

## ORIGINAL ARTICLE

# Diaminodiphenylmethane Sensitization in north-eastern Italy from 1996 to 2012

F. Zuliani,<sup>1,\*</sup> A. Prodi,<sup>1</sup> A.B. Fortina,<sup>2</sup> M.T. Corradin,<sup>3</sup> M. Bovenzi,<sup>1</sup> F. Larese Filon<sup>1</sup><sup>1</sup>Clinical Unit of Occupational Medicine, University of Trieste, Trieste, Italy<sup>2</sup>Dermatology Unit, Department of Paediatrics, University of Padua, Padua, Italy<sup>3</sup>Dermatology Unit, S. Maria degli Angeli Hospital, Pordenone, Italy

\*Correspondence: F. Zuliani. E-mail: francescazuliani@hotmail.com

## Abstract

**Background** 4,4'-Diaminodiphenylmethane (DDM) is an aromatic amine used as a hardener, insulator and anticorrosive. Exposure implies risk of being sensitized and developing contact dermatitis.

**Objective** The aim of this study was to determine the occurrence of contact sensitization to DDM among patients with contact dermatitis and the role of occupational exposure.

**Patients and Methods** From 1996 to 2012, 24 056 consecutive patients with suspected allergic contact dermatitis were patch tested in north-eastern Italy. Individual characteristics were collected through a standardized questionnaire in eight departments of dermatology and occupational medicine.

**Results** The overall prevalence of DDM sensitization was 2.5% ( $n = 599$ ) with a decreasing trend in considered years. Trieste area had the higher prevalence of sensitization (3.2%). Mechanics and chemical industry workers had a significant higher risk of being sensitized to DDM.

**Conclusion** DDM sensitization is decreasing in years and is associated with some occupational exposures.

Received: 15 July 2016; Accepted: 15 September 2016

## Conflicts of interest

None declared.

## Funding sources

None declared.

## Introduction

4,4'-Diaminodiphenylmethane (DDM) is an aromatic amine used in rubber products, in synthetic textiles, as a hardener to cross-link epoxy resins, as a catalyst in the production of polyurethanes. Exposure to DDM may occur in production of rubber, plastics, synthetic resins, polymeric thermoplastic materials, colorants and paints, boats, automobiles, germicides, insecticides, in waterproofing of tissues and in recycling of plastic materials.<sup>1,2</sup> DDM sensitivity has been proposed to be a marker for diphenylmethane diisocyanate (MDI) contact sensitization.<sup>3,4</sup>

Workers primarily at risk are those employed in naval, mechanical, electric and electronic industry; they were affected by allergic contact dermatitis on hand, isolated or in association with face, trunk, arms and/or legs.

A positive patch test reaction to DDM in dermatological patients range between 0.8 and 8.5% with differences between countries<sup>1</sup> and exposure characteristics<sup>4-6</sup> and is related with the contact/exposure with substances containing DDM. In 2001, our group reported data on previous sensitization to

DDM in Italian patch tested population finding a prevalence of 1.9%.<sup>7</sup>

The aim of our study was to verify prevalence of DDM sensitization in a patch tested population from north-eastern Italy between 1996 and 2012, in order to:

- analyse the temporal trend of this sensitization during this period;
- evaluate involved sites and gender distribution
- study cross-reactivity with other haptens
- find associations between DDM sensitization and occupations in our geographical area.

## Patients and Methods

### Patients

From 1996 to 2012, we patch tested 24056 consecutive patients (16215 women and 7841 men) with suspected contact dermatitis in five departments of dermatology or occupational medicine in north-eastern Italy (Trieste, Pordenone, Padova, Rovigo,

Bolzano-Trento). All of them were given a standardized questionnaire, aimed at gathering information about individual characteristics, occupational history and personal/family history of atopic diseases (asthma and/or allergic rhino-conjunctivitis with at least one positive prick test to relevant aeroallergens). All subjects underwent a dermatological examination and occupational contact dermatitis was defined by the physician.<sup>8</sup>

We excluded 3150 patients with missing responses to personal and occupational history; so, only 20906 patients were finally included in the evaluation of work-related sensitization. All patients were assigned to occupational categories, aggregating related job groups into larger one (e.g. 'Health Care Workers' category). Some categories were reserved for specific jobs (such as carpenters or painters, extrapolated from the generic group of artisans) in order to give a special attention to occupations that, according to literature and clinical practice, represent a high risk of exposure to DDM, although numerically unrepresentative. We chose as a reference group, the white-collar workers (employees in office work), since presumably their sensitization to DDM is not related to occupational exposure.

#### Patch tests

All patients were patch tested using the European baseline series 6 and DDM 1% using haptens produced by F.I.R.M.A. (Italy) and Finn Chambers<sup>®</sup> on Scampor<sup>®</sup> (Epitest Ltd, Tuusula, Finland).<sup>6</sup>

Patches were applied on the upper back and removed after 48 h. The sites were examined on removal and 24 or 48 h after removal, according to International Contact Dermatitis Research Group guidelines.<sup>9</sup>

Reactions of grades +, ++ and +++ in the second examination were considered to be positive. Doubtful reactions ( $\pm$ , '?') were considered negative.

#### Statistical analysis

Data analysis was performed with software STATA v. 12.0 (Stata Corp., LP, College Station, TX, USA). Results of the patch test were analysed by means of multivariate logistic regression analysis in relation with sex, age, profession of patients and year of patch testing (according to calendar periods: 1996–1998, 1999–2001, 2002–2004, 2005–2007, 2008–2010, after 2010). Odds ratios and 95% confidence intervals were estimated from the coefficients and the standard errors of logistic regression output. Trend test across ordered groups has been performed via the Cuzick's test for trend.

A  $P < 0.05$  was established as the limit of statistical significance.

#### Results

The study population included 16 215 women (67.4%) and 7 841 men (32.6%) and their ages ranged from 16 to 97 years and

**Table 1** DDM sensitization in different body sites

	Female <i>n</i> = 403 %	Male <i>n</i> = 196 %	Total <i>n</i> = 599 %	OR	95% CI
Hand/Forearm Dermatitis	31.75	41.88	35.16	1.55	1.04–2.30
Leg	8.25	12.50	9.68	1.59	0.86–2.94
Face	22.54	8.75	17.89	0.33	0.18–0.61
Other sites	38.10	36.88	37.68	0.95	0.64–1.41

the mean age was  $42.6 \pm 17.3$  for females and  $42.7 \pm 17.5$  for males. Padua area had the largest number of patients (32.9%) and Rovigo had the smallest one (3.8%).

Five hundred and ninety-nine (2.49%) of the patients showed sensitization to DDM with percentages similar in both sexes. Sensitization was higher in Trieste (3.21%) and lower in the other areas (range 2.1–2.3%).

DDM Dermatitis most frequently involved hands among males with OR = 1.55; CI 95% 1.1–2.3 (Table 1) and less frequently, the face with OR = 0.3; CI 95% 0.2–0.6.

The prevalence of DDM sensitization did not show significant difference in females and males (OR = 0.9; CI 95% 0.7–1.1). Sensitization was significantly more frequent in older groups of patients (OR = 1.02; CI 95% 1.0–1.1), with a prevalence from 1.1% (16–25 years) to 3.8% (59–97 years) (Fig. 1).

The temporal trend of sensitization shows a stable prevalence from the beginning of the study (3.1%) to 1999–2001 (3.19%) and decreasing in the last years (1.4% after 2010) (Fig. 2).

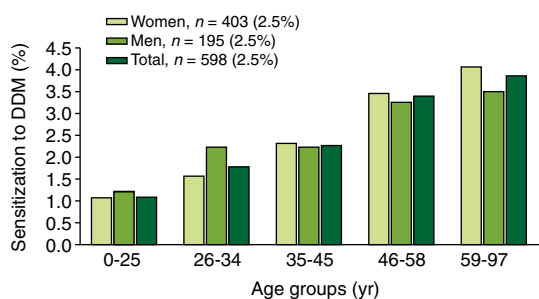
Significative concurrent sensitization for many haptens was observed in patients with positive patch test reaction to DDM (Table 2).

The association between sensitization to DDM and occupations were evaluated using multinomial logistic analysis, using as reference category, white-collar workers (Table 3). We found a significant association with mechanical work (3.3% OR = 1.67; CI 95% 1.1–2.5) and chemical industry work (4.2% OR = 2.2; CI 95% 1.0–4.5).

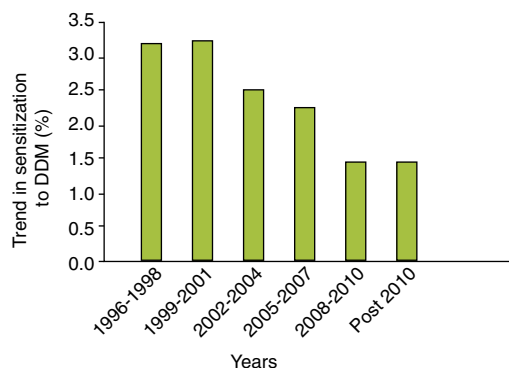
#### Discussion

This study investigated the prevalence of DDM sensitization in a database of 24506 subjects (the largest in Italy) with suspected allergic contact dermatitis, patch tested during 1996–2012, allowing us to have important knowledge about temporal trend of sensitization of DDM in north-eastern Italy.

The overall prevalence of DDM sensitization from 1996 to 2012 was 2.5% and was higher than the 1.1% found by Liippo *et al.*,<sup>4</sup> by Tarvainen (0.8%)<sup>6</sup> and Engfeldt *et al.* in Sweden (0.89%)<sup>1</sup> that analysed general dermatological patients patch tested. Our prevalence resulted lower than that found by Uter (8.5%),<sup>10</sup> in subjects sensitized to 'para-amino compounds' and by Engfeldt *et al.*<sup>1</sup> in Belgium (3.6%). Differences in sensitization that Engfeldt *et al.*<sup>1</sup> had attributed to the cross-reactivity



**Figure 1** Sensitization to DDM in different age groups.



**Figure 2** Trend in sensitization to DDM in considered years.

**Table 2** Concurrent sensitization between DDM and other haptens. Data are reported as Odds ratio (OR) and 95% confidence intervals (CI)

Hapten	OR	95% CI
Benzocaine	24.24	17.57–33.42
Cobalt chloride	1.83	1.46–2.29
Colophonium	2.00	1.27–3.17
Disperse Yellow 3	5.58	3.54–8.74
Disperse Blue 124	1.80	1.22–2.69
Epoxy resin	2.33	1.22–4.45
Fragrance mix	1.80	1.40–2.32
IPPD	2.85	1.61–5.06
Mercaptobenzothiazole	3.05	1.59–5.85
Paraben mix	3.01	1.87–4.86
para-Phenylenediamine	20.9	17.3–25.4
Primin	1.78	1.16–2.72
Thiuram mix	1.73	1.06–2.84

between DDM and p-phenylenediamine sensitization, that was more common in Belgium population.

Prevalence of sensitization decreased from 3.1% in 1996 to 1.4% in 2012, and this is plausibly attributable to an improvement of safety measures over the years, which has reduced the occupational exposure in younger ages. Trieste area had the highest prevalence of sensitization, because the average age was

**Table 3** Sensitization to DDM and association with occupation evaluated with multinomial logistic analysis using as reference category white-collar workers. Data are reported as Odds ratio (OR) and 95% confidence intervals (CI)

Job	Total n	DDM positive n (%)	OR	95% CI
White-collar workers	107	1.97	1	
Healthcare workers	61	2.42	1.16	0.85–1.60
Maids and restaurant	13	1.48	0.73	0.40–1.30
Personal care workers	1	3.33	1.46	0.20–10.9
Barbers and hairdressers	7	2.54	1.42	0.65–3.06
Shop assistants	1	1.59	0.67	0.09–4.94
Farmers and fishers	6	2.87	1.21	0.52–2.80
Construction workers	23	2.13	0.99	0.63–1.58
<b>Mechanics</b>	<b>37</b>	<b>3.30</b>	<b>1.67</b>	<b>1.14–2.47</b>
Woodworkers	10	2.89	1.44	0.75–2.80
Other artisans	13	2.49	1.20	0.67–2.16
Food processing workers	2	1.98	1.00	0.24–4.13
<b>Chemical industry workers</b>	<b>8</b>	<b>4.17</b>	<b>2.16</b>	<b>1.04–4.53</b>
Professional drivers	7	2.94	1.41	0.65–3.10
Domestic workers	9	2.99	1.30	0.65–2.60
Household workers	97	3.45	1.06	0.78–1.46
Students	1	0.56	0.43	0.06–3.15
Retired	135	3.95	0.88	0.63–1.24
Unemployed	8	2.17	1.06	0.51–2.20

DDM, 4,4'-Diaminodiphenylmethane. Significant associations are reported in bold.

higher than in other areas. In fact, in both sexes, sensitization was more frequent among patients aged 59–97 years (3.8%) than in younger group of workers (OR = 1.0; CI 95% 1.0–1.1).

Hands were the most frequently involved skin area by contact dermatitis (this body site was involved in 35.2% of our patients sensitized to DDM) and this is in accordance with a relevant occupational role of this sensitization.<sup>4,7</sup> Involvement of the hands (69%) together with facial symptoms (60%) were reported in subjects with occupational contact dermatitis related to epoxy chemicals.<sup>11</sup>

We find a significant association between DDM sensitization and occupation in chemical industry (OR = 2.2; CI 95% 1.1–4.5) because these workers are exposed to epoxy resins or other cross-reacting chemicals belonging to the para-amino group and also to isocyanate glue or varnishes. A significant association was found also in mechanics (OR = 1.7; CI 95% 1.1–2.5), who are exposed to epoxy resins, glues, polymeric thermoplastic materials and plastic materials.<sup>1,2</sup>

Moreover, we find strong association between DDM sensitization and other haptens with a similar molecular structure.<sup>7,12,13</sup> Between the 'para-amino compounds' benzocaine and p-phenylenediamine strongly cross-reacted with DDM sensitization (OR = 24, CI 95% 17.6–33.4 and OR 20.9, CI 95% 17.3–25.4 respectively) as already reported in other studies<sup>7,14,15</sup>. The last one is surely the most important in terms of

prevalence of sensitization in the population tested. Many other haptens resulted associated to the sensitization to DDM, in line with previous analysis<sup>7,14,15</sup> due to similar chemical structure (azo-dyes, parabens, primin) or to the sharing of some metabolic derivative such as eugenol and isoeugenol in fragrance mix<sup>7</sup> or to concomitant sensitization that can be suggested for epoxy resins that use DDM as hardener.

This is the largest study of DDM sensitization in Italy and the results are interesting showing the decrease in sensitization, probably due to the reduction of the use of cross-reactive products such as p-phenylenediamine in hair dyes.<sup>14</sup>

Nevertheless, some limitations of this study deserve attention. Although based on a large sample of individuals, the study population included patients who attended health services for suspected allergic dermatitis, and, for this reason, our results may be affected by selection bias. Another possible limitation of this study is related to its multi-centric design that may affect the data recording in different centres although all participants accepted a standardized protocol.

### Acknowledgement

We acknowledge the EU Horizon 2020 COST action StanDerm (TL-1206).

### Conclusion

Our study demonstrated a reduction in DDM sensitization over time in our geographical area. The evaluation of the distribution of sensitization in various occupational categories, permitted to define a higher sensitization in operators of chemical industry and in mechanics.

### References

- 1 Engfeldt M, Goossens A, Isaksson M, Zimerson E, Bruze M. The outcome of 9 years of consecutive patch testing with 4,4'-diaminodiphenylmethane and 4,4'-diphenylmethane diisocyanate. *Contact Dermatitis* 2013; **68**: 98–102.
- 2 Goossens A, Detienne T, Bruze M. Occupational allergic contact dermatitis caused by isocyanates. *Contact Dermatitis* 2002; **47**: 304–308.
- 3 Estlander T, Keskinen H, Jolanki R, Kanerva L. Occupational dermatitis from exposure to polyurethane chemicals. *Contact Dermatitis* 1992; **27**: 161–165.
- 4 Liippo J, Lammintausta K. Contact sensitization to 4,4'-diaminodiphenylmethane and to isocyanates among general dermatology patients. *Contact Dermatitis* 2008; **59**: 109–114.
- 5 Romaguera C, Garcia-Perez A, Martin-Pascual A, Miranda A. Diaminodiphenylmethane in standard patch tests. *Contact Dermatitis* 1981; **7**: 347–348.
- 6 Tarvainen K. Analysis of patients with allergic patch test reactions to a plastics and glues series. *Contact Dermatitis* 1995; **32**: 346–351.
- 7 Fortina AB, Piaserico S, Larese F *et al.* Diaminodiphenylmethane (DDM): frequency of sensitization, clinical relevance and concomitant positive reactions. *Contact Dermatitis* 2001; **44**: 283–288.
- 8 Rui F, Bovenzi M, Prodi A *et al.* Nickel, cobalt and chromate sensitization and occupation. *Contact Dermatitis* 2010; **62**: 225–231.
- 9 Isaksson M, Brandão F, Bruze M, Goossens A. Recommendation to include budesonide and tixocortol pivalate in the European standard series. *Contact Dermatitis* 2000; **43**: 41–42.
- 10 Uter W, Lessmann H, Geier J, Becker D, Fuchs T, Richter G. IVDK Study Group; German Contact Dermatitis Research Group (DKG) The spectrum of allergic (cross-)sensitivity in clinical patch testing with 'para amino' compounds. *Allergy* 2002; **57**: 319–322.
- 11 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.
- 12 Jolanki R, Kanerva L, Estlander T, Tarvainen K. Concomitant sensitization to triglycidyl isocyanurate, diaminodiphenylmethane and 2-hydroxyethyl methacrylate from silk-screen printing coating in the manufacture of circuit boards. *Contact Dermatitis* 1994; **30**: 12–15.
- 13 Schnuch A, Brasch J, Uter W. Polysensitization and increased susceptibility in contact allergy: a review. *Allergy* 2008; **63**: 156–167.
- 14 Rudzki E, Rebandel P, Zawadzka A. Sensitivity to Diaminodiphenylmethane. *Contact Dermatitis* 1995; **32**: 303.
- 15 Holness DL, Nethercott JR, Adams RM *et al.* Concomitant positive patch test results with standard screening tray in North America 1985–1989. *Contact Dermatitis* 1995; **32**: 289–292.