

Acrylates in Contact Dermatitis

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Acrylates are plastic materials that are formed by the polymerization of monomers derived from acrylic or methacrylic acid. They have found numerous applications in paints, varnishes and adhesives, in the printing industry, in the medical and dental professions, and in artificial nails. Beginning in the 1950s, many reports of occupational and non-occupational allergic contact dermatitis to (meth)acrylate monomers have been published. These molecules are strong irritants, and patch testing can induce active sensitization. When patch tested, acrylate-allergic patients often display multiple positive tests. These reactions may represent cross-reactions, or concomitant reactions due to the presence, in the products responsible for sensitization, of impurities not disclosed in material safety data sheets. (Meth)acrylates are volatile and unstable chemicals, as demonstrated by their rapid disappearance from commercially available patch test allergens when exposed to air for more than a few hours.

SIMPLEST OF the carboxylic acids, acrylic acid was synthesized in 1843, while Frankland and Duppa produced methacrylic acid in 1865.¹ Acrylates, salts (esters) of acrylic acid, were polymerized for the first time by German chemists Fittig and Paul in 1877.¹ In 1927, Rohm and Haas AG in Germany began commercial production of polymethyl acrylate (PMA),² and in 1933, they patented the name Plexiglas for a crystal-clear, shatterproof, and weather-resistant glass substitute made of polymethyl methacrylate (PMMA).

Polymethyl methacrylate was used extensively during World War II in airplane canopies, machine gun turrets, periscope lenses, and others. Nowadays, it is used in windowpanes, skylights, car lights and windshields, street lamp casings, lighthouse lenses, motorcycle helmet visors, aquarium panel, and others. Polymethyl methacrylate and other acrylate polymers have found countless applications in the manufacture of plastic outdoor signs, electric insulators, compact discs, paints and adhesives including instant glues and anaerobic sealants, printing inks, cosmetics, and artificial nails. Medical uses include contact and intraocular lenses, dental prostheses and filling compounds, bone cement, and hearing aids, among others. Polymethyl acrylate can absorb many times its weight in water and has found uses in disposable diapers and sanitary pads.

This article will review the basic chemistry of commonly used acrylates, their cutaneous adverse effects and methods of preven-

tion, the selection of patch testing screening series, as well as some technical aspects of testing with acrylates.

CHEMISTRY

Acrylic polymers are thermoplastic resins, meaning that can be melted and molded at high temperatures. When the temperature is lowered, they become rigid and the desired shape is retained. These polymers may, however, be converted into thermosetting (infusible) resins by cross-linking.³ Their monomeric building blocks include acrylic and methacrylic acid, their corresponding esters acrylates and methacrylates, cyanoacrylic acid and its esters, as well as acrylonitrile and acrylamide.⁴ Acrylic acid ($\text{H}_2\text{C}=\text{CH}-\text{COOH}$) results from the combination of a carboxyl radical to a vinyl group. Polymerization is an addition reaction where linkage of the monomeric units occurs through an opening of the vinyl double bond. If a single monomer is used, the final product is a homopolymer, whereas a copolymer is formed by the addition of different monomers. Polymerization is usually carried out with heat or at room temperature, a process that usually requires the presence of an initiator (benzoyl peroxide, etc) and accelerator (*N,N'*-dimethyl-*p*-toluidine) or by exposure to ultraviolet (UV) light in the presence of a photoinitiator such as benzophenone.⁴ Polymerization with ionizing radiation does not require priming by a photoinitiator. Anaerobic sealants polymerize in the absence of oxygen. Spontaneous polymerization of the various preparations is prevented by the addition of an inhibitor, often hydroquinone.

Mono (Meth)Acrylates

Monofunctional (meth)acrylates are colorless liquids and each molecule contains only 1 vinyl group (Fig. 1). Their polymers are linear and slide along each other to melt when heated. Ethyl and

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butyl acrylate (EA and BA) are used in the production of acrylate rubber.² Butyl acrylate may be found in some spectacle frames.⁴ Hearing aids and dentures are most often polymers of methyl methacrylate (MMA). Artificial nails are traditionally “sculpted” over the existing nail plate using a 2-part mixture of liquid monomer and polymer powder. The mixture polymerizes at room temperature under ambient light.⁵ In recent years, “gel nails” have become popular owing to the ease of application of the multiple layers of gel, which are then polymerized by exposure to UV light. Both types contain multiple mono (meth)acrylates, most commonly MMA. Because of its sensitizing potential, in the United States, the Food and Drug Administration banned MMA in 1974 for use in artificial nails, although it can still be found in many imported resin systems.⁶ Other compounds include EA, ethyl methacrylate (EMA), 2-hydroxyethyl acrylate (2-HEA), 2-hydroxyethyl methacrylate (2-HEMA), and 2-hydroxypropyl acrylate and methacrylate (2-HPA, 2-HPMA).⁷ Ultraviolet-cured inks and printing plates make use of the same compounds.

Poly (Meth)Acrylates

Multifunctional acrylates harbor 2 or more reactive acrylic groups (Fig. 2). Their varying viscosity and volatility make them excellent reactive diluents for various resin systems such as dental composite materials, artificial nail compounds, and UV-cured inks. Their main role, however, is to serve as cross-linking agents between polymer chains, thereby increasing their rigidity and durability while making them thermosetting.⁸ Compounds used for dental restoration and prostheses are mostly dimethacrylates such as ethyleneglycol dimethacrylate (EGDMA), diethyleneglycol dimethacrylate (DEGDMA), triethyleneglycol dimethacrylate (TREGDMA), and 1,4-butanediol dimethacrylate (BUDMA).⁴ Artificial nails resins contain trimethylol propane trimethacrylate, 1,6-hexanediol diacrylate (HDDA), and triethyleneglycol diacrylate (TREGDA), as well as EGDMA and DEGDMA. 1,6-Hexanediol diacrylate is a frequent component of UV-cured inks, along with pentaerythritol triacrylate (PETA) and trimethylpropane triacrylate (TMPTA), 2 closely related compounds that differ only by the presence of a methyl group in the latter molecule.

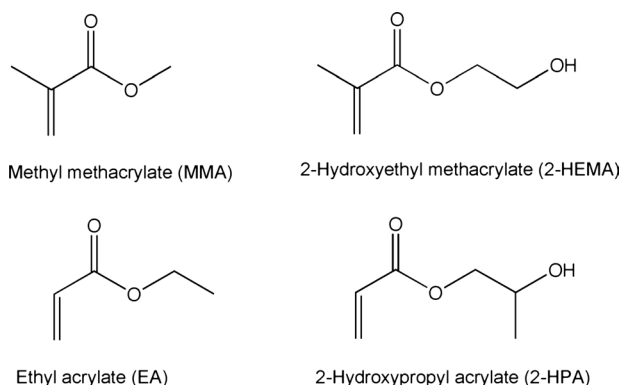


Figure 1. Examples of monofunctional methacrylates and acrylates.

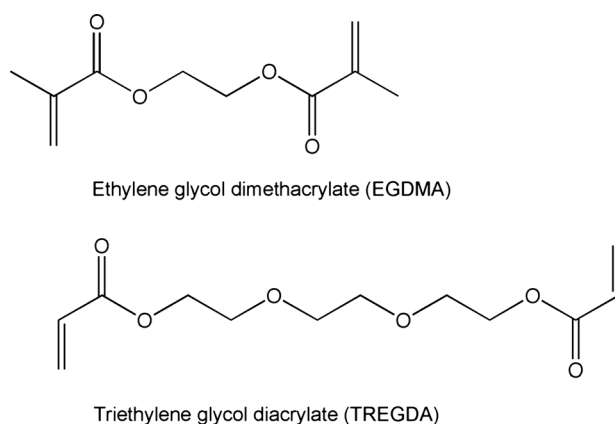


Figure 2. Polyfunctional methacrylate and acrylate.

Prepolymers

Prepolymers are low-molecular weight polymers that can be converted into larger polymers through chain extension or cross-linking. They allow liquid or paste formulations to be molded before hardening into a thermosetting plastic. These hybrid molecules result from the addition of acrylic or methacrylic acid with epoxy, urethane, or polyester resins. Although some become polymerized by exposure to air moisture (window sealants, grout) or with a catalyst such as benzoyl peroxide, most are found in UV-curable processes. Commonly used in dentistry are the prepolymers based on bisphenol A and (glycidyl)methacrylate (GMA), collectively known as epoxy acrylates: BIS-GMA (Fig. 3), BIS-EMA, and BIS-MA.⁴

Cyanoacrylates

Invented in 1942, these fast-acting glues include methyl-2-cyanoacrylate and ethyl-2-cyanoacrylate (Fig. 4), better known as Krazy Glue or Super Glue, whereas *n*-butyl- and 2-octyl-cyanoacrylate are found in medical adhesives such as Histoacryl and Dermabond skin glues. Polymerization occurs rapidly, is sometimes complete within 1 minute, and is triggered by moisture on the surfaces to be bonded. Cyanoacrylates form very strong bonds with metals, ceramic, glass, rubber, plastics, and biologic tissues.

CUTANEOUS EFFECTS

Acrylic monomers are responsible for most of the documented cutaneous reactions. Fully cured acrylate polymers are hard or

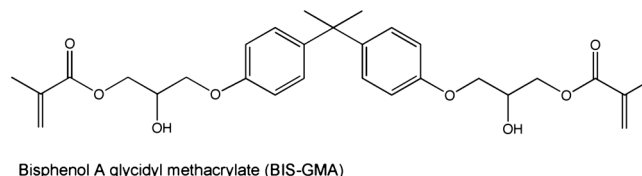
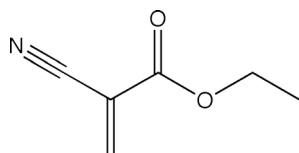


Figure 3. An epoxy acrylate based on bisphenol A, commonly used in dentistry.



Ethyl cyanoacrylate (ECA)

Figure 4. Cyanoacrylates are used in instant glues.

flexible, high-molecular weight compounds that are relatively inert. It should be remembered, however, that trace amounts of residual monomers are almost always present in the lattice of polymerized acrylates.⁹

Irritation

Irritant contact dermatitis has been described with various acrylates. Shimizu et al¹⁰ reported the case of a chemistry student who developed an acute, blistering chemical burn within 24 hours after she spilled GMA on the dorsum of her foot. Printers exposed to tetraethylene glycol diacrylate (TTEGDA) in UV-cured printing inks have developed bullous lesions shortly after exposure.¹¹ Other investigators have also noted delayed irritant reactions from TTEGDA.¹² Four workers in a chemical plant had accidental cutaneous exposure to TTEGDA without immediate reaction, followed by the appearance of a vesicular reaction 2 to 3 days later.¹² One female worker subsequently developed allergic contact dermatitis, which was later proven by patch testing, manifested by the development of a generalized eczematous dermatitis 3 weeks later. Malten et al¹³ had already described an epidemic of delayed irritancy in 20 workers exposed to hexanediol and butanediol diacrylate in the coating department of a door factory. The bullous lesions appeared 12 to 14 hours after skin contact, and none of the affected workers became sensitized. From these publications and from animal experimentation, it can be concluded that diacrylates are strong irritants, monoacrylates are moderate irritants, and their corresponding methacrylates are nonirritant or are weak irritants.⁸

Calnan¹⁴ described an outbreak of airborne irritant contact dermatitis. Five female workers in an electronic factory complained of a burning sensation or itchiness of the eyes, eyelids, and face, with or without erythema and swelling. This reaction occurred when the workers were exposed to vapors of cyanoacrylate glue. Patch tests were negative, and the symptoms disappeared when the relative humidity in the working environment was raised to 55% as water vapor in the air quickly polymerized airborne cyanoacrylate.

Allergy

All types of acrylates have been shown to sensitize. Their sensitizing potential parallels their irritancy: multifunctional acrylates are potent sensitizers and monoacrylates are moderate sensitizers. Their methylated counterparts are much weaker allergens.⁸ Numerous publications have described allergic contact dermatitis from acrylates, with most cases being of occupational origin.

Dentistry

Dental personnel such as dentists, dental assistants, orthodontists, and dental prosthetists are at high risk of allergic sensitization to acrylics.¹⁵ Numerous reports and case series have documented occupational allergic contact dermatitis from MMA, 2-HEMA, TREGDMA, DEGDMA, EGDMA, and the epoxy acrylates BIS-GMA, BIS-EMA, and BIS-MA.^{16–28} In general, dental technicians and prosthetists become sensitized to MMA and the polyfunctional cross-linking methacrylates EGDMA, DEGDMA, and TREGDMA, whereas sensitization to 2-HEMA and the epoxy acrylates predominates in dentists and dental technicians.²⁷ The dermatitis involves the pulp of the fingers, most often the thumb, index, and middle finger. Desquamation and painful fissures characterize the dermatitis that may become very incapacitating. Lesions are sometimes widespread or airborne in dental technicians exposed to particles projected by grinding operations on prostheses.^{29,30} Immediate hypersensitivity has been occasionally reported, manifested by occupational rhinitis, conjunctivitis, pharyngitis, or bronchial asthma.^{31,32} No patient had positive prick tests to acrylates and the pathogenesis of these reactions remains elusive. Mathias et al have reported the puzzling case of a laboratory technician who developed allergic contact dermatitis from 2-HEMA associated with nausea and diarrhea.³³ The gastrointestinal symptoms recurred when the patient underwent patch testing.

Nonoccupational exposure has led to sensitization in dental patients. Kanerva and Alanko³⁴ described allergic contact stomatitis and perioral dermatitis from several epoxy di(meth)acrylates in dental composite resin. Their patient had experienced multiple episodes of oral and perioral dermatitis after visits to the dentist. Patch testing revealed concomitant strong reactions to epoxy resin. Koch's³⁵ patient experienced chronic stomatitis after placement of provisional dental bondings. Also in this case, patch testing revealed contact sensitization to BIS-GMA and to epoxy resins. Two teenagers, reported by Connolly et al,³⁶ developed severe lip swelling and perioral dermatitis within 24 hours of having dental braces glued with a UV-cured bonding agent. Both were found to be allergic to BIS-GMA as well as to epoxy resin. A woman subsequently found to be allergic to MMA and EGDMA presented with labial and gingival lichenoid lesions. This reaction appeared in the weeks that followed reinforcement of her old dental prosthesis with a composite resin.³⁷ An 81-year-old woman attributed her long-standing burning mouth and loss of taste sensation to changing her dentures.³⁸ Patch testing showed positive reactions to MMA, EMA, EA, 2-HEMA, 2-HEA, and EGDMA. Her symptoms improved after removal of the dentures. Uncommon reactions have included labial edema as a manifestation of delayed allergy to various methacrylates in dentures³⁹ and chronic widespread urticaria without mucosal lesion.⁴⁰

Adhesives and Coatings

Acrylates have found widespread application in glues, paints, lacquers, and varnishes. Consequently, workers who manufacture

these products and those who use them are at risk for allergic sensitization.⁴¹ Dempsey⁴² reported the first cases of occupational allergic contact dermatitis from anaerobic sealants. These 3 factory workers presented with hand dermatitis and reacted to various ingredients of Sta-Lok and Loctite adhesives, namely GMA and polyurethane dimethacrylate. Three women working on electric or electronic assembly lines became sensitized to Loctite 222 or 290.⁴³ When patch tested, they reacted to polyethylene glycol dimethacrylate (PEGDMA), the main component of the “200” series of Loctite anaerobic sealants. A machine assembler consulted for work-related hand dermatitis.⁴⁴ He had been exposed to various Loctite anaerobic sealants and the investigation elicited sensitizations to PEGDMA, 2-HEMA, and 2-HPMA. Of the 7 patients discussed above who were allergic to anaerobic sealants, only 1 reacted to MMA. More recently, Aalto-Korte et al⁴⁵ reviewed the files of 10 patients with allergic reactions to acrylic monomers caused by exposure to glues at work. Nine had used anaerobic sealants, 3 used cyanoacrylate glues, and 1 used a 2-component instant adhesive. All workers were allergic to 2-HEMA and EGDMA; 9, to 2-HPMA; 7, to TREGDMA and tetrahydrofurfuryl methacrylate (THFMA); and 5, to EMA and TREGDA. Interestingly, 4 patients reacted to MMA.

Acrylates in UV-cured adhesives have also been responsible for numerous cases of occupational allergic contact dermatitis. An epidemic occurred in a plant manufacturing video display units.⁴⁶ Electrical coils were glued with an acrylate-based UV-cured adhesive, and the entire process was automated. The workers, however, had to manually disassemble defective coils. Patch testing was performed in 21 workers who developed hand dermatitis. Of those, 12 reacted to acrylates, but only 3 had positive reactions to a component of the glue, β -carboxy-ethyl acrylate. Other workers reacted to diethylene glycol diacrylate (DEGDA), TREGDA, HDDA, and 1,4-butanediol acrylate that were not present in the glue. These reactions could represent cross-reactions or concomitant reactions to impurities in the adhesive system.

Additional sources of allergy to UV-cured acrylates include paints. A worker in a paint factory became sensitized when his clothes became contaminated during the canning process.⁴⁷ He displayed a 2+ reaction to a 0.2% dilution of the paint that contained dipropylene glycol diacrylate. Unfortunately, the patient could not be tested to this particular acrylate, but he reacted to DEGDA, TREGDA, and 1,4-butanediol acrylate. A worker painting metal parts in a car factory developed a unilateral dermatitis on the hand holding the parts that were painted.⁴⁸ He reacted to an unspecified acrylic monomer present in the paint, as well as to DEGDA. Resins used to repair windshields and adhesives for glass are also cured by exposure to UV light and have induced allergic contact sensitization.^{49–51}

Printing Industry

Printing techniques have evolved tremendously since Gutenberg's first experiments with wooden blocks. Modern processes, such as

Letterflex, Nyloprint, and Napp use UV-cured acrylates in the production of printing plates from photographic negatives. These plates can then be mounted on rotary or flatbed presses to print large numbers of newspapers, magazines, or books. Ultraviolet-cured inks are also used in silkscreen printing, where ink is squeezed through a mesh stencil and quickly dried by UV exposure. This technique is especially useful to print labels or pictures on plastic, fabric, wood, glass, or metal.

Magnusson and Mobacken⁵² are credited with the first description of allergic contact dermatitis from acrylates in a printing plant. Beurey et al¹¹ reported not only irritation but also allergic contact dermatitis from the multifunctional acrylate TTEGDA. Numerous additional publications later followed these early reports.^{53–63} Emmett⁵³ described 4 workers, employed in a plant that manufactured UV-cured printing ink, who developed allergic contact dermatitis on the hands, forearms, trunk, and face from sensitization to PETA and TMPTA. Nethercott's⁵⁵ 7 patients held various positions in a similar plant. They presented with dermatitis involving the hands, forearms, face, abdomen, and thighs. All were sensitized to PETA and 2 were also allergic to TMPTA. In the study by Björkner et al,⁵⁷ 6 printing press operators developed allergic contact dermatitis of the hands, forearms, and face. When patch tested with the ink constituents, all reacted to TMPTA, 3 reacted to polyester acrylate, and 2 reacted to epoxy acrylate. In addition, 4 had positive patch tests to PETA; 2, to 2-EHA and BA; and 1, to EA—compounds not present in the ink. Malten and Bende⁵⁶ investigated 5 patients with allergic contact dermatitis on the hands and forearms, acquired after exposure to a photopolymer mixture in the plate-making department of a newspaper printing plant. Of the 4 patients subsequently tested, all reacted to 2-HEMA and 2 reacted to TREGDMA and DEGDA. Similarly, the main sensitizer in the Napp printing plate process was found to be 2-HEMA.^{60,61}

A number of publications have documented the occurrence of allergic contact dermatitis in silkscreen printers.^{64–68} The first reported case was allergic to TPGDA and to PETA.⁶⁴ The 2 patients described by Whitfeld and Freeman⁶⁵ had predominantly facial involvement. Both were allergic to the ink from the workplace at a dilution of 0.5% in alcohol. The second patient could not be tested further, but the first reacted to TPGDA, a component of the ink. The printer investigated by Isaac et al⁶⁶ had a pruritic dermatitis of the hands and eyelids. He reacted to the UV-cured ink from the workplace, 1% in petrolatum (pet), to TMPTA, PETA, and BUDA. Only the first 2 substances were present in the ink. A 40-year-old printer was making stencils for printing T-shirts when he developed allergic contact dermatitis on the hands and wrists.⁶⁸ He had positive patch tests to his own ink (as is, semiopen test) to TPGDA, BIS-GMA, EGDMA, and epoxy resin. The presence of EGDMA in the ink could not be confirmed. Likewise, the patient evaluated by Skotnicki and Pratt⁶⁹ was allergic to TPGDA, the only ingredient listed in the material safety data sheets (MSDS) of the ink, but also reacted to TREGDA, TREGDMA, DEGDA, PETA, BUDA, and epoxy resin.

In summary, printers are exposed to a variety of acrylates that can be strong irritants and sensitizers, and once sensitized, they often react to multiple (meth)acrylates when patch tested but rarely to MMA. This is exemplified by the patient reported by Morgan and Fewings,⁷⁰ who became sensitized after a single accidental exposure to an ink containing HDDA. When patch tested, he reacted not only to HDDA but also to DEGDA, HEA, and BUDA. These positive tests may represent cross-reactions, but also concomitant reactions, because these inks often contain other (meth)acrylates than those stated on the MSDS.⁶⁷ Facial involvement is common: workers may transfer the sensitizing ink from the hands to the face; however, true airborne exposure does occur through a phenomenon known as “ink fly” in which rapidly moving printing presses aerosolize the ink.⁶⁵

Artificial Nails

Artificial nails are either preformed plastic pieces that are glued with a cyanoacrylate instant adhesive on an existing nail, or sculptured, that is, built from a paste made by mixing liquid acrylic monomer with polymer powder and cured at room temperature. More recently, photobonded nails have become very popular: they are made by applying multiple layers of acrylic gel, each layer hardened by brief exposure to a weak UV light source.⁷¹ The contact dermatitis literature is replete with case reports of allergic sensitization to acrylates from artificial nails in customers as well as in beauticians, with the earliest reports dating back to the 1950s.^{5,7,71–81}

In their 1957 publication, Fisher et al described 4 patients who developed severe, painful paronychia dermatitis within 2 to 4 months of regular application of acrylic nails.⁷¹ All patients were sensitized to the MMA liquid monomer but not to the powder polymer. Numerous reports of sensitization to MMA eventually led, in 1974, to a Food and Drug Administration ban of this chemical for use in artificial nails. The industry replaced MMA with related acrylates, such as EMA, DEGDM, EGDMA, *N*-butyl methacrylate, and others. These molecules were soon found to cross-react with MMA.^{72,73} In sensitized customers, the dermatitis most often involves the periungual area, including the nail folds and the hyponychium, sometimes the nail bed and the hyponychium. Occasionally, lesions may occur on the eyelids, face, and neck, from manual transfer of the allergenic monomer to these areas. More rarely, widespread lesions involving the hands, arms, trunk, and face have been reported.⁷⁵ The culprits are usually 2-HEMA, EA, EMA, EGDMA, and DEGDM.^{77,78}

Allergic contact dermatitis is an occupational hazard for manicurist and beauticians who apply artificial nails.^{74,79,81} The lesions tend to be more widespread than in customers, involving the fingers, hands, wrists, and often the face, eyelids, and neck.^{5,77,79} It is believed that in these cases, the facial dermatitis is secondary to airborne exposure from the dust generated by filing the hardened nail.⁵

Allergic sensitization to acrylates from artificial nails may have unsuspected consequences. A 50-year-old female dentist devel-

oped a pruritic fingertip dermatitis within days of applying acrylic nails.⁷⁶ Her patch tests were positive to MMA. When she subsequently returned to work, her hand dermatitis relapsed from exposure to dental bonding agents. Similarly, patients who had been previously sensitized from artificial nails were found to develop severe stomatitis after exposure to dental materials containing 2-HEMA and BIS-GMA.^{82,83}

Paronychia, onycholysis, and onychodystrophy are common accompaniments of allergic contact dermatitis from acrylic artificial nails. The nails may remain friable, ridged, and distorted long after the initial dermatitis has resolved. Prolonged and even permanent loss of nails has been described.^{71,77,84,85} Still more bothersome are the painful paresthesia that sometimes supervene.⁷¹ This finding was first reported in orthopedic surgeons handling bone cement.⁸⁶ It presents as a burning or throbbing pain, often associated with tingling or numbness.⁸⁷ As with onychodystrophy, this distressing sensation, for which there is no effective treatment, may persist for years. Most of the time, paresthesia is seen with allergic contact dermatitis, but sensitization does not seem to be a prerequisite for its occurrence. The patient of Baran and Schibli⁸⁸ complained of immediate pain when the MMA paste was applied and a persistent feeling of pressure once the nails were in place. When the nails fell off a few months later, she was left with severe onychodystrophy and long-lasting paresthesia that was not relieved by nail avulsion. Patch tests were negative with 3 dilutions of MMA. Methyl methacrylate is a powerful lipid solvent and can therefore penetrate tissues rapidly, causing direct damage to the free nerve endings that are abundant in the periungual region.⁸⁹

Miscellaneous, but Mostly Medical, Sources of Exposure

Orthopedic surgeons and nurses are at risk for sensitization to MMA in bone cement.⁹⁰ Recipients of cemented orthopedic endoprostheses are rarely sensitized,⁹¹ possibly because exposure that bypasses the skin induces tolerance.

Parts of insulin pump infusion sets have been responsible for contact sensitization to acrylates.^{92–94} Two patients presented with allergic contact dermatitis under the plastic butterfly of the device. They were sensitized to phenoxypoly(ethyleneoxy)ethylacrylate, isobornyl acrylate, and β -carboxyethyl acrylate, present in the Loctite 302 glue used to fix the metal needle to the plastic part.⁹² Another patient, using the same infusion sets, developed similar lesions.⁹³ When patch tested, however, she reacted to multiple acrylates from the Chemotechnique Diagnostics (Vellinge, Sweden) series, including TREGDMA, TREGDA, MMA, EMA, 2-HEMA, EGDMA, and PETA. A fourth patient became allergic to the catheter linking the needle apparatus to the pump.⁹⁴ She also reacted to numerous acrylates including MMA, EMA, MA, EA, 2-HEMA, and BUDMA. Chemical analysis of the catheter revealed the presence of MA.

An acute contact dermatitis erupted on the back of a 35-year-old nurse who was using a transcutaneous electrical nerve

stimulator (TENS).⁹⁵ Her patch tests were positive to the conductive “hydropad” covering the electrodes, to 2-HEMA, 2-HPMA, and EGDMA. The hydropad was found to contain a copolymer of 2-HEMA. Weber-Muller et al⁹⁶ reported on 2 patients who developed eczematous lesions under the electrodes of a TENS. The first patient reacted to the conductive gel as well as to EGDMA and EA. The second patient had a negative test to the electrode but was positive to 2-HEA, 2-HEMA, 2-HPMA, and TREGDA. A more recent case reacted to 2-HEMA, 2-HPMA, EGDMA, and HDDA.⁹⁷ The conductive gel of electrocardiogram electrodes has also caused allergic contact dermatitis in a patient who reacted to EA, 2-HEA, urethane diacrylate (UDA), and BUDA.⁹⁸ The gel contained 90% acrylic derivatives.

Disposable electrosurgical grounding plates stick to the skin by means of pressure-sensitive adhesive that contains 2-HEMA and 2-HEA. One week after a surgical procedure, a 69-year-old farmer developed a rectangular eczematous plaque over his right buttock, corresponding to the area of contact with a grounding plate.⁹⁹ Patch tests were positive to MMA, 2-HEMA, TREGDMA, EGDMA, EA, BA, and 2-HEA. He was likely sensitized by exposure during the surgical procedure. The 2 patients described by Woollons et al¹⁰⁰ reacted to MMA and 2-HEMA, but Jagtman’s¹⁰¹ 4 patients reacted to numerous (meth)acrylates, including 2-HEMA, but not to MMA.

Other sources of sensitization include spectacle frames,¹⁰² where butyl acrylate was the sensitizer, and hearing aids.^{103,104} The patient of Dutree-Meulenberg et al¹⁰³ with hearing aid dermatitis became sensitized to UDA, EGDMA, TREGDMA, DEGDMA, and TREGDA but showed no reaction to MMA. The resin of the hearing aid contained a mixture of urethane (meth)acrylates. Similarly, the patient reported by Sood and Taylor¹⁰⁴ became allergic to a hearing aid that contained 2-HEMA and PEGDMA. She reacted to 2-HEMA, 2-HPMA, EGDMA, PEGDMA, TMPTA, and PETA but not to MMA. In addition, she reacted to ethyl-cyanoacrylate that was used to glue a face plate to the shell of the hearing aid. A 47-year-old woman, with a past history of allergy to acrylic nails and dental crowns, presented with an acute vulvar and perineal dermatitis after using incontinence pads that contained polyacrylate in their absorbent layer.¹⁰⁵ Her patch tests were positive to 9 (meth)acrylates, including MMA and EA. The material of the pad was not analyzed but likely contained unpolymerized acrylate monomers.

Occupational allergic contact dermatitis has been reported in 3 chemistry laboratory workers handling Lowicril electron microscopy embedding medium, a mixture of various (meth)acrylates.¹⁰⁶ One worker was patch tested and reacted to 2-HEA, one of the known components of the medium. A 40-year-old histology technician became sensitized to Technovit resins, based on MMA and 2-HEMA.¹⁰⁷ She reacted to 2-HEMA, 2-HPMA, and EGDMA but not to MMA. Occupational hand dermatitis occurred in 2 factory workers involved in the manufacture of acrylic contact lenses.¹⁰⁸ The resins used were 2-HEMA, 2-HEA, and EGDMA. One patient reacted to 2-HEA; the other, to

2-HEA and 2-HEMA. The manufacturing process is now fully automated, and workers are no longer exposed, except those involved in the maintenance of the machines. One such worker developed a fingertip dermatitis and showed positive patch test reactions to 2-HEMA, 2-HPA, EGDMA, and MMA.¹⁰⁹ Sensitization to tetrahydrofurfuryl acrylate occurred in 2 factory workers exposed to a new adhesive used in the assembly of surgical needles.¹¹⁰

Cyanoacrylates

Cyanoacrylates polymerize almost instantaneously in the presence of water and bind immediately to surface keratins. Calnan¹⁴ therefore believed that it was almost impossible for cyanoacrylates to induce allergic contact sensitization. This firmly entrenched belief has since been refuted by many publications that described cases of sensitization to this type of glue in various settings.^{111–120} A patient using Krazy Glue to strengthen her nails developed a truncal dermatitis mimicking small plaque parapsoriasis.¹¹¹ Patch testing with the dried glue produced a vesicular reaction and the dermatitis cleared with avoidance of the glue. A 14-year-old boy became sensitized after 20 days of applying a cyanoacrylate glue to his retroauricular areas in an attempt to correct protruding ears.¹¹² Belsito¹¹³ described 3 women, with mainly periungual dermatitis, who were allergic to ethylcyanoacrylate (ECA) in Krazy Glue used for nail wrapping. Tomb et al¹¹⁴ saw a 20-year-old hairstylist with severe facial dermatitis. She was using 2 cyanoacrylate glues to fix wigs to customers’ remaining hair. Both glues contained more than 99.6% ECA and gave positive patch tests reactions at dilutions of 1% in pet. Fitzgerald et al¹¹⁵ also reported ectopic dermatitis in a manicurist applying preformed artificial nails with a glue that contained ECA and isopropyl-2-cyanoacrylate. Her lesions involved the fingers, dorsum of the hands, eyelids, and trunk, and she reacted to the glue and to ECA. Guin et al¹¹⁶ described 3 women who had been using preformed artificial nails glued with ECA and developed onychodystrophy, onycholysis, and subungual hyperkeratosis. All were allergic to ECA, and one had positive patch tests to clippings of her own fingernails 2 months after discontinuing use of the glue. Severe fingertip dermatitis and onychodystrophy led in 1 case to months of sick leave before the cause could be uncovered.¹¹⁷ Allergic contact dermatitis from octylcyanoacrylate (OCA) occurred 2 weeks¹¹⁸ and 4 weeks¹¹⁹ after surgical wound closures with Dermabond skin adhesive.

It is generally agreed that cyanoacrylates and (meth)acrylates do not cross-react.^{87,117,121} However, among the 11 patients studied by Koppula et al,⁷ who were allergic to artificial nails, all reacted to various (meth)acrylates and 5 also had positive patch tests to ECA. Similarly, a 24-year-old manicurist with hand eczema reacted to MMA, EA, EMA, 2-HEMA, 2-HPMA, EGDMA, and her cyanoacrylate glue.¹²⁰ It is possible, however, that these patients have acquired concomitant reactions from exposure to multiple nail products.

PRACTICAL CONSIDERATIONS

Protective Equipment

Adequate protective gloves should be worn when handling unpolymerized acrylates. Latex gloves are rapidly permeated by MMA, as demonstrated by Pegum and Medhurst.¹²² Exposure of different glove materials in a diffusion chamber showed very short breakthrough times of less than 1 to 4 minutes for most materials, vinyl being inferior to natural rubber latex.¹²³ Using standardized methods, Mäkelä and Jolanki¹²⁴ confirmed the lack of protection afforded by latex and vinyl gloves, but also by polyethylene, thin nitrile, chloroprene, and styrene-ethylene-butadiene rubber. Trilaminated gloves made of polyethylene/ethylene vinyl alcohol/polyethylene gave excellent results, but these gloves are inelastic and hinder dexterity. It is suggested to wear them under standard latex gloves for better fit.

Munksgaard¹²⁵ showed that regular gloves do not fare better when exposed to 2-HEMA and TREGDMA, with breakthrough times of 1 to 3 minutes for vinyl gloves and 5 to 8 minutes for latex gloves. These gloves have a better resistance against BISGMA and UDMA, with breakthrough times of 20 minutes for vinyl and 80 minutes for latex. For dental work involving UV-cured acrylates, it is recommended to wear a double layer of nitrile gloves for tasks lasting 15 to 30 minutes. For longer work, a polyethylene glove should be worn under a nitrile glove.¹²⁴

Screening Series

Some authors have tried to devise screening series that would pick up most cases of allergic sensitization with a small number of patch test allergens. Kanerva et al¹²⁶ reviewed the 1985 to 1995 data from the Finnish Institute of Occupational Health. Among their 48 patients who reacted to at least 1 of 30 (meth)acrylates, the most common sensitizers were 2-HEA, 2-HPMA, and 2-HEMA. More recently, Goon et al¹²⁷ added 5 (meth)acrylates to the baseline series used in 2 centers in Singapore and Sweden. They found that testing with 2-HEMA, TREGDA, and EGDMA would pick up 97% of (meth)acrylate-allergic patients. A Canadian retrospective study analyzed the data from 44 patients allergic to 1 or more (meth)acrylate.¹²⁸ Testing with EA and MMA would have detected 73% of the allergic patients, whereas the addition of 2-HEMA would have increased the detection rate to 91%.

For patients sensitized from artificial nails, Koppula et al⁷ mentioned that MMA is not a good screening allergen. However, EA alone would have been positive in 91% of their 11 patients. They suggest to also test 2-HEA, EGDMA, TREGDA, and ECA. Constandt et al⁵ state that testing with 2-HEMA and ECA would screen most cases.

In the occupational setting, Geukens and Goossens²⁶ recommend testing with EGDMA, 2-HEMA, TREGDMA, and MMA. Aalto-Korte et al²⁸ reviewed their files for the period 1994 to 2009 and found 66 acrylate-allergic patients. Testing with EGDMA, DEGDA, 2-HPMA, and PETA would have revealed sensitization in

93% of these patients. It seems therefore that no screening series fits every situation and that MMA alone is insufficient.

Active Sensitization and Patch Test Concentrations

Acrylates and methacrylates must be diluted to avoid irritant patch test reactions. Even at low concentrations, active sensitization can occur. Kanerva et al¹²⁹ sensitized 1 patient to EA and BA 1% in pet and 3 patients to EA, 2-HEA, and 2-HPA 0.5% pet. They eventually lowered the concentration of their patch tests acrylates to 0.167% pet. Cavelier et al^{130,131} also reported active sensitization from acrylates. The current patch testing concentration for acrylates is 0.1% pet, 2% pet for methacrylates, and 10% pet for cyanoacrylates.

Vehicles and Test Chambers

Petrolatum is the preferred patch test vehicle. Attempts at induction and elicitation of sensitization to acrylates in guinea pigs were much less successful when acetone or alcohol was used, possibly because of polymerization of the acrylate in the vehicle.¹³² When testing cyanoacrylates, Bruze et al¹³³ obtained false-negative reactions with Finn Chambers and acetone as a vehicle. They attributed this finding to rapid polymerization of ECA, with aluminum catalyzing the reaction. This phenomenon did not occur with plastic chambers or with Finn Chambers when ECA was diluted in pet. Björkner et al⁴ recommend the use of plastic chambers regardless of the vehicle.

Cross-Reaction or Coreactions?

Most patients sensitized to a small number of (meth)acrylates display multiple positive reactions when patch tested to an extended series of allergens. These positive tests most likely represent cross-reactions. It is felt that sensitization to methacrylates may induce cross-reactivity to acrylates but not the opposite.²⁸ However, Kanerva et al¹³⁴ and Henriks-Eckerman and Kanerva¹³⁵ performed chemical analysis of a large number of commercial products containing (meth)acrylates, using gas chromatography coupled with mass spectrometry. They were able to demonstrate the presence of multiple compounds that were not declared in the MSDS, sometimes in concentrations up to 46% of the total weight of the product. Therefore, it is likely that many of the multiple patch test reactions are in fact concomitant reactions.

True cross-reactions have been reported between MA, EA, and dimethyl fumarate or its isomer, dimethyl maleate.^{136–138} Dimethyl fumarate is the ill-fated fungicide that was responsible for the Chinese sofa epidemic of severe allergic contact dermatitis in Finland, the United Kingdom, and France^{136,138} and later caused a second epidemic of shoe contact dermatitis in Spain.¹³⁷ Maleates are used in the pharmaceutical industry and as ingredients in polyvinyl acetate glues and polyester resins.^{137,139}

Purity and Conservation of Patch Test Allergens

Henriks-Eckerman and Kanerva¹⁴⁰ verified the purity of commercially available (meth)acrylate patch test allergens. The

dimethacrylates were very pure, but diacrylates and triacrylates contained between 9% and 19% impurities, mostly the corresponding monoacrylates or hydroxyacrylates. These impurities may account for some of the cross-reactions described in the literature.

By high-performance liquid chromatography, Goon et al¹⁴¹ measured the concentration of 5 (meth)acrylates used for patch testing in 9 centers from around the world, and compared their results with the concentration stated by the suppliers of the allergens. The analyzed allergens included MMA, 2-HEMA, 2-HPA, EGDMA, and TREGDMA. All of the EGDMA and TREGDMA samples were within the accepted range, but 4 of 5 2-HPA syringes were below the acceptable range. The worst performer was MMA with only 1 sample having an acceptable concentration. Methyl methacrylate is the most volatile of the tested substances and may have evaporated from the pet vehicle. Samples with the lowest concentrations of allergens were those that were past their expiry date.

The same authors then evaluated the effect of air transport on the final concentration of MMA, 2-HEMA, and EGDMA.¹⁴² These allergens, in capped syringes and in preloaded IQ chambers (Chemotechnique Diagnostics, Vellinge, Sweden), were sent from Malmö to Singapore and back. The concentrations remained stable in the syringes, but allergens sent in IQ chambers had almost completely disappeared at the end of travel. Even more thought provoking are the results from this group's latest publication.¹⁴³ They studied the same 5 (meth)acrylates as in their first experiment,¹⁴¹ kept in syringes, and loaded in IQTM chambers. These allergens were stored at room temperature, refrigerated, and frozen (allergens in syringes only). Their concentrations were measured over time. Obviously, frozen samples were more stable than those stored in the refrigerator, and the latter kept better than those left at room temperature. Syringes containing 2-HEMA, EGDMA, and TREGDMA retained more than 80% of their initial concentrations after 128 days, regardless of the temperature of storage. However, syringes containing MMA kept at room or in the refrigerator were below the 80% mark between 8 and 10 days. 2-HPA fared a little better, plunging below the 80% concentration by day 21 if kept at room temperature and at day 105 when refrigerated. All allergens were rapidly lost when stored in IQ chambers. Whether stored at room temperature or refrigerated, MMA and 2-HPA drop below the 80% acceptable concentration after a single day. 2-HEMA and EGDMA follow suit after 2 days. TREGDMA is slightly more stable: it takes 5 days for samples kept at room temperature to reach 80% of their initial concentrations, and more than 1 month when refrigerated.

These findings send the following warnings to the patch testing community: (a) (meth)acrylates should be used before their expiry date, (b) they should be kept in the freezer or at least in the refrigerator, and (c) they should be applied to chambers only at the time of testing and not in advance.

CONCLUSIONS

Nowadays, acrylates and methacrylates are ubiquitous materials. Their range of application is very broad and includes dentistry, the printing industry, artificial nails, as well as diverse adhesives such as anaerobic sealants and instant glues. They are irritant and also strong allergens, as demonstrated by the plethora of case reports of allergic contact dermatitis that have been published since the 1940s. Most cases of sensitization would be picked by a screening series comprising MMA, 2-HEMA, EA, EGDMA, TREGDA, and ECA. Testing with extended series and the patients' own products may be necessary, keeping in mind the risk of active sensitization. Cross-reactions are common, but could represent concomitant sensitization, considering the inadequate information provided by MSDS and the impurities found in most products. Finally, it is important to remember that these molecules are quite labile and that the concentration of commercial allergens may vary over time depending on their storage conditions.

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