

## 2-Hydroxyethyl methacrylate (2-HEMA) sensitization, a global epidemic at its peak in Spain?

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### Abstract

**Background:** A global epidemic of allergic contact dermatitis to (meth)acrylates has been described in relation to the widespread use of manicure products.

**Objectives:** To evaluate the frequency of sensitization to 2-hydroxyethyl methacrylate (2-HEMA) among consecutively patch tested patients with eczema in Spain; the percentage of current relevance; the MOAHLFA index; and, the potential sources of exposure to (meth)acrylates.

**Methods:** From January 2019 to December 2022, 2-HEMA 2% pet. was prospectively patch tested in 24 REIDAC (Spanish Allergic Contact Dermatitis Registry) centres.

**Results:** Six thousand one hundred thirty-four patients were consecutively patch tested with 2-HEMA 2% pet. 265/6134 (4.3%) were positive. Positive reactions of current relevance were identified to involve 184/265 (69%). The efficiency (number of patch tests needed to detect relevant positive patch test reactions) was 34 (6134/184). The variable 'occupational' was found to be significantly associated with a higher risk for relevant positive reactions to 2-HEMA (OR: 10.9; 95% CI: 8.1–14.9).

**Conclusion:** (Meth)acrylate sensitization is a prevalent health issue in Spain. 2-HEMA 2% pet. has been identified to be a highly effective (meth)acrylate allergy marker in

the GEIDAC baseline series. The responsible authorities should implement policies guaranteeing accurate labelling of industrial, medical, and consumer materials while ensuring the enforcement of said labelling through appropriate legal means.

#### KEYWORDS

(meth)acrylates, 2-hydroxyethyl methacrylate, acrylates, acrylic nails, allergic contact dermatitis, beauticians, occupational, patch test, prevalence, semi-permanent nail polish

## 1 | INTRODUCTION

Acrylic resins are plastic materials formed by the polymerisation of monomers containing an acrylic group derived from acrylic acid (acrylates) or methacrylic acid (methacrylates).<sup>1</sup> Hereafter, we will refer to both as (meth)acrylates.

Allergic contact dermatitis (ACD) from (meth)acrylates has been described in both the occupational and non-occupational settings for more than 50 years.<sup>2–6</sup> The use of manicure materials containing (meth)acrylates, especially semi-permanent nail polish, also known as ‘long-lasting nail polish’, ‘gel polish’ or ‘permanent polish’ to the consumer has experienced an increase throughout the last 15 years, causing a global epidemic of ACD to (meth)acrylates across many countries around the world.<sup>7,8</sup>

REIDAC is a research project of the Spanish Contact dermatitis Group (GEIDAC) that collects the results of epicutaneous test performed on patients studied in various dermatology services of public hospitals in Spain.

In previous retrospective observational research, conducted from 1 January 2013 to 30 June 2016 (3.5 years) in four Departments of the Spanish Contact Dermatitis Research Group (GEIDAC), we found a frequency of 1.82% of ACD to (meth)acrylates in semi-permanent nail polish among consecutively patch tested patients with eczema in Spain.<sup>9</sup> The three most frequent (meth)acrylates involved were 2-hydroxyethyl methacrylate (2-HEMA), hydroxypropyl methacrylate (HPMA) and tetrahydrofurfuryl methacrylate (THFMA) and 100% of cases would have been diagnosed had they only been patch tested with 2-HEMA and HPMA.<sup>9</sup> Subsequently, in another prospective multicentre study where 2-HEMA, HPMA and THFMA were systematically patch tested in 10 GEIDAC centres for 1 year (2017–2018), we found 2-HEMA sensitization to involve 3.6% (81/2194)<sup>10</sup> of consecutively patch tested patients with eczema. According to further research (conducted from 2008 to 2017), the frequency of sensitization to 2-HEMA in consecutively patch tested patients with eczema was found to be 2.3% (66/2844 patients).<sup>11</sup> Patch tests with 2-HEMA were also systematically performed in The United Kingdom (UK),<sup>12</sup> Italy<sup>13</sup> and Denmark,<sup>14</sup> and a frequency of reactions to 2-HEMA were reported to be 1.7%, 1.5% and 2.4%, respectively.

Subsequently, it was recommended that 2-HEMA 2% in petrolatum (pet.) was applied to consecutively patch tested patients with eczema according to data provided by the European Contact Allergy Surveillance System (ESSCA)<sup>15</sup> and the GEIDAC.<sup>16</sup> 2-HEMA was, thus,

added to the Extended European and Spanish Baseline Series in January 2019 and January 2022, respectively.

According to Hernández-Fernández et al., the frequency of sensitization to 2-HEMA in patients patch tested with the Extended Spanish Baseline Series, including 2-HEMA, was 3.66% in Spain (a multicentre REIDAC research conducted from January 2019 to December 2020).<sup>16</sup> We hereby report the results of an extension of said REIDAC research, to calculate the frequency of sensitization to 2-HEMA in consecutive patients patch tested within a 4-year period (from January 2019 to December 2022) in 24 REIDAC centres. We additionally describe the epidemiological features (including the occupation and geographical distribution) of the sensitized patients as well as possible sources of (meth)acrylates exposure.

## 2 | MATERIALS AND METHODS

Consecutive patients ( $n = 6134$ ) were routinely patch tested with 2-HEMA 2% pet. from 1 January 2019 to 31 December 2022 in 24 Spanish REIDAC centres.<sup>16</sup> Initially, it was patch tested as a European Society of Contact Dermatitis (ESCD) candidate allergen; and, subsequently (from January 2022), as a component of the Spanish baseline series.

Allergens were supplied by Chemotechnique Diagnostics or AllergEAZE based on its availability in each centre. Exposure times (48 h) and scoring readings on days (D) 2 and D4 and relevance assessment were conducted according to the ESCD guidelines.<sup>17</sup> An additional reading on D7 was performed in some patients.

Last reading made (D4 or D7, depending on the cases) was recorded. Only reactions scored as (+), (++) or (+++) were considered to be positive. The most frequent occupations of 2-HEMA-positive and relevant 2-HEMA-positive-patients were analysed.

Some cases suspected to be related to manicure products were reported to the Spanish Agency of Medicines and Medical Devices (AEMPS) cosmetovigilance surveillance system. The minimum criteria for notification were a significant injury requiring systemic treatment with corticosteroids; the inability to perform usual tasks at work; or, the need for sick leave. More specific information regarding possible sources of exposure to (meth)acrylates or additional clinical data (registered as free text) was also analysed. The registry and uses of the data were approved by the Complejo Hospitalario Universitario Insular-Materno Infantil Ethics Committee (2017/964) and its

operation complies with the Declaration of Helsinki. All patients signed informed consent to participate forms.

## 2.1 | Statistic methods

Online platform OpenClinica version 3.12 (OpenClinica LLC and collaborators, Waltham, MA, USA) and REDCap (<https://projectredcap.org/resources/citations/> RRID:SCR\_003445) was used by REIDAC to record data<sup>16</sup> and analysed with the programme Stata version 16 (StataCorp LLC, Texas, RRID:SCR\_012763).

## 3 | RESULTS

From January 2019 to December 2022, 6134 consecutive patients were patch-tested with 2-HEMA 2% pet. in 24 centres. 265/6134 (4.3%) patients were positive to 2-HEMA. 253/265 (95%) patients were female. Half (134/265, 51%) were older than 40 years old (Table 1). Relevance of positive patch test reactions was considered to be current in 184/265 (69.4%); past in 25/265 (9.4%); and unknown in 56/265 (21.1%) (Table 2). The efficiency (number of patch

tests needed to detect relevant positive results to 2-HEMA) was 34 (6134/184).

No significant differences were identified in the sensitization to 2-HEMA prevalence throughout the years in the study period: (3.7% in 2019; 4.7% in 2020; 4% 2021; and, 4.7% in 2022) according to the homogeneity ( $p = 0.47$ ) and trend ( $p = 0.27$ ) statistic tests.

200/265 patients (75.5%) developed moderate-to-strong (++ or +++) patch test reactions to 2-HEMA. Additionally, nine patch tests were doubtful (+?) and one was considered to be irritative. No evidence of active sensitization or other side effects such as leukoderma were identified.

The demographic characteristics of the 2-HEMA-sensitized patients regarding the MOAHLFA index as well as the results of the crude analysis are shown in Table 1. The variable 'occupational' was found to be significantly associated with a higher risk of positive patch tests to 2-HEMA (OR: 7.7; 95% CI: 5.9–10.1); and, especially to relevant positive patch tests to 2-HEMA (OR: 10.9; 95% CI: 8.1–14.9). The most frequent occupations among patients with positive patch tests to 2-HEMA were: beautician and/or hairdresser (31%); office worker (12%); health worker (9%); student (7%); and, other (41%). The most frequent occupations among patients with relevant positive patch tests to 2-HEMA were also beautician and/or hairdresser (38%);

**TABLE 1** Demographic characteristics and results of logistic analysis of the total patients, patients with positive patch tests to 2-HEMA and patients with current relevant positive patch tests to 2-HEMA patients regarding MOAHLFA index.

MOAHLFA variables	Total patch tested population, n (%)	Positive test to 2-HEMA, n (%)	OR positive test	95% CI	p-Value	Current relevant positive test to HEMA, n (%)	OR positive test	95% CI	p-Value	Negative test to 2-HEMA, n (%)
Male	1860 (30)	12 (5)	9.7	5.4–17.4	<0.01	7 (4)	11.7	5.5–24.9	<0.01	1848 (31.5)
Occupational (main)	580 (10)	108 (41)	7.7	5.9–10.1	<0.01	91 (50)	10.9	8.1–14.9	<0.01	472 (8)
Atopy	1054 (17)	29 (11)	0.6	0.4–0.9	<0.01	17 (9)	0.5	0.3–0.8	<0.01	1025 (17.5)
Hand	1869 (31)	195 (75)	7.3	5.5–9.8	<0.01	158 (87)	17.1	11.0–26.5	<0.01	1674 (28.5)
Leg	328 (5)	3 (1)	0.2	0.1–0.6	<0.01	1 (1)	0.1	0.01–0.7	<0.05	325 (5.5)
Face	1338 (22)	22 (8)	0.3	0.2–0.5	<0.01	11 (6)	0.2	0.1–0.4	<0.01	1316 (22.4)
Age	4136 (68)	134 (51)	0.5	0.4–0.6	<0.01	88 (48)	0.4	0.3–0.6	<0.01	4002 (68.2)
Total	6134	265				184				5869

Note: n = number of patients, (%) percentage of total number of patients in each category.

Abbreviations: CI, confidence interval; HEMA, 2-hydroxyethylmethacrylate; MOAHLFA, male, occupational dermatitis, atopic dermatitis, hand dermatitis, leg dermatitis, face dermatitis, age  $\geq$  40 years; OR, odds ratio.

**TABLE 2** Hydroxyethylmethacrylate patch test reaction: strength and relevance.

Strength	Current relevance, n (%)	Past relevance, n (%)	Unknown relevance, n (%)	Total, n (%)
Any (+, ++ or +++)	184 (69.4)	25 (9.4)	56 (21.1)	265 (100)
+	35 (19)	10 (40)	20 (35.7)	65 (24.5)
++	108 (58.7)	8 (32)	29 (51.8)	145 (54.7)
+++	41 (22.3)	7 (28)	7 (12.5)	55 (20.8)
Doubtful (+?)	2	0	7	9
Irritative				1

Note: n = number of patients, (%) percentage with respect to the total of patients in each category.

**TABLE 3** Main occupation of HEMA-positive patients (n: 265).

Occupations	HEMA-positive patients, n (%)	OR positive test (95% CI)	p-Value	Current relevant HEMA-positive patients, n (%)	OR positive test (95% CI)	p-Value
Hairdresser or beautician	83 (31)	Reference		70 (38)	Reference	
Office worker	33 (12)	0.08 (0.05–0.12)	<0.01	25 (14)	0.07 (0.04–0.12)	<0.01
Health worker	23 (9)	0.08 (0.05–0.14)	<0.01	17 (9)	0.07 (0.04–0.13)	<0.01
Student	18 (7)	0.05 (0.03–0.08)	<0.01	8 (4)	0.03 (0.01–0.05)	<0.01
Others	108 (41)	0.04 (0.03–0.06)	<0.01	64 (35)	0.03 (0.02–0.04)	<0.01

Note: n = number of patients, (%) percentage of total number of patients in each category. Abbreviations: CI, confidence interval; HEMA, 2-hydroxyethylmethacrylate; OR, odds ratio.

office worker (14%); health worker (9%); student (4%); and, other (35%) (Table 3).

Another MOAHLFA variable found to be associated with 2-HEMA sensitization was 'Hand dermatitis' (OR: 7.3; 95% CI: 5.5–9.8). Conversely, variables significantly associated with a lower risk for 2-HEMA sensitization were identified to be: Female (OR: 9.7; 95% CI: 5.4–17.4); 'face dermatitis' (OR: 0.3; 95% CI: 0.2–0.5); 'age >40' (OR: 0.5; 95% CI: 0.4–0.6) and 'atopy' (OR: 0.6; 95% CI: 0.4–0.9). (Table 1).

All products notified to AEMPS cosmetovigilance system were semi-permanent nail polish products. No other manicure materials (such as acrylic nail or gel nail or fake nail adhesives) were notified to AEMPS cosmetovigilance. Notifications to the AEMPS were not uniform throughout the years with zero, four, and three notifications being identified in 2020, 2021 and 2022 respectively. In 2021, we identified three notifications involving consumers who self-applied semipermanent nail polish at home and one notification regarding one beautician who also self-applied semi-permanent polish.

Seven cases of onycholysis were recorded. Thirteen patients admitted to self-applying semi-permanent nail polish at home. Other possible sources of exposure to (meth)acrylates were identified to be dental materials in 6 cases; glues or paints involving construction workers and mechanics in five cases; and superabsorbent materials (sanitary napkins and incontinence pads) in five cases.

## 4 | DISCUSSION

The overall frequency of sensitization to 2-HEMA in the 4-year study period was identified to be 4.3%, which is higher than the frequency found by prior research conducted by GEIDAC<sup>10</sup> (3.6%) (2017–2018) and by research conducted in other regions: 1.7% in the UK<sup>12</sup> (2016–2017); 1.5% in Italy<sup>13</sup> (2017–2018); 2.4% in Denmark<sup>14</sup> (2017–2019) and 2.3% according to recent research on the frequency of the European baseline allergens conducted in 53 departments across 13 European countries (including GEIDAC) (2019–2020).<sup>18</sup> The percentage of positive reactions to HEMA was likely underestimated since D7 readings were only performed in a low proportion of cases.

Evidence for a significant progressive increase in the frequency of sensitization to 2-HEMA throughout the study period was, however, not identified (according to the homogeneity and trend statistic tests).

As expected, women become sensitized to 2-HEMA more often than men through the exposure to manicure materials. The proportion of women involved (95% in positive cases vs. 68% in negative cases) was higher than previously reported (e.g., a fourfold frequency involving female patients according to Italian research).<sup>13</sup>

2-HEMA was detected to be a highly efficient allergen<sup>19</sup> since we found 34 patch tests to be required to detect one relevant positive result. Additionally, the proportion of relevant patch test reactions was high compared to most baseline series allergens.<sup>16</sup> The relevance/source of exposure were, however, unknown in a notable proportion of cases (21%) and past relevance was 9.4%.

According to the statistical analysis, risk factors for sensitization to 2-HEMA were identified to be: female, a diagnosis of occupational dermatitis; the occupation of hairdresser/ beautician; and hand dermatitis. On the other hand, protector factors were found to be male, face dermatitis, age older than 40, and a history of atopy.

We found the frequency of occupational cases to be very high (41% in positive cases vs. 8% in negative cases), although slightly lower than in other series. Studies, however, may not be comparable due to methods being heterogeneous (45%–67.6%).<sup>6,14</sup> Regarding occupations, professional beauticians/ hairdressers predominate among patients positive to 2-HEMA (31%) and patients positive to 2-HEMA with a current relevance 38%. The proportion of patients with professions other than beautician and/or hairdresser (69%) was high, suggesting that the number of patients becoming sensitized as consumers of manicure, or other (meth)acrylic materials is notable. Most patients developed moderate-to-strong patch test reactions. We did not identify any cases with reactions suggestive of active sensitization or other side effects. According to REIDAC policy, however, secondary effects of the patch tests may only be identified in the follow-up and recorded as free text, thus said events may have been missed in some cases. Most cases of active sensitization to (meth)acrylates<sup>20</sup> were, however, reported in the '1980s' when highly concentrated patch test preparations of acrylates (1%) and (meth)acrylates (10%) were applied.<sup>21</sup> Active sensitization can be difficult to differentiate from late<sup>22</sup> reactions. Accordingly, the 2% pet. preparation of 2-HEMA was found to be adequate (sensitive and safe) for systematic patch testing.

Only a small proportion of cases were notified to the AEMPS cosmetovigilance system. Consumers who self-apply manicure products

at home, and beauticians, both tend to bring in a large number of nail polish products. Most are purchased online, and are often more difficult to be identified in the AEMPS cosmetovigilance system, due to the scarcity of information provided on the labels. The vast majority of consumers who get manicure in beauty salons do not provide any products or information, which makes it difficult to complete the identification process.

According to additional information provided by some researchers as free text, onycholysis, as the predominant clinical manifestation, was described to involve at least seven cases (including one patient initially misdiagnosed with psoriasis for 3 years). Additionally, one consumer of acrylic nails, gel nails and semi-permanent nail polish, presented with eyelid eczema without any reactions on her hands.

At least 13 patients self-applied long-lasting nail polish at home. Five of them presented with symptoms post 2020 (the point in time when manicure materials with 2-HEMA were restricted to be used only by professionals in the EU and should no longer be available to be purchased by the general public<sup>23</sup>). This may indicate that some consumers may self-apply at home manicure products with 2-HEMA marketed for professional use. However, sensitization from products marketed for domestic use acquired before the restrictions were implemented, is not possible to be ruled out nor elicitation of dermatitis due to cross-reactivity to other (meth)acrylates.

It is often troublesome to identify the source of exposure to (meth)acrylates in industrial, medical or other consumer products (e.g., inks, glues, sanitary napkins, medical devices, etc.) because information regarding their composition and cooperation of manufacturers is usually deficient.<sup>24-26</sup> Some patients were exposed to (meth)acrylates in dental materials<sup>24</sup> including a dentist and a dental prosthetist who were occupationally exposed to (meth)acrylates at their workplaces; a dental assistant and consumer of acrylic manicure products who developed airborne reactions and systemic symptoms; one patient diagnosed with burning mouth syndrome who experienced worsening of her symptoms after using a denture adhesive with acrylates; one patient with night oral soreness for 2 years which she related to new dental covers and one patient with reactions from a removable denture who improved with avoidance measures. Five of twelve male patients sensitized to 2-HEMA worked in the construction sector or as mechanics. All recalled worsening of their reactions secondary to performing work tasks and improvement during holidays.<sup>25</sup> Five patients recalled genital pruritus or eczema from superabsorbent materials (sanitary napkins and incontinence pads). Two of them never used manicure materials with acrylates (previously published).<sup>26,27</sup> Incontinence pads have been described as possible causes of eczema in (meth)acrylate-sensitized patients.<sup>28-31</sup> One patient developed scaly eczematous fingertip reactions following contact with glues and different materials while making miniature models. One patient sensitized to 2-HEMA recalled eczematous reactions from the exposure to a specific brand of running shoes. Unfortunately, the presence of (meth)acrylates could not be studied in the shoes. The shoes were suspected to be involved in the reactions because the patient regularly used semi-permanent nail polish and acrylic nails with good tolerance.

One possible limitation of REIDAC is that the sources of contact with (meth)acrylates and relevant assessment details are not mandatorily recorded (only some researchers provided the exposure sources as free text). Additionally, sequelae of (meth)acrylate sensitization such as onychodystrophy may not be recorded by some REIDAC researchers thus they might have been underreported. According to our results, sensitization to 2-HEMA is a concerning health issue in Spain. The inclusion of 2-HEMA as a (meth)acrylate allergy screening marker in the GEIDAC baseline series has proven to be highly effective and, apparently safe. A great deal of work, however, remains to be done to fight this epidemic currently at its peak in Spain. For instance, there is a dire need to improve the policies regulating the cooperation from manufacturers to provide transparent labelling of industrial materials, medical devices and other consumer products. Finally, authorities should implement monitoring procedures to ensure that the legal standards are enforced.

#### AUTHOR CONTRIBUTIONS

**María Elena Gatica-Ortega:** Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; supervision; resources; data curation.

**María Antonia Pastor-Nieto:** Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; data curation; supervision; resources.

**Ana María Giménez-Arnau:** Writing – review and editing; resources; methodology; investigation.

**Pedro Mercader-García:** Investigation; methodology; writing – review and editing; resources.

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## CONFLICT OF INTEREST STATEMENT

Ana María Giménez-Arnau is or recently was a speaker and/or advisor for and/or has received research funding from Ammiral, Amgen, Astra-Zeneca, Avene, Celldex, Escient Pharmaceuticals, Genentech, GSK, Instituto Carlos III- FEDER, Leo Pharma, Menarini, Mitsubishi Tanabe Pharma, Novartis, Sanofi-Regeneron, Servier, Thermo Fisher Scientific, Uriach Pharma/Neucor. Pedro Mercader-García reports lectures and advisory boards from Sanofi, Leo Pharma, Lilly and AbbVie, outside the submitted work.

## DATA AVAILABILITY STATEMENT

Research data are not shared.

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