Received: 5 August 2023 | Revised: 8 September 2023 | Accepted: 14 September 2023

DOI: 10.1111/cod.14430

REVIEW

CONTACT DERMATITIS WILEY

2-Hydroxyethyl methacrylate (HEMA): A clinical review of contact allergy and allergic contact dermatitis. Part 2. Cross- and co-sensitization, other skin reactions to HEMA, position of HEMA among (meth)acrylates, sensitivity as screening agent, presence of HEMA in commercial products and practical information on patch test procedures

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Abstract

This is the second part of a literature review of the clinical aspects of contact allergy to and allergic contact dermatitis from 2-hydroxyethyl methacrylate (HEMA). Topics include cross- and co-sensitization, atypical manifestations of contact allergy, frequency of positive patch tests to HEMA compared with other (meth)acrylates, sensitivity of HEMA as a screening agent, the presence of HEMA in commercial products, and practical information on patch testing procedures. Primary sensitization to methacrylates including HEMA may result in methacrylate and acrylate cross-sensitization. There is a strong cross-allergy between HEMA, ethylene glycol dimethacrylate (EGDMA), and hydroxypropyl methacrylate; many reactions to EGDMA are cross-reactions to primary HEMA sensitization. Rare atypical manifestations of HEMA-allergy include lichen planus, lymphomatoid papulosis, systemic contact dermatitis, leukoderma after positive patch tests, and systemic side effects such as nausea, diarrhoea, malaise, and palpitations. The occurrence of respiratory disease caused by methacrylates such as asthma is not infrequent. HEMA is the most frequently patch test-positive methacrylate. It is a good screening agent for allergy to other (meth) acrylates. Patch test sensitization to HEMA 2% pet. is extremely rare. There are (some) indications that HEMA is frequently used in dental products and nail cosmetics.

KEYWORDS
2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, acrylates, cross-reactivity, dental products, ethylene glycol dimethacrylate, HEMA, methacrylates, nail cosmetics

Abbreviations: ACD, allergic contact dermatitis; BUDA, 1,4-butanediol diacrylate; ECA, ethyl cyanoacrylate; EGDMA, ethylene glycol dimethacrylate; HEA, 2-hydroxyethyl acrylate; HEMA, 2-hydroxyethyl methacrylate; HPA, 2-hydroxypropyl acrylate; HPMA, 2-hydroxypropyl methacrylate; IVDK, Information Network of Departments of Dermatology, Germany, Austria, Switzerland; (M)A, (meth)acrylate(s); MMA, methyl methacrylate; MSDS, material safety data sheet(s); OACD, occupational allergic contact dermatitis; TREGDA, triethylene glycol diacrylate; TREGDMA, triethylene glycol dimethacrylate; THFMA, tetrahydrofurfuryl methacrylate.

1 | INTRODUCTION

This is the second part of a literature review of the clinical aspects of contact allergy to and allergic contact dermatitis (ACD) from 2-hydroxyethyl methacrylate (from here on mostly termed HEMA, its International Nomenclature Cosmetic Ingredient [INCI] name). In

part 1 of the article, the epidemiology of HEMA contact allergy was discussed and detailed information on published case series and case reports was presented. It was found that HEMA is currently an important cause of contact allergy and ACD in North America and Europe with recent prevalences of 3.2% in the United States + Canada[1] and 1.5%–3.7% In Europe.[2] The rising importance of HEMA as a cause of ACD in Europe was well noted and, therefore, in January 2019, the European Society of Contact Dermatitis included HEMA in the European baseline series for routine testing.[3,4] Soon thereafter, a multicentre study in 13 European countries found a rate of 2.3% positive reactions in 7675 patients suspected of contact dermatitis routinely tested with HEMA 2% pet.[5]

Another observation was that the profile of products causing ACD related to HEMA and other (meth)acrylates in the last 20 years or so has shifted from the 'classic' (meth)acrylate culprit products dental materials, glues, sealants, adhesives, paints, and printing inks to nail cosmetics including acrylate nails, gel nails, and, more recently, long-lasting nail polish (gel lacquer).[6–16] Indeed, in recent studies, the large majority (64% to >80%) of reactions to HEMA were related to cosmetic nail products.[9,10,17–19] Both professional nail stylists were affected and consumers. Twenty-seven to 100% of all patients with ACD to HEMA or other (meth)acrylates were beauticians[6,7,9,12,19] and nail stylists/nail technicians/beauticians mostly formed the majority (56%–97%) of all patients with occupational ACD (OACD).[4,9,10,19,20] As a consequence of the major role of cosmetics in ACD to HEMA, currently the large majority to nearly all of these patients are female.[2]

In our literature review, we have found 24 studies presenting case series of patients with ACD attributed to HEMA. However, in only 10 of these series, the causative role of HEMA was established by identifying HEMA as an ingredient in the culprit product from information in the material safety data sheet (MSDS), ingredient label, from information obtained from the manufacturer or from chemical analyses. We also found 168 case reports of ACD and OACD in patients allergic to HEMA, but in only 54 of these was the presence of HEMA in the product causing ACD established. Most of the authors of the other case reports judged the reaction to HEMA to be 'relevant' (i.e., that HEMA had caused the dermatitis or contributed to it) without knowing whether HEMA was present in the product. Therefore, we urge that investigators make the utmost effort to verify that HEMA is indeed an ingredient before rating the HEMA-positive patch test as relevant.[2]

In this Part 2 of the article, cross- and co-sensitization with HEMA will be discussed; atypical skin reactions to HEMA presented; it will be assessed whether HEMA is the most frequent (meth)acrylate allergen and how sensitive HEMA is as a screening agent; the presence of HEMA in commercial products will be investigated; and practical information on patch testing procedures provided.

2 | MATERIALS AND METHODS

All issues of the journal *Contact Dermatitis* were hand searched for relevant articles from July 2023 (volume 89, issue 1) back to February 1975 (volume 1, issue 1), as were all issues of the journal *Dermatitis/American Journal of Contact Dermatitis* from May/June 2023 (volume 34, issue 3) back to March 1990 (volume 1, issue 1). An electronic database search was conducted in PubMed/MEDLINE, Web of Science Core Collection, Scopus, and Embase using as key words 'hydroxyethyl methacrylate', 'HEMA' and 'acrylate' (the latter in PubMed only), in combination with 'contact allergy' and 'allergic contact dermatitis'. The bibliographies of all relevant studies identified were hand searched for additional eligible publications.

3 | CROSS-REACTIONS AND CO-REACTIONS

Most patients in case reports of ACD to (meth)acrylates have multiple sensitizations when patch tested, although they have probably not been exposed to all of the positive compounds.[7,21] Allergy to just one (meth)acrylate occurs infrequently, which is especially the case in sensitization to isobornyl acrylate.[22] Most often, the finding of multiple positive reactions is explained as the result of cross-allergy. Indeed, it is generally acknowledged that primary sensitization to methacrylates may result in both methacrylate and acrylate cross-sensitization. Conversely, patients sensitized to acrylates may cross-react to other acrylates but are unlikely to show cross-sensitization to methacrylates.[23,24] There is a strong cross-allergy between HEMA, ethylene glycol dimethacrylate (EGDMA), and 2-hydroxypropyl methacrylate (HPMA).[23] The association between these methacrylates is discussed in Section 3.1.

Another possible explanation for multiple positive patch test reactions is concomitant sensitization. Acrylic compounds used in commercial products are generally rather impure.[25] Studies with chemical analyses have shown the presence of multiple (meth)acrylates in such products that were not declared in the MSDS, sometimes in concentrations of >40% of the total weight of the product.[26,27] Therefore, it cannot be excluded and may be likely that a number of the multiple patch test reactions are in fact concomitant reactions.[24] In individual cases it is difficult to assess which of the two alternatives is more probable.[25] Formerly, impurities in patch test preparations may also have led to false interpretation of patch test results.[28]

3.1 | Cross-reactions between HEMA, EGDMA, and HPMA

In many groups of selected patients patch tested with a series of (meth)acrylates, HEMA, EGDMA, and HPMA were the most commonly patch test positive monomers[24,29] (see also Section 6). It was also found that there are very frequent co-reactions between HEMA and EGDMA and between HEMA and HPMA, as detailed in Tables 1 and 2.

This may indicate cross-reactivity, the possibility of which has been confirmed in animal studies.[41] HEMA and EGDMA are produced by esterifying ethylene glycol with methacrylic acid. HEMA is the

TABLE 1 Relationship between positive patch test reactions to HEMA and to EGDMA.

Number of patients reacting to HEMA[a]	Number of HEMA-positive patients reacting to EGDMA and percentage, *n* (%)	Number of patients reacting to EGDMA[a]	Number of EGDMA-positive patients reacting to HEMA and percentage, *n* (%)	Reference
		81	81 (100)	11[b]
51	41 (80)	43	41 (95)	30
47	30 (64)	30	30 (100)	31
29	26 (90)	28	26 (93)	8
23	20 (87)	20	20 (100)	32
21	18 (86)	18	18 (100)	25
18	14 (78)	15	14 (93)	33
10	10 (100)	10	10 (100)	34
9	8 (89)	8	8 (100)	35
8	7 (88)	10	7 (70)	36
7	6 (86)	6	6 (100)	37
6	5 (83)			38[b]
Range	64%–100%		70%–100%	
Average	81% (95% CI 75%–85%)		97% (95% CI 94%–99%)	

[a]Only studies with >5 HEMA/EGDMA-positive patients were included.
[b]This study was not included in the relative risk calculations, because it only has one-sided information.

TABLE 2 Relationship between positive patch test reactions to HEMA and to HPMA.

Number of patients reacting to HEMA[a]	Number of HEMA-positive patients reacting to HPMA and percentage, *n* (%)	Number of patients reacting to HPMA[a]	Number of HPMA-positive patients reacting to HEMA and percentage, *n* (%)	Reference
		99	97 (98)	11[b]
51	42 (82)	52	42 (81)	30
41	38 (93)	43	38 (88)	24
39	38–39 (97–100)	41	37–39 (90–95)	39
30	28 (93)	29	29 (100)	7
29	26 (90)	29	26 (90)	8
21	16 (76)	16	16 (100)	25
14	9 (64)	9	9 (100)	40
10	9 (90)	9	9 (100)	34
9	7 (78)	7	7 (100)	35
8	8 (100)	11	8 (73)	36
7	3 (43)			37[b]
Range	43%–100%		73%–100%	
Average	87% (95% CI 82%–90%)		93% (95% CI 89%–95%)	

[a]Only studies with >5 HEMA/HPMA-positive patients were included.
[b]This study was not included in the relative risk calculations, because it only has one-sided information.

mono-ester of ethylene glycol and EGDMA the di-ester. HEMA can be present as an impurity in EGDMA and EGDMA can be present as an impurity in HEMA. Furthermore, EGDMA can be metabolized to HEMA in the skin and body by enzymatic hydrolysis in cells and plasma, but HEMA cannot be metabolized to EGDMA.[31,42] In some studies, it was found that the strength of the positive reactions to HEMA was either greater than or equal to the strength of the positive reaction to EGDMA.[31] The significance of these findings is still undetermined, but may explain the frequent co-reactivity of HEMA and EGDMA[42] and may indicate that HEMA is often the sensitizer and EGDMA the cross-reacting substance, for example, by local release of HEMA in the patch test skin.[41]

Further evidence for this hypothesis can be found in data assessing the co-reactivity between HEMA and EGDMA in various studies,

which is shown in Table 1. In patients with positive patch tests to HEMA 81% (95% confidence interval [CI] 75%–85%) on average also have a positive reaction to EGDMA. Conversely, of patients who react to EGDMA, 97% (95% CI 94%–99%) on average co-react to HEMA. With a relative risk of 0.85 (95% CI 0.79%–0.91; $p < 0.001$, using a fixed and random effects meta-analysis model), more EGDMA-positive patients co-react to HEMA than HEMA-positives co-react to EGDMA. This may indicate that a large number of EGDMA-positives are the result of cross-reactivity to HEMA-sensitization.

A similar, but far less pronounced, picture arises in the co-reactivity data between HEMA and HPMA (Table 2). In patients with positive patch tests to HEMA 87% (95% CI 82%–90%) on average also have a positive reaction to HPMA. Conversely, of patients who react to HPMA 93% (95% CI 89%–95%) co-react to HEMA. More HPMA-positive patients co-react to HEMA than HEMA-positives co-react to HPMA. The relative risk for HEMA-positive patients to co-react to HPMA is 0.97% (95% CI 0.90%–1.04%, using a fixed and random effects meta-analysis model). The difference is not significant ($p = 0.3648$). On the basis of these data, we cannot speculate on the relationship between HEMA and HPMA in terms of sensitizer and cross-reactor.

3.2 | Other cross-reactions

3.2.1 | Cyanoacrylates

It is generally assumed that there are no cross-reactions from (meth) acrylates to ethyl cyanoacrylate (ECA) and other cyanoacrylates or vice versa.[43–46] In an earlier US study, 5 of 11 patients with positive reactions to (meth)acrylates related to artificial nails co-reacted to ECA, tested as a commercial glue containing nearly 100% ECA. This led the authors to conclude that these reactions were cross-reactions to other (meth)acrylates.[47] In a subsequent letter to the Editor, a Finnish dermatologist and expert in acrylate allergy suggested that the reactions to ECA had been the result of independent sensitization rather than cross-reactivity.[48] He had found in his own data that of 68 patients tested with a series of (meth)acrylates and ECA 2%, many had positive patch tests to one or more methacrylates including HEMA, but none reacted to ECA; he concluded that there is no cross-reactivity between them. Nevertheless, he stated that '… patients have their own, individualized pattern of cross-reactivity, and it cannot be excluded that some individuals may show cross-reactions between cyanoacrylates and (meth)acrylates'.[48] This led to a rather fierce rebuttal in which the authors maintained their opinion of cross-reactivity and suggested that the Finnish colleague should try using a higher concentration of ECA, as this might give more positive reactions. Interestingly, they extensively argued that their reactions to ECA, tested as nearly dried commercial glue, were not irritant, whereas the Finnish colleague had not even suggested this (which he rightfully could have).[49]

Since then, this topic does not seem to have been discussed any more. Co-reactions of ECA and (meth)acrylates have been observed several times, but in these cases, the sensitizations could readily be explained by both contact with nail cosmetics containing (meth)acrylates and cyanoacrylate glues used for fixation of false eyelashes, false nails or for other applications.[12,50,51]

3.2.2 | Dimethyl fumarate

In patients with contact allergy to the fungicide dimethyl fumarate, especially those with high degree of patch test reactivity, cross-reactions have been observed to the low-molecular weight (meth) acrylates ethyl acrylate, methyl acrylate and—to a far lesser extent—methyl methacrylate.[52–55] Unfortunately, HEMA was not tested in these studies.[52,53]

3.2.3 | Epoxy acrylates

Aliphatic acrylates do not seem to cross-react with epoxy acrylates such as bisphenol A diglycidyl methacrylate.[47,56–58]

3.2.4 | 4-Acryloylmorpholine

In control testing for 4-acryloylmorpholine sensitization, three patients proved to be allergic to both HEMA (from allergy to manicure products) and to 4-acryloylmorpholine, and a fourt became sensitized to both chemicals by the patch test. This synchronicity could be an indirect proof of cross-reactions between the two compounds. However, if cross-reactions to HEMA were the reason for the 4-acryloylmorpholine positive results in these controls, one would expect HEMA to yield stronger reactions than 4-acryloylmorpholine in them, which occurred in only one of four cases.[59]

4 | OTHER SKIN REACTIONS CAUSED BY HEMA

4.1 | Atypical manifestations of ACD

Lichen planus of the nail apparatus may have been induced by ACD to acrylates in gel nails and worsened by HEMA in gel nail lacquer used on preformed nails. However, cyanoacrylates may also have contributed, but these were not patch tested.[60]

(Meth)acrylates in gel nails may have caused lymphomatoid contact dermatitis of the eyelids resembling lymphomatoid papulosis. A patch test to HEMA was strongly positive and the histology and immunochemistry of a skin biopsy taken from the positive HEMA patch test were also consistent with lymphomatoid papulosis.[61]

A widespread eruption on the trunk and extremities has been observed in a patient allergic to HEMA after having her teeth varnished to reduce dentin hypersensitivity.[62] In another patient presented by the same authors, a rash on both arms appeared after

dental fillings containing HEMA had been applied.[63] In both cases, which are described in more detail in Section 6.2 in Part 1 of this article, absorption of HEMA through the oral mucosa was held responsible for the distant eruptions, diagnosed as systemic contact dermatitis (systemic allergic dermatitis).[62,63]

4.2 | ACD with systemic side effects

A 28-year-old male laboratory technician developed dermatitis of his hands related to contact with a solution containing 80% HEMA in absolute alcohol associated with nausea and diarrhoea, which was also noted during two separate patch testing sessions.[64] A 51-year-old woman described four episodes of discomfort of the buccal mucosa along with nausea, malaise, and palpitations following repeated exposures to temporary fillings used during complicated root canal treatment.[65] Both patients proved to be allergic to HEMA. Their case descriptions can be found in Sections 6.2 and 6.4 in Part 1 of this article.

4.3 | Miscellaneous skin reactions to HEMA

A 24-year-old woman had twice, during dental appointments, developed flushing of the face and presternal region, generalized tremor, perioral sensations, and itching of both hands. On both visits, the dentist had treated her with composite materials and a dentin-bonding agent and the reaction had appeared after application of the bonding agent, which contained, as one of the ingredients, HEMA. A type-I allergic reaction was suspected, but scratch tests with HEMA 1% pet. were negative after 20 min. However, on two occasions, the scratch test became positive after 8–9 h. The first time, the reaction persisted for 14 days. The second time also the dental bonding agent became positive after 8 h, but both reactions had now disappeared 12 h later. The authors were uncertain whether the observed reactions should be interpreted as a very late type-I reaction or as an allergic reaction 'in between a type-I and a type-IV allergy'. Patch tests were not performed.[66]

Several cases of leukoderma following at the sites of previous positive patch tests to HEMA and other methacrylates have been observed.[39,67–69] The pathogenesis of acquired leukoderma is not fully understood.

5 | RESPIRATORY DISEASE

It has been well documented that methacrylates may induce respiratory complications including asthma, rhinitis, and rhinoconjunctivitis.[70] These reactions have mostly been reported in dental personnel, despite the fact that these professionals usually have low and short-term exposure to volatile methacrylates that are below established limits.[71] Prevalence studies suggest a possible increasing trend in methacrylate sensitivity with estimates ranging from 1.3% to 25% in dental workers. Asthma-like symptoms usually appear after a long latency period of over 10 years. The exact mechanism is uncertain, but it is neither immediate-type nor delayed-type allergy. It is assumed that the asthma may be induced via different immunologic mechanisms.[70] A more detailed discussion of asthma, rhinitis, and conjunctivitis caused by methacrylates is considered to fall outside the scope of this article.

6 | IS HEMA THE MOST FREQUENTLY POSITIVE HAPTEN IN PATCH TESTING WITH A SERIES OF (METH)ACRYLATES?

Patients patch tested with a series of (meth)acrylates often react, when allergic, to many monomers. Various authors have observed that HEMA was the most frequently positive or one of the most frequent reactors. Relevant data on this topic are detailed in Table 3.

In 7 of 17 (41%) studies, HEMA had rank position 1; in 5, HEMA shared first place, in 4 with EGDMA and in one with HPMA. Thus, in 12 of 17 (71%) investigations, HEMA was the most frequently positive methacrylate. In the 5 other studies, HEMA was second in 2, tied for second and third place with EGDMA in another 2 investigations and had rank position 8 in the fifth.[36] Thus, generally speaking, HEMA is the most frequently positive methacrylate in patients tested with a (meth)acrylates series. In 12 of 17 studies (71%), EGDMA was in the 'Top-3′: 2 times first, 4 times first with HEMA, 4 times second, and 2 times third. This high score may be directly related to the many positives to HEMA (see Section 3.1). HPMA was present in the top-3 in 11 of 16 studies, but was not tested in one investigation.[31]

There was no obvious correlation between rank order of HEMA and the selection criteria of the patients patch tested. However, in six of seven studies involving patients who had contact with acrylate nail cosmetics and who had proven or suspected contact allergy to (meth)acrylates, HEMA had rank number 1 or shared first and second place; in the seventh investigation, HEMA held second place after HPMA (Table 3).

7 | SENSITIVITY OF HEMA AS MARKER FOR (METH)ACRYLATE ALLERGY

As shown above, HEMA is, generally speaking, the most frequently positive monomer in patch testing with a series of (meth)acrylates. Therefore, many authors have suggested that HEMA would be a good screening agent ('marker') for allergy to (meth)acrylates.[3,31,32,40,74] Studies providing data on the sensitivity of HEMA as a marker, that is, the percentage of (meth)acrylate-allergic patients in which HEMA is positive, are summarized in Table 4.

They are ordered according to culprit product categories. The mean sensitivity of all these studies together was 86% (95% CI 75%–92%), ranging from 33% to 100%. The sensitivity of HEMA was significantly different between the different culprit categories ($p < 0.012$; using a χ^2 test). Glues had the highest sensitivity with all patients being HEMA-positive. Next were dental materials and nail cosmetics with sensitivities of 91% (95% CI 51%–99%) and 90%

TABLE 3 Frequency of positive reactions to HEMA compared with other (meth)acrylates.

Years and country	No. of. patients tested	Selection criteria	No. of (M)A tested	Rank order of positive reactions to HEMA[a]	Ref.
2013–2016 Spain	43	Allergy to acrylate nail cosmetics	17	1 HPMA ($n = 41$); **2 HEMA** ($n = 39$); 3 THFMA (31/39 tested)	39
2007–2016 Sweden	16	Nail technicians with (M)A allergy	16	**1–2 HEMA** ($n = 10$); 1–2 EGDMA ($n = 10$); 3–4 HPMA ($n = 9$); 3–4 BUDA ($n = 9$)	72
2002–2015 UK	475	Susp. (M)A allergy	28	1 HEA ($n = 32$); **2–3 HEMA** ($n = 29$); 2–3 HPMA ($n = 29$)	8
2006–2013 Portugal	122	Susp. (M)A allergy	15–17	**1 HEMA** ($n = 30$); 2 HPMA ($n = 29$); 3 HEA ($n = 20$)	7
2004–2013 IVDK	75	Nail artists/cosmetologists with self-suspected OACD from nail cosmetics	12	**1 HEMA** ($n = 27$ of 74 tested)[b]; 2 HPMA ($n = 26$); 3 EGDMA ($n = 24$)	30
1993–2013 Australia	14	Beauticians with (M)A allergy	>13	**1 HEMA** ($n = 14$); 2 EGDMA ($n = 11$); 3 HPMA ($n = 9$)	40
1993–2012 NL	148–151	Susp. (M)A allergy	29	1 HPA (12/148); 2 HEA (12/148); **8 HEMA** (8/151)	36
1994–2009 Finland	66	(M)A allergic patients	36	1 EGDMA ($n = 43$); **2–3 HEMA** ($n = 42$); 2–3 HPMA ($n = 42$)	24
1981–2008 Spain	15	Beauticians with (M)A allergy from acrylate nails	15	**1–2 HEMA** ($n = 13$); 1–2 EGDMA ($n = 13$); 3 TREGDMA ($n = 7$)	73
1994–2006 Finland	10	Patients with OACD from acrylates in glues	35	**1–2 HEMA** ($n = 10$); 1–2 EGDMA ($n = 10$); 3 HPMA ($n = 9$)	34
1994–2006 Finland	32	Dental personnel with (meth)acrylate allergy	26	**1–2 HEMA** ($n = 24$); 1–2 EGDMA ($n = 24$); 3 HPMA ($n = 23$)	21
2002–2005 Sweden	1609	Routine testing	5	**1 HEMA** ($n = 16$); 2 TREGDA ($n = 12$); 3 HPA ($n = 11$)	42
<2005 Belgium	27	Susp. (M)A allergy from nail cosmetics	1–24	**1 HEMA** ($n = 25$); 2 EGDMA ($n = 20$ of 26 tested)	74
2001–2004 Israel	55	Susp. (M)A allergy from nail cosmetics	13	**1–2 HEMA** ($n = 17$); 1–2 HPMA ($n = 17$); 3 EGDMA ($n = 13$)	75
1995–2004 Sweden	1632	Susp. (M)A allergy in dental patients and personnel	11[c]	**1 HEMA** ($n = 47$); 2 EGDMA ($n = 30$); 3 TREGDMA ($n = 13$)	31
1995–1999 Germany	126	Dental technicians with dermatitis	24	1 EGDMA ($n = 20$); **2 HEMA**[b] ($n = 19$); 3 HPMA ($n = 16$)	58
1995–1998 Sweden	109	Dental personnel with (M)A allergy	11[c]	**1 HEMA** ($n = 23$); 2 EGDMA ($n = 20$); 3 MMA ($n = 16$)[c]	32

Abbreviations: BUDA, 1,4-butanediol diacrylate; EGDMA, ethylene glycol dimethacrylate; HEA, 2-hydroxyethyl acrylate; HEMA, 2-hydroxyethyl methacrylate; HPA, 2-hydroxypropyl acrylate; HPMA, 2-hydroxypropyl methacrylate; IVDK, Information Network of Departments of Dermatology, Germany, Austria, Switzerland; M(A), methacrylate(s); MMA, methyl methacrylate; NL, Netherlands; susp., suspected; THFMA, tetrahydrofurfuryl methacrylate; TREGDA, triethylene glycol diacrylate; TREGDMA, triethylene glycol dimethacrylate; UK, United Kingdom.

[a]HEMA in bold letter type.

[b]Tested at 1% pet.

[c]HPMA was not tested in this study.

TABLE 4 Sensitivity of HEMA as a marker for (meth)acrylate allergy.

Years and country	Selection criteria (S); sources of sensitization/ACD	No. of patients positive to: (meth) acrylates/HEMA		Sensitivity (%)	Reference
Culprit products: Nail cosmetics					
2012–2018 Portugal	S: suspected (meth)acrylate allergy; sources: probably all nail cosmetics	39	38	97	16
2016–2017 United Kingdom	S: routine testing (HEMA) and targeted testing of a (meth) acrylate series; sources: 135/140 nail cosmetics	140	102	73	10
2008–2017 Spain	S: suspected (meth)acrylate allergy; sources: all nail cosmetics	66	64	97	14
2013–2016 Spain	S: patients allergic to gel nail polish; sources: gel nail polish	42	37	88	39
2007–2016 Sweden	S: nail technicians with (meth)acrylate allergy; sources: nail cosmetics	16	10	63	72
2013–2015 EECDRG	S: patients with ACD from nail acrylates; sources: nail cosmetics.	135	124	92	11
1993–2013 Australia	S: beauticians with (meth)acrylate allergy; sources: nail cosmetics	14	14	100	40
1981–2008 Spain	S: beauticians allergic to acrylate nails; sources: nail cosmetics	15	13	87	73
<2005 Belgium	S: suspected allergy from nail cosmetics; sources: nail cosmetics	27	25	93	74
2001–2004 Israel	S: suspected allergy from nail cosmetics; sources: nail cosmetics	21	17	81	75
Culprit products: Mixed group					
2002–2015 United Kingdom	S: suspected (meth)acrylate allergy; sources: 22 nail cosmetics, 12 glues, 7 medical dressings, 2 paints, 2 dental materials	52	29	56	8
2013–2014 Italy	S: suspected (meth)acrylate allergy; sources: 5 dental materials, 3 artificial nails	7	7	100	37
2008–2014 UK	S: suspected (meth)acrylate allergy; sources: 46 nail cosmetics, 4 dental materials, 2 adhesives, 1 printing ink	54	44	81	6
2006–2013 Portugal	S: suspected (meth)acrylate allergy; sources: 28 artificial nails, 3 dental materials, 4 dental prostheses	37	30	81	7
1993–2012 NL	S: suspected (meth)acrylate allergy; sources: 8 nail cosmetics, 5 glues, 3 printing inks, 2 dental materials, 5 paints/lacquers	24	8	33	36
1994–2009 Finland	S: patients allergic to (meth)acrylates; sources: 34 dental workers, 12 glue, 3 artificial nails, 4 printing ink, 3 paints	66	42	64	24
Culprit products: Dental materials					
1994–2006 Finland	S: dental personnel with OACD from (meth)acrylates; source: dental products	32	24	75	21
1995–2004 Sweden	S: suspected (meth)acrylate allergy in dental patients and dental personnel; sources: dental materials	48	47	98	31
1978–1999 Belgium	S: patients with OACD to (meth)acrylates; sources: 14 dental materials, rest not specified/unclear	31	14	45	76
1995–1998 Sweden	S: dentists and dental nurses allergic to (meth)acrylates; sources: dental materials	23	23	100	32
Culprit products: Glues					
1994–2006 Finland	S: patients with OACD from (meth)acrylates in glues; sources: glues	10	10	100	34
Culprit products: Unknown					
2002–2005 Sweden	S: routine testing plus additional targeted (meth)acrylate testing; sources: not stated	38	17	45	42

Abbreviations: ACD, allergic contact dermatitis; HEMA, hydroxyethyl methacrylate; OACD, occupational allergic contact dermatitis.

(95% CI 82%–95%), respectively. The lowest HEMA-sensitivity was found in the mixed group (59% [95% CI 51%–83%]) and the study where the culprit product was unknown (45% [95% CI 29%–62%]).

It can be concluded that, as previously suggested by many authors, HEMA is a good screening agent for contact allergy to (meth) acrylates, especially for patients with reactions to nail cosmetics and dental products. Although glues had a 100% score, the low number of patients in this study and the lack of corroborating data do not permit to draw firm conclusions as to the sensitivity of HEMA for (meth)acrylate sensitivity in patients sensitized by glues.

8 | PATCH TEST SENSITIZATION

Several cases of patch test sensitization to HEMA have been observed, both from application of HEMA-containing products in (too) high concentrations.[77–80] and from commercial patch test preparations containing 2% HEMA in petrolatum.[59,81–83]

8.1 | Sensitization from inadequate patch testing

A 39-year-old female dermatologist was patch tested with a glue containing HEMA (unknown concentration) and other unidentified (meth) acrylates at 1%, 5%, and 10% pet. No irritation was observed, but 2 weeks after the patch tests, the regions showed positive reactions which lasted for the next 10 days. One year later, patch tests were repeated and the patient now had positive reactions to HEMA 1% pet., EGDMA 2% pet. and MMA 2% pet. at D3 and D7.[79]

A 38-year-old dental nurse developed vesicular dermatitis on her hands and fingers, and simultaneously paresthesia of fingers 1–3 of her right hand. Patch testing was performed with the European standard series and three acrylate resins to which she had been exposed, including two components of a dental adhesive system. These acrylate compounds were tested undiluted. At D4, there were no positive reactions. Later, the patient was patch tested again and now had positive reactions to the two components of the dental adhesive system tested 1% pet. (20 controls negative), HEMA 2% pet. and EGDMA 2% pet. Both methacrylates were present in the two components of the dentin-bonding system in concentrations of 48% and 29% (HEMA) respectively 0.8% and 13% (EGDMA). The patient was considered to have been sensitized to these methacrylates by the patch tests with undiluted dentin-bonding products.[77,78]

A patient was sensitized to HEMA from a 'use test' on intact skin with undiluted glass ionomer material. According to the MSDS the primer of this material contained 37%–41% HEMA and the liquid 18%–20% HEMA.[80]

8.2 | Patch test sensitization from adequate patch testing

A 45-year-old woman was tested with a dental screening series because of pain and white streaks on her oral mucosa. After 2 and 4 days, there were no positive reactions. One month later, she reported that since a few days after the last reading, she had noticed itching and redness in the test area. A red infiltration could be seen on her back. Because it was impossible to localize the causative allergen with any accuracy, repeat patch tests with the entire dental screening series were performed. At both D2 and D4, there was a ++ reaction to camphoroquinone 1% pet., without any other reactions. However, 10 days after application of these tests, the patient noticed two new red infiltrations which could be localized as due to EGDMA 2% pet. and HEMA 2% pet. Retesting now showed positive reactions to both methacrylates at D2 and D4.[83] In this case, two test sessions in a short period of time may have facilitated patch test sensitization.

A patient suspected of contact allergy to (meth)acrylates was patch tested with the European standard series, the dental series, and the (meth)acrylate series. There were no positive reactions at D4, but on D13 four positive reactions were visible, identified as HEMA, HPMA, EGDMA, and *N*,*N*-dimethylaminoethyl methacrylate (all tested 2% pet.). Retesting now showed that all four induced positive patch tests reactions at D4.[81]

One patient tested with (meth)acrylates and—as a control—with 4-acryloylmorpholine had late reactions to HEMA 2% pet. and 4-acryloylmorpholine 0.5% pet. on D18, which had a crescendo pattern for more than 2 weeks. Three months later, she was retested and now reacted positively to both chemicals at D2 and D4.[59]

A woman was patch tested with a (meth)acrylate series for palatal lesions related to the wearing of a plastic dental prosthesis. After 2 and 4 days, all tests were negative, but 3 weeks later, the patient reattended for erythematous areas on her back, corresponding to the area of application of the (meth)acrylates series. Repeated patch testing with this series now showed +++reactions at D4 to HEMA and methyl methacrylate (both tested 2% pet.) and to butyl and ethyl acrylate 0.1% pet.; there were also +reactions to EGDMA and TREGDMA at 2% pet. It was concluded that the patient had become sensitized to these (meth)acrylates by the first patch test session.[82]

9 | PRESENCE OF HEMA IN COMMERCIAL PRODUCTS

9.1 | General

There are few data in literature regarding the qualitative and quantitative presence of HEMA in commercial products. For many substances and products, information on the contents can be found on the MSDS, which, in the EU, should be provided to downstream users and distributors when the substance or mixture is classified as hazardous. However, if the substance or mixture is also sold to the general public, an MSDS does not need to be provided.[84] Other potential sources of information on the contents of a product are the product information sheet or, in the case of cosmetics, the ingredient labelling information on the product, packaging, or separate labels. Previously, in Finland, it has been found by chemical analyses of various acrylic products such as dental composite resins and bonding materials, glues,

paints, lacquers, and UV-cured coatings, that many of these products contained undeclared (meth)acrylates, sometimes in very high concentrations, up to 46%. In addition, declared concentration ranges of specific (meth)acrylates were sometimes found to be inaccurate. The information provided in the safety data sheets therefore may often be unreliable and needs to be improved.[26,27,77,85,86] Possible causes for inaccuracies are: raw materials may contain hidden impurities; final product may contain starting materials; decomposition of components; contamination of residues; manufacturing process may be poorly controlled; and undeclared components may be added intentionally.[26] It should be noted that, with the exception of ref. 85 (Australia, 2007) this information dates back 20–25 years and was all established in one country, Finland.

Quite remarkably, some authors, in articles presenting patients with ACD from HEMA, make statements on the presence of HEMA in certain products without providing any evidence for it. Example 1: 'Most gel nails contain 2-HEMA, which is not included in sculptured nails'.[87] The first claim is unsubstantiated, the second wrong. Example 2. '…apart from 2-HEMA, that is always used in gel nails (source article cited)…'[88] No confirming data provided in the cited article. Example 3. 'Monomeric acrylates are similar to those used in acrylic nails, with the exception of 2-HEMA, which is present only in gel nails'.[89] No confirming data, but the authors refer to another article, where this statement is indeed made, but also without any substantiation.[90]

Currently, in the European Union, the use of HEMA in nail cosmetics is permitted in products for professional use only and is forbidden in consumer products. The warning texts 'for professional use only' and 'can cause an allergic reaction' must be stated on the package of professional nail products containing HEMA.[91]

9.2 | Data on the presence of HEMA in substances and products

In the Netherlands, in July 2023, a market survey was performed investigating the presence of HEMA in modern nail cosmetics (acrylate nails, gel nails, and gel nail polish). Relevant products shown at www.bol.com were screened for the presence of information on the ingredients. These products are not sold directly by bol.com, but by the manufacturers or importers of these products. Whenever possible, the ingredients were verified by searching the websites of the manufacturers/importers. Of 448 nail cosmetics investigated, product information was lacking in 54. Of the 394 products in which the ingredients could be established, 229 (58%) contained HEMA. The frequency of the presence of HEMA in various product types (primer, base coat, polish, top coat, builder gel et cetera) ranged from 24% to 74% (I. M. Steunebrink, A. C. de Groot, T. Rustemeyer. Presence of HEMA in nail cosmetics. Article in preparation).

In the United States, in 2019, acetone extracts of 16 medical adhesives (7 medical/surgical tapes, 4 wound closure tapes, 2 hydrocolloid dressings, 1 transparent dressing, 1 transparent dressing with non-adherent pad, and 1 bandage) were analysed using ultrahigh-performance liquid chromatographic mass spectrometry (MS). Fifteen of the 16 samples contained at least one detectable acrylate, most often TREGDMA. HEMA was not identified in any of the 16 products.[92]

In 2018, four patients with ACD from long-lasting nail polish were reported from Spain.[93] All four patients were sensitized to 2-hydroxyethyl acrylate, and three of them were sensitized to HEMA, HPMA, and EGDMA. HEMA was listed on the labels of six of the nine brands of nail polish that these four patients had used.[93]

Between 2013 and 2016, in 4 dermatology departments in Spain, 43 patients were diagnosed with ACD caused by (meth)acrylates in long-lasting nail polish. The most frequently reacting patch test allergens were HEMA, HPMA, and THFMA. These three allergens were also the methacrylates most frequently identified on the labels of the patients' products, including HEMA in 7/13 (54%).[39]

In the Netherlands, in 2015, the ingredient labels of 91 gel nail polishes, both for professional and consumer use, were screened for the presence of (meth)acrylates. HEMA was the most frequently identified, being present in 46 products (51%), followed by HPMA (44/91, 48%), and di-HEMA trimethylhexyl dicarbamate (43/91, 47%). Specific data for professional and consumer products were not provided.[94]

In a 2007 review from Belgium of the chemical composition of dental adhesives commonly used at that moment, the ingredients of 65 such products were shown.[95] These adhesives were mostly produced in the United States, Japan, Germany, and Liechtenstein. In a group of 15 three-step etch and rinse adhesives 11 (73%) contained HEMA (5× in two components, 4× in one component, and 2× in three components). In a group of 23 two-step etch and rinse adhesives, 18 (78%) contained HEMA. In a group of 11 two-step self-etch adhesives, all 11 (100%) contained HEMA, in 7 cases both in the primer and in the bonding. Finally, in a group of 16 one-step self-etch adhesives, 8 (50%) contained HEMA. The amounts of HEMA in these products were not given.[95]

In 2005, in Belgium, 25 patients with ACD from acrylic nails or gel nails had positive reactions to HEMA. It was not specified how many products used by the patients actually contained HEMA, but it was stated that 'some acrylic nails did not contain 2-HEMA on their ingredient list', which leads to the conclusion that most products indeed did contain HEMA.[74]

In a 2005 systematic review of the chemical aspects of self-etching enamel–dentin adhesives, it was stated that of the monomers used in these adhesives, HEMA was the most frequently applied monomer. However, in adhesives with improved hydrolytic stability, HEMA was replaced by new, strongly acidic adhesive monomers.[96]

In Finland, in 2001–2002, commercial dental restorative materials commonly used there were analysed in order to obtain information about the occurrence of sensitizing acrylates. Acetone-soluble methacrylates of seven bonding materials, eight composite resins, and two glass ionomers were identified by gas chromatography with mass-selective detection and quantified by liquid chromatography with ultraviolet detection. HEMA was detected in five of seven bonding materials in concentrations (w/w) ranging from 0.3% to 28%, median 17%. Its presence was declared in MSDS in only two of the five products. Of the eight composite resins, only one product contained

HEMA, in a concentration of 7% (not declared on the MSDS) and it was identified in both glass ionomers (0.2% and 23%, one declared in an MSDS).[86]

Also in Finland, in 1997, 10 acrylic products (dental composite resins and bonding materials, glues, paints, lacquers, and UV-cured coatings) were analysed by gas chromatography–MS for the presence of (meth)acrylates. HEMA was found in two products: a dental adhesive (concentration 6.8%) and an acrylic adhesive (26%).[27]

10 | PATCH TEST CONSIDERATIONS

10.1 | Concentration used for patch testing

Patch testing is mostly performed with a concentration of 2% in petrolatum, available from Chemotechnique (www.chemotechnique.se) and SmartPracticeCanada (www.smartpracticecanada.com). In some countries, including Germany, Austria, and Switzerland, 1% pet. is the concentration used in the baseline series of the Deutsche Kontaktallergie-Gruppe (DKG).[97] This concentration is also used at the Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark.[9] This patch test material is available from SmartPracticeCanada and SmartPracticeEurope (www.smartpracticeeurope.com). Recent investigations to establish whether one of these test concentrations performs better than the other were not found.

10.2 | Late appearing patch test reactions to HEMA

In several studies, it was found that HEMA and other (meth)acrylates are not infrequently positive on D7 for the first time (i.e., negative at the first reading on D3/D4). As a consequence, when a late reading is not performed, sensitizations may be missed. Therefore, several authors have recommended to perform patch test readings on both D3/D4 and on D7.[31,35,42,98] Unfortunately, there are few data available on the frequency of these late reactions to HEMA.

In a 2005–2007 study from Sweden, 1609 consecutive patients suspected of contact dermatitis were patch tested with HEMA 2% pet. and there were 16 positive reactions, 8 of which were relevant.[42] Of these 8, 6 positives at D7 had been negative ($n = 3$) or ?+ ($n = 3$) at D3/D4. This means that, without a late reading, 3/8 (38%) relevant sensitizations to HEMA would have been missed and in another 3 the ?+ reactions at D3/D4 would have been difficult to interpret correctly.[42]

The same group of investigators performed a retrospective study in a group of 1632 patients who had been tested with the 'dental patient series' or the 'dental personnel series' during 1995–2005.[31] If only one reading had been made (on D3 and not also on D7), 7/29 (24%) HEMA-positive dental patients would have been missed. In the group of dental personnel, If only one reading had been made on D3/D4, 3 of 18 (17%) HEMA-positive dental personnel would have stayed undetected.[31]

In a third study from this research group, 1 of 18 (6%) positive patch test to HEMA in a group of patients tested with the acrylate/methacrylate series and/or the nail series would have been missed when a late reading on D7 had not been performed.[35]

At the Mayo Clinic, Scottsdale, USA, between 2001 and 2020, 543 patients were patch tested with HEMA 2% pet. and 15 (2.8%) had late positive reactions (D8 or later). Twelve had weak (+) and 3 had strong (++) reactions. Of the 15 reactions 4 (27%) were considered to be relevant.[99] In an earlier study from the Mayo Clinic in Rochester, performed between 1997 and 2006, 2 of 148 patients (1.4%) had late-appearing positive reactions at D7 or later.[100] Repeat patch tests were not performed, and therefore it remains unknown whether some of these reactions were due to patch test sensitization rather than representing late-appearing positive reactions.[99,100] However, positive test reactions to HEMA emerging after 10 days do not automatically imply active sensitization (see Section 10.3).[98]

Finally, in Germany, 522 patients were patch tested with HEMA 1% pet. and reactions were read at D3 and D7. At D3, there were 14 positive reactions. Only one reaction was observed at D7 for the first time, indicating that 7% of positive patch tests to HEMA (1% pet.) would have been missed when no D7 reading is performed.[101]

Whether the numbers of missed reactions in these studies are high enough to warrant a routine late reading on or around D7 can be a matter of debate. However, HEMA is currently included in the European baseline series.[35] As this series contains a number of other haptens that more or less frequently are positive at the D7 reading for the first time, such as neomycin, corticosteroids, epoxy resin, and methylchloroisothiazolinone/methylisothiazolinone[101] and, in the European Society of Contact Dermatitis guideline for diagnostic patch testing, a late reading at or around D7 is part of the 'optimum' reading time schedule,[102] it seems advisable, whenever possible, to perform late readings.[31,35]

10.3 | Long duration of positive patch tests

In a study in three centers in Sweden, 12 patients with known contact allergy to HEMA and EGDMA were tested with HEMA and EGDMA in dilution series of 2% v/v in alcohol 99.5% v/v, with a dilution factor of 10 down to 2×10^{-9}%. Eleven had again positive patch tests to HEMA, which were positive at D3 in 10/11. In the 11th patient, the reaction was first visible at the D14 reading. It was concluded that late-appearing positive patch tests are not necessarily the result of active sensitization (patch test sensitization).[98]

When investigating the course of the positive reactions, the authors of this study found that in 10/11 patients, the patch test to the 2% concentration of HEMA was still positive at D28 (and two reactions positive at D28 to the 0.2% concentration). It was concluded that patch test reactions to HEMA are long-lasting.[98] However, it should be appreciated that HEMA had been tested with alcohol as vehicle, in a dilution series with 10 patches, that they were also tested with a dilution series of the cross-reacting methacrylate EGDMA (also with many positive reactions) and that the patients had previously displayed positive patch tests to HEMA 2% pet. These factors may well have excessively stimulated the immune system and facilitated persistence of the reactions. Whether single positive patch tests to HEMA (e.g., in a baseline series) are also long-lasting, has apparently not been investigated.

10.4 | Concentrations of HEMA in commercial patch test materials

Acrylates and methacrylates are volatile substances, and it has been demonstrated that volatile allergens may disappear from petrolatum patch test preparations. In a study investigating the correlation between stated and measured concentrations of acrylate and methacrylate allergens in patch test preparations, seven of eight samples that were collected from centres in various parts of the world that had been used there, showed a concentration of 80%–90% of the stated concentration, which is within the range considered to be acceptable.[103] In another study, of six fresh HEMA patch test preparations obtained from three major suppliers, four were in accordance with the stated concentrations, ranging from 95% to 108% of this concentration. One had 88% of the stated concentration (which is considered acceptable), the sixth 71%, which is too low.[104] These same authors also investigated fresh samples of HEMA 2% pet. from Chemotechnique and found that they contained an average of 1.91% HEMA, with four of six samples containing the stated concentration.[105]

10.5 | Stability of HEMA in commercial patch test materials

In Sweden, the variation in allergen content over time was measured for HEMA in commercial patch test materials (syringes). When stored at room temperature, the concentration had dropped to 80% of the initial concentration (the minimum considered acceptable) after some 4–5 months. However, when stored in a freezer or refrigerator, concentrations of HEMA were well over 80% at D256 (8.5 months).[106]

In another investigation, the variation in time of the concentration of HEMA in patch test material loaded in IQ chambers™, IQ Ultimate™ chambers (Chemotechnique Diagnostics), and Van der Bend® transport containers (Van der Bend BV, Brielle, The Netherlands) was investigated. It was demonstrated that the initial concentration remains stable for 8 h in all three chambers, at least when stored in the refrigerator.[105]

The same group of investigators showed that there is a heterogeneous distribution of HEMA in fresh commercial patch test preparations. In some syringes, the concentration was lower in their frontal segment.[104]

10.6 | Practical patch testing advice

The following practical advice for patch testing (meth)acrylates (not specifically for HEMA) has been given.[54,89,106–108] The patch test preparations must be stored in a refrigerator in capped syringes. They should be used before their expiry date and they should be loaded in the patch testing chambers immediately before application to patients' backs.[54,89,107,108] If the materials are prepared earlier, it should be on the day of use[106] and the test materials must be stored in the refrigerator until actual use.[105] In addition, some authors have recommended to discard the initial extrusion from a syringe with (meth)acrylates, as the concentration of the material may be decreased at the syringe tip due to sample volatility.[104,109] When a false-negative patch test is suspected, a new sample should be obtained, and the patient should be retested.[107]

11 | PROTECTION AGAINST HEMA OFFERED BY GLOVES

People working with (meth)acrylates usually wear gloves for protection. Unfortunately, many (meth)acrylate monomers, including HEMA, can penetrate most surgical rubber and polyvinyl chloride (PVC) gloves (especially vinyl and latex), sometimes within minutes.[110–117] Double gloving with nitrile gloves, or polyethylene gloves under nitrile gloves, affords adequate protection for tasks that do not exceed 30–60 min.[108,118] However, the breakthrough time may be <15–20 min with higher concentrations of (meth)acrylates or when these substances are dissolved in particular solvents.[54] An in vivo method has been developed which may show whether certain gloves are sufficiently protective against (meth)acrylates under working conditions.[119]

The best protection is provided by Silver Shield®/4H® gloves (Honeywell Safety Products, USA), a 5-layer laminate, which can inhibit the penetration of acrylates and provides protection for several hours.[8,12] Unfortunately, the rigidity of these (very expensive) gloves hinders the performance of tasks that require dexterity and tactility (e.g., nail shaping), and so these gloves are not widely used by beauticians, currently the largest professional group at risk of sensitization to (meth)acrylates. An alternative possibility is to wear fingers cut from the 4H gloves under more flexible disposable gloves, although this may still impede the proper performance of the fine tasks required in nail aesthetics.[73]

Some protection at work (primary and secondary prevention) can further be provided by allergen avoidance, working hygiene (including keeping occupational object surfaces clear from residues), 'non-touch' techniques, face masks, face shields or goggles, suitable clothing and frequently changing disposable gloves.[11,39,120] The most effective measures are elimination of the hazard (the [meth]acrylates) or substitution (replacing the hazard). However, in dentistry, the cosmetic nail industry and other industries where contact with (meth)acrylates exists, these chemicals are ubiquitous and essential. Replacement by different non-hazardous materials will rarely be possible and replacement by other (meth)acrylates non-effective because of the sensitizing potential of other (meth)acrylates and extensive cross-reactivities.[70]

12 | DISCUSSION

Most patients who are contact allergic to (meth)acrylates have multiple positive patch tests; this is usually attributed to cross-allergy. Primary sensitization to methacrylates may result in both methacrylate and acrylate cross-sensitization. Conversely, patients sensitized to acrylates may cross-react to other acrylates but are unlikely to show cross-sensitization to methacrylates.[23,24] There is a strong cross-allergy between HEMA, EGDMA, and HPMA[23] and it is likely that many reactions to EGDMA are cross-reactions to primary HEMA sensitization (Section 3.1).

However, acrylic compounds used in commercial products are generally rather impure (97) and products often contain more (meth) acrylates than stated in the MSDS.[26,27] Thus, multiple positive reactions may also be caused by concomitant sensitization rather than cross-allergy.[24] There appears to be no cross-reactivity between (meth)acrylates and cyanoacrylates (Section 3.2).

Rare atypical manifestations caused by HEMA-allergy include lichen planus of the nail apparatus,[60] lymphomatoid papulosis,[61] systemic contact dermatitis (systemic allergic dermatitis),[62,63] and ACD with systemic side effects such as nausea, diarrhoea, malaise, and palpitations.[64,65] Several cases of leukoderma following at the sites of previous positive patch tests to HEMA and other methacrylates have been observed.[39,67–69] Respiratory diseases such as asthma and rhinoconjunctivitis caused by methacrylates are not infrequent, especially in dental personnel; the mechanism of such reactions is unclear.[70]

HEMA is the most frequently positive methacrylate in patients tested with a (meth)acrylates series (Section 6). It is a good screening agent (marker) for allergy to other (meth)acrylates, especially in patients sensitized to such chemicals in dental materials and nail cosmetics, for which it has a sensitivity of 90% (Section 7).

Several cases of patch test sensitization to HEMA have been observed, both from application of HEMA-containing products in (too) high concentrations[77–80] and from commercial patch test preparations containing 2% HEMA in petrolatum.[59,81–83] However, active sensitization to HEMA 2% pet. appears to be extremely rare. Investigators from Malmö, Sweden, in 2011 stated that they had used HEMA 2% pet. for over 20 years without observing any cases of active sensitization.[103]

Few recent data regarding the qualitative and quantitative presence of HEMA in commercial products can be found in literature. There are some indications that HEMA is frequently used in dental products[86,95] and nail cosmetics.[74,94] For patch testing, HEMA is commercially available in 1% and 2% preparations; comparisons between the two are not available. Late-appearing positive patch tests at D7, which were negative at D3/D4, are not exceptional and may be missed when D7 readings are not performed.[31,35,42,99] (Meth) acrylates are volatile materials. To avoid lowering of the concentration in patch test material, the patch test preparations must be stored in a refrigerator in capped syringes. They should be used before their expiry date and they should be loaded in the patch testing chambers immediately before application to patients' backs.[54,89,107,108] If the materials are prepared earlier, it should be on the day of use[106] and the test materials must be stored in the refrigerator until actual use.[105]

HEMA can penetrate most surgical rubber and PVC gloves (especially vinyl and latex), sometimes within minutes. Double gloving with nitrile gloves, or polyethylene gloves under nitrile gloves, affords adequate protection for tasks that do not exceed 30–60 min.[108,118] The best protection is provided by Silver Shield®/4H® gloves (Honeywell Safety Products, USA),[8,12] but the rigidity of these (very expensive) gloves hinders the performance of tasks that require dexterity and tactility (Section 11).

A summary of key information on 2-hydroxyethyl methacrylate (HEMA) data found in this review and recommendations are provided in Box 1.

BOX 1 Summary of key information on 2-hydroxyethyl methacrylate (HEMA) data found in this review and recommendations.

- Generally speaking, HEMA is the most frequently positive methacrylate in patients tested with a (meth)acrylates series.
- HEMA is a good screening agent for contact allergy to (meth)acrylates, especially for patients with reactions to nail cosmetics and dental products, identifying 85%–90% of all cases of (meth)acrylate sensitizations.
- Most patients allergic to (meth)acrylates have multiple sensitizations when patch tested, which is usually explained as the result of cross-allergy. Indeed, it is generally assumed that primary sensitization to methacrylates may result in both methacrylate and acrylate cross-sensitization. Conversely, patients sensitized to acrylates may cross-react to other acrylates but are unlikely to show cross-sensitization to methacrylates.
- Acrylic compounds used in commercial products are generally rather impure and may contain multiple (meth)acrylates not declared in the material safety data sheet(s). Consequently, a number of the multiple patch test reactions may in fact be the result of concomitant sensitizations rather than of cross-allergy.
- There is a strong cross-allergy between HEMA, ethylene glycol dimethacrylate (EGDMA), and 2-hydroxypropyl methacrylate. There are indications that a large number of EGDMA-positives are the result of cross-reactivity to primary HEMA-sensitization.
- It is generally assumed that there are no cross-reactions from (meth)acrylates to ethyl cyanoacrylate and other cyanoacrylates or vice versa.
- Commercial patch test preparations are available in concentrations of 2% in petrolatum and 1% pet. It is unknown which performs better, and whether 1% pet. may result in (occasional) false-negative reactions. Studies to investigate this topic are easy to perform and we urge this should be pursued without delay.
- HEMA and other (meth)acrylates may show positive patch tests at D7 for the first time (i.e., negative at the first reading on D3/D4). As a consequence, when a late reading is not performed, sensitizations may be missed. Unfortunately, there are few data available on the frequency of these late reactions to HEMA, and this should be investigated in more detail to provide information on which an advice of routine readings at D7 or D8 can be based. In the meantime, in patients with a history suggestive of sensitivity to (meth)acrylates, it may be worthwhile to schedule a late reading, when patch tests are negative at D3 or D4.
- Active sensitization to HEMA 2% pet. appears to be extremely rare.
- Few recent data regarding the qualitative and quantitative presence of HEMA in commercial products can be found in literature. There are some indications that HEMA is frequently used in dental products and nail cosmetics, in the latter category possibly in >50% of products.
- Methacrylates may not infrequently induce respiratory complications including asthma, rhinitis, and rhinoconjunctivitis, especially in dental personnel. Asthma-like symptoms usually appear after a long latency period of over 10 years; their exact mechanism is uncertain.

AUTHOR CONTRIBUTIONS

Anton C. de Groot: Conceptualization; formal analysis; methodology; visualization; project administration; writing—original draft; writing—review and editing; resources. **Thomas Rustemeyer:** Conceptualization; methodology; data curation; investigation; validation; resources; writing—review and editing.

ACKNOWLEDGEMENTS

The authors wish to thank Wouter Ouwerkerk, PhD, Department of Dermatology, Amsterdam UMC, University of Amsterdam, Amsterdam Infection & Immunity Institute, Amsterdam, The Netherlands and National Heart Centre Singapore, Singapore, for performing the statistical analyses. The authors wish to thank Iemke Steunebrink for collecting the data on the presence of HEMA in nail cosmetics.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable.

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How to cite this article: de Groot AC, Rustemeyer T. 2-Hydroxyethyl methacrylate (HEMA): A clinical review of contact allergy and allergic contact dermatitis. Part 2. Cross- and co-sensitization, other skin reactions to HEMA, position of HEMA among (meth)acrylates, sensitivity as screening agent, presence of HEMA in commercial products and practical information on patch test procedures. *Contact Dermatitis*. 2023;1-16. doi:10.1111/cod.14430