Recommendation to include hydroxyethyl (meth)acrylate in the British baseline patch test series*

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Summary

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Background (Meth)acrylates are potent sensitizers and a common cause of allergic contact dermatitis (ACD). The frequency of (meth)acrylate ACD has increased with soaring demand for acrylic nails. A preliminary audit has suggested a significant rate of positive patch tests to (meth)acrylates using aimed testing in patients providing a clear history of exposure. To date, (meth)acrylates have not been routinely tested in the baseline patch test series in the U.K. and Europe.

Objectives To determine whether inclusion of 2-hydroxyethyl methacrylate (2-HEMA) 2% in petrolatum (pet.) in the baseline series detects cases of treatable (meth)acrylate ACD.

Methods During 2016–2017, 15 U.K. dermatology centres included 2-HEMA in the extended baseline patch test series. Patients with a history of (meth)acrylate exposure, or who tested positive to 2-HEMA, were selectively tested with a short series of eight (meth)acrylate allergens.

Results In total 5920 patients were consecutively patch tested with the baseline series, of whom 669 were also tested with the (meth)acrylate series. Overall, 102 of 5920 (1·7%) tested positive to 2-HEMA and 140 (2·4%) to at least one (meth)acrylate. Had 2-HEMA been excluded from the baseline series, (meth) acrylate allergy would have been missed in 36 of 5920 (0·6% of all patients). The top (meth)acrylates eliciting a positive reaction were 2-HEMA (n = 102, $1\cdot7\%$), 2-hydroxypropyl methacrylate (n = 61, $1\cdot0\%$) and 2-hydroxyethyl acrylate (n = 57, $1\cdot0\%$).

Conclusions We recommend that 2-HEMA 2% pet. be added to the British baseline patch test series. We also suggest a standardized short (meth)acrylate series, which is likely to detect most cases of (meth)acrylate allergy.

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- A significant rate of sensitization to (meth)acrylates has been demonstrated worldwide
- Increasing demand for acrylic nail fashion is putting consumers and nail technicians at risk of sensitization to (meth)acrylates.

What does this study add?

- Inclusion of 2-hydroxyethyl methacrylate (2-HEMA) 2% in petrolatum (pet.) in the baseline series detects treatable (meth)acrylate allergic contact dermatitis (ACD).
- Identifying (meth)acrylate ACD is important as it can have adverse health consequences for patients who require composite fillings, surgical glue and bone cement, all of which contain (meth)acrylates.
- We recommend that 2-HEMA 2% pet. be added to the British baseline patch test series, and to baseline series used in other countries.

Acrylates and methacrylates are monomers that polymerize to make acrylic plastics. Their use is widespread including in orthopaedic surgery, dentistry and the printing and beauty industries. (Meth)acrylates are potent sensitizers and are a common cause of allergic contact dermatitis (ACD).

The frequency of (meth)acrylate allergy has increased in recent years, with a shift in occupational and recreational exposure towards the beauty industry. There is soaring demand for longer-lasting nail fashion compared with traditional varnish. Acrylic, sculpted, gel and gel polish nails such as Shellac (a popular brand of gel polish in the U.K.) all contain (meth)acrylates, and nail glue contains cyanoacrylates. There are numerous stages during the application process whereby beauticians in nail bars and their clients are at risk of becoming sensitized.

In the U.K., the rate of (meth)acrylate allergy in Leeds tripled between 2008 and 2014.² In Birmingham, U.K., there was a shift in exposure from industrial sources towards acrylic nails between 2002 and 2015.⁴ The Health and Occupation Research Network found that (meth)acrylates were the most frequently cited source of ACD in beauticians between 1999 and 2011.³ A similar pattern has been observed internationally. In Portugal, from 2006 to 2013, nail (meth)acrylates were responsible for 76% of (meth)acrylate-related ACD,⁵ and this pattern has been replicated in international studies.^{6,7} (Meth)acrylates were named Contact Allergen of the Year by the American Contact Dermatitis Society in 2012 and were included in their baseline series in 2017.⁸ Methyl methacrylate has been banned in nail cosmetics in some states in the U.S.A.

To date, (meth)acrylates have not been routinely included in the baseline patch test series in the U.K. and Europe. Our preliminary retrospective audit was carried out in nine U.K. dermatology centres between 2008 and 2015, using selective

patch testing to acrylates based on a clear history of exposure. We found the frequency of sensitization to any (meth)acrylate to be a minimum of 1.3%, with a frequency of 0.7% to 2-hydroxyethyl methacrylate (2-HEMA), the most commonly sensitizing (meth)acrylate. The European Society of Contact Dermatitis (ESCD) suggests that an allergen might be included in the baseline series when the proportion of consecutively patch tested patients with a positive test to a specific allergen exceeds 0.5-1.0%. 10 As 0.7% was likely to be an underestimate, we set up a further prospective audit, including 2-HEMA in the extended baseline patch test series. We aimed to identify cases of (meth)acrylate ACD that would otherwise have been missed and to identify the most common (meth) acrylate allergens to test positive, with the intention of recommending a shortened (meth)acrylate series for testing in the U.K.

Materials and methods

During a 12-month period between December 2016 and November 2017, data were collected from 15 U.K. and Irish dermatology departments (Bath, Birmingham, Cardiff, Cork, Dundee, East Kent, Imperial College London, Leeds, Leicester, Newport, Oxford, Portsmouth, The Royal Free Hospital London, Sheffield and South Tees). In total 5920 consecutive patients with eczema referred to a dermatology clinic for patch testing were tested to the extended British baseline patch test series including 2-HEMA 2% in petrolatum (pet.). Patients with a history of (meth)acrylate exposure, for example those working in the dental, printing or nail and beauty industries, were selectively tested with a short series of eight (meth)acrylate allergens. Those who tested positive to 2-HEMA at the day 2 reading had the series of eight (meth)acrylates added on day 2.

The eight (meth)acrylate allergens tested in the short series were 2-hydroxypropyl methacrylate (2-HPMA); ethyl acrylate (EA); ethylene glycol dimethacrylate (EGDMA); tetraethylene glycol dimethacrylate (TEGDMA); 2-hydroxyethyl acrylate (2-HEA); 1,6-hexanediol diacrylate (1,6-HDDA); ethyl cyanoacrylate (ECA) and triethylene glycol diacrylate (TREGDA).

The allergens were obtained from Chemotechnique Diagnostics (Vellinge, Sweden). All departments used the same test materials. The allergens were stored and dispensed according to the manufacturer's instructions. (Meth)acrylate allergens were transported in airtight tubes and prepared by experienced patch test nurses immediately prior to application, to reduce any evaporation of the volatile (meth)acrylate compounds, which could lead to a falsely low rate of reactions. The amount of allergen applied was enough to fill the well of the disc but not extrude when the patch was applied to the patient's back. Patches were applied for 48 h under occlusion.

Readings were carried out according to the ESCD guidelines on day 2 and day 4 by dermatologists experienced in interpreting patch tests. 10 Patients who had the short (meth) acrylate series added at day 2 were asked either to return for a day 7 reading or to contact their patch test centre for a further reading if any new patch test sites became positive. Allergic patch test reactions were scored according to the International Contact Dermatitis Research Group criteria. 10

We recorded which patients had the short (meth)acrylate series added at day 2, after a positive screening test to 2-HEMA, to distinguish them from those predicted to have (meth)acrylate allergy by history, who had the short series added at day 0. Some units tested to other (meth)acrylate allergens, not included in the series of eight, and any reactions were recorded. Demographic details recorded were age, sex, occupation, history of atopy and history of use of nail products, in particular those known to the U.K. consumer as Shellac® (gel polish), gel nails, nail products requiring curing by ultraviolet (UV), or nail glues. The primary site of dermatitis was recorded, or where multiple sites were involved, such as 'hands and feet', this was documented.

Results

In total 5920 consecutive patients with eczema were patch tested to the extended baseline series, including 2-HEMA, at 15 U.K. centres (Table S1; see Supporting Information). Of these, 669 selected patients with a history of (meth)acrylate exposure (n = 633), or who tested positive to 2-HEMA in the baseline series (n = 36), were tested to the short (meth)acrylate series. Overall, 140 patients tested positive to at least one (meth)acrylate allergen, with a total of 416 positive reactions; 102 patients tested positive to 2-HEMA.

Of the 140 patients with proven (meth)acrylate ACD, 104 had the (meth)acrylate series added at day 0, as they had a clear history of (meth)acrylate exposure. Thirty-six patients who had provided no history of (meth)acrylate exposure had the series added at day 2, following a positive reaction to 2-HEMA in the baseline series. In these 36 patients a diagnosis

of (meth)acrylate ACD would have been missed, had 2-HEMA not been included in the baseline series.

The top (meth)acrylates eliciting a positive reaction were 2-HEMA (n = 102, 1.7%), 2-HPMA (n = 61, 1.0% minimum predicted value if tested in all patients) and 2-HEA (n = 57; 1.0% minimum predicted value if tested in all patients) (Table 1). Irritant reactions were recorded in two patients, one to both 2-HEMA and EGDMA and the other to 2-HEMA.

Thirty-four patients with (meth)acrylate ACD did not test positive to 2-HEMA in the baseline patch test series, but had been suspected to have (meth)acrylate allergy based on their history. Of the allergens included in our short (meth)acrylate series, ECA recorded the highest number of positive reactions (n = 16) in these patients.

Positive reactions to (meth)acrylates not included in our short (meth)acrylate series were as follows: diethylene glycol diacrylate (DEGDA) 0.1% pet. in 23 patients, methyl methacrylate (MMA) 2% pet. in 16 patients and ethyl methacrylate (EMA) 2% pet. in 11 patients. Four patients tested positive exclusively to DEGDA. DEGDA, MMA and EMA were not tested in all patients with suspected (meth)acrylate allergy, so no data on the comparative frequency of sensitization were available.

Table 1 Number and percentage of patients who patch tested positive to each (meth)acrylate allergen, and predicted minimum percentage rate of allergy if tested in the baseline series in unselected patients (n = 5920)

(Meth)acrylate allergen (in order of most common allergen to test positive)	No. of patients who tested positive to each (meth)- acrylate allergen	% of patients who tested positive to each (meth)- acrylate allergen ^a	*
2-HEMA 2% pet.	102	N/A	1.7
2-HPMA 2% pet.	61	9.1	1.0
2-HEA 0·1% pet.	57	8.5	1.0
EA 0·1% pet.	51	7.6	0.9
EGDMA 2% pet.	50	7.5	0.8
TEGDMA 2% pet.	32	4.8	0.5
ECA 10% pet.	24	3.6	0.4
1,6-HDDA 0·1% pet.	22	3.3	0.4
TREGDA 0·1% pet.	17	2.5	0.3

2-HEMA, 2-hydroxyethyl methacrylate; 2-HPMA, 2-hydroxypropyl methacrylate; 2-HEA, 2-hydroxyethyl acrylate; EA, ethyl acrylate; EGDMA, ethylene glycol dimethacrylate; TEGDMA, tetraethylene glycol dimethacrylate; ECA, ethyl cyanoacrylate; 1,6-HDDA, 1,6-hexanediol diacrylate; TREGDA, triethylene glycol diacrylate; pet., petrolatum; N/A, not applicable. aOf the 669 selected patients tested to the short (meth)acrylate series. ^bPredicted percentage of the 5920 patients tested to the extended baseline series.

A striking female predominance was noted in patients with (meth)acrylate ACD: 94% (n = 131) of all 140 patients with positive reactions to (meth)acrylates were female and 6% (n = 9) were male. The mean age was $41\cdot2$ years, median 38, range 15–73. Fifty-six of these 140 patients (40%) were atopic. The mean duration of dermatitis was 24 months, median 24, range 2–216. Hands were the most common primary site of dermatitis, in 68 patients (49%), followed by the face in 25 patients (18%) (Fig. 1). Many patients had more than one site affected.

Of the 140 patients with proven (meth)acrylate ACD, 76 (54%) stated that they had been exposed to (meth)acrylates in UV-cured nails, 75 (54%) in gel nails, 51 (36%) in Shellac[®] (gel polish nails), 26 (19%) in nail glue, 10 (7%) in dentistry, four (3%) in orthopaedics and one (1%) in the printing industry (Fig. 2). Many patients had been exposed to (meth) acrylates in multiple nail products; a minority had also had exposure from other sources such as dental procedures.

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. Nonoccupational exposure alone, due to professional application of cosmetic nails containing (meth)acrylates, was recorded in 97 (69%) patients, three of whom also used home gel nail kits. The remaining five patients positive to 2-HEMA had other nonoccupational sources of exposure, three from surgical glue and two from medical dressings: one a stoma adhesive device and one a transcutaneous electrical nerve stimulation adhesive device. There were no patients for whom the source of exposure was unidentified.

Discussion

This large multicentre prospective audit has determined that the proportion of consecutively patch tested patients in the U.K. with a positive patch test to 2-HEMA is 1·7%, well above the ESCD recommended threshold of 0·5-1·0% for inclusion in a baseline patch test series. ¹⁰ We have shown an increase in the number of cases of (meth)acrylate ACD identified when 2-HEMA is included in the baseline series, rather than relying on history alone. We would have missed almost one-third of cases of (meth)acrylate ACD had 2-HEMA not been incorporated into the baseline series. It is important not to miss (meth)acrylate allergy, to avoid cases of recalcitrant undiagnosed cosmetic allergy.

The ability of 2-HEMA testing to detect most cases of (meth)acrylate ACD is widely recognized. As we anticipated, 2-HEMA was the most frequent (meth)acrylate allergen to test positive. Although a number of other (meth)acrylates were positive in many patients due to coupled reactivity, most (73%, 102 of the 140 cases) would have been identified as having (meth)acrylate allergy using 2-HEMA alone as a screening agent. The short (meth)acrylate series tested in this audit included the most common (meth)acrylate allergens to test positive.

There were four patients who reacted exclusively to DEGDA. A diagnosis of DEGDA ACD would have been missed in these patients, despite screening with 2-HEMA and testing to the short series of eight (meth)acrylate allergens. Additionally, isobornyl acrylate has recently been reported to cause ACD in indwelling glucose monitors; this is a (meth)acrylate not present in routinely commercially available (meth)acrylate allergen series. 11-13 Hence, we feel that supplemental (meth)-

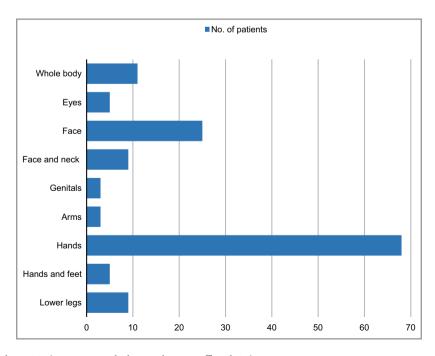


Fig 1. Primary site of dermatitis (many patients had more than one affected site).

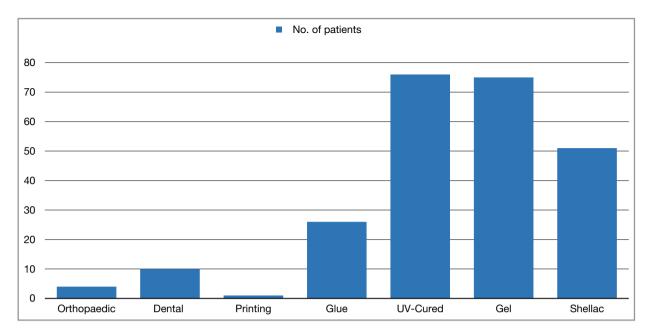


Fig 2. Source of (meth)acrylate exposure reported by patients. Acrylic nails, including gel polish (Shellac®), gel and ultraviolet-cured nails, were the predominant source of exposure, compared with historical sources of exposure such as the printing industry and dentistry. Many patients reported more than one source of exposure.

acrylate allergens should be added to the shortened series to avoid missing relevant allergy. We suggest adding the following six: DEGDA, 1,4-butanediol dimethacrylate (1,4-BDMA), EMA, MMA, triethylene glycol dimethacrylate (TREGDMA) and tetrahydrofurfuryl methacrylate (THFMA) (Table 2). The addition of these six extra allergens is based on the results of our audit and a literature review of recently published studies demonstrating the most frequent (meth)acrylates to cause allergy in Europe. 1,5-7,14-16 Once isobornyl acrylate becomes commercially available as a patch test allergen, we plan to add this to our recommended series of 14.

Routinely testing 2-HEMA and adding a shortened (meth) acrylate series, if the history indicated, would detect most cases of ACD to (meth)acrylates. Testing to a shortened (meth)acrylate series would avoid some patch test-associated morbidity due to coupled reactivity giving multiple strongly positive reactions. Commercial patch test allergen providers supply multiple (meth)acrylate series for testing, depending on the likely source of (meth)acrylate exposure, some of which have up to 24 (meth)acrylate allergens. We feel that it is simpler to have one series to cover all types of (meth)acrylate exposure.

Coupled reactivity among the acrylate class is well documented^{5,14-17} and is reflected in our patient population, where 416 positive reactions were recorded in 140 patients. Acrylic nail products contain a number of different acrylic allergens that can cause concomitant sensitization, and therefore it is difficult to elicit the exact allergen to which an individual is sensitized. Some allergens are more likely to show coupled reactivity than others, in particular 2-HEMA, which again supports its use as a screening allergen.

Table 2 Recommended British Society for Cutaneous Allergy short series of 14 (meth)acrylates. We recommend supplementing this list with isobornyl acrylate when it becomes commercially available as a patch test allergen

Allergen	CAS number
1,4-Butanediol dimethacrylate (1,4-BDMA) 2% pet.	2082-81-7
Ethyl cyanoacrylate (ECA) 10% pet.a	7085-85-0
Ethylene glycol dimethacrylate (EGDMA) 2% pet. ^a	97-90-5
1,6-Hexanediol diacrylate (1,6-HDDA) 0·1% pet.a	13048-33-4
2-Hydroxypropyl methacrylate (2-HPMA) 2% pet. ^a	27813-02-1
Triethylene glycol diacrylate (TREGDA) 0·1% pet. a	1680-21-3
Tetrahydrofurfuryl methacrylate (THFMA) 2% pet.	2455-24-5
Ethyl acrylate (EA) 0·1% pet.a	140-88-5
Ethyl methacrylate (EMA) 2% pet.	97-63-2
Diethylene glycol diacrylate (DEGDA) 0·1% pet.	4074-88-8
2-Hydroxyethyl acrylate (2-HEA) 0·1% pet.a	818-61-1
Methyl methacrylate (MMA) 2% pet.	80-62-6
Tetraethylene glycol dimethacrylate	109-17-1
(TEGDMA) 2% pet. ^a	
Triethylene glycol dimethacrylate	109-16-0
(TREGDMA) 2% pet.	

Pet., petrolatum. aEight allergens included in the short (meth)acrylate series, which were tested from day 0 in patients whose history suggested (meth)acrylate allergy and from day 2 in patients with a positive test to 2-hydroxyethyl methacrylate (2-HEMA) at day 2.

ACD to cyanoacrylates occurs less frequently than that to (meth)acrylates. Cyanoacrylates, used as nail, eyelash, surgical and instant glue [such as ECA (Superglue®) and 2-octyl cyanoacrylate (Dermabond®)] do not usually show concomitant sensitization to (meth)acrylates including 2-HEMA. Ten of our patients (9%) with (meth)acrylate ACD reacted to ECA alone, and were not detected by testing to 2-HEMA. Although we cannot rely on 2-HEMA to detect allergy to cyanoacrylates, the history of cyanoacrylate ACD is often more obvious, with the patient observing that the use of glue led to a localized cutaneous reaction, such as a reaction following application of false eyelashes, or one localized to a surgical wound. The combination of a thorough history and the addition of 2-HEMA alone as a screening allergen should detect most cases of (meth)acrylate allergy, including those sensitized to cyanoacrylate, who would have the short methacrylate series added based on a clear history of a glue reaction.

The authors recognize that (meth)acrylates are potent sensitizers and, as such, patch test sensitization may occur. This has been largely attributed to the higher concentrations at which (meth)acrylates were historically tested. 10,19,20 Since the use of lower patch test concentrations, the problem of patch test sensitization has diminished. None of the recent studies in our selective literature review, covering the last two decades, reported any cases of active sensitization. (Meth)acrylates sometimes cause irritant reactions, which can be difficult to distinguish from true positive results. As experienced clinicians interpreted the results in all of our participating units, and as the ESCD guidelines were followed in the reading and interpretation of positive patch test results, we believe that misinterpretation of patch test findings was kept to a minimum. 10

There are numerous points during the application of acrylic nails whereby a consumer is at risk of sensitization: pushing back the cuticle and nail fold, which can breach the epidermal barrier; soaking nails in highly irritant acetone to aid removal; and inadequately polymerizing acrylic monomers by using the incorrect wavelength of UV. Those working in the nail and beauty industry may additionally be using no gloves, or gloves that (meth)acrylates can penetrate, and may be exposed to airborne (meth)acrylate allergens while filing nails, in some cases causing respiratory symptoms. Soaring demand for acrylic nails, which are durable and perceived as aesthetically pleasing, has led to nail bars being ubiquitous on every high street. Two-thirds of our patients with (meth)acrylate ACD were sensitized by cosmetic use of acrylic nails and almost one-third via their occupation in the nail and beauty industry. Nail technicians are often young, inadequately trained and working in poor, sometimes slave-like conditions, as highlighted in recent media reports. 21,22 It is unlikely that these establishments are adequately training nail technicians to protect themselves from the risks mentioned above. Additionally, there is an identified increase in consumers buying easily accessible home nail kits, which may have the incorrect wavelength of UV. 23-25

In the European Union, the Scientific Committee on Consumer Safety (SCCS) provides opinions concerning health and safety risks of nonfood consumer products. Surprisingly, the SCCS stated that 2-HEMA is unlikely to pose a risk of sensitization when applied appropriately to the nail plate at concentrations up to 35% – supporting this by stating that the normal

nail plate acts as a good barrier to the penetration of chemical substances and that 2-HEMA polymerizes rapidly under UV curing, leaving little chance for monomers to be absorbed. Leaving little chance for monomers to be absorbed. It determined that any risk of sensitization is posed by inappropriate application by a consumer, or constant exposure in a nail technician. In the U.S.A., some states ban the use of MMA in cosmetics and there is some public awareness of acrylate allergy. The epidemic of allergy to (meth)acrylates, if not controlled, could mirror the recent epidemic of allergy to the preservative methylisothiazolinone. It is our role as dermatologists to raise the alarm. 30,31

In July 2018, the British Society for Cutaneous Allergy (BSCA) added 2-HEMA to the British baseline series. Recently there has been a decision to add 2-HEMA to the European baseline series, ^{32,33} and the ESCD recommends routinely screening with 2-HEMA from January 2019. ³⁴

In conclusion, we have conclusively demonstrated that (meth)acrylate ACD is being missed in the U.K. and Ireland. The BSCA have recently updated their guidance by including 2-HEMA in the British baseline series. These data clearly show that testing 2-HEMA in the baseline patch test series will help to identify treatable disease, avoid further morbidity and provide evidence to regulators that preventable cosmetic and occupational allergy is occurring.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1. Total number of patients patch tested to the baseline and short (meth)acrylate series at each centre.

Powerpoint S1. Journal Club Slide Set.

Video S1 Author video.