatives of 1,3-BDMA was based on patch testing an ingredient mixture for epoxy hardeners, Aradur® 3277 BD, which contained 30–60% derivatives of 1,3-BDMA and 3–7% 1,3,5-tris(3-dimethylamino)propyl-s-hexahydro-1,3,5-triazine. As the patients showed positive patch test reactions to Aradur® 3277 BD at concentrations as low as 0.0005%, we conclude that the allergen or allergens in Aradur® 3277 BD and the epoxy hardeners are likely to be one or several components of the derivatives of 1,3-BDMA, the concentration of which is at least 10 times that of 1,3,5-tris(3-dimethylamino)propyl-s-hexahydro-1,3,5-triazine. In further support of this, derivatives of 1,3-BDMA bear a close structural resemblance to MXDA, also known as 1,3-BDMA, a known contact allergen (6, 7). A single molecular structure for derivatives of 1,3-BDMA cannot be given, since it consists of a mixture of derivatives. Derivatives of 1,3-BDMA are described in a dossier of the European Chemicals Agency (ECHA) (13). The dossier presents some molecular structures for derivatives of 1,3-BDMA. However, as the ECHA dossier relates to a different epoxy hardener product from those that our patients were exposed to, it is uncertain whether the molecular structures presented in the dossier are applicable to the hardener products of our patients. According to the dossier, a murine local lymph node assay was performed with a test material representing derivatives of

1,3-BDMA. This yielded positive results, which indicates that the derivatives of 1,3-BDMA are sensitizers. As the hardener ingredient is a technical product that contains a mixture of derivatives of 1,3-BDMA, further studies are needed to clarify the molecular structures of the actual allergens in derivatives of 1,3-BDMA.

Only 3 of our patients showed allergic reactions to MXDA. Therefore, patch testing with MXDA may not reliably indicate patients with contact allergy to derivatives of 1,3-BDMA. Instead, patch testing with the patient's own epoxy hardener product or a hardener ingredient that contains derivatives of 1,3-BDMA is necessary to diagnose this allergy. Another novel contact allergen in epoxy hardeners, 2-methylpentane-1,5-diamine, was recently described (14). It is therefore important to bear in mind

that previously unrecognized or novel contact allergens might be present in epoxy resin systems.

To our knowledge, contact allergy to derivatives of 1,3-BDMA has not been previously described. It is of note that, although the two hardeners containing derivatives of 1,3-BDMA that our patients had been using were products from the same manufacturer, several other manufacturers' epoxy hardener products that contain derivatives of 1,3-BDMA are available on the market.

We conclude that derivatives of 1,3-BDMA represent a previously unknown contact allergen in epoxy resin systems, the detection of which requires detailed exposure data and patch testing, not only with commercially available and previously known contact allergens, but also with the patients' workplace materials.

References

- 1 Pham H Q, Marks M J. Epoxy resins. In: *Ullmann's Encyclopedia of Industrial Chemistry*, 7th edition: Weinheim, Wiley-VCH Verlag GmbH & Co, 2012: pp. 156–211.
- 2 Pesonen M, Jolanki R, Larese Filon F et al. Patch test results of the European baseline series among patients with occupational contact dermatitis across Europe – analyses of the European Surveillance System on Contact Allergy network, 2002–2010. *Contact Dermatitis* 2015; **72**: 154–163.
- 3 Aalto-Korte K, Pesonen M, Suuronen K. Occupational allergic contact dermatitis caused by epoxy chemicals: occupations, sensitizing products, and diagnosis. *Contact Dermatitis* 2015; **73**: 336–342.
- 4 Nixon R, Cahill J, Jolanki R. Epoxy resins. In: *Kanerva's Occupational Dermatology*, 2nd edition, Rustemeyer T, Elsner P, John S M, et al. (eds): Berlin, Heidelberg, Springer-Verlag, 2012: pp. 559–581.
- 5 Kanerva L, Jolanki R, Estlander T. Allergic contact dermatitis from epoxy resin hardeners. *Am J Contact Dermat* 1991; **2**: 88–97.
- 6 Aalto-Korte K, Suuronen K, Kuuliala O et al. Contact allergy to epoxy hardeners. *Contact Dermatitis* 2014; **71**: 145–153.
- 7 Geier J, Lessmann H, Hillen U et al. Sensitization to reactive diluents and hardeners in epoxy resin systems. IVDK data 2002–2011. Part I: reaction frequencies. *Contact Dermatitis* 2015: doi:10.1111/cod.12491.
- 8 Johansen J D, Aalto-Korte K, Agner T et al. European Society of Contact Dermatitis guideline for diagnostic patch testing – recommendations on best practice. *Contact Dermatitis* 2015; **73**: 195–221.
- 9 Frick-Engfeldt M, Isaksson M, Zimerson E, Bruze M. How to optimize patch testing with diphenylmethane diisocyanate. *Contact Dermatitis* 2007; **57**: 138–151.
- 10 Nixon R, Cahill J, Jolanki R. Epoxy resins. In: *Kanerva's Occupational Dermatology*, Rustemeyer T, Elsner P, John S M, Maibach H I (eds): Heidelberg, Springer, 2012: pp. 559–581.
- 11 Dahlquist I, Fregert S. Allergic contact dermatitis from volatile epoxy hardeners and reactive diluents. *Contact Dermatitis* 1979; **5**: 406–407.
- 12 Breuer K, Uter W, Geier J. Epidemiological data on airborne contact dermatitis – results of the IVDK. *Contact Dermatitis* 2015; **73**: 239–247.
- 13 ECHA registration Dossier 4140: 1,3-Benzenedimethanamine, N-(2-phenylethyl) derivs. Available at: <http://echa.europa.eu/en/registration-dossier/-/registered-dossier/4140> (last accessed 27 May 2016).
- 14 Darr-Foit S, Geier J, Elsner P, Schliemann S. Occupational contact allergy to the epoxy resin hardener 2-methylpentane-1,5-diamine. *Contact Dermatitis* 2016; **74**: 115–116.