

# Sensitization to ethylenediamine dihydrochloride in patients with contact dermatitis in northeastern Italy from 1996 to 2021

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## Abstract

**Background:** Ethylenediamine dihydrochloride is a versatile aliphatic amine found in numerous medications and industrial compounds and is a known sensitiser. The sensitization prevalence is affected by geographical and socio-cultural factors.

**Objectives:** The objectives are to analyse the temporal trend of sensitization to ethylenediamine dihydrochloride in northeastern Italy and to investigate associations with occupations.

**Methods:** Between 1996 and 2021, 30 629 patients with suspected allergic contact dermatitis were patch tested with the Triveneto baseline series. Individual characteristics were collected through a standardised questionnaire.

**Results:** The overall prevalence of ethylenediamine dihydrochloride sensitization was 1.29% with percentages similar in both sexes. We observed a significant decreasing trend over time ( $p < 0.001$ ), yielding a sensitization prevalence  $< 1\%$  in recent years. Among departments, residence in Pordenone area was protective for sensitization. No significant associations were observed with specific occupations. We found significant associations between ethylenediamine dihydrochloride sensitization and being 26–35 years old (odds ratio [OR], 1.47; 95% confidence interval [CI]: 1.05–2.08), and sensitization for many haptens, such as paraben mix (OR, 5.3; 95% CI: 3.3–8.5), epoxy resin (OR, 5.1; 95% CI: 3.0–8.7), neomycin sulphate and mercaptobenzothiazole.

**Conclusions:** Our study showed a downward time trend of ethylenediamine dihydrochloride sensitization in northeastern Italian population and pointed to an update of the Triveneto baseline series.

## KEYWORDS

contact dermatitis, epidemiology, ethylenediamine dihydrochloride, sensitization, time trend analysis

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## 1 | INTRODUCTION

Ethylenediamine dihydrochloride (EDD), CAS no. 333-18-6, is a chemical compound synthesised by reacting ethylenediamine (EDA) with hydrochloric acid or hydrogen chloride gas.<sup>1</sup> Because of its versatility, it has been widely used as chemical intermediate in the production of many industrial compounds and may be found in pharmaceutical products.<sup>2</sup>

EDD is a potent sensitising agent producing contact dermatitis (CD).<sup>3</sup> More rarely, sensitization to it may lead to rhinitis and asthma, systematically induced dermatitis, and urticarial reactions.<sup>4–6</sup>

CD due to EDD was first described in the late 1950s in pharmacists handling aminophylline suppositories that contain this substance as increaser of solubility of active component (theophylline).<sup>7,8</sup> Sensitization to EDD was also occasionally reported among nurses preparing and administering injectable aminophylline.<sup>9,10</sup>

EDD has been a common sensitiser due to its wide use as a stabiliser in topical preparations.<sup>3</sup> Frequent sensitizations in general population were described in the 1960–1970s due to its presence in Mycolog (tri-actocortyl in the United Kingdom, Kenacomb in Australia and Assocort in Italy), an antifungal/corticosteroid combination cream containing neomycin, nystatin, gramicidin and triamcinolone.<sup>11–13</sup> Because of these reports, a reformulation of the cream without the allergen was made in 1985 (Mycolog II),<sup>13</sup> and subsequently EDD was removed from many other topical medications. However, certain generic formulations of nystatin-containing creams may still contain this sensitiser.<sup>3,14–16</sup>

In sensitised subjects, the systematic administration of aminophylline may cause allergic reactions,<sup>4,17</sup> and, recently, a case of urticarial reaction has been described due to aminophylline compound used for mesotherapy.<sup>6</sup> In addition, an entire family of antihistamines is derived from EDA (hydroxyzine, pyrilamine and tripelemamine), and some cross-reactions have been reported systematically and topically.<sup>4,18</sup> Although rare, the allergic reactions to these EDA derivatives may result in significant morbidity.<sup>17</sup>

Occupational CD (OCD) to EDD has been reported much more rarely than non-OCD,<sup>16,19</sup> despite being present in numerous industrial processes. It is used as a stabiliser in rubber latex, corrosion inhibitor in antifreeze solutions and cooling fluids, epoxy curing agent, accelerator in colour development baths in photography, solvent for casein, albumin and shellac. Other industrial applications are in the preparation of electroplating and electrophoretic gels, dyes, insecticides, floor polish removers, synthetic waxes and textile lubricants.<sup>19–21</sup>

In industrial scenarios, OCD caused by EDD was described in metallurgical engineering after exposure to coolant oils<sup>22,23</sup> and lubricants.<sup>24,25</sup> English et al.<sup>26</sup> reported a case of OCD, also to a floor polish remover in which the allergen was present. EDD sensitivity and cross-reactions were also found for OCD with epoxy resin hardeners.<sup>27–29</sup> Then, Corazza et al.<sup>21</sup> reported OCD in a goldsmith using an industrial detergent, in which EDD acts as a sequestering agent for metal ions except gold and silver.

Although its widespread use and its sensitising potential, EDD has over the years become clinically less important and has, therefore, been displaced from the European baseline series and only included in a medicament series.<sup>30</sup> However, the specific standard/baseline series

vary according to the locality of the patch-testing centres,<sup>31</sup> and many still include this hapten as considered appropriate for the population being tested—as is the case in North-East Italy Contact Dermatitis Group (NEICDG).<sup>32</sup>

Recent data on contact sensitization to EDD in Italy are not available. This study aimed to analyse the temporal trend of sensitization to EDD between 1996 and 2021 in northeastern Italian population patch tested for suspected allergic CD (ACD) and to investigate possible associations with occupations.

## 2 | MATERIALS AND METHODS

The Triveneto patch test database has been already described in several publications.<sup>32–34</sup> In the period between 1 January 1996 and 31 December 2021, a total of 30 629 consecutive patients with symptoms and/or signs of suspected CD were clinically assessed and patch tested in one of the departments of dermatology or occupational medicine constituting the NEICDG (Padua, Trieste, Pordenone, Belluno, Rovigo and Trento-Bolzano; the latter being aggregated for analysis). All of them underwent a clinical examination and were given a standardised questionnaire to collect information about individual characteristics, personal and family history of atopic diseases (asthma and/or allergic rhinoconjunctivitis with at least one positive prick test to relevant aeroallergens) and occupational history. All patients were assigned to occupational categories, aggregating related job groups into larger one (e.g., ‘Health workers’ category). Subjects without formal employment were subdivided into the three categories of students, retired and unemployed. Clerks were chosen as reference group, since presumably their sensitization profiles are not related to job exposure. Similarly to job categories, specific body sites (e.g., fingers, palms and dorsa of hands) were aggregated into larger categories (e.g., ‘hands’). Sex and age differences were taken into account to minimise confounding factors, as described in the section ‘Statistical analysis’. All patients underwent patch testing for diagnostic purposes and gave written informed consent.

### 2.1 | Patch tests

Finn Chambers on Scanpor tape (Epitest Ltd, Tuusula, Finland) and a selection of haptens from FIRMA (Firenze, Italy) and SmartPractice Italy (Roma, Italy) were used to perform patch tests on patients with the Triveneto baseline series.<sup>35</sup> The tested allergens included EDD 1% pet. Patches were applied on the upper back and removed after 48 h (day [D] 2). The sites were examined on removal (D2) and after 72 (D3) or 96 h (D4) according to ICDRG guidelines.<sup>36</sup> Reactions of grades +, ++ and +++ in the second examination were considered to be positive. Doubtful reactions (± and ‘?’) were considered to be negative.

### 2.2 | Statistical analysis

Data analysis was performed with the software STATA v. 14.0 (Stata Corp., LP, College Station, Texas, USA). Categorical data were

**TABLE 1** Characteristics of patients sensitised and not sensitised to ethylenediamine dihydrochloride.

Characteristics	Ethylenediamine dihydrochloride-positive (n = 396)	Ethylenediamine dihydrochloride-negative (n = 30 233)	Total (n = 30 629)	p
Age, years ± SD	44.5 ± 16.8	43.8 ± 17.2	43.8 ± 17.2	ns
Males, n (%)	134 (33.8)	9801 (32.4)	9935 (32.4)	ns
Occupational dermatitis, n (%)	37 (9.3)	2483 (8.2)	2520 (8.2)	ns
Atopic eczema, n (%)	39 (11.2)	2729 (10.1)	2768 (10.1)	ns
Hand localization, n (%)	122 (38.5)	9392 (36.3)	9514 (36.3)	ns
Leg localization, n (%)	21 (6.6)	2098 (8.1)	2119 (8.1)	ns
Face localization, n (%)	67 (21.1)	5048 (19.5)	5115 (19.5)	ns
Age ≥ 40 years, n (%)	220 (55.6)	16 162 (53.5)	16 382 (53.5)	ns

Note: Some percentages do not sum to the total because of missing data. Abbreviations: ns, not significant; SD, standard deviation.

cross-tabulated into  $k \times k$  contingency tables and compared using the chi-square test. Sensitization to EDD as an outcome was analysed by multivariate logistic regression analysis considering, as independent variables, sex, age (as a continuous variable) and patient occupation (with clerks as reference category). Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated from the coefficients and the standard errors of logistic regression output. An EDD sensitization trend test across ordered groups was performed with Cuzick's test for trend. Patients with missing data for relevant variables were excluded from the analysis. A  $p$  value of  $<0.05$  was established as the limit of statistical significance.

### 3 | RESULTS

The study population included 20 694 women (67.6%) and 9935 men (32.4%). The mean age of the population was higher for males ( $44.1 \pm SD 17.3$  vs.  $43.6 \pm 17.2$  years;  $p < 0.05$ ). There was a higher frequency of occupational dermatitis in males (10.1%) than in females (7.4%) ( $p < 0.05$ ), and dermatitis most frequently involved the hands in both sexes (39.9% in males versus 34.6% in females,  $p < 0.05$ ), followed by the face, more often in women (22.9% in females versus 12.5% in males;  $p < 0.05$ ). The overall prevalence of EDD (1% per.) sensitization was 1.29% with percentages similar in both sexes. No significant difference in mean age, occupational dermatitis (9.0% in males vs. 9.5% in females), and involvement of hand (38.1% in males vs. 38.7% in females) and face (20.0% in males vs. 21.7% in females) was observed between EDD-sensitized women and men. MOAHLFA (Male, Occupational dermatitis, Atopic dermatitis, Hand dermatitis, Leg dermatitis, Facial dermatitis, Age > 40 years) index values for patients with ACD caused by EDD and those who were not allergic to EDD are shown in Table 1. The former group was older and presented more hand and face dermatitis, but no significant differences emerged. Examination by logistic regression did not find that increased patient age affected the risk of EDD-sensitization.

Details of patch test results are reported in Figure S1: 40% of patients reacted on D2, mainly with + reactions (19.5%), whereas the

**TABLE 2** Sensitization to ethylenediamine dihydrochloride in different dermatological centres.

Centre	Sensitized, n	Total, n	%	OR	95% CI
Padua	148	9562	1.55	1	
Pordenone	78	7471	1.04	<b>0.67</b>	<b>0.51–0.88</b>
Trieste	129	9963	1.29	0.83	0.66–1.06
Others	41	3633	1.13	0.73	0.51–1.03
Total	396	30 629	1.29		

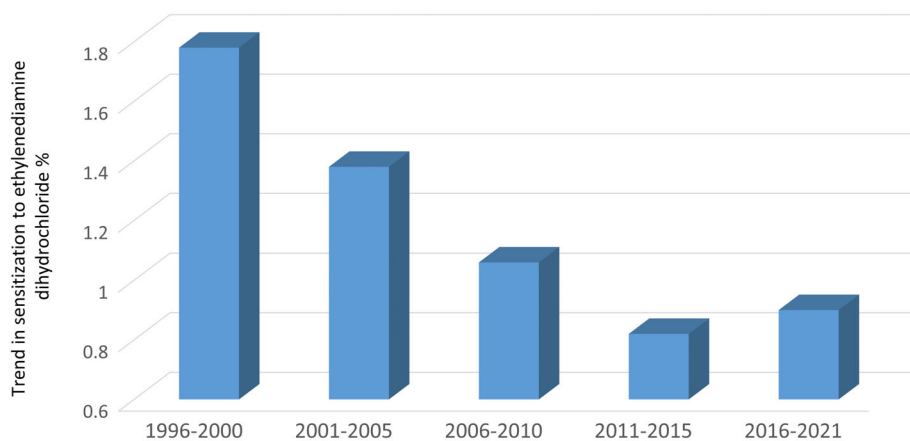
Note: Statistically significant results are in bold. Abbreviations: CI, confidence interval; OR, odds ratio.

readings on D3 and D4 yielded + reactions in 47.3%, ++ reactions in 33.6% and +++ reactions in 19.1%.

EDD sensitization in different occupational groups, investigated by means of multivariate logistic regression and using clerks as reference category, is shown in Table S1. Among the general population of 30 629 patients, 69 were excluded from analysis because of lack of information concerning their jobs. Of the 396 sensitized patients, 352 were distributed among the various occupational categories, and for 44 patients no detailed occupational data were available. No significant associations were observed between EDD sensitization and specific occupations.

The numbers of patients collected by the departments that participated in the survey were 9963 (32.5%) for Trieste, 9562 (31.2%) for Padua, 7471 (24.4%) for Pordenone and 3633 (11.9%) for others. Among the 396 sensitized cases, 148 were diagnosed in Padua, 129 in Trieste, 78 in Pordenone and 41 in the other centres. The prevalence of sensitization in Pordenone was significantly lower than that in Padua (OR, 0.67; 95% CI: 0.51–0.88) (Table 2).

The temporal analysis for EDD sensitization showed a significant decreasing trend over time, from 1.78% in 1996–2000 to 0.82% in 2011–2015 and 0.9% after 2016 (1996–2000 vs. after 2016;  $p < 0.001$ ) (Figure 1). Regression analysis revealed significantly lower prevalence of positive patch test reactions for each of the periods considered (2001–2005, 2006–2010, 2011–2015 and after 2016) (Table S2).



**FIGURE 1** Trend in sensitization to ethylenediamine dihydrochloride in considered years.

**TABLE 3** Sensitization to ethylenediamine dihydrochloride in different age groups.

Age (years)	Sensitised, n	Total, n	%	OR	95% CI
<26	51	5073	1.01	1	
26-35	95	6433	1.48	<b>1.47</b>	<b>1.05-2.08</b>
36-45	72	5787	1.24	1.24	0.86-1.77
46-55	71	5073	1.40	1.40	0.97-2.01
56-65	50	4208	1.19	1.18	0.80-1.75
>65	57	4055	1.41	1.40	0.96-2.05
Total	396	30 629	1.29		

Note: Statistically significant results are in bold.

Abbreviations: CI, confidence interval; OR, odds ratio.

The prevalence of sensitization in different age groups showed a fluctuating trend (Table 3), with a significantly increased prevalence in subjects aged 26-35 years (OR, 1.47; 95% CI: 1.05-2.08).

Significant concurrent sensitization for many haptens was observed in EDD-sensitized subjects (Table 4). The strongest association was found for paraben mix (OR, 5.3; 95% CI: 3.3-8.5), followed by epoxy resin (OR, 5.1; 95% CI: 3.0-8.7), neomycin sulphate and mercaptobenzothiazole.

Multiple reactions among EDD-sensitized patients are summarized in Figure 2. Thirty-one percent were monosensitized to EDD. Most of the co-sensitized subjects reacted to one other hapten (25%), followed by those who reacted to two other haptens (17.4%), whereas only a few were sensitized to  $\geq 3$  other haptens.

## 4 | DISCUSSION

Epicutaneous patch testing is the primary diagnostic tool for identifying allergens that cause ACD. Most countries or regions have a recommended standard series (also referred to as baseline or screening series) comprising allergens that most commonly cause ACD in the population being patch-tested. The standard series forms the core

series of contact sensitizers that may be expanded by patch testing with other series specifically chosen on the basis of patient history, physical examination and/or environmental/occupational exposure.<sup>31</sup>

The Triveneto standard patch test series, as recommended by the NEICDG, is a modified European baseline series according to local epidemiological profile and pattern of contact sensitization; our tested allergens included EDD 1% pet. Similarly in Europe, the Spanish Contact Dermatitis and Skin Allergy Research Group provides its own standard series retaining several allergens appropriate to the Spanish setting that are not present in the European series (e.g., EDD).<sup>37</sup> Ongoing surveillance on the prevalence of contact sensitization contributes to maintaining an up-to-date standard series comprising the most relevant allergens for routine patch testing in different countries and geographical areas.<sup>38</sup>

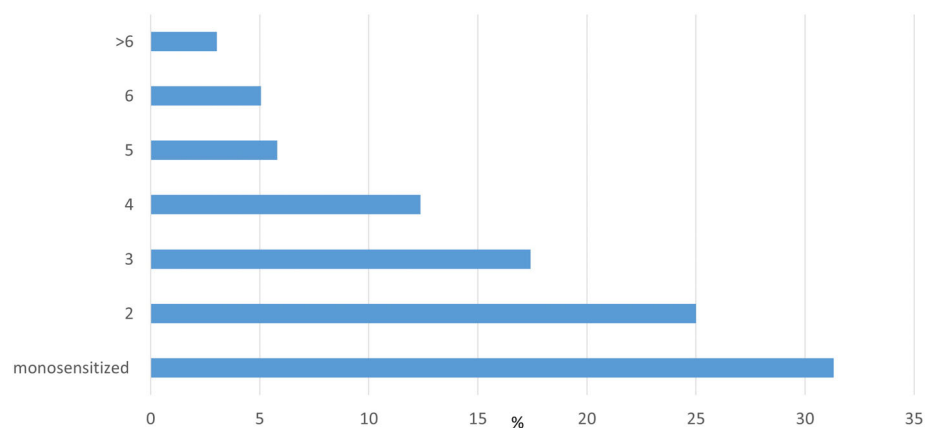
This study investigated the prevalence of EDD sensitization in a database of 30 629 subjects (the largest in Italy) with suspected ACD, patch tested during 1996-2021, allowing us to have important knowledge about the time trend of EDD sensitization in northeastern Italy. The overall prevalence of EDD sensitization in this period was 1.29%. Our percentage of positive reactions was still higher compared to that found over 20 years ago in Central Europe (0.3%),<sup>39</sup> which had led to no longer including EDD in the European standard series.<sup>30</sup> In contrast to the rest of Europe, the frequency of reactions to EDD has always been higher in southern Europe. In Italy, Angelini et al.,<sup>40</sup> who investigated 8230 southern Italian patients with suspected ACD between 1968 and 1983, found EDD sensitization in 3.0%. In Spain, Romaguera et al.<sup>41</sup> patch-tested 4600 patients in the period 1973-1977 and found a sensitization prevalence of 2.5% for EDD.

In our study, the temporal trend of sensitization showed a higher prevalence (1.78%) at the beginning of the study (in 1996-2000) and a gradual significant decrease over time reaching 0.82% in 2011-2015, followed by a slight increase after 2016 (0.9%). Similarly to our figures in recent years, the European Surveillance System on Contact Allergies results, presented by Uter et al.<sup>38,42</sup> in two studies, found an overall low prevalence (0.81% and 0.88% in 2015-2018 and 2019-2020, respectively) in those departments that have used the TRUE test system as a part of their baseline patch test series. The TRUE test

**TABLE 4** Concurrent sensitization to ethylenediamine dihydrochloride and other haptens (all in pet., except where indicated otherwise).

Haptens	Ethylenediamine dihydrochloride-positive (n = 396)	Ethylenediamine dihydrochloride-negative (n = 30 233)	OR	95% CI
Paraben mix 1%, n (%)	19 (4.8)	285 (0.9)	<b>5.3</b>	<b>3.3–8.5</b>
Epoxy resin 1%, n (%)	15 (3.8)	232 (0.8)	<b>5.1</b>	<b>3.0–8.7</b>
Neomycin sulphate 20%, n (%)	36 (9.1)	665 (2.2)	<b>4.4</b>	<b>3.1–6.3</b>
Mercaptobenzothiazole 2%, n (%)	10 (2.5)	178 (0.6)	<b>4.4</b>	<b>2.3–8.3</b>
Diaminodiphenylmethane 0.5%, n (%)	33 (8.3)	702 (2.3)	<b>3.8</b>	<b>2.7–5.5</b>
Disperse yellow 3 1%, n (%)	11 (2.8)	225 (0.7)	<b>3.8</b>	<b>2.1–7.1</b>
Lanolin alcohol 30%, n (%)	22 (5.6)	479 (1.6)	<b>3.6</b>	<b>2.3–5.7</b>
Mercapto mix 2%, n (%)	9 (2.3)	194 (0.6)	<b>3.6</b>	<b>1.8–7.1</b>
Benzocaine 5%, n (%)	11 (2.8)	237 (0.8)	<b>3.6</b>	<b>1.9–6.6</b>
Quaternium-15 1%, n (%)	6 (1.5)	139 (0.5)	<b>3.3</b>	<b>1.5–7.6</b>
Chinoline mix, n (%)	4 (1.0)	1 (0.003)	<b>3.1</b>	<b>1.2–8.2</b>
IPPD, n (%)	9 (2.3)	236 (0.8)	<b>2.9</b>	<b>1.5–5.8</b>
Euxyl K400 0.5%, n (%)	19 (5.0)	526 (1.9)	<b>2.8</b>	<b>1.7–4.4</b>
p-phenylenediamine 1%, n (%)	36 (9.1)	1060 (3.5)	<b>2.7</b>	<b>1.9–3.9</b>
Thiuram mix 1%, n (%)	16 (4.1)	491 (1.6)	<b>2.5</b>	<b>1.5–4.2</b>
Disperse Blu 124 1%, n (%)	22 (5.6)	758 (2.5)	<b>2.3</b>	<b>1.5–3.5</b>
Fragrance mix-I 8%, n (%)	54 (13.6)	2147 (7.1)	<b>2.1</b>	<b>1.5–2.8</b>
Formaldehyde 1% (aq), n (%)	22 (5.6)	879 (2.9)	<b>2.0</b>	<b>1.3–3.0</b>
Kathon GC 0.01%, n (%)	33 (8.4)	1294 (4.3)	<b>1.9</b>	<b>1.4–2.7</b>
Primin 0.01%, n (%)	12 (3.0)	498 (1.6)	<b>1.9</b>	<b>1.04–3.3</b>
Colophonium 20%, n (%)	12 (3.0)	512 (1.7)	<b>1.8</b>	<b>1.01–3.2</b>
Carba mix 3%, n (%)	24 (6.1)	1062 (3.5)	<b>1.8</b>	<b>1.2–2.7</b>
Cobalt chloride 1%, n (%)	60 (15.1)	2818 (9.3)	<b>1.7</b>	<b>1.3–2.3</b>
Balsam of Peru 25%, n (%)	38 (9.6)	1792 (5.9)	<b>1.7</b>	<b>1.2–2.4</b>
Thimerosal 0.1%, n (%)	35 (9.0)	1783 (6.0)	<b>1.5</b>	<b>1.1–2.2</b>
Potassium dichromate 0.5%, n (%)	39 (9.8)	2010 (6.7)	<b>1.5</b>	<b>1.1–2.1</b>
4-tert-butylphenolformaldehyde resins 1%, n (%)	6 (1.5)	335 (1.1)	1.4	0.6–3.1
Nickel sulphate 5%, n (%)	122 (30.8)	7950 (26.3)	<b>1.2</b>	<b>1.01–1.5</b>

Note: Some percentages do not sum to the total because of missing data. Statistically significant results are in bold. Abbreviations: CI, confidence interval; OR, odds ratio.

**FIGURE 2** Percentages of ethylenediamine dihydrochloride-sensitized patients reacting to a growing cumulative number of haptens.

(thin-layer rapid use epicutaneous patch test) is an FDA-approved pre-packaged allergen system used by many dermatologists as a valuable first-line screening tool instead of the traditional testing system (syringes and Finn chambers); it now comprises 35 haptens diverging from the European standard series in some aspects (e.g., inclusion of EDD).<sup>43</sup>

Our analysis did not find an occupational role of EDD in our geographical area. This finding, showing that sensitization in work circumstances is rather rare, is in agreement with previous findings,<sup>2,16,19,30</sup> and confirms the main role of EDD as a non-occupational source of allergy. Surprisingly, though not statistically significant, we observed an increased prevalence of EDD sensitization in tannery, leather and shoe industry workers (OR, 1.98; 95% CI: 0.62–6.36) compared with clerks (reference category). To the best of our knowledge, no other studies have addressed an association as such before. This increased prevalence may be partially explained by the several steps related to leather production and shoe processing that involve exposure to a wide range of chemicals such as fungicides, dyes, rubber and adhesive components, which may contain EDD.<sup>20</sup>

Besides, a small, not significant, increased prevalence was observed in domestic workers (OR, 1.46; 95% CI: 0.70–3.02), other artisans (including textile workers, upholsterers) (OR, 1.32; 95% CI: 0.63–2.73), hairdressers, barbers and beauticians (OR, 1.35; 95% CI: 0.62–2.93), and mechanics (OR, 1.20; 95% CI: 0.76–1.90). In UK, consultant dermatologists of the occupational skin disease surveillance (EPIDERM 1993–2012) reported 44 cases of work-related skin disease attributed to EDD between 1993 and 2012; occupations reporting reactions to EDD included beauticians/hairdressers, engineers, chemical process operators, nurses, machine fitters, machine tool operators and cleaners/domestics.<sup>44</sup> In north-central Italy, the local health authority, who investigated 286 cases of confirmed ACD between 1995 and 1997, found a prevalence of sensitization to EDD of 1.7% (similarly to our figure in the first years) involving the health, cleaning and metalworking sectors.<sup>45</sup> Both these studies found some categories in which sensitization to EDD was believed to be job related, although they did not compare EDD sensitization in such professions with a reference category. Regarding health sector, skin sensitization was observed in pharmaceutical workers and nurses handling aminophylline preparations,<sup>7–10,19</sup> of which EDD along with theophylline are components. Our analysis did not find an increased sensitization to EDD in health workers, probably as a result of the improvement of protective measures in this sector and the replacement of theophylline-containing products with others, which are not dissolved in EDD.<sup>17</sup> In metallurgical engineering, OCD has been reported from EDD after exposure to coolant oils and lubricants, and even an epidemic occupational sensitization in a wire-drawing factory has been described.<sup>22–25</sup> Among industrial and laundry detergents, there are a number of notable products that can contain EDD as bleach activator,<sup>3</sup> which may explain the sensitization observed in cleaners/domestics and also in hairdressers, as frequently performed the cleaning of the hairdressing salon.<sup>46</sup> EDA sensitivity may also be attributable to cross-reactivity to other amines, as previously demonstrated,<sup>27–29</sup> and reactions to EDD observed in beauticians/

hairdressers may even be a result of cross-reactions of paraphenylenediamine and related amines in hair dyes.<sup>3,47</sup>

Our data showed an increased sensitization, albeit not significant, in retired individuals (OR, 1.10; 95% CI: 0.80–1.52). We think there may be different reasons for this increased prevalence. It may be partially explained by exposure at a young age to EDD from antifungal/steroid combination creams (e.g., Mycogol) before it was gradually removed in the 1980–1990s, and partially by the presence of comorbidities, such as venous insufficiency, the treatment of which may involve the use of topical medications, which may still contain EDD.<sup>16,40</sup> In fact, EDD may be a hidden allergen as inactive ingredient of certain topical products—nystatin creams in particular, especially generic formulations—as recently observed by Iammatteo et al.<sup>3</sup>

Hence, the prevalence of EDD allergy has been declining in Europe, probably as a result of the legislative measures regarding EDD content in commercial topical medications,<sup>13,14</sup> but cases of EDD allergy are still being observed. Recently, a retrospective study of patch test results in Greece found that 11% of construction workers had positive patch test reactions to EDD.<sup>48</sup> Similarly, Mowitz et al.<sup>49</sup> in Sweden observed 12.5% of EDD sensitization among workers manufacturing precast concrete elements. In this latter case, the reactions to EDD have been attributable to cross-reactivity to other aliphatic amines added to the cement, which have similar chemical structures. In both these studies, the high prevalence of sensitization to EDD along with other allergens appeared to be due to a poor adherence of such workers to protective measures. Anyway, these ‘epidemic’ occupational sensitivities are a reminder of the high sensitising potential of EDD, and strongly emphasise the importance of prevention.

Deeply analysing the characteristics of subjects sensitised to EDD, the most frequently involved sites were primarily hands/forearms followed by the face, as parts of the body most exposed to external agents, which is in line with other studies.<sup>19,32,34,50</sup> However, there was no significant difference in the MOAHLFA body localizations if compared with the EDD-negative group. Typically, wherever there is a relevant occupational role of sensitization, there is also a significant involvement of hands.<sup>34,50</sup> Hence, our finding supports the idea that EDD sensitization is mainly from non-occupational contact with externally used preparations. Moreover, we failed to find an increased risk of having atopic eczema, which is in line with other studies in Italy, where the prevalence of atopic dermatitis is lower when compared, for instance, with northern European countries.<sup>32,46,51,52</sup>

Despite the decreasing trend of EDD sensitization, our data showed a significantly increased risk (OR, 1.47; 95% CI: 1.05–2.08) for young adults (26–35 years old) to be sensitised when compared with subjects less than 26 years old. We think that young adults are the age class most exposed to sensitization as they are the most active sector of the population. Otherwise, our analysis demonstrated a fluctuation in EDD sensitization in different ages and no differences between women and men were observed, showing that exposure to EDD might occur from multiple sources according to its wide usage.

With respect to different geographical areas, the Padua Centre had the higher prevalence of sensitization (1.55%), whereas residence

in the Pordenone area was protective for sensitization to EDD (OR, 0.67; 95% CI: 0.51–0.88). These findings may be explained by their own geographical characteristics. In Pordenone, there is a predominance of small towns and very large rural areas, and therefore a prevailing exposure to contact allergens different from EDD.<sup>53</sup>

The evaluation of multiple sensitivities in patients with contact allergy to EDD showed that a larger proportion was monosensitized (31%), followed by those who had a reaction to only one contact allergen apart from EDD (25%), and those who reacted to two additional other haptens (17.4%). Concomitant sensitivities are often observed and may be the result of co-sensitization due to concomitant exposure to unrelated allergens, or cross-reactivity due to structural similarities between allergens.<sup>54</sup> We found a significant association between EDD positivity and positivity for many other haptens, mainly antimicrobial preservatives, such as paraben mix and neomycin sulphate, but also resins, such as epoxy resin and diaminodiphenylmethane, and rubber accelerators, such as mercaptobenzothiazole. Concurrent sensitization between neomycin sulphate and EDD was reported by several authors<sup>2,49,55</sup>; these haptens are often used together in the same topical products to enhance the antimicrobial activity. Coupled reactivity between EDD and other amines in epoxy resin system has already been reported,<sup>2,3,24</sup> probably due to similar amino structure. Moreover, EDD may be present as an additive in cement, which often contain many other contact allergens.<sup>48,49</sup> In many workers, concurrent sensitization to some of these haptens may also depend on the use of rubber protective equipment (gloves and shoes) that may contain EDD among additives.<sup>17,56</sup> Furthermore, in adhesive sensitivities, coupled reactivity has been reported between colophony, rubber components and EDD, due to the chemical N, N'-disalicylidene-1, 2-diaminopropane, which is hydrolyzed to a derivative of EDA.<sup>57</sup>

Our study has some limitations. 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, the results may be affected by selection bias. The merging of smaller groups into larger ones—because of the statistical limitations of small group analysis—may also have led to some loss of data, although we paid more attention to categories previously reported in the literature and/or having a higher prevalence than the average. Another possible limitation is related to the multi-centric design of the study that may have affected the data recording in different centres, though all participants accepted the use of a standardised protocol. Despite such possible limitations, this study is, in our best knowledge, the largest and longest that reports data on EDD sensitization in Italy.

Our study adds some important data regarding EDD sensitization prevalence in the northeastern Italian population and points to an update of the Triveneto standard patch test series. The downward time trend probably reflects the results of the removal of EDD content in topical preparations most commonly used in Italy, and the promotion of a culture of risk prevention at workplace, which includes the training and vocational education, and the use of proper personal and collective protective equipment by workers. Contact allergy to EDD has become clinically less relevant in northeastern Italy, yielding a prevalence of sensitization <1% in recent years, and we, therefore,

consider no longer justifiable to include this hapten in our baseline patch test series. Nevertheless, it is important to remember the possibility of EDD allergy in any patient presenting with skin eruption or unexpected worsening of previous skin eruption after application of topical medicaments and/or contact with adhesives.

## AUTHOR CONTRIBUTIONS

**Linda Piapan:** Writing – original draft; conceptualization; investigation; methodology; data curation. **Anna Belloni Fortina:** Investigation. **Erika Giuliani:** Investigation. **Francesca Larese Filon:** Supervision; formal analysis; writing – review and editing; conceptualization; investigation; software; validation; data curation.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, F. L. F., upon reasonable request.

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