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REVIEW

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2-Hydroxyethyl methacrylate (HEMA): A clinical review of contact allergy and allergic contact dermatitis—Part 1. Introduction, epidemiology, case series and case reports

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Abstract

2-Hydroxyethyl methacrylate (HEMA) has been increasingly recognised as a contact allergen and was added to the European baseline series in 2019. In this article (2 parts), the results of an extensive literature review of the clinical aspects of contact allergy/allergic contact dermatitis to HEMA are presented. In part 1, the epidemiology of HEMA contact allergy is discussed and detailed information on published case series and case reports presented. HEMA is an important cause of contact allergy/allergic contact dermatitis in North America and Europe with recent prevalences of >3% in the USA + Canada and 1.5%–3.7% in Europe. Currently, most cases are caused by nail cosmetics, both in consumers and professional nail stylists. In our literature review, we have found 24 studies presenting case series of patients with allergic contact dermatitis attributed to HEMA and 168 case reports. However, the presence of HEMA in the products causing ACD was established in only a minority. Part 2 will discuss cross- and co-sensitisation, and other skin reactions to HEMA, will assess whether HEMA is the most frequent (meth)acrylate allergen and how sensitive HEMA as a screening agent is, investigate the presence of HEMA in commercial products and provide practical information on patch testing procedures.

KEYWORDS
2-hydroxyethyl methacrylate, acrylates, allergic contact dermatitis, contact allergy, dental nurse, dentist, glue, HEMA, methacrylates, nail cosmetics, nail stylists, occupational allergic contact dermatitis

1 | INTRODUCTION

Acrylates and methacrylates (together often termed 'acrylates' or '(meth)acrylates') are the esters and salts of acrylic acid and methacrylic acid, respectively.[1] Monomers may polymerize into polymers by a process called curing or hardening. Curing may be achieved by adding chemical catalysts (initiators/accelerators), by ultraviolet or LED light, by heat, by absence of oxygen, by ionizing radiation or spontaneously (self-curing).[2] The products of these reactions are called plastics or plastic resins, which can be shaped into various products. Ninety years ago, the first commercial application of acrylates was a light-weight, shatter-resistant glass alternative composed of polymethyl methacrylate, termed plexiglass (generic name) or Plexiglas® (trade name).[3] Today, acrylates are used in an extremely broad range of products for industrial, consumer, medical and dental uses (Table 1).[2–4]

Acrylates are well-known causes of contact allergy and allergic contact dermatitis. The haptens are the low molecular weight monomers.

Abbreviations: ACD, allergic contact dermatitis; BUDA, 1,4-butanediol diacrylate; EA, ethyl acrylate; 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); NACDG, North American Contact Dermatitis Group; OACD, occupational allergic contact dermatitis; TREGDA, triethylene glycol diacrylate; TREGDMA, triethylene glycol dimethacrylate; TENS, transcutaneous electrical nerve stimulator; THFMA, tetrahydrofurfuryl methacrylate.

TABLE 1 Potential sources of (meth)acrylates.

Industrial products	Adhesives (glues, tapes); coatings (glass, leather, rubber, textiles, woods, etc.); computer disks; fibreglass; glues; insulators; lacquers; paints; plastics and plastic products; printing inks; printing plates; repair of windshields and windowpanes; sealants.
Consumer products	Cleaning products (polishes, waxes); contact lenses; disposable diapers; fitness devices; glues; incontinence pads; sanitary pads; spectacle frames; textiles; water-based paints.
Medical products	Adhesive tape; bone cement for arthroplasty; conducting gels in diathermy pads, transcutaneous electrical nerve stimulators (TENS) and ECG electrodes; glucose sensors; glue for electrosurgical earthing plate; hearing aids; insulin pumps; intraocular contact lenses, acrylic ocular prostheses; microporous biomaterials; orthopaedic prostheses; polymethyl methacrylate-based material for cranioplasty; surgical glues; tissue embedding medium for light microscopy; wound dressings.
Dental products	Crowns; dental prostheses; dentures; desensitising dental swabs; fillings; occlusal splint; orthodontic adhesive; restorations; veneers.
Cosmetics/ aesthetics	Dermal filler; glue for false eyelashes, eyelash extensions, hair extensions and fixation of wigs and hairpieces; glue for preformed nails (press-on nails); nail cosmetics (acrylate nails, gel nail polish, gel nails, nail hardeners)

Note: Adapted from Refs. 2–4.

Acrylic acid and methacrylic acid themselves have a negligible role in contact allergy to (meth)acrylates.[5] The cured end products of acrylic resin systems do not normally sensitise or cause symptoms in previously sensitised individuals, as they do not contain enough reactive monomers.[6] However, especially when curing is incomplete (e.g., with improper curing technique), residual monomers may be present in the final product and may occasionally induce contact allergy or elicit allergic contact dermatitis (ACD). Previously, mostly dental personnel (dentists, dental nurses, dental technicians),[7–14] printers,[12,15–18] painters and workers in paint factories[18] and machinists and other industry workers exposed to glues, sealants and adhesives[7,19] were at risk of becoming sensitized.

However, during the last 2 decades, in many studies, a shift has been observed in many or most cases of contact allergy and ACD from acrylates being caused by nail cosmetics (acrylate nails, gel nails, long-lasting nail polish [gel lacquer]). These reactions are observed in both nail technicians/beauticians (inducing occupational ACD) and in consumers of these cosmetic products, either clients of nail technicians or women who apply the nail products themselves at home.[1,20–22]

In many studies in which patients were patch tested with a tray of (meth)acrylates, the most frequently reacting molecule was 2-hydroxyethyl methacrylate (HEMA).[9,11,20,23–25] From here on, its INCI name HEMA will mostly be used. Many investigators also found that HEMA generally is a good screening agent for contact allergy to other (meth)acrylates.[1,9,23,26] In addition, HEMA showed frequent positive patch test reactions in both unselected[27] and selected patient groups[1,20,25,28,29] in European countries. Therefore, in January 2019, HEMA was included by the European Society of Contact Dermatitis in the European baseline series for routine testing.[30,31]

Because of its presence in the baseline series, the expected high rates of cases of contact allergy detected by patch tests, and because of the serious implications that sensitisation to HEMA may have for patients, it is important that dermatologists and other physicians performing patch tests should be well-informed of the clinical and patch test aspects of HEMA or at least have access to such information. The comprehensive clinical review presented here aims to facilitate these goals and at the same time is intended to provide a detailed bibliography of relevant published studies for future authors of HEMA/acrylate-related scientific articles.

In this part 1 of the article, the epidemiology of contact allergy to and allergic contact dermatitis from HEMA will be presented as well as detailed information on published case series and case reports. Part 2 will discuss cross- and co-sensitisation, and other skin reactions to HEMA, will assess whether HEMA is the most frequent (meth)acrylate allergen and how sensitive HEMA as a screening agent is, investigate the presence of HEMA in commercial products and provide practical information on patch testing procedures.

2 | MATERIALS AND METHODS

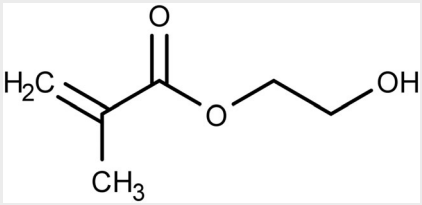
All issues of the journal *Contact Dermatitis* were hand searched for relevant articles from July 2023 (volume 89, issue 1) back to February 1975 (volume 1, issue 1), as were all issues of the journal *Dermatitis/ American Journal of Contact Dermatitis* from May/June 2023 (volume 34, issue 3) back to 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' (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 | PROFILE OF HEMA

HEMA is the 2-hydroxyethyl ester of methacrylic acid. It was first synthesised around 1925. Common methods of synthesis are (i) reaction of methacrylic acid with ethylene oxide; and (ii) esterification of methacrylic acid with a large excess of ethylene glycol. Both these methods give also some amount of ethylene glycol dimethacrylate.

HEMA is a plastic material used in printing industry, artificial nail modelling systems such as gel nails and long-lasting nail polish, dental plastic fillings and many other applications. The substance is applied in a viscous monomeric form and cured into a solid polymeric structure most often with ultraviolet light. HEMA as a monomer has been considered both as strongly allergenic[6,32] and as a weak to moderate sensitizer[33]; once fully cured it is safe.[6] The structural formula and other characteristics of HEMA are shown in Table 2.

TABLE 2 Characteristics of 2-hydroxyethyl methacrylate.[33–35]

Chemical class	Methacrylates
Function(s) in plastics	Monofunctional monomer; diluent
Function in cosmetics	Nail sculpting, film forming
IUPAC name	2-Hydroxyethyl 2-methylprop-2-enoate
INCI name	HEMA
Other names	Glycol methacrylate; glycol monomethacrylate; 2-HEMA; ethylene glycol methacrylate; methacrylic acid, 2-hydroxyethyl ester; (hydroxyethyl)methacrylate (Wikipedia)
CAS registry number	868-77-9
EC number	212-782-2
Molecular formula	$C_6H_{10}O_3$
Molecular weight	130.14 g/mol
Structural formula	
Physical form	Colourless viscous liquid
Water solubility	Miscible with water and soluble in common organic solvents
Purity	97.0% to >99%
Impurities/ accompanying contaminants	Diethylene glycol monomethacrylate: <2.0% Ethylene glycol dimethacrylate: <0.2% Water: <0.04% Methacrylic acid: <0.04% Ethylene oxide: <0.001% Hydroquinone monomethyl ether (4-methoxyphenol): 40–80 ppm (additive for prevention of polymer formation); in commercial nail products for professional and for non-professional use, its content will be at maximum of 200 ppm; similar polymerisation inhibitors may also be used

4 | PATCH TESTING WITH HEMA IN GROUPS OF PATIENTS

4.1 | Patch testing in consecutive patients suspected of contact dermatitis: Routine testing

Results of studies performing routine patch testing with HEMA (testing in consecutive patients suspected of contact dermatitis) are shown in Table 3.

HEMA has been included in the screening tray of the North American Contact Dermatitis Group (NACDG) since 2007; the NACDG publishes their patch test results biannually. In the period 2007–2014, the prevalence of sensitisation to HEMA in North America (USA + Canada) has been fairly constant between 2.0% and 2.6%.[44–47] Relevance rates ranged from 28% to 44% for 'definite + probable' relevance (for which the criteria are rather strict). In the period 2015–2016, the prevalence of positive reactions reported by the NACDG increased to 3.4%.[43] In the most recent 2019–2020 NACDG study, the prevalence again was high with 3.2%, which was a statistically significant increase compared with the pooled proportions of positive reactions of HEMA over the previous 10 years (2009–2018).[36]

Results of routine testing with HEMA in Europe are available from Sweden,[24] United Kingdom,[27] Italy,[40,42] Denmark,[39] Spain[38] and a multicentre study from 13 European countries.[37] In the post-2015 studies, rates of positive reactions to HEMA were around 1.6% in the UK[27] and Italy.[40,42] In Denmark in the period 2017–2019, 2.4% of female patients had positive reactions to HEMA (the male population was excluded, as there was only 1 reaction in a man).[39] Nearly the same percentage (2.3%) was found in the multinational 2019–2020 study.[37] The highest prevalence has been found in 2019–2020 in Spain, with 69 of 1884 patch-tested individuals (3.7%) reacting to HEMA.[34]

In recent studies in which relevance data were specified, the large majority (64%, 73%, 80%, 80% and >80%) of reactions to HEMA were related to cosmetic nail products.[27,39,40,42,43] Professional nail stylists were affected as were consumers, who either had their nails done in a nail salon by professionals or applied the acrylic nails, gel nails or long-lasting nail polish themselves at home. In the group of patients with occupational allergic contact dermatitis, nail stylists/nail technicians/beauticians formed the majority: 56%,[39] 64%[42] and 97%.[27] Many of these professionals also used acrylic cosmetics themselves, which inevitably will have led to an increased risk of sensitisation.[27] In the Danish study, it was found that the proportion of HEMA test-positive patients with a history of using UV nail polish increased from 50% in 2017 to 85% in 2018 and 100% in 2019.[39] As a consequence of this major role of nail cosmetics, the large majority of patients sensitised to HEMA are currently female, in one study even 31/32 (97%).[39]

4.2 | Patch testing in groups of selected patients

Results of testing HEMA in groups of *selected* patients (e.g., professional manicurists, patients suspected of allergy to (meth)acrylates, students in dental medicine, dental technicians, patients with dental occupations who had occupational allergic contact dermatitis, patients assessed for possible sensitisation to (meth)acrylates used in manicures) back to 1994 are shown in Table 4 (ordered by selection criteria). The table with studies in chronological order is shown in Table S1.

All these studies had a retrospective design and the investigated populations varied widely in selection parameters and the degree of selection. Therefore, it is not surprising that the rates of

TABLE 3 Results of patch testing in consecutive patients suspected of contact dermatitis (routine testing).

Years and Country	Test conc. and vehicle	Number of patients		Relevance (R)[a]; Comments (C)	References
		Tested	Pos. (%)		
2019–2020 NACDG	2% pet.	4111	130 (3.2%)	R: definite + probable relevance: 42%[a]; statistically significant increase in percentage positive reactions compared with the pooled proportions of positive reactions of HEMA over the previous 10 years (2009–2018)	36
2019–2020 13 European countries	2% pet.	7675	178 (2.3%)	R: not stated; C: 53 departments	37
2019–2020 Spain	2% pet.	1884	69 (3.7%)	R: 48 (70%)	38
2017–2019 Denmark	1% pet.	1293[b]	31 (2.4%)	R: currently relevant $n = 22$ (71%), past relevance $n = 5$ (16%); 16/22 relevant cases (73%) were caused by artificial nail modelling systems; 9/22 (41%) were occupational and 13 (59%) non-occupational; 5/9 occupational cases were in beauticians; C: all patients were female (in the study group there was only one male patient and therefore only women were included); a history of use of UV-nail polish resulted in a crude odds ratio of 9.7 for positive patch tests to HEMA; the proportion of HEMA test-positive patients with a history of using UV nail polish increased from 50% in 2017 to 85% in 2018 and 100% in 2019	39
2018 Italy	2% pet.	436	7 (1.6%)	R: 5/7 reactions (71%) were relevant, 4 from acrylic nails and 1 from a dental prosthesis	40
2017–2018 NACDG	2% pet.	4935	127 (2.6%)	R: definite + probable relevance: 36%[a]	41
2016–2018 Italy, 8 centres	2% pet.	4025	61 (1.5%)	R: 41 (67%, in women 72%, in men 38%); culprit products were acrylic nails (33/41, 80%), dental prostheses (5/41, 12%) and glues ($n = 3$, 7%); 27 patients had ACD (89% by acrylic nails) and 14 had OACD (64% by acrylic nails)	42
2016–2017 UK, 15 centres	2% pet.	5920	102 (1.7%)	R: not specified for HEMA; of 140 patients with proven (M)A ACD, 76 (54%) had been exposed to (meth)acrylates in UV-cured nails, 75 (54%) in gel nails, 51 (36%) in gel nail polish, 26 (19%) in nail glue, 10 (7%) in dentistry, four (3%) in orthopaedics and one (1%) in the printing industry; many patients had been exposed to (meth)acrylates in multiple nail products; C: of the 140 patients with proven (meth)acrylate ACD, occupational exposure was recorded in 38 (27%); apart from one patient who was a printer, all patients with occupational exposure worked in the nail and beauty industry, and in addition all of these used acrylic nails recreationally; almost one-third of cases of (M)A ACD would have been missed if HEMA had not been present in the baseline series.	27
2015–2016 NACDG	2% pet.	5594	188 (3.4%)	R: definite + probable relevance: 25%[a]; C: in 64%, sources of pos. HEMA patch tests were artificial nails (47%), nail care products (6.5%), nail polish (6.5%), or nail adhesives (4%)	43
2013–2014 NACDG	2% pet.	4859	128 (2.6%)	R: definite + probable relevance: 28%[a]	44
2011–2012 NACDG	2% pet.	4230	83 (2.0%)	R: definite + probable relevance: 34%[a]	45
2009–2010 NACDG	2% pet.	4301	(2.0%)	R: definite + probable relevance: 30%[a]	46
2007–2008 NACDG	2% pet.	5065	(2.4%)	R: definite + probable relevance: 44%[a]	47
1998–2008 Canada	2% pet.	3991	30 (0.8%)	R: 26 (87%): 10 in artificial nails, 8 in dental products, 5 in adhesives, 2 in feminine hygiene pads and 1 in a leg prosthesis	48

TABLE 3 (Continued)

Years and Country	Test conc. and vehicle	Number of patients		Relevance (R)[a]; Comments (C)	References
		Tested	Pos. (%)		
2005–2007 Sweden	2% pet.	1609	16 (1.0%)	R: 8/16 (50%) reactions were relevant for contact with (meth)acrylates: 6 nail technicians, 3 dental workers, 3 men working with UV-cured acrylates and 2 acrylic nail users; not specified for HEMA	24
2005–2007 Singapore	2% pet.	1181	3 (0.3%)	R: one reaction was relevant	24

Abbreviations: ACD, allergic contact dermatitis; conc., concentration; (M)A, (meth)acrylate; NACDG, North American Contact Dermatitis Group (USA, Canada); OACD, occupational allergic contact dermatitis; pos., positive.
[a]NACDG criteria: current relevance *definite*: use test with the suspected item was positive, or a patch test to the object or product was positive; current relevance *probable*: the antigen could be verified as present in known skin contactants and clinical presentation was consistent.
[b]All female patients; only the results of routine testing in females are presented, as there was only one man with a positive patch test to HEMA.

TABLE 4 Patch testing in groups of patients: Selected patient groups (ordered by selection criteria).

Years and country	Test conc. and vehicle	Number of patients		Selection of patients (S); Relevance (R); Comments (C)	References
		Tested	Positive (%)		
Selection for contact with nail cosmetics					
2008–2017 Spain	2% pet.	89	64 (72%)	S: patients assessed for possible sensitisation to (meth)acrylates used in manicures; R: not stated; C: 46 of 66 patients (70%) with one or more positive reactions to (meth)acrylates were nail professionals, 9 (14%) professionals and also users (consumers) and 11 (17%) consumers	49
<2017 Poland	2% pet.	93	1 (1.1%)	S: professional manicurists working in a beauty salon, recruited by a questionnaire, surveying the occurrence of skin, ocular, nasal and respiratory symptoms; R: not specified; C: only 7 had some dermatosis of the hands, but none had (active) dermatitis	50
2007–2016 Sweden	2% pet.	28	10 (36%)	S: nail technicians patch tested because of dermatitis; R: 100%; C: all patients were female	51
2001–2016 NACDG	2% pet.	482	273 (56.7%)	S: patients with more than 1 allergic patch test reaction associated with a nail care product; R: 70% current, 30% past; C: 45/273 (16%) patients had occupational ACD/contact allergy; the frequency of HEMA-reactions associated with nail care increased throughout the study period	52
2004–2013 IVDK	1% pet.	172	39 (22.7%)	S: female consumers in who nail cosmetics were considered to be the cause of their dermatitis	25
	1% pet.	73	16 (22%)	S: female nail artists/cosmetologists in whom nail cosmetics were not suspected as the cause of their dermatitis	25
	1% pet.	74	27 (36%)	S: female nail artists/cosmetologists in whom nail care/sculpturing material was considered to be the cause of their dermatitis	25
2001–2004 Israel	2% pet.	55	17 (31%)	S: patients suspected of reactions to acrylic nails and tested with a nail (meth)acrylate series; R: all reactions were considered to be relevant; C: 8 reactions were OACD in professional beauticians specialising in nail sculpturing	53
Selection for dental professionals and products					
2001–2018 NACDG	2% pet.	217	18 (8.3%)	S: patients with dental occupations who had occupational allergic contact dermatitis; R: 100%; patients were selected on the basis of occupationally relevant reactions	54

(Continues)

TABLE 4 (Continued)

Years and country	Test conc. and vehicle	Number of patients		Selection of patients (S); Relevance (R); Comments (C)	References
		Tested	Positive (%)		
2001–2015 IVDK	1% pet.	188	40 (21.3%)	S: dental technicians suffering from occupational contact dermatitis and tested with HEMA; R: 'we have no reliable data on the patients' individual exposures; hence, we cannot comment on the clinical relevance of the sensitisations in every case'	55
<2013 Bulgaria	0.2% pet.	108	29 (26.8%)	S: advanced students in dental medicine (n = 72) and dental professionals (n = 36); not specified how they were selected, but most of them had no skin pathology; R: not stated; C: 9/29 (31%) also reacted to formaldehyde, tested at 0.1% aqua (!); in a group of 29 occupationally unexposed dental patient controls 11 (38%) had a positive reaction to HEMA, which is astonishing, especially considering the low concentration of HEMA of 0.2% (which is probably incorrect and should be 2%); probably unreliable study	56
1995–2004 Sweden	2% pet.	1632	47 (2.9%)	S: patients tested with a dental series or dental personnel series; R: not stated	9
2004 Finland	1% pet.	86	3 (3.5%)	S: dental nurses participating in a clinical examination after telephone interviews; R: in all 3 the reactions were considered the cause of occupational ACD	57
2001 Korea	2% pet.	22	1 (4.5%)	S: dental technicians with contact dermatitis; R: not stated; C: only few reactions to HEMA and other acrylates because few patients had serious dermatitis and many cases were probably irritant contact dermatitis	58
1995–1999 Germany	1% pet.	126	19 (15.1%)	S: dental technicians with dermatitis referred by insurers for legal compensation; R: 6/19 (32%)	59
1997–1998 Sweden	2% pet.	147	7 (4.8%)	S: dentists who had eczema recruited by a questionnaire; R: not stated; C: most of the patients with acrylate allergy did not have serious medical, social or occupational consequences	60
1995–1998 Sweden	2% pet.	109	23 (21.1%)	S: dentists and dental nurses with skin disease; R: not stated	11
1993–1994 Germany	2% pet.	55	18 (33%)	S: dental technicians reported to the insurer suspected of occupational contact dermatitis; R: not specified	14
Patients suspected of (meth)acrylate allergy/tested with a (meth)acrylate or similar series					
2012–2015 UK	2% pet.	251	12 (4.8%)	S: patients tested with a limited or extensive (meth) acrylate series; R: 10/12 (83%); culprit products were gel nails (*n* = 5), false nails (*n* = 2), adhesive drapes (*n* = 2) and dental (*n* = 1); 2 reactions were not relevant; C: all but one were female; all five patients with reactions from gel nails were beauticians or nail technicians and 3 of these had occupational allergic contact dermatitis; the other 2 also had gel nails themselves and may have become sensitised this way	29
2008–2015 UK, nine centres	2% pet.	1306	125 (9.6%)	S: patients with a history of (meth)acrylate exposure; R: not specified for HEMA; of 120 patients with reactions to one or more (M)A, 68	28

TABLE 4 (Continued)

Years and country	Test conc. and vehicle	Number of patients		Selection of patients (S); Relevance (R); Comments (C)	References
		Tested	Positive (%)		
				had OACD (58 in the nail and beauty industry) and 52 had recreational exposure from acrylic nail products (110:120 = 92% nail cosmetics); C: 92% of the patients were female	
2002–2015 UK	2% pet.	475	29 (6.1%)	S: patients suspected of contact allergy to (meth) acrylates R: not specified; C: 24/47 (meth) acrylate-allergic patients (51%) had occupational ACD; 23/47 (49%) were related to nail cosmetics; a shift in exposures away from manufacturing and towards acrylic nail sources was observed	21
2008–2014 UK	2% pet.	455	44 (9.7%)	S: patients tested with an acrylate series; R: all reactions were considered to be relevant; of 54 patients reacting to a (meth)acrylate (of which 44 were HEMA-positive), 45 (83%) were related to nail cosmetics, of who 15 (33%) were beauticians	1
2006–2013 Portugal	2% pet.	122	30 (24.6%)	S: patients with a history of acrylate exposure and reactions; R: all reactions were considered to be relevant; C: in 28 of 37 (76%) patients with positive patch tests to (M)A the reactions were related to artificial acrylic nails (13 technicians, 8 users, and 7 technicians and users), in 4 (11%) to dental prostheses, and in 3 (8%) to occupational contact with dental material (1 dentist and 2 dental prosthetics technicians); 25/37 (68%) patients with reactions to (M)A had occupational ACD, of who 20 (80%) were nail beauticians	20
2004–2013 IVDK	1% pet.	10 089	309 (3.1%)	S: women tested with (meth)acrylates; R: not stated	25
1993–2012 NL	2.0% pet.	151	8 (5.3%)	S: strong suspicion of (meth)acrylate contact allergy; R: not specified for individual chemicals; C: HEMA had rank order 8 in (meth)acrylates series; of 24 patients with one or more reactions to (M)A, 21 (88%) had (certain, probable or possible) OACD: 8 nail stylists, 4 assembly line workers, 3 printers, 2 laboratory technicians, 2 dental technicians, one painter and one dairy farmer	61
1994–2009 Finland	1% pet.	541	42 (7.7%)	S: patients patch tested with a (meth)acrylate series; R: 40 had been exposed to methacrylates and 0 to acrylates	7
2000–2007 USA	2% pet.	442	28 (6.3%)	S: patients patch tested with glues and plastics series; R: 23/28 (82%)	62
1983–1998 UK	2% pet.	330	26 (7.9%)	S: patients with a history of contact with (meth) acrylates; R: not stated	12
1985–1995 Finland	2% pet.	273	31 (11.4%)	S: patients with a history of (meth)acrylate exposure; R: not stated; C: overlap with the data in ref 64	63
1991–1994 Finland	2% pet.	124	13 (10.5%)	S: patients with a history of (meth)acrylate exposure; R: not stated C: overlap with the data in ref. 63	64
Other selection criteria					
2000–2019 IVDK	1% pet.	417	4 (1%)	S: male painters with OD tested with a resin and glue series; R: not stated.	65
2001–2018 NACDG	2% pet.	259	7 (2.7%)	S: patients with medical adhesives (miscellaneous health aids/tapes/band-aids/adhesive aids/	66

(Continues)

TABLE 4 (Continued)

Years and country	Test conc. and vehicle	Number of patients		Selection of patients (S); Relevance (R); Comments (C)	References
		Tested	Positive (%)		
				suture glue) documented as the sources of positive patch test reactions; R: 1/7 (14%); 6 were *possibly* relevant	
2010–2013 Germany	1% pet.	250	1 (0.4%)	S: consecutive cemented arthroplasty-bearing patients suspected of having allergic reactions to the implant materials; R: not stated	67
2001–2010 Australia	2% pet.	504	48 (9.5%)	S: not stated; R: 65%	68
1994–2010 NACDG	2% pet.	?	? (?)	S: hairdressers/cosmetologists; R: in a group of 57 patients who had at least one relevant occupationally related reaction, 15 (26%) reacted to HEMA; C: the high rate of positive reaction was ascribed to the fact that nail technicians, who are occupationally exposed to (meth) acrylates, were coded as 'cosmetologists'	69
1993–2010 Australia	NS	164	8 (4.9%)	S: hairdressers and apprentice hairdressers presenting at an occupational dermatology clinic; R: 100%	70
1994–2009 Finland	1% pet.	66	42 (64%)	S: group of patients with pos. patch tests to one or more (meth)acrylates; R: 40 had been exposed to methacrylates and 0 to acrylates	7
2000–2004 USA	2% pet.	77	4 (5.2%)	S: patients with a presenting symptom of oral disease or oral symptoms; R: 75%	71
<2001 Finland	2% pet.	2446	69 (2.8%)	S: suspected contact dermatitis of the oral mucosa or lips, or suspected occupational or non-occupational contact reactions caused by dental products; R: not stated	72
2000 Spain	NS	520	3 (0.6%)	S: patients with dental prostheses, complaints not mentioned; R: all reactions were considered to be relevant	73

Abbreviations: ACD, allergic contact dermatitis; IVDK, Information Network of Departments of Dermatology, Germany, Austria, Switzerland; (M)A, (meth) acrylate(s); NACDG, North American Contact Dermatitis Group; NL, Netherlands; NS, not stated; OACD, occupational allergic contact dermatitis; OCD, occupational contact dermatitis; OD, occupational dermatitis; UK, United Kingdom.

positive reactions to HEMA vary widely between 0.6%[73] and 72%.[49] At the low end of the spectrum, in a group of patients who had a dental prosthesis and who were tested with HEMA, there were hardly any positive patch test reactions.[73] This could have been anticipated, as it is well known that dentures rarely cause allergic problems because of the absence of free HEMA monomers in adequately hardened dentures or very low content of HEMA monomers. At the high end of the spectrum, it is equally unsurprising that in a retrospectively selected group of patients assessed for possible sensitisation to (meth)acrylates used in manicures, of who the majority were nail professionals, 72% showed positive patch tests to HEMA.[49] Indeed, possible allergic contact dermatitis to nail cosmetics is easily recognized, HEMA and other (meth)acrylates are virtually the only sensitizers in these modern nail cosmetics, HEMA is present in many nail cosmetics (unpublished observations from currently conducted market survey; see also paragraph 9.2 'Data on the presence of HEMA in substances and products' in Part 2 of this article) and HEMA is a good screening agent for contact allergy to other (meth)acrylates (see paragraph 7 'Sensitivity of HEMA as marker for (meth)acrylate allergy' in Part 2).

The influence of selection is beautifully shown in a 2004–2013 study performed by the Information Network of Departments of Dermatology (IVDK)[25]: 3.1% positive reactions to HEMA in women tested with (meth)acrylates, versus 22.7% in female consumers in who nail cosmetics were considered to be the cause of their dermatitis. Twenty-two per cent positives to HEMA in female nail artists/cosmetologists in whom nail cosmetics were *not* suspected as the cause of their dermatitis versus 36% in those in whom nail care/sculpturing material was considered to be the cause of their dermatitis.[25]

4.2.1 | Selection for nail cosmetics

In studies with selection towards reactions to nail cosmetics, high rates (22%–72%) of positive reactions to HEMA were observed in 5 of 6 studies (Table 4). Virtually all patients were female and many

were nail professionals,[25,49,51,53] in a Spanish study representing >80% of patients.[49] In a 2001–2016 study performed by the NACDG in patients with more than 1 allergic patch test reaction associated with a nail care product, the frequency of reactions to HEMA increased throughout the study period.[52] In a study from Poland only 1% of professional manicurists working in a beauty salon and recruited by a questionnaire reacted to HEMA, which may easily be explained by the fact that none had active dermatitis and most had not any skin symptoms at all.[50]

4.2.2 | Selection for dental products and dental professionals

In studies with a selection of dental professionals and dental products, rates of positive reactions ranged from 2.9% to 33% (Table 4). The highest frequencies of sensitisation were found in dental technicians reported to the insurer suspected of occupational contact dermatitis (33%),[14] dental technicians suffering from occupational contact dermatitis (21.3%),[55] dentists and dental nurses with skin disease (21.1%)[11] and dental technicians with dermatitis referred by insurers for legal compensation (15.1%).[59] A study from Bulgaria also showed a high rate of 26.8% positive reactions to HEMA, but was most likely unreliable (Table 4).[56] Patch testing with a dental series or dental personnel series (possibly liberal, not selected for strong suspicion of [meth]acrylate allergy) yielded only 2.9% reactions to HEMA in a 1994–2004 study from Sweden.[9]

4.2.3 | Selection for suspicion of (meth)acrylate allergy

Many studies have reported the results of testing HEMA and other (meth)acrylates in special series in patients suspected of (meth) acrylate allergy. Most had scores of HEMA-positives in the 5%–11% range (Table 4). A very high rate of 24.6% positive reactions to HEMA was observed in Portugal, in which all patients tested had both a history of (meth)acrylate exposure and a history of reactions to the acrylate-containing products. As might be expected, in 76% of the patients the reactions were related to artificial acrylic nails, of whom 2/3 were nail technicians.[20] In other recent studies, 70%[29] and 92%[28] of the relevant reactions were related to nail cosmetics; in one of these studies, nearly 50% of the patients were nail stylists with OACD.[28] As a result, the large majority of patients were female.[20,28,29] In an investigation from the UK, a shift in exposures away from manufacturing and towards acrylic nail sources was observed during the study period 2002–2015.[21]

4.2.4 | Other selection criteria

Low rates of HEMA positives were observed in painters with occupational dermatitis (1%),[65] patients with reactions to medical adhesives (2.7%),[66] consecutive cemented arthroplasty-bearing patients suspected of having allergic reactions to the implant materials (0.4%),[67] and patients with dental prostheses (0.6%).[73] The highest score (64%) was found in a study from Finland; selection of patients with positive patch tests to one or more (meth)acrylates understandably led to this result.[7]

5 | CASE REPORTS AND CASE SERIES

In this section, case series and case reports of allergic contact dermatitis from HEMA are presented with descriptions of clinical and patch testing data.

5.1 | Case series

Case series are groups of patients (usually 3 or more) with allergic contact dermatitis, who have positive patch test reactions to HEMA, in whom the investigators attributed the dermatitis to the established HEMA hypersensitivity. To diagnose 'ACD from HEMA', the presence of HEMA in the products that have caused the allergic skin reaction must, strictly speaking, be ascertained, for example, from information on the ingredient label or material safety data sheet. In many of the case series presented below, this condition may not—always—have been fulfilled. It is very likely that many investigators score a positive patch test reaction to HEMA as 'relevant' (indicating that HEMA has caused the dermatitis or has contributed to it), when the patient has used products known to contain (meth)acrylates at the site of the dermatitis, also when it is unknown whether these products actually contained HEMA itself. In such cases, the ACD may well have been caused by one or more other (meth)acrylates that cross-react to or from HEMA, which possibility must be taken into account when assessing the reports below.

At the end of this section, key data of the *proven cases* of ACD or OACD from HEMA are summarised in tabular form (Table 5).

5.1.1 | Artificial nails

2018 EECDRG

A retrospective study in 11 European Environmental Contact Dermatitis Research Group (EECDRG) clinics collected information on cases of ACD caused by nail acrylates diagnosed by aimed testing between 2013 and 2015.[26] Among 18.228 studied patients, 136 (0.75%; 135 women, one man) had ACD caused by nail acrylates. One hundred thirty-five patients had been tested with HEMA 2% pet. and there were 124 (92%) positive reactions. Exact data on the relevance of the positive patch tests was not provided, but 'HEMA and/or many other (meth)acrylates were present in the gels used for nail sculpting procedures and for long-lasting gel nail lacquers from many different brands, mostly depending on the country of origin'.[26]

2017 Portugal

In a retrospective study, 13 departments in Portugal identified 230 cases of allergic contact dermatitis caused by (meth)acrylates used in nail products between 2011 and 2015, representing 2% of all patients patch tested in that period.[74] Fifty-five (24%) were occupationally exposed, 56 (24%) were consumers, and 119 (52%)) were exposed both as consumers and occupationally. HEMA was tested in 220 individuals and was positive in 198 (90%). It was not mentioned how many of these had used products actually containing HEMA.[74]

2017 Canada

In a 1-year-period in 2015–2016, six female nail technicians with dermatitis were seen at a major referral centre for suspected occupational ACD in Canada.[75] Patch tests, read at D2, D4 and D7, yielded positive reactions to HEMA, 2-hydroxypropyl methacrylate (HPMA), ethylene glycol dimethacrylate (EGDMA) and 2-hydroxyethyl acrylate (HEA) in all six, and five had positive reactions to another 1–3 (meth)acrylates. All were diagnosed with occupational ACD from (meth)acrylates in nail cosmetics. No information was provided on the composition of the materials the patients worked with.[75] However, the relevance of HEMA was indicated by the statement: 'Acrylic and gel nails, as well as shellac nail polish, are all known to contain HEMA …', apparently based on Le et al.[76] However, in that article, HEMA is indeed mentioned as a (possible?) ingredient of all tabulated nail cosmetics, but (i) without the specific statement that *all* these products contain HEMA and (ii) without any sources to substantiate these data. Also, in a 2005 study from Belgium (presented below in this paragraph), the ingredient lists of products used by patients who had experienced skin reactions from acrylic nails were checked and it was found that 'some acrylic nails did not contain 2-HEMA on their ingredient list',[23] which implies that *not all* acrylic nails are known to contain HEMA.

2016, 2011 Belgium

HEMA was stated to be the (or an) allergen in 13 patients in a group of 603 individuals suffering from cosmetic dermatitis, seen in the period 2010–2015 in Leuven, Belgium.[77] In the same centre in Belgium, HEMA was responsible for 7 out of 959 cases of non-fragrance cosmetic allergy where the causal allergen was identified in the period 2000–2010. The culprit cosmetic products were nail cosmetics. This study overlaps with the previous one for the time period January–November 2010.[78]

2016, 2009, 2008 Spain

A Spanish study published in 2016[79] reported that, in the period 1996–2013, in a tertiary referral centre in Valencia, 5419 patients were patch tested. Of these, 608 individuals had allergic contact dermatitis and 20 photoallergic contact dermatitis to cosmetics. HEMA was listed as the responsible allergen in 28 cases. In total, 40 patients were allergic to one or more (meth)acrylates, of who 27 (68%) were beauticians, who had occupational allergic contact dermatitis from contact with porcelain nails, gel nails, and/or long-lasting nail polish.[79]

A previous study from the same clinic in Valencia, Spain, published in 2009, reported 202 patients with allergic contact dermatitis caused by cosmetics seen in the period 2000–2007.[80] Therefore, the data presented were also included in the 2016 study.[79] In the group of 202 patients with ACD from cosmetics, there were 10 beauticians with occupational allergic contact dermatitis of the hands, who reacted to multiple (meth)acrylates from their presence in artificial nail materials. Of these 10 individuals, seven reacted to HEMA, which reactions were apparently relevant.[80]

One year earlier, in 2008, the investigators from this clinic in Spain had presented data on 15 patients with ACD to (meth)acrylates in artificial nails.[81] All were women; 14 were professional beauticians and 1 was a client who had her nails done with acrylates. All were tested with 15 (meth)acrylates. Seven reacted to 2 (meth)acrylates, the others to 3–8 monomers. HEMA and EGDMA were the most frequent positives, each reacting in 13 of 15 patients. The authors considered the reactions to *all* (meth)acrylates to be relevant. However, it was also mentioned that some positive patch tests were cross-reactions (ergo: contradictory with all relevant) and no information was provided on the ingredients of the used (meth)acrylate materials.[81]

2005 Belgium

In a study in two hospitals in Belgium (study period not mentioned), 27 patients who had experienced skin reactions from acrylic nails, of who 16 were professional beauticians, were patch tested with 1–24 (meth)acrylates and 25/27 (93%) reacted to HEMA. It was not specified how many products used actually contained HEMA, but it was stated that 'some acrylic nails did not contain 2-HEMA on their ingredient list', so most of them indeed did.[23]

1996 Austria

Five women with UV-cured acrylic nails presented with a pruritic and painful perionychial and subonychial dermatitis for several months.[82] Monthly renewal of the nails caused a strong exacerbation of the dermatitis the next day. A change to 'hypoallergenic' commercial products declared to be free of acrylates by the manufacturers of three patients did not yield considerable improvement in any of them. Patch tests were positive to HEMA 0.6% pet., HPMA 0.6% pet. and EGDMA 2% pet. Some had positive reactions to other (meth)acrylates and all reacted to one or more 'acrylate-free' commercial products. The exact composition of the products used was not mentioned, but the presence of the positively reacting (meth)acrylates (including HEMA) was implied: 'All acrylates present in the commercial formula were positive on patch testing and should be considered relevant allergens'.[82]

See also Aalto-Korte and Suuronen[83] in Section 5.1.3 for two cases of sensitisation to HEMA in nail products.

5.1.2 | Long-lasting nail polish

2018 Spain

In 2018, four patients with ACD from long-lasting nail polish were reported from Spain. All four patients were sensitised to 2-hydroxyethyl acrylate, and three of them were sensitised 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.[84]

2017 Spain

Between 2013 and 2016, in four dermatology departments in Spain, 43 patients were diagnosed with ACD caused by (meth)acrylates in long-lasting nail polish (1.8% of all patients tested, 2.8% of all women tested).[85] All were female, and all had hand dermatitis. Patients were mostly less than 40-years-old and 40/43 (93%) were beauticians who had an occupational cause of their dermatitis. The most frequently reacting patch test allergens were HEMA (39/43, 91%), HPMA (41/43, 95%) and tetrahydrofurfuryl methacrylate (THFMA) (31/39 tested, 79%). These three allergens were also the methacrylates most frequently identified on the labels of the patients' products: HEMA in 7/13 (54%); di-HEMA trimethylhexyl dicarbamate in 5/13 (38%) and HPMA also in 5 (38%). In all cases, multiple positive reactions were recorded, and most of these reactions were strong (2+) or extreme (3+) positive.[85]

2015 Australia

Four cases of allergic contact dermatitis from Shellac® nail products/polish, involving three beauticians and one consumer, were reported from Australia. All reacted to HEMA and three of them also to one or more other methacrylates. It is likely (based on the data in Dahlin et al.[86]) that the products in one or more of the patients contained HEMA.[76]

2014 Sweden

During 2014, in Sweden, 65 reports concerning undesirable effects from the use of a UV-curing nail polish of one brand (very likely Shellac®) were received by the Swedish Medical Products Agency.[86] Eight patients who had suffered serious skin reactions from the use of the acrylate-based UV-curing nail polish for home use were investigated and patch tested with its ingredients. Six of these individuals, among whom a nail technician, had positive reactions to HEMA. All six also reacted to the ingredients di-HEMA trimethylhexyl dicarbamate 2% pet. and to 'urethane acrylates' (0.1% pet.), as well as to the base coat and the coloured coat, both tested at 1% pet. The authors considered the possibility that HEMA was the main sensitizer, and that the other reactions were cross-reactions resulting from the structural similarities: di-HEMA trimethylhexyl dicarbamate is a mixture of two molecules, both containing the HEMA structure, and urethane acrylates is a mixture containing hydroxyethyl acrylate. Another possibility offered was that the reactions to the other acrylate-containing ingredients were caused by HEMA present as a contaminant in the test material. This kit was subsequently prohibited by the Swedish Medical Products Agency and was no longer available from July 2014 onwards.[86]

5.1.3 | Dental products

2021 Finland

In the period 2010–2019, at the Finnish Institute of Occupational Health (where all patients have a suspected occupational skin disease), 55 patients tested positive to one or more acrylic compounds.[83] HEMA was the most commonly positive allergen with 21 cases (38%), and 13 of these (62%) had specific exposure to HEMA. Four of these 13 patients had OACD from HEMA in anaerobic sealants (a plumber, an assembler of trucks, an assembler of hospital beds, and an assembler of motor parts); three dental assistants had OACD from HEMA in dental adhesives and other acrylate-containing products; three (a glazier, windscreen assembler and a car mechanic) had OACD from HEMA in UV-cured adhesives and repair resins; a pedicurist and a beautician were sensitised to nail products containing HEMA; and a car painter had OACD from HEMA in car paint products.[83]

2007 Finland

In the period 1994–2006, 32 patients working in dentistry who had allergic reactions to acrylic monomers were examined at the Finnish Institute of Occupational Health: 15 dental nurses, 9 dentists, and 8 dental technicians.[10] The most commonly positive allergens were HEMA and EGDMA, both in 24 cases (75%), and HPMA in 23 cases (72%). The clinical records of 1 dental nurse were not found. All of the other 31 patients had hand dermatitis, and 25 of them had had fingertip dermatitis typical of methacrylate allergy. The methacrylate allergy was considered occupational in all 31 patients whose clinical records were available. Eight of 9 dentists (89%) were allergic to HEMA. In 5 of them, the presence of HEMA was mentioned in the safety data sheets (SDS) of subjects' own products and in one it was demonstrated by chemical analysis. Twelve of the 15 nurses (80%) were allergic to HEMA. In 8 of them, the presence of HEMA was mentioned in the SDS of subjects' own products and in one it was demonstrated by chemical analysis. Four of the 8 dental technicians (50%) had a positive patch test to HEMA and the methacrylate was identified in the own products of one of the technicians.[10]

1996 Poland

In the period 1990–1994, in Lodz, Poland, 1619 patients suspected of occupational contact dermatitis were investigated. Occupational ACD to acrylates was observed in 9 individuals: 4 dental technicians, 4 dentists and a textile printer. HEMA was patch test positive in four of these (not in the textile printer). Whether these patients actually had contact with HEMA was not mentioned.[13]

1994 Finland

In the Finnish Institute of Occupational Health, between 1988 and 1994, 10 patients with suspected OACD and one with pharyngitis caused by dentin-bonding systems (primer and adhesive) were investigated.[87] Pulpitis was the typical clinical feature, that is, dry, cracking, thickened fingertips, of fingers 1–3 of the left hand. Seven patients

complained of paresthesia. Seven of these patients (all allergic to HEMA, EGDMA and HPMA) had been reported previously.[88–90] The 'new' patients were three dentists and one dental nurse who all had dermatitis of the fingertips. Two of these (the dental nurse and a dentist) reacted to one or both components of the dentin-bonding system tested at 1% pet. (negative in 20 controls), two to HEMA and to other (meth)acrylates including EGDMA (one was not tested with HEMA). The primer contained, according to the material safety data sheets (MSDS), 30%–65% HEMA and the adhesive 40%–50% HEMA. GC–MS showed 48% HEMA in the primer and 32% in the adhesive. EGDMA was found to be present by GC–MS in a concentration of 0.8% in the primer and of 13% in the adhesive, which was not mentioned in the MSDS.[87]

1991 Finland

In 1991, six patients sensitised to a new dental adhesive system were reported from the Finnish Institute of Occupational Health.[88] Five had repeatedly relapsing dermatitis, the sixth patient had respiratory problems only (previously described in ref. 89). Three complained of paresthesia. The 5 patients with OACD were 3 dental nurses and 2 dentists. Four had dermatitis limited to the fingers and one had eyelid eczema. Patch tests were positive in all 5 to HEMA 2% pet., EGDMA 2% pet., HPMA and to the two components of the adhesive system, tested 1% pet. (negative in 20 controls). According to the material safety data sheets, the primer contained 30%–65% HEMA and the second component 50%–60% HEMA.[88] Later, in a study in which these six patients were described once more, it was shown by GC–MS that the primer contained 48% HEMA and 0.8% EGDMA, and that the adhesive component contained 29% HEMA and 13% EGDMA.[87]

5.1.4 | Other products

2008 Finland

In the period 1994–2006, 10 patients seen at the Finnish Institute of Occupational Health were examined who had occupational allergic contact dermatitis from methacrylates in glues (in nine cases from anaerobic glues).[19] They all displayed multiple positive patch tests to acrylates (acrylates and/or methacrylates and/or epoxy acrylates). The contents of the glues were examined by reading the Safety Data Sheets and by chemical analyses (gas chromatography with a mass selective detector). All patients reacted to HEMA and EGDMA and 9 to HPMA. However, in only two of these, HEMA was the causative allergen. The first was a plumber who had ACD from a pipe sealant containing 17.8% HEMA and the second was a measurement technician reacting to a bicomponent glue containing HEMA and methyl methacrylate (MMA) (quantities not stated). Two others had contact with products containing 0.01% and 0.12% HEMA, but these glues contained high concentrations of other acrylates to which these patients were also allergic. Most cases of OACD to glues (7/10) were caused by various dimethacrylates.[19]

1998 Netherlands

In The Netherlands, four patients developed ACD with intense red reactions from contact with electrosurgical earthing plates during operations, which contain an adhesive to fix the grounding plate to the skin.[91] Patch tests in these four individuals were positive to the electrosurgical earthing plate 'as is' (all +++), to 2-hydroxyethyl acrylate 0.1% pet. (+++), to HEMA 1% pet. (all ++) and to 2 or 3 other (meth)acrylates. Three of the four patients had probably previously become sensitised by sculptured nails. The manufacturer stated that the adhesive contained 2-hydroxyethyl acrylate and HEMA. Since these reports, a warning to acrylate-sensitive patients has been added to the information sheet of the earthing plate. The author suggested that reactions to such electrosurgical earthing plates after operations may be more frequent, as they are probably mistakenly interpreted as burns, because of the intense red reactions.[91]

1998 Sweden

In Sweden, during 1996–1997, a survey of occupational dermatoses, based on a questionnaire, clinical examination and patch testing, was carried out among present and former employees in a plant producing binders for glues and paints, the binders being based on vinyl acetate and/or acrylates. Eighty-seven individuals (76 present and 11 former employees) participated in the clinical examination and patch testing, which was conducted with a standard test series and chemicals from the work environment. Occupational allergic contact dermatitis was demonstrated in 16 (former) employees. In 12, the allergen was MCI/MI (preservative for the binders), in one formaldehyde and in 3 HEMA and 1–3 other methacrylates.[92]

1983 Denmark

Three printers working in newspaper production developed hand eczema related to their work.[16] Patch tests with scrapings of uncured printing plates that they worked with, tested as is, were positive. Testing with three chemical fractions obtained from chloroform extracts of the plates were positive to one fraction of 1% in alcohol in all three patients. Chemical analyses of this fraction by means of infrared spectrophotometry, nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) and elemental analysis (combustion analysis) showed this fraction to be HEMA. Patch tests with HEMA 1% pet. were also positive in the three printers.[16]

1979 Netherlands

Five workers involved in a photoprepolymer printing plate procedure developed dermatitis mainly on their hands and forearms. Four of them were patch tested with the 11 ingredients of the photoprepolymer mixture. All 4 reacted to HEMA 0.1% alc., 2 to triethylene glycol dimethacrylate (TREGDMA) 1% MEK (methyl ethyl ketone) and 2 to the ingredient DEGDM 1% MEK.[93]

5.1.5 | Summaries of case series

In Table 5, short summaries are provided of the cases of *proven* ACD and OACD from HEMA presented in Sections 5.1.1–5.1.4.

TABLE 5 Summaries of case series of allergic contact dermatitis caused by HEMA.

Year and country	Number of patients	Culprit product(s)	Occupation/work task/consumer	References
2021 Finland	4	Anaerobic sealants	1 plumber, 1 assembler of trucks, 1 assembler of hospital beds, 1 assembler of motor parts	83
	3	Dental adhesives and other dental products	Dental nurses	
	3	UV-cured adhesives and repair resins	1 glazier, 1 windscreen assembler, 1 car mechanic	
	2	Nail products	1 pedicurist, 1 beautician	
	1	Car paint	Car painter	
2016 Sweden	5	Gel nail polish	Consumers	86
	1	Gel nail polish	Nail technician	86
2008 Finland	2	Glues	1 plumber, 1 measurement technician	19
2007 Finland	5	Dental products	Dentists	10
	9	Dental products	Dental nurses	
	1	Dental products	Dental technician	
1998 Netherlands	4	Adhesive on electrosurgical earthing plate	Consumers/patients	91
1998 Sweden	3	Binders for glues and paints	Production workers	92
1994 Finland	2	Dental bonding system	1 dentist, 1 dental nurse	87
1991 Finland	5	Dental adhesive system	3 dental nurses, 2 dentists	88
1983 Denmark	3	UV-cured printing inks	Printers	16
1979 Netherlands	4	Photo-prepolymer mixture for printing ink	Production workers	93

Note: In all cases in this table, the presence of HEMA in the product(s) causing ACD was established from information found in material safety data sheets (MSDS), ingredient listing, data obtained from the manufacturer or from chemical analyses.

6 | CASE REPORTS OF ALLERGIC CONTACT DERMATITIS CAUSED BY HEMA

In this section, case reports of allergic contact dermatitis (ACD) from HEMA in (mostly) single patients are presented. To qualify for inclusion, the presence of HEMA in the product causing ACD must have been firmly established, for example, from information found in material safety data sheets (MSDS), ingredient listings, data obtained from the manufacturer, or from chemical analyses. At the end of this section, these cases are very shortly summarised in tabular format (Table 6 [occupational contact] and Table 7 [non-occupational contact]).

Cases where patients suffering from ACD caused by a (meth)acrylate-containing product had a positive patch test to HEMA, but where the presence of this specific methacrylate in the culprit product was not ascertained, are not included here, but presented in Section 7.

6.1 | Nail cosmetics

A 41-year-old professional manicurist presented with a 1-year history of itchy erythema and papules on her hands, fingertips and forearm. Thereafter, vesicles and fissures appeared in the same location. Similar symptoms were evident on the head, face and neck 4 months after onset of the lesions on her hands. Patch tests were positive to HEMA, EGDMA, ethyl acrylate (EA) and HEA. A colour gel for gel nails contained HEMA. An open test with this material was negative.[94]

Another 41-year-old woman developed acute eczema on the hands with secondary generalisation affecting both wrists, forearms and thighs, as well as the lateral abdomen, neck, chest and lower back, following the application of acrylic (porcelain) nails with a home kit for beginners. Patch tests were positive to HEMA and several other (meth)acrylates. HEMA was present in the composition of the acrylic liquid—as shown on the label—bought by the patient.[95]

A 35-year-old manicurist, presenting with hand eczema with severe pulpitis and nail plate dystrophy, had occupational allergic contact dermatitis from HEMA present in several artificial nail materials she used. The presence of HEMA was not indicated on the labels, but by gas chromatography–mass spectrometry (GC–MS), the methacrylate was detected in the products used by the patients in concentrations ranging from 0.012% to 9.1%.[96]

A 26-year-old woman had been applying artificial nails to herself for 3 years when she developed dermatitis of her nail folds and fingertips. Patch testing showed positive reactions to HEMA, HPMA, 2 other methacrylates (all tested 2% pet.) and to her nail hardener, nail liquid and nail gel (all tested at 0.1% and 1% pet.) at readings on days 2, 3 and 7. Material safety data sheets indicated

that the nail hardener and the nail gel contained HEMA and the nail liquid HPMA.[97]

A 52-year-old manicurist developed dermatitis affecting her fingertips, nail folds and eyelids. The manicurist noticed that the airborne powder formed after filing the clients' artificial nails irritated her face and neck. The patient gave positive patch test reactions to HEMA, MMA, EGDMA and HPMA. The MSDS indicated that the patient's nail liquid, the nail strengthener, and the UV-curing gel contained HEMA, HPMA and EGDMA. This was a case of occupational, partly airborne, allergic contact dermatitis.[97]

A 47-year-old man, working as a demonstrator of application of artificial gel nails, developed dermatitis in the palm of both hands, on the fingertips, face and neck. He had positive patch tests to an UV-curing gel that he used containing HEMA (concentration of HEMA and test concentration of the gel not stated) and to HEMA 2% pet.[18]

A 26-year-old non-atopic female florist with no previous skin disease or allergies presented for evaluation of bilateral chronic palmar hand eczema of 2 years' duration.[98] Patch testing with the European baseline series and the extended baseline series, as well as single allergens for chrysanthemum, propolis, tulipalin A, selected flowers, plants and her own products revealed an unexpected positive test reaction (++) to HEMA only. It turned out that the patient applied acrylic nails, such as gel nails, as well as long-lasting nail polish on herself and others in her leisure time. She was then tested with the acrylic nail test series and there were positive reactions to three acrylates and four methacrylates. Signs and symptoms of hand eczema disappeared when exposure to acrylates was removed. The title of this article 'Palmar eczema from secondary HEMA exposure—the artificial nail grip sign' shows that the dermatitis was attributed by the investigators to HEMA in the products used. However, no mention was made of the composition of her products other than 'HEMA is used in gel nails and long-lasting nail polish'. Therefore, this case report should actually not be included in this section, but because of the title, it was decided to present it anyway.[98]

A 40-year-old woman presented with multiple splinters haemorrhages with slight subungual hyperkeratosis in the distal areas of all the nails of the hands, without any lesions around the nail or skin. She reported having regularly used permanent nail polish for the past 3 years, without using UV or LED lamps for curing the nail polishes. In the last 2 years, she noticed nail itching. Patch tests were positive to HEMA 1% pet, other methacrylates and her own products. HEMA and the other methacrylates were identified on the labels of these products.[99]

See also Ref. 100 in Section 6.2 for another nail technician with ACD from HEMA in the products she used at work and also applied on her own nails.

6.2 | Dental products

A 28-year-old woman had her teeth varnished with a product containing HEMA which was tolerated well.[101] One month later, the patient developed a genital dermatitis at the sites of contact with her feminine hygiene pads, which contained polyacrylates. The eruption progressed to spread symmetrically to her arms and legs over the course of 10 days. The patient did not use the pads again. Five months later, she had her teeth again varnished to reduce dentin hypersensitivity. Within 24 h, the patient experienced gingival inflammation, hyperemia and ulcerations on her buccal mucosa and gingiva. This once more became widespread symmetrically on her trunk and extremities and lasted over 4 months. Patch tests showed positive reactions to many (meth)acrylates including HEMA. The patient was diagnosed with spreading ACD, presumably from HEMA in sanitary pads and systemic contact dermatitis from HEMA in varnish after sensitisation from the first application of the varnish.[101]

A 39-year-old woman presented with oedema, erythema and ulceration of the mucosa of the upper lip. Six days earlier, she had attended her dentist, who had used acrylates for dental work on her front teeth. The symptoms had started 1–2 days later. Two years earlier, the patient had suffered a similar reaction after dental work involving acrylates. The materials used contained HEMA both in the primer and in the adhesive system. Patch tests were positive to HEMA and to TREGDMA. The source of sensitisation was considered to be the previous treatment.[102]

A 30-year-old dental nurse developed occupational fingertip dermatitis typical of allergic contact dermatitis caused by acrylate compounds.[103] Her dermatitis healed during vacations but relapsed on re-exposure. She suspected that a light-cured hybrid-glass ionomer caused the symptoms, because the dermatitis had started within months of this ionomer being adopted for use. Patch testing revealed that she had become sensitised to several acrylics, including HEMA. Her hybrid-glass ionomer primer and liquid, tested at 1% pet. also provoked an allergic patch test reaction, but not the powder. The MSDSs of these products showed the primer to contain 37%–41% HEMA and the liquid contained 18%–20%. HEMA was not mentioned on the MSDS of the powder.[103]

A 61-year-old woman had worked for 28 years as a dental technician.[100] In the last 3 years, she had been the owner of a nail salon where she applied artificial nails and long-lasting nail polish on customers. The patient was also a self-user of artificial nails and had previously experienced periungual eczema on the right first and second finger. Recently, dental plastic fillings had been applied to the buccal surfaces of five teeth on the right side of her oral cavity. Five hours after the procedure, she had developed an itchy rash on both arms. Two days later, the patient noticed a rash and swelling on her right cheek. Patch tests showed positive reactions to HEMA (++) and three other (meth)acrylates. Of these, only HEMA was found to be present in both her dental plastic fillings and the products used in her nail salon. The patient was diagnosed with systemic allergic dermatitis and local allergic contact dermatitis from HEMA in dental fillings after previous sensitisation to HEMA (or other acrylates) in acrylic nail products.[100] This is an unusual case, as allergic contact dermatitis to dental plastic fillings is rare.[39] Elicitation in this patient was explained by the authors by a high local and systemic exposure load to HEMA as (a) she had five dental plastic fillings done simultaneously and (b) the fillings were applied to the neck of the teeth, resulting in risk of contaminating the adjacent mucosa and the saliva. Another factor may be

incomplete curing of dental plastic fillings causing them to leak HEMA monomers. Incomplete curing may occur when an insufficient wavelength is applied, or insufficient time is used in the curing process.[100]

A 47-year-old female dentist had been working in general dentistry for 22 years performing dental fillings, orthodontics, prosthetics and dental surgery.[104] She had had symptoms of rhinoconjunctivitis and sneezing for 12 years, cough attacks for 10 years, and shortness of breath for 2 years. Furthermore, she had had hand and face dermatitis for 3 years. The symptoms were work-related and disappeared during weekends and holidays. Occupational asthma was diagnosed by an inhalation challenge test in which the patient handled liquid dental methacrylates (MAs) for 30 min. The provocation test also resulted in rhinoconjunctivitis. On patch testing, positive reactions were provoked by several methacrylates including HEMA, to which the patient was occupationally exposed. In addition, patch testing induced itching, swelling and soreness of the eyelids, maximal during the 3-day patch test reading. An optometrist's consultation indicated that the symptoms were in accordance with delayed allergic conjunctivitis.[104]

A 55-year-old woman developed marked symmetrical lip and gingival oedema and erythema within days of the start of treatment with a 'desensitising dental swab' for sensitive teeth containing HEMA. Two days after she recommenced use of the products, her lips flared again and treatment was discontinued. Patch tests were positive to the swab (pure and 10% water), HEMA and various other (meth) acrylates. The patient had probably become sensitised to acrylates previously from the use of artificial fingernails and had mild fingertip and neck dermatitis when she started using the dental swab.[105]

A 63-year-old female patient had her teeth restored with a crown containing unspecified acrylates covered with a UV-cured adhesive lacquer containing 2-HEMA.[106] The night after this intervention the patient experienced painful blisters, oral erythema and oedema of the inner lip on the adjacent mucosa. When symptoms persisted after 8 days, she visited her dentist. The dentist cleaned the provisional crown and again covered it with the HEMA-containing adhesive lacquer, which severely aggravated the symptoms. Patch tests were positive to HEMA and EGDMA dimethacrylate. The patient had become sensitised from the use of artificial nails 3 years previously when an eczematous reaction to sculptured nails of the 'photobonded' type had appeared.[106]

A 57-year-old female patient presented with facial oedema, cheilitis and stomatitis that started after three overnight applications of a home tooth-whitening kit. The whitening kit included an individualised plastic dental mould, which is prepared by the dentist, and a whitening gel, which contains HEMA. HEMA is used to create a gel-like substance and to stabilise the pH, to improve bleaching efficacy. Patch tests were positive to HEMA and EGDMA on D4. The primary source of sensitisation was not mentioned.[107]

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. Initially, symptoms developed on the day after insertion of the filling. However, with repeated exposure, the onset became more rapid, occurring within hours after the fourth exposure. The temporary filling consists of a base and a catalyst, the base containing HEMA. Patch testing resulted in ++ reactions to HEMA and to HPMA on D4. Previous temporary fillings without reactions were considered to be a likely cause of sensitisation.[107]

Allergic stomatitis with painful mucosal erythema and oedema developed in two patients, one with OACD and another with ACD to acrylic nails and with a positive patch test to HEMA and other (meth) acrylates, after application of dental crowns attached with an acrylate-based cement containing HEMA.[53]

A female patient had worked as a dentist for 24 years when she developed dermatitis on her left forefinger and thumb. Extensive patch testing showed her to be allergic to HEMA present in a dentin primer that she had started to use before the dermatitis first appeared. She also reacted to another dentin primer that contained MMA and a third containing TREGDA and had positive patch tests for all these (meth)acrylates.[108]

A 27-year-old man presented with eczema on the volar aspect of his left hand, associated with itching and burning. Recurrences always appeared at the same site. The patient had worn dentures for years and he used to apply a dental fixation agent over his left hand and then use it in the oral cavity. As he used latex gloves during this procedure, he did not consider this to be unsafe. Patch tests were positive to HEMA and the dental bonding agent 1% pet. The product proved to contain HEMA and dimethacrylate monomer.[109]

A 58-year-old non-atopic dental nurse had been occupationally exposed to dental acrylics for 19 years when she developed dermatitis and moderately severe paresthesia of fingertips I–III of both hands. Patch tests were positive to HEMA 2% pet., 8 other (meth)acrylates, a primer 5% pet. and a dentin/enamel bonding resin 2% and 5% pet. Gas chromatographic-mass spectrometric analysis showed 16% HEMA in the primer and 31% HEMA in the resin, along with other acrylics. The material safety data sheet (MSDS) of the primer did not indicate the presence of HEMA (actually contained 16%) and HEMA was stated to be present in a concentration of 1%–5% in the resin (actually contained 31%).[110]

After the instillation of a temporary crown of her left first molar, a 47-year-old woman developed marked swelling, erythema, and pruritus of her lips, as well as at the crown site.[111] A similar reaction occurred a few weeks later after the permanent crown was inserted. Patch tests were positive to HEMA and many other (meth)acrylates. The permanent crown was made of metal alloy and was fixed with a glass ionomer luting cement containing HEMA, the temporary crown contained various (meth)acrylates. The patient had previously become sensitised by acrylic nails. Later, she developed ACD at the site of incontinence pads. These contained polyacrylates, more detailed information was not provided by the manufacturer.[111]

A 38-year-old woman presented with stomatitis and painful ulcers in the oral cavity following dental treatment. Her medical history included severe contact dermatitis due to artificial nails at 18 years of age. Patch tests were positive to HEMA, HPMA and EGDMA. The safety data sheets for the unspecified dental products showed that three contained (meth)acrylates, of which one HEMA. After removing the dental products from the patient's oral cavity, her

stomatitis and oral ulcers improved. After having been sensitised to HEMA in nail cosmetics, this patient was re-exposed to it during dental treatment, and allergic symptoms developed as a result.[112]

A 47-year-old woman presented with swelling and discomfort of the lips, tongue and gingival tissues of the maxillary anterior teeth.[113] A resin-bonded fixed partial denture replacing a maxillary central incisor had been related with a composite luting agent by her dentist the previous day, and symptoms began several hours post-dental treatment. On examination, the chin, lips, tongue, and anterior hard palate were swollen, with blister formation. Contact materials included a resin-based adhesive and composite luting agent containing unpolymerised methacrylate ester monomers, HEMA, and bis-phenol glycidyl dimethacrylate. Patch tests were positive to HEMA and seven other methacrylates. The patient probably had become sensitised during a previous similar dental procedure.[113]

A 32-year-old female dentist developed severe fingertip dermatitis, typical of acrylics allergy, and associated paronychia. On patch testing, she was positive to eight acrylics, including HEMA, EA, MMA, EGDMA and TREGDMA, which were also shown by gas chromatography/mass spectrometry to be present in the particular dental products that she herself used at work, to which she had also positive patch test reactions.[114]

A 30-year-old dentist, after having used a HEMA-containing dentin primer for 3 years, started to experience allergic reactions such as redness, pruritus, sclerosis, and oedema on his fingertips whenever he handled the 2-HEMA solution. An atypical patch test with the solution at 35% and 100% was positive. The concentration of HEMA in the solution was not mentioned.[115]

A 56-year-old female patient complained of redness and oedema of the tongue and small vesicles of the gums with local burning and itching, several hours after the placement of an acrylic dental prosthesis made of HEMA and catalytic powder. Lesions remained for 24 h and reappeared 2 days later, just after the replacement of the dental prosthesis. A patch test to HEMA 2% in olive oil was negative. In a second session, HEMA was tested at 5%, 10% and 20%, yielding a positive result to the 20% concentration at 4 days only. Twenty controls were negative.[116]

A 55-year-old woman presented after undertaking a series of home dental bleaching treatments.[117] Tooth sensitivity led to the use of desensitising dental swabs. Marked symmetrical lip and gingival oedema and erythema were noted within days of treatment. The patient had mild fingertip and neck dermatitis at the time of treatment and was noted to wear artificial fingernails. A ROAT with the dental swab solution, containing HEMA, resulted within 3 h in a vesicular, eczematous reaction. Patch tests were positive to HEMA 2% and to the desensitising solution as is and 10% water. The patient had become sensitised to acrylates from artificial nails and eczema was elicited by the desensitising swab.[117]

6.3 | Glues–adhesives–sealants

A 38-year-old woman had been working for 6 years in the production of car rear-view mirrors. Her job was to glue the mirrors to the windscreen.[118] Three months before consultation, she developed a dry and fissured dermatitis on fingers III and IV of both hands, that spread to the other fingers and the palms and later to the lower arms, chest, neck and face, and she developed rhinitis and tenderness of the mucous membranes of the nose. She also had paresthesia of the fingertips and gastrointestinal complaints. In her work, the patient had frequent contact with a 2-component adhesive based on acrylate compounds. According to the MSDS, it contained 15%–25% HEMA, 20%–30% isobornyl acrylate and 20%–30% polyurethane acrylate resin, a copolymer containing HEMA. On patch testing, she reacted to her own glue (2%, 0.6%, 0.2% pet.) and to many (M)As including HEMA. Prick tests and inhalation tests (because of the rhinitis) were negative. The patient was not able to continue her work.[118]

A 44-year-old man working as a window replacer presented with a 5-month history of intermittent scaling of the dorsal hands and distal phalanges, including the fingertips, where fissuring extended under the nails ([119]). Around that time, a new process had been introduced whereby ready-cut pieces of bevelled glass were affixed to a new glass sheet with a two-stage UV-cured glue. Patch tests were positive to HEMA, five other methacrylates and the glue 0.5% pet. The material safety data sheet indicated that the glue contained HEMA and ethylhexyl methacrylate at 50% and 37%, respectively.[119]

A 60-year-old male veterinarian had suffered from persistent hand and facial eczema for several months. Patch tests were positive to HEMA. The source was a glue based on acrylates containing HEMA, which was used by the patient on a daily basis to adhere blocks under the hooves of large cattle. The patient subsequently discontinued performing the procedure himself and supervised his colleagues instead, but then, the lesions on his face still persisted. Only after avoiding all contact, the lesions disappeared completely after some months. The patient was diagnosed with OACD and airborne ACD to HEMA in glue.[120]

A self-employed 57-year-old car windscreen repairer presented with a 6-month history of fingertip dryness, vesicles and desquamation. His work frequently involved the use of UV-cured products as an adhesive during the repair process of the windscreens. Safety data sheets showed one resin to contain HEMA and other methacrylate monomers. Patch tests were positive to HEMA 2% pet. only. The patient was given avoidance instructions and advised to use nitrile gloves, which resulted in great improvement of the symptoms.[121]

A 40-year-old man developed itchy dermatitis on his hands 3 months after he started assembling CD ROM drives (parts of a personal computer) with UV-cured acrylic glue without any skin protection measures. Patch tests were positive to the glue 10%, 5% and 1% diluted in petrolatum, to HEMA and to EGDMA. The manufacturer confirmed the presence of HEMA in the glue.[122]

A highly (meth)acrylate-allergic patient underwent surgery because of nodular struma. Three days after her operation she developed an oozing, highly pruritic dermatitis, 8 × 19 cm in width on her left thigh, at the site where an electrosurgical earthing plate had been used during the surgery. It was revealed that the pressure-sensitive adhesive of the pad contained HEMA, to which the patient earlier had

had an allergic patch test reaction. He was negative on patch testing to other (meth)acrylates present in the pad.[123]

A 62-year-old man who had been a machine assembler for 18 years presented with hand dermatitis of 10 months' duration, that had almost completely cleared on a recent 3-week vacation.[124] He had been assembling hydraulic machines for plastic moulding injectors and had come in contact with various anaerobic sealants. Patch testing gave positive reactions to three anaerobic sealants tested at 1% in pet. or olive oil (19 controls were negative) and three methacrylate monomers in the cosmetic tray. In a second session, materials provided by the manufacturer of the sealants were tested which yielded positive reactions to HEMA and HPMA, both tested at 5%, 1% and 0.1% pet. One of these sealants contained both methacrylates, and the other two sealants contained polyethylene glycol dimethacrylates, to which patch tests were also positive.[124]

A 42-year-old female squash player underwent surgery to repair her ruptured Achilles tendon.[125] During surgery, a disposable blue diathermy pad was applied to her right thigh. At 6 h, she experienced itching under the pad. By 72 h, she had developed some erythema in an area conforming to the shape of the diathermy pad. At 7 days, she had marked erythema, scaling and fissuring, which subsequently took 5 weeks to resolve. An enquiry made to the manufacturers of the disposable blue diathermy pad revealed the presence of two potential allergens, 2-hydroxyethyl acrylate and HEMA, in the conducting gel and the blue polyurethane foam. Patch tests were positive to the foam as is, to HEA, HEMA and EGDMA, all tested 2% pet. The patient revealed that she had used artificial sculptured acrylic nails several years before, which had resulted in periungual dermatitis (55). The authors also presented a second patient with a virtually identical history, clinical presentation and patch test results. Interestingly, she had also a positive patch test to an acrylate co-polymer nail varnish resin present in the authors' "nail varnish series", which was thought to be a cross-reaction to the other acrylates.[125]

A 69-year-old man had a bilateral aortofemoral by-pass operation.[126] A week later, an erythematous, oedematous, vesicular plaque appeared in the right gluteal region, where a surgical earthing plate had been applied during the operation to allow electrosurgery. This earthing plate had a disposable adhesive conductor composed of a layer of polyethylene foam 1.5 mm thick and a sheet of aluminium foil coated in pressure-sensitive adhesive (PSA), protected by disposable silicon paper. The adhesive was acrylic and contained 2-hydroxyethyl acrylate and HEMA. Patch tests were +++ positive to HEMA 2% pet and to 2-hydroxyethyl acrylate 0.1% pet. There were also positive reactions to 5 other (meth)acrylates.[126]

A 33-year-old woman presented with a 4-month history of a dry and intensely itching fingertip of the middle finger of the left hand with a painful burning sensation. The lesions worsened gradually, and the fingertip became scaly and fissured. Her job consisted of attaching a sort of spring to an industrial relay with the use of an acrylates adhesive. Patch tests were positive to HEMA, HPMA and 4 other (meth) acrylates. The material safety data sheet of the adhesive confirmed the presence of HPMA and HEMA as ingredients.[127]

A 50-year-old man underwent orthopaedic surgery due to a cervical spinal stenosis.[128] Two weeks later, erythema, oedema and scaling developed exactly at the previous site of an electrosurgical grounding plate on the left thigh. Patch testing revealed positive reactions to the electrosurgical plate (+++/+++, bullous reaction and papules surrounding the test chamber site) and its components hydroxyethyl acrylate 2% (+++/+++) and HEMA 2% pet. (−/++). The patient had never had any contact with dental materials or glues containing acrylates before and no acrylic bone cement had been used during surgery. Therefore, the patient was probably sensitised by HEA, HEMA or both from contact with the acrylate-containing adhesive on the grounding plate used to fix the electrodes on the skin.[128]

A 56-year-old plumber developed dermatitis of the hands and paresthesia of the fingers. The lesions were caused by an anaerobic sealant used to secure the joints of metal, water and gas pipes. Patch tests were positive to the sealant components HEMA and HPMA and to the sealant itself, tested at 2% and 5% pet.[129]

A 51-year-old man had developed severely painful stomatitis including aphthae.[130] He had worn dentures for years without any problems. Five weeks before the presentation, his denture had loosened. In order to fix his denture the patient had used a common acrylate-based superglue. The next day he suffered from swollen lips and a painful red mouth. Since the denture was still loosened, the patient used some special adhesive he had bought in a dental laboratory. Within the next day, he had developed more severely painful mucosal lesions. Patch tests were positive to HEMA, which was present in the second glue the patient had used.[130]

A 25-year-old woman was referred for treatment of a 'burn' on her left thigh. She had had a routine orthopaedic operation and the diathermy pad had been inadvertently left on overnight. On examination, there was a well-demarcated erythematous patch of eczema on her left thigh with mild scaling. The borders of the rash corresponded to the dimensions of the diathermy pad. The manufacturers of the diathermy pads disclosed HEA and HEMA as the two possible allergens in the conductive adhesives on the diathermy plates. Patch tests were positive to HEMA 1% pet. and MMA 2% pet.[131]

A 42-year-old woman was referred for treatment of a 'diathermy burn' sustained after a routine gynaecological operation. The diathermy pad had been in contact with the skin for approximately 2 hours. Examination showed a well-demarcated patch of eczema on the left thigh corresponding to the dimensions of the diathermy pad used. Patch tests were strongly positive to HEMA and MMA. The presence of HEMA in the conductive adhesives of the plate was confirmed.[131]

6.4 | Other products

A 38-year-old factory worker presented with eczema initially localised to the face, wrists and dorsum of the hands, which subsequently spread widely.[132] Six weeks before the onset, he had started a new

job as a model maker for a company manufacturing model body parts and surgical training devices. Because he had no direct contact with products during their manufacture, an airborne allergen was suspected. Patch tests were positive to HEMA and HPMA, both 2% pet. A thorough review of his working environment identified the artificial skin used in the surgical models to contain both methacrylates. The key property of the artificial skin was that it allowed the use of diathermy. This was identified as the potential source despite having been manufactured in an adjoining room.[132]

A 25-year-old female worker in a paint factory developed eczema on the eyelids, the neck and both wrists. Patch tests were positive to a paint containing HEMA (concentration of HEMA and test concentration of the gel not stated) and to HEMA 2% pet.[18]

A 55-year-old woman presented with perioral cutaneous inflammation.[133] Two years earlier, a dermal filler substance containing 40% HEMA and EMA suspended in 60% hyaluronic acid had been injected during corrective surgery of skin depressions. Months later, she experienced palpable nodules in both cheeks. The responsible aesthetic surgeon evacuated the filler leaving the areas of swelling. Afterwards, three dermal injections of corticosteroids were performed with good results, although perioral inflammation persisted. Patch tests were positive to HEMA 2% in pet. but negative to EMA 2% in pet. It is unknown whether the patient had previous occupational or dental exposure to HEMA.[133]

A pathology embedding medium and a chemical research laboratory have been mentioned as primary sources of sensitisation to HEMA in one or more patients with positive patch tests to HEMA. Patient or patch testing details were not provided.[134]

A 28-year-old male laboratory technician developed dermatitis in his hands related to contact with a solution containing 80% HEMA in absolute alcohol used in the preparation of a tissue embedding medium for light microscopy.[135] Three separate outbreaks occurred at approximately 2 months intervals, each progressively worse. The third outbreak was associated with nausea and diarrhoea. The patient also noted mild paresthesia of the fingertips which had persisted since the initial outbreak. Patch tests were positive to HEMA 5% in alcohol 97%. He noted nausea and mild diarrhoea commencing within 4 h of initial application of patch tests and persisting for 24 h. Nineteen controls tested with HEMA 5% in alcohol 97% were negative, and none developed nausea or diarrhoea. Later, patch tests with a piece of vinyl glove and latex surgical glove between the patch with HEMA and the skin were also positive—indicating that HEMA penetrated the materials—and again resulted in diarrhoea and nausea.[135]

After 9 months of work in a factory manufacturing disposable contact lenses, a 36-year-old man presented with a 4-month history of a work-related, recurrent, bilateral dermatitis affecting the tips of his fingers and thumbs. Personal protective equipment included safety boots, latex gloves and goggles. Patch tests were positive to HEMA, 2-hydroxypropyl acrylate (HPA), EGDMA, MMA and own acrylate monomers 1% and 2% pet. The constituent monomers used in the contact lens manufacture were HEMA, EGDMA and glycerol monomethacrylate.[136]

A 48-year-old woman had been working as a silk-screen printer for 12 years before she got the first symptoms of dermatitis on her wrists and lower arms.[137] The symptoms were mild until she developed dermatitis on her face and eyelids 3 years later. Since then, she has repeatedly developed severe skin symptoms within a few days of returning to work. In silk-screen printing work, she used both one- and two-component inks. Patch tests were positive to diaminodiphenyl methane (DDM), HEMA, several other (meth)acrylates, several epoxy compounds and three components of the solder-resistant silk-screen printing coatings handled by the patient: two hardeners and an ink. Patch testing with the ingredients of these materials revealed contact allergy to DDM in one hardener, to triglycidyl isocyanurate in the second and to HEMA in the one-component ink.[137]

Nine months after starting treatment with transcutaneous electrical nerve stimulation (TENS) for chronic low back pain, a 35-year-old nurse developed a florid eczema immediately beneath the electrode pads, which recurred at new sites of electrode application. Her skin improved when she discontinued the use of the system, but recurred when she resumed its use. Patch tests revealed positive reactions to the TENS hydropad (inner surface), HEMA, HPMA and EGDMA, all 2% pet. The hydropad conductive gel contained a methacrylate copolymer consisting in part (50/181) of HEMA.[138]

A 29-year-old woman working in the manufacture of contact lenses and exposed to (meth)acrylate monomers presented with recurrent hand dermatitis localised to the sides of the fingers and palms after 6 weeks of work. Symptomatic relief was experienced during holidays. Patch tests were positive to HEA 0.1% pet. and HEMA 1% and 0.1% pet. Samples of the constituents of the lenses provided by the manufacturer contained HEA, HEMA and EGDMA. The purity of HEA and HEMA was 98% as determined by HPLC analyses.[139]

A 65-year-old woman presented with bilateral external auditory canal dermatitis of 6 years in duration that began 3 months after she purchased 'in-the-canal' hearing aids for mild sensorineural deafness. She developed a pruritic weeping eczema that resolved within 2 weeks if she discontinued wearing the hearing aids. Patch tests were positive to scrapings of the hearing aid (shell material, finish coat), to HEMA, to polyethylene glycol dimethacrylate, to ethyl cyanoacrylate and to four other (meth)acrylates. The manufacturer confirmed the presence of HEMA and polyethylene glycol dimethacrylate in the outer coating applied to the hearing aid shell. Ethyl cyanoacrylate was used in the adhesive used for bonding the faceplate with the shell.[140]

See also Sauder and Pratt[101] in Section 6.2 for allergic contact dermatitis to HEMA in sanitary pads.

6.5 | Sort summaries of case reports

Sort summaries of the case reports discussed in Sections 6.1–6.4 are presented in Table 6 (occupational contact with [meth]acrylates) and Table 7 (non-occupational contact).

TABLE 6 Summaries of case reports of allergic contact dermatitis caused by HEMA in patients with occupational contact with (meth) acrylates.

Product category	Sex, age	Culprit product(s)	Occupation/work task	References
Nail cosmetics	F 41	Colour gel	Manicurist	94
	F 35	Artificial nails	Manicurist	96
	F 52	Nail liquid, strengthener, and gel	Manicurist	97
	M 47	Gel	Demonstrator of artificial gel nails	18
	F, 61	Artificial nails, gel nail polish	Manicurist	100
Dental products	F, 30	Hybrid-glass ionomer primer and liquid	Dental nurse	103
	F, 47	Dental materials	Dentist	104
	F, 53	Dentin primer	Dentist	108
	F, 58	Primer and bonding resin	Dental nurse	110
	F, 32	Dental products	Dentist	114
	M, 30	Dentin primer	Dentist	115
	NS	Acrylate-based cement for attaching crown	Unspecified dentistry personnel	53
Glues–adhesives–sealants	F, 38	2-Component adhesive	Production of car rear-view mirrors	118
	M, 44	Two-stage UV-cured glue	Window replacer	119
	M, 60	Glue to adhere blocks under hooves	Veterinarian	120
	M, 57	UV-cured adhesive	Car windscreen repairer	121
	M, 40	UV-cured glue	Assembler of CD ROM drives	122
	M, 62	Anaerobic sealant	Machine assembler	124
	F, 33	Adhesive	Attaching a spring to an industrial relay	127
	M, 56	Anaerobic sealant	Plumber	129
Other products	F, 25	Paint	Worker in paint factory	18
	M, 28	Solution containing 80% HEMA in alcohol	Laboratory technician	135
	M, 36	Contact lenses	Production of disposable contact lenses	136
	F, 48	One-component ink	Silk-screen printer	137
	F, 29	Contact lenses	Manufacture of contact lenses	139
	M, 38	Artificial skin	Model maker for model body parts and surgical training devices	132

Note: In all cases in this table, the presence of HEMA in the product(s) causing ACD was established from information found in material safety data sheets (MSDS), ingredient listing, data obtained from the manufacturer, or from chemical analyses.
Abbreviation: NS, not stated.

7 | CASE REPORTS OF ALLERGIC CONTACT DERMATITIS POSSIBLY CAUSED BY HEMA

Far more frequent than published cases of ACD caused by HEMA (i.e., where the presence of HEMA in the culprit product was established) are reports of patients with an allergic reaction to one or more (meth)acrylate-containing products who had a positive patch test to HEMA, scored as 'relevant', without having been identified in these products. Key data of these cases of ACD *possibly* caused by HEMA are shown in Table 8.

8 | DISCUSSION

This literature study shows that HEMA is currently an important cause of contact allergy and allergic contact dermatitis in the USA and Europe. In the USA, where HEMA was already included in the NACDG screening series in 2007,[47] 3.2% of patients routinely patch tested by the members of the NACDG were positive to it during 2019–2020, which was significantly higher than the pooled results of the preceding 10 years.[36] In Europe, prevalences of positive patch tests to HEMA in studies performed since 2015 have ranged from 1.5% to 3.7%.[27,37–40,42] The rising importance of HEMA as the cause of ACD was well noted and, therefore, in

TABLE 7 Summaries of case reports of allergic contact dermatitis caused by HEMA in patients with non-occupational contact with (meth) acrylates.

Product category	Sex, age	Culprit product(s)	References
Nail cosmetics	F, 41	Liquid for acrylic nails	95
	F, 26	Nail hardener and nail gel	97
	F, 40	Permanent nail polish	99
Dental products	F, 28	Teeth varnish to reduce dentin hypersensitivity	101
	F, 39	Primer and adhesive system for dental restoration	102
	F, 61	Dental plastic fillings	100
	F, 55	Desensitising dental swab	105
	F, 63	UV-cured adhesive lacquer on a crown	106
	F, 57	Whitening gel	107
	F, 51	Temporary fillings	107
	M, 27	Fixation agent for dentures	109
	F, 47	Glass ionomer luting cement	111
	F, 38	Unspecified dental products	112
	F, 47	Composite luting agent	113
	F, 56	Acrylic dental prosthesis	116
	F, 55	Desensitising dental swabs	117
	NS	Acrylate-based cement for attaching crown	53
Glues–adhesives–sealants	?	Adhesive for electrosurgical earthing plate	123
	M, 69	Adhesive for electrosurgical earthing plate	126
	F, 42	Conducting gel and polyurethane foam of diathermy pad	125
	F, 53	Diathermy pad	125
	M, 50	Adhesive on electrosurgical grounding plate	128
	M, 51	Adhesive for dentures	130
	F, 25	Adhesive on diathermy plates	131
	F, 42	Adhesive on diathermy plates	131
Other products	F, 55	Dermal filler substance	133
	F, 35	Electrode pads of transcutaneous electrical nerve stimulation (TENS)	138
	F, 65	Outer coating of hearing aids	140

Note: In all cases in this table, the presence of HEMA in the product(s) causing ACD was established from information found in material safety data sheets (MSDS), ingredient listing, data obtained from the manufacturer, or from chemical analyses.
Abbreviation: NS, not stated.

January 2019, the European Society of Contact Dermatitis included HEMA in the European baseline series for routine testing.[30,31] 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.[37] This provided sound evidence that the addition of HEMA to the baseline series was certainly well-justified, in terms of the overall frequency of sensitisation.[37,236] Indeed, the rate of positive reactions to HEMA found since 2019 was high enough for continued inclusion in the 2023 European baseline series.[237] Previously, HEMA had already been added to the British baseline series (July 2018[27]) and the Italian SIDAPA (Società Italiana Dermatologia Allergologica Professionale Ambientale) baseline series (2016[40]). The Spanish baseline series followed in 2022.[238] Somewhat surprisingly, HEMA was not added to the revised 2019 baseline series of the International Contact Dermatitis Research Group (ICDRG).[239] This is because the ICDRG bases its recommendations solely on investigations performed by their own members, and HEMA has not been a subject of the ICDRG's investigations yet (An Goossens, email communication, June 2023).

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).[1,20,21,26–29,39,48,49,240,241] Indeed,

TABLE 8 Case reports of allergic contact dermatitis *possibly* caused by HEMA.

Year and country	Sex, age	Culprit products	Comments/other information	References
2023 Spain	F, $n = 3$	Acrylic nails	2 consumers, 1 nail stylist	141
2023 Spain	M, 41	Additive in fresh concrete	Uncertain whether the additives contained (meth) acrylates; not mentioned in the Safety Data Sheets	142
	M, 62	Repair mastic	Uncertain whether the mastic contained (meth)acrylates; not mentioned in the Safety Data Sheet	142
2023 Spain	F, 23	Hygiene pad	ACD each time of menstruation and using feminine hygiene pads	143
2023 UK	F, 28	Dental acrylates	Dentist; she would mix acrylate preparations on the glove surface, directly overlying the site of dermatitis and used her non-dominant hand as a 'manual tray' to access the acrylate during procedures	144
2023 Spain	F, 89	Incontinence pad	The product was known to contain ethylhexyl acrylate, which was not tested	145
2022 Spain	M, 17	Glucose sensor	Strong reaction to isobornyl acrylate, a known constituent of the sensor; HEMA reacted weakly and IBOA therefore was the (main) sensitizer	146
2022 Croatia	F, 34	Artificial nails	Both occupational contact and wearer of acrylic nails; also asthma	147
2022 Ireland	F 51	Artificial nails	Nail technician; psoriasis-like clinical picture on the central palms and fingers with marked hyperkeratosis, erythema, with deep fissuring; also on the soles of the feet; complete resolution after avoidance of acrylates; the localisation under the feet was not explained and koebnerisation of psoriasis was not considered	148
2021 Belgium	F, 40	Hybrid gel nail polish	Periungual dermatitis and onycholysis; hybrid means that no UV-curing was required, curing by daylight; the product contained HEMA-base methacrylate copolymers but apparently no HEMA monomers	149
2021 Netherlands	M, 69	Bone cement	Bullous pemphigoid on the right leg starting 3 weeks after replacement surgery of the right knee; spontaneous healing after 6 months attributed to self-limiting diffusion of methacrylate monomers from the bone cement into the surrounding tissues	150
2021 USA	F, 55	Headphone	Apple AirPods contain trace amounts of (meth)acrylates; the patient had previously become sensitised from medical adhesives or gel nails	151
2021 Italy	F, 14	Gel nails	Also eczema on the face	152
2021 Spain	F, 36	Gel nail polish	Occupational ACD from gel nail polish in beautician; after 2 years of asthma	153
2020 UK	F, $n = 2$	Gel nail products	No dermatitis, only 'pseudopsoriatic' nail changes: discolouration, brittleness, onycholysis, splinter haemorrhages; one was a beautician	154
2020 UK	M, 61	TENS hydrogel	(Meth) acrylate in conductive hydrogel sheet of transcutaneous electrical nervous stimulation machine	155
2020 Italy	M, 82	ECG electrodes	Positive patch test reaction to the inner side of the electrode; 'acrylic' was an ingredient of the adhesive backing material	156
2020 Italy	F, 10	Gel nail polish	Positive patch tests to HEMA, other methacrylates and the gel nail polish 1% pet.	157
2020 Israel	F, 25	Acrylic nails	Leukoderma followed the positive patch tests	158
2020 Spain	F, 56	ECG gel	ECG electrode hydrogel	159
2020 Portugal	F, 11	Nail aesthetics	Child of a professional nail beautician, playing with her mother's products	160
2020 Tunisia	F, 30	Glue	Worker in 'electric factory'; occupational ACD, rhinoconjunctivitis and life-threatening severe asthma	161

(Continues)

TABLE 8 (Continued)

Year and country	Sex, age	Culprit products	Comments/other information	References
2019 Bulgaria	F, 37	Nail cosmetics	Hand eczema and airborne face dermatitis; professional manicurist	162
2019 Germany	F, 58	Dental fillings	Prior sensitisation to acrylic nails; erosive lichen oris from dental filling	163
2019 UK	M, 64	Glue	Glue is used to secure the cow hoof to a plastic orthopaedic shoe to take off the weight of damaged hoofs; occupational ACD in a farmer	164
2019 USA	F, 41	Nail polish	Acrylates in gel nails may have caused or worsened lichen planus of the nail apparatus; HEMA was used in nail polish applied to preformed nails; doubtful whether this prolonged lichen planus; more likely was sensitisation in glues used to fix the preformed nails, but patch test with cyanoacrylates were not performed	165
2018 Japan	F, 42	Acrylic accessories	Acrylic accessories are for example earrings and necklaces	166
2018 UK	F, 22	Hairspray	Dermatitis of the face, neck and shoulders from using hairspray on the hair and face (to fix the make-up); apparently not ascertained that the hairspray contained acrylates	167
2018 UK	F, 22	Glue for press-on nails	Lupus-like plaques on the face, later spreading to the trunk and legs	168
2018 Belgium	F, 32	Wound dressing	(Meth)acrylate-containing glue in wound dressing to fixate a Hickman catheter	169
2018 Spain	F, 40	Gel nails	(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	170
2017 USA	F, 28	Acrylic nails	Distal onycholysis of all fingernails; history of periungual eczema, nails became normal after ceasing the use of acrylic nails	171
2017 USA	F, 33	Gel nails/polish	Sensitised by gel nails, ACD from gel nails and later nail polish	172
2017 Portugal	F, 45	Gel nails	Only eyelid and periorbital dermatitis	173
2016 Spain	M, 40	Acrylic nails	Professional flamenco guitarist who applied acrylic material to strengthen the nails; no ACD but nail dystrophy, onycholysis and paronychia	174
2016 UK	F, 40	Acrylic nails and gel nail polish	Dental work with composite fillings containing (meth) acrylates was repeatedly uneventful	175
2016 Spain	F, $n = 3$	Gel nail lacquer	All three had hand dermatitis, 2 lip oedema and cheilitis	176
2016 Sweden	F, 37	Nail cosmetics	Professional nail technician; also relevant reaction to HPMA	177
2015 Belgium	F, 49	Gel nail polish	The patient had episodes of non-pruritic cheilitis and lip oedema over the course of several months, but around the nails only mild erythema	178
2015 UK	F, 13	Dental adhesive	Acrylate-containing adhesive was used to fix the patient's braces and caused lip swelling, which was at its worse in the morning and settled throughout the day	179
2015 Spain	F, 23	Dental adhesives, composite resins	Also paresthesia and decreased thermoalgesic sensitivity in fingertips and the region of positive methacrylates patch tests	180
2015 Canada	F, 30	Bonding solution	Dermatitis of the back of the right hand from placing drops of bonding solution on the gloved hand	181
2014 Italy	F, 35	Acrylic nails	Hobby manicurist; also contact allergy to ethyl cyanoacrylate from contact with hair extension glues	182

TABLE 8 (Continued)

Year and country	Sex, age	Culprit products	Comments/other information	References
2014 Japan	F, 45	Dental prosthesis and filings	Ulcers and erosions of the oral mucosa, multiple sharply defined round bullous erythemas on the hands, diagnosed as 'fixed eruption caused by methacrylate'; the patient was patch test positive to '2-hydroxy methacrylate', which does not exist and was likely HEMA	183
2014 Spain	F, 27	Gel nails	Manicurist; fingertip dermatitis, nail dystrophy	184
	F, 52	Gel nails	Manicurist; airborne dermatitis to nail sanding dust; fingertip dermatitis	184
	F, 59	Gel nails	Manicure client; fingertip dermatitis	184
2014 Turkey	F, 28	Self-adhesive electrodes	ACD from electrodes with positive patch tests to these electrodes; positive reaction to butyl acrylate? + to HEMA (not read at D7); also nickel allergy, which may or may not have contributed to ACD	185
2014 The Netherlands	F, 65	Gel nails	Consumer; periungual rhagades and squamae of the fingertips	186
2014 Italy	F, 38	Acrylic nail cosmetics	Nail operator; also asthma; HEMA tested at 5% pet.; the reaction to HEMA was only + with many strong reactions to other (meth)acrylates, and therefore HEMA was unlikely to be a or the culprit	187
2013 Poland	F, 32	Nail cosmetics	Manicurist; hand dermatitis; bullous lesions on fingers; airborne ACD	188
2013 India	M, 28	Superglue	Very dubious report; the discussion is all about cyanoacrylates; it seems as if the authors think that HEMA is a cyanoacrylate	189
2013 UK	F, 68	Wound dressings		190
2012 Portugal	F, $n = 3$	Acrylic nails	Two were both customers and professional nail beauticians; one had periungual eczema, the second eczema + airborne pattern, the third only dermatitis localised to the face and eyelids	191,192
2012 UK	F, 48	Acrylate nail polish	Applications led to exacerbations of recurrent swelling, redness and itching of the eyelids, which had started after having used false eyelashes; the glue contained ethyl 2-cyanoacrylate, to which the patient was allergic	193
2012 UK	F, 53	Acrylic nails	Nine months after patch testing, the patient had persisting acquired leukoderma at the patch test sites of HEMA and 4 other methacrylates	194
2012 USA	F, 62	Dental adhesive	Intermittent swelling of the lips and gums; worsening after acrylic nails; later persistent swelling of the upper lip	195
2012 UK	F, 49	Gel nails and polish	Nail dystrophy, subungual hyperkeratosis, erythema of the nail folds	196
2012 Spain	F, $n = 3$	Nail cosmetics	All 3 were professional manicurists/beauticians	197
2012 Italy	F, $n = 2$	Nail cosmetics	Professional beauticians; pulpitis with erythema, hyperkeratosis, fissures	198
2012 UK	FM, $n = 2$	Dental materials	Orthodontic nurse and dentist; atypical locations from wiping off uncured bonding/restorative material to a particular location on the natural rubber latex gloves, where it penetrated the glove and caused ACD of the underlying skin	199
2012 Spain	F, 40	Gel nails		200
2010 UK	M, 59	Acrylic nails	Occupational ACD in professional classical guitar player who had acrylic nails for better playing technique	201
2009 Germany	F, 38	Nail cosmetics	Professional nail technician; ACD and distal onycholysis	202

(Continues)

TABLE 8 (Continued)

Year and country	Sex, age	Culprit products	Comments/other information	References
2009 France	F, 44	Nail cosmetics	Professional beautician who also wore acrylic nails herself; also asthma	203
2008 Portugal	F, $n = 3$	Gel nails	Two customers, one beautician who also had gel nails herself	204
2008 USA	F, 48	Acrylic nails	Contact allergy resulted in hyperpigmentation and pterygium inversum unguium of most of the fingers	205
2007 Sweden	F, 51	Dental materials	Eczema of the face from airborne exposure to methacrylates	206
2007 Australia	F, 33	Acrylic nails	Persistent paresthesia despite removal of nails and healing of dermatitis	207
2007 France	F, 37	Glue	Glue for fixating preformed press-on nails	208
2007 Italy	F, 43	Eye mask	Sensitisation by temporary restoration material; same patient as in Ref. 210	209
2005 Germany	F, 43	Eye mask	Sensitisation by denture; same patient as in Ref. 209	210
2005 Spain	F, 28	Acrylic nails	Both occupational ACD and occupational rhinitis from (meth)acrylates	211
2005 USA	F, 56	Temporary crown	Poor quality article; HEMA was termed 2-hydroxyethyl acrylate; the patient was diagnosed with ACD from HEMA leached from temporary crown material, but the material safety data sheet indicated the presence of 'multifunctional methacrylates' (which HEMA is not)	212
2004 France	M, 54	TENS electrode	Possibly, the TENS contained ethyl acrylate	213
2004 Spain	F, 26	Acrylic nails	Professional nail stylist	214
2003 Poland	F, 40	Dental materials	Dental nurse	215
2002 Canada	F, 47	Incontinence pad	Previous sensitisation by acrylic nails and later reaction to dental product; the pad contained polyacrylates but details on monomers were not provided by the manufacturer	111
2001 Australia	M, 71	Denture	Allergic contact stomatitis; the problem was solved by boiling the dentures, thereby probably polymerising the residual monomers	216
2001 Portugal	F, 64	Bone cement	Nurse working in operating room of orthopaedic hospital; the patient also had a positive test to methyl methacrylate, which is the likely culprit	217
2001 UK	M, 55	Electrosurgical earthing plate	The patient had previously become sensitised to acrylates from occupational exposure to (M)A in glues used for windscreen repair	218
2000 UK	M, 37	UV-cured varnish	Printer; ACD and airborne ACD; flare-up while in dental surgery, presumably from small amounts of acrylates present in the surgery room from previous treatments	219
2000 UK	F, 79	Dental material	Lichenoid reaction healed after replacement of restorations by HEMA-free materials	220
1999 Canada	FM, $n = 3$	Dental products	Three dentists with hyperkeratotic fissured distal fingertip dermatitis	221
1999 Australia	M, $n = 2$	Ink in banknotes	Two men, 60 and 68	222
1998 Sweden	M, 26	Window repair glue	Sensitisation to HEMA and MMA after 6 working with the glue for 6 weeks	223
1998 Finland	?	Dental products	Dental nurse; contact leukoderma after fierce positive patch test to undiluted dental acrylate products	224
1998 France	F, 28	Acrylic nails	Subungual hyperkeratosis, onycholysis, perionyxis, pachyonychia and splinter haemorrhages	225
1996 Belgium	F, 38	Glue for insulin pump infusion set	Positive patch tests to HEMA and 10 other (meth) acrylates	226

TABLE 8 (Continued)

Year and country	Sex, age	Culprit products	Comments/other information	References
1996 Germany	F, 36	Glue in grounding plate	Previous sensitisation to HEMA and HPMA from artificial nails	227
1995 Finland	F, 69	Dental prosthesis	Stomatitis with burning, itching and erythema of the oral mucous membranes	228
1995 Austria	F, 30	Artificial nails	Designer of artificial nails; the material contained 'hydroxy-functional' methacrylates; very strong reaction to HEMA down to 0.06% pet.; relevance of HEMA highly likely; this patient was also presented in ref. 82	229
1989 Spain	M, 51	Varnish	High-resistance varnish used on lower-leg prosthesis	230,231
1988 Spain	$n = 6$	Anaerobic sealant	2 mechanics and 4 workers in a car assembly line	232
1986 Spain	F, 17	Artificial nails		233
1983 Sweden	M, 60	Printing plate		234
1977 Netherlands	$n =$?	Printing plate manufacturing		235

Abbreviations: ACD, allergic contact dermatitis; TENS, transcutaneous electrical nervous stimulation; UK, United Kingdom; USA, United States of America.

in recent studies, in which HEMA was tested in consecutive patients suspected of contact dermatitis, the large majority of reactions to HEMA were related to cosmetic nail products: 64%,[43] 73%,[39] 80%,[40] 80%[42] and >80%.[27] The same trend has been observed in most studies among patients suspected of allergy to (meth)acrylates tested with a series of these chemicals: 49% (despite the relatively low percentage, the authors stated that 'a shift in exposure away from manufacturing and towards acrylic nail sources was observed'),[21] 70%,[29] 76%,[20] 83%[1] and 92%.[28]

Both professional nail stylists were affected and consumers, who either had their nails done in a nail salon or applied the acrylic nails, gel nails or nail polish themselves at home. The percentage of all patients with ACD to HEMA or other (meth)acrylates who were beauticians varied strongly: 27%,[42] 31%,[39] 33%,[1] 74%[20] and 100% (only five patients).[29] Among groups of patients with occupational allergic contact dermatitis from HEMA, nail stylists/nail technicians/beauticians mostly formed the majority: 56%,[39] 64%,[42] 80%,[20] 85%[28] and 97%.[27] Many of these professionals also used acrylic cosmetics themselves, which inevitably will have led to increased risk of sensitisation.[27] In the UK, in the period 1996–2017, an exponential growth in the number of beauticians with acrylate-related occupational ACD was observed.[22] It was also found that hairdressers and beauticians working with HEMA-containing nail products and glues have a ninefold increased risk of developing contact allergy to HEMA compared with controls.[242]

Up to 2014, most nail cosmetics causing ACD were acrylate nails or gel nails. Since 2016, ACD from long-lasting nail polish is being reported increasingly.[39,76,84–86] In a study from Denmark, it was found that the proportion of HEMA test-positive patients with a history of using UV nail polish increased from 50% in 2017 to 85% in 2018 and 100% in 2019.[39] As a consequence of the major role that nail cosmetics play in ACD and OACD to HEMA and other (meth)acrylates, currently the large majority to nearly all[39] of HEMA/(meth)acrylate-sensitised patients are female.[28,29,39,240]

In response to the large numbers of patients with contact allergy to HEMA in nail cosmetics and dermatologists' calls to action, in November 2020, in the European Union, the use of HEMA in nail cosmetics was restricted in the context of the EU Cosmetics Regulation (EC 1223/2009), permitting only professional use. The warnings 'for professional use only' and 'can cause an allergic reaction' must be stated on the package of nail products containing HEMA.[243]

The causative role of HEMA in patients with a positive patch test to HEMA, who have ACD from products containing (meth) acrylates, deserves special attention. To diagnose 'ACD from HEMA', the presence of HEMA in the products that have caused the allergic skin reaction must, strictly speaking, be ascertained, for example, from information on the material safety data sheet, ingredient label, from information obtained from the manufacturer or from chemical analyses. It is very likely that many investigators score a positive patch test reaction to HEMA as 'relevant' (indicating that HEMA has caused the dermatitis or has contributed to it), when the patient has used products known to contain (meth)acrylates at the site of the dermatitis, also when it is has not been established that these products actually contain HEMA itself. In such cases, the ACD may well have been caused by one or more other (meth)acrylates that cross-react to or from HEMA. That this latter scenario is far from inconceivable, is shown clearly in a study from the Finnish Institute of Occupational Health (FIOH). The investigators had collected 10 patients with occupational allergic contact dermatitis from (meth)acrylate-containing glues.[19] All patients reacted to HEMA. However, when the MSDS had been examined and chemical analyses had been performed, only in 2 of these 10 cases was HEMA proven to be the causative allergen. Hence, in the other eight cases, the

BOX 1 Summary of key information on HEMA and data found in this review

- (Meth)acrylates are well-known causes of contact allergy and allergic contact dermatitis, for example, from their presence in dental materials, glues, printing inks, paints and nail cosmetics;
- Formerly, many sensitised patients had occupational allergic contact dermatitis (dental personnel, printers, and industry workers in contact with glues);
- The most frequently reacting (meth)acrylate appears to be HEMA (further discussed in Part 2 of this article);
- In January 2019, HEMA was included by the European Society of Contact Dermatitis in the European baseline series for routine testing; HEMA has been part of the screening tray of the North American Contact Dermatitis Group (NACDG) since 2007;
- Recent prevalences of positive reactions to HEMA in North America were 2.0%–2.6% in the period 2007–2014, rising to 3.2% in 2019–2020;
- Recent prevalences of positive reactions to HEMA in Europe range from 1.6% to 3.7%; a multinational study found an average of 2.3%;
- Based on these data, it can be concluded that HEMA is currently an important cause of contact allergy and allergic contact dermatitis;
- During the last two decades, a shift has been observed to nail cosmetics being the culprit products causing allergic reactions; Indeed, the large majority (64% to >80%) of reactions to HEMA are related to cosmetic nail products (acrylate nails, gel nails, long-lasting nail polish [gel lacquer]);
- Such reactions are observed in both nail technicians/beauticians (inducing occupational ACD) and in consumers of these cosmetic products, either clients of nail technicians or women who apply the nail products themselves at home;
- Among groups of patients with occupational allergic contact dermatitis from HEMA, nail stylists/nail technicians/beauticians form the majority (56%–97%); many of these professionals also use acrylic cosmetics themselves, leading to increased risk of sensitisation;
- As a consequence of the major role of nail cosmetics, the large majority of patients sensitised to HEMA are currently female (up to 97%);
- In response to the large numbers of patients with contact allergy to HEMA in nail cosmetics and dermatologists' calls to action, in November 2020, in the European Union, the use of HEMA in nail cosmetics was restricted in the context of the EU Cosmetics Regulation (EC 1223/2009), permitting only professional use. The warnings 'for professional use only' and 'can cause an allergic reaction' must be stated on the package of nail products containing HEMA;
- Patch testing in selected patient groups has shown rates of positive reactions to HEMA varying widely between 0.6% and 72%; the results are entirely dependent on the selection parameters and the degree of selection;
- 24 case series of patients with allergic contact dermatitis attributed to HEMA have been reported; in 14, nail cosmetics were the culprit products, in 5 dental products and in 5 other products; in only 10 of these case series, the causative role of HEMA was ascertained;
- 54 single cases of allergic contact dermatitis ($n = 28$) and occupational allergic contact dermatitis ($n = 26$) in which the causative role of HEMA was established, have been published; the culprit products were nail cosmetics in 8 patients, dental products in 21, glues in 16 and others in 9;
- The authors also found 115 cases of allergic contact dermatitis in patients allergic to HEMA, in which ACD or OACD has been ascribed to HEMA, without proof of HEMA being present in the culprit products. The implicated products were nail cosmetics in 57 cases, dental products in 18, glues in 14 and other products in 26, including 7 to medical equipment such as ECG- or TENS-electrodes and glucose sensors;
- The (possible) causative role of HEMA in patients with a positive patch test to HEMA, who have ACD from products containing (meth)acrylates, deserves more attention; a detailed search for the composition of these products and the allergens contained therein should be an integral part of the patch test procedure.

positive patch test was not relevant, it only had a marker function for allergy to other (meth)acrylates that were the actual causes of the OACD.[19]

This problem is manifested in many case series and case reports. We have found 24 case series of patients with ACD attributed to HEMA; in 14, nail cosmetics were the culprit products, in 5 dental products and in 5 other products (presented in Sections 5.1.1–5.1.4). In only 10 of these case series, the causative role of HEMA was ascertained (Table 5).

We have also identified 54 single cases of ACD ($n = 28$) and OACD ($n = 26$) in which the causative role of HEMA was established. The culprit products were nail cosmetics in 8 patients, dental products in 21, glues in 16 and others in 9 (Sections 6.1–6.5, Tables 6 and 7). However, next to these well-documented cases, we also found 115 cases of ACD in patients allergic to HEMA, in which (in the great majority) ACD or OACD had been ascribed by the authors to HEMA without proof of HEMA being present in the culprit products (Table 8). The implicated products were nail

cosmetics in 57 cases, dental products in 18, glues in 14 and other products in 26, including 7 to medical equipment such as ECG- or TENS-electrodes and glucose sensors.

We consider a detailed search for the composition of products that have caused ACD and the allergens contained therein an essential part of the patch test procedure. We are well aware that this can be laborious and frustrating, for example, when the manufacturer of the product is uncooperative. However, rating a reaction to HEMA as relevant without investigating whether the causative product actually contains this substance may be considered suboptimal practice by some. Most cases are currently caused by cosmetic products, the ingredients of which should not be that hard to find.

Notwithstanding the uncertainties and lack of data, there can be no doubt that HEMA is an important causative allergen, especially in nail cosmetics and dental products, in which it is a frequent ingredient. This and other topics related to HEMA allergy will be discussed in part 2 of this article. A summary of key information on HEMA and data found in the current review is shown in Box 1 (previous page).

AUTHOR CONTRIBUTIONS

Anton de Groot: Conceptualization; methodology; formal analysis; project administration; writing – original draft; writing – review and editing; resources. **Thomas Rustemeyer:** Conceptualization; methodology; resources; writing – review and editing.

DATA AVAILABILITY STATEMENT

Data sharing not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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