Cross-reactions of multifunctional methacrylates and acrylates

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Kanerva L. Cross-reactions of multifunctional methacrylates and acrylates. Acta Odontol Scand 2001; 59:320–329. Oslo. ISSN 0001-6357.

Dental acrylic monomers (that is, acrylates and methacrylates) are important occupational sensitizers. Acrylic monomers may also cause allergic reactions in dental care. Unfortunately, acrylic monomers cross-react—that is, allergic sensitization induced by one acrylic compound extends to one or more other acrylic compounds. Therefore, sensitized individuals are often multiallergic and, accordingly, cannot be exposed to any of the compounds. In the present review aspects of cross-reactivity in general and data from animal studies of cross-reactivity of multifunctional methacrylates and acrylates are summarized. A multitude of acrylic monomers is used in dentistry, and when patients or dental personnel become sensitized, it is of great importance to identify the dental acrylic preparations to which the sensitized individual can be exposed. Sensitized dental workers are known to have ceased working in dentistry owing to occupational allergic contact dermatitis or asthma, caused by dental acrylic monomers. Unfortunately, cross-reactivity of acrylic monomers used in dentistry is not sufficiently mapped to enable selection of an appropriate compound for the sensitized person. Another important aspect is that product declarations of dental acrylic materials should show all acrylic compounds present in the products—even acrylic monomers/impurities with lower concentrations than 1%. This could help to select a product that the sensitized individual could use. ☐ *Acrylate; acrylic monomers; animal study; asthma; cross-reactivity; dentistry; 2-hydroxyethyl methacrylate; multifunctional methacrylate; occupational dermatitis; sensitization*

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The term cross-sensitization denotes the phenomenon in which an allergic sensitization induced by one compound extends to one or more other compounds (1, 2). The allergen causing the primary reaction is called the primary allergen or primary sensitizer. The compounds that cause cross-sensitization are called secondary allergens and are usually related to the primary allergens. There are several mechanisms by which cross-reactions may occur. 1) The structural similarities between the primary and secondary allergens are so close that the immune system cannot distinguish between them and reacts as if they were identical. 2) The primary allergen is metabolized or converted in vivo into a compound that is identical or structurally so closely related to it (see above) that sensitized cells cannot differentiate between them. 3) The secondary allergen is transformed in vivo into compounds closely related to the primary allergen. 4) Both the primary and the secondary allergens are converted in vivo into identical or closely related chemicals. 5) Primary and secondary allergens combine in vivo with a carrier and are subsequently modified to form an antigen with similar determinants (1, 2).

Cross-reactivity has been reported between a great number of chemicals, some examples of which are given in Table 1 (2). Cross-reactivity is well known between, for example, para-amino compounds (Fig. 1) (2), corticosteroids (3), local anesthetics (4), and acrylic monomers (5, 6).

Methacrylates

The following acrylates, methacrylates, and epoxy acrylates are called acrylic monomers and are widely used in dentistry. Allergic contact dermatitis (ACD) caused by acrylic monomers is well known in dental personnel (6). Acrylic monomers are also an important occupational hazard to the respiratory system of dental workers (7). Important acrylic monomers in dentistry are: monomethacrylates, such as methyl methacrylate (MMA) and 2-hydroxyethyl methacrylate (2-HEMA), and multifunctional methacrylates, including such dimethacrylates as ethyleneglycol dimethacrylate (EGDMA) and triethyleneglycol dimethacrylate (TEGDMA). The multifunctional monomers act as cross-linkers and 'diluents' for high molecular weight monomers, such as 2,2-bis[4-(2-hydroxy-3-methacryloyloxypropoxy) phenyl]propane (BIS-GMA). All these can cause occupational ACD and, in dental patients, allergic reactions. The clinical picture of dermatitis is usually pulpitis of the fingertips or dermatitis of the face, caused by airborne acrylic monomers (6).

From patch testing it is well known that patients with ACD from acrylic monomers often show reactions to several acrylic monomers (Fig. 2) even though exposure and sensitization probably has not occurred to all the patch test-positive acrylic monomers (5, 6). Table 2 shows patch test results for acrylic monomers of six patients sensitized by dental composite resins (6). All patients show an individual patch test pattern. This may be because patients have different exposure histories to dental acrylics. Another reason is that each individual usually develops his/her own cross-sensitivity pattern (1).

Dental personnel have the highest risk of developing

Table 1. Cross-reactivity between some common chemicals (see Ref. 2)

Compound	Uses of compound	Cross-reacting compound
Alantolactone	Antihelminthic, naturally occurring	Frullanolide
p-Aminoazobenzene	Leather dye	*p*-Amino compounds
p-Aminoazotoluene	Topical medication	*p*-Phenylenediamine (PPDA)
p-Aminobenzoic acid	Naturally occurring	*p*-Phenylenediamine (PPDA)
Aniline	Dyes, inks	*p*-Amino compounds
Aniline black	Fur dye	*p*-Amino compounds
Benadryl	Antihistamine	Antistine
Benzaldehyde	Dyes, perfumery, naturally occurring	Vanillin
Benzocain	Local anesthetic	Procain
Benzoyl peroxide	Resins, ointments	Ethyl benzoate
Bismark brown	Dyes	*p*-Amino compounds
Bisphenol A	Synthesis of epoxy resins	Diethylstilbestrol
Bithionol	Antiseptic	Chlorinated salicylanilide
Chloral hydrate	Ointments	Chlorobutanol
Chloroxylenol	Creams, lotions	Chlorocresol
Chlorpromazine	Antipsychotic agent	Phenothiazine
Coniferyl benzoate	Benzoin present in Balsam of Peru	Benzyl cinnamate
Diaminodiphenylmethane	Antioxidant	*p*-Phenylenediamine (PPDA)
Diethylstilbestrol	Synthetic estrogen	Dienestrol
1-Chloro-2,4-dinitrobenzene (CDNB)	Model electrophile, used, e.g., in experimental contact dermatitis	1-Fluoro-2,3-dinitrobenzene
Epichlorhydrin	Synthesis of epoxy resins	Propylene oxide
Ethylenediamine	Creams, lotions	Antistine
Fuchsin	Dye, antifungal agent	*p*-Amino compounds
Hexachlorophene	Disinfectant, fungicide	Bithionol
Hexamethylenetetramine	Antiseptic, rubber chemical	Formaldehyde
Hexylresorcinol	Disinfectant, creams, mouth wash	Resorcinol
Hydroquinone	Antioxidant	Pyrocatechol
Hydroquinone-*O*-benzyl ether (Benoquin®)	Antioxidant	Hydroquinone
N-isopropyl-*N*′-phenyl-*p*-phenylenediamine	Antioxidant	*p*-Phenylenediamine (PPDA)
Pyrogallol	Dyes, tar	Resorcinol
Sudan IV	Coloring agent	*p*-Aminoazotoluene
Tetrachlorosalicylanilide (TCSA)	Soaps	Hexachlorophene
Umbelliferone	Sunscreening agent	Psoralen
Usnic acid	Naturally occurring in lichen acids comprising oak moss	Atranorin

ACD to acrylic monomers. The most common acrylic monomers provoking allergic patch test reactions are given in Table 3 (8). An individual's history of exposure to various acrylic monomers is difficult to establish. First, dental personnel have been exposed to a great number of dental acrylic monomers during their working life. Second, even if the exposure history were known, the dental products containing acrylic monomers contain many undeclared potentially cross-reactive compounds (9–11) (Table 3). Differences can probably occur even between batches of acrylic materials, and it is therefore difficult to determine a dental worker's occupational exposure, especially over a long period.

Animal studies of allergenicity and cross-reactivity of diacrylates and dimethacrylates

When discussing cross-reactivity or cross-sensitivity in animal studies, it is important to be certain that the primary and secondary allergens are pure. A chemical cannot be classified as an allergen unless the pure substance is used for both induction and challenge. In many acrylic compounds a high level of purity is difficult to obtain. Therefore, sensitization to impurities cannot be excluded, although positive reactions caused by them are probably infrequent.

Chung & Giles (12) studied cross-sensitivity of methyl, ethyl, and *n*-butyl methacrylates in guinea pigs already in the 1970s but did not examine the sensitizing capacity or cross-reactivity of di(meth)acrylates. Parker & Turk (13) investigated the ability of acrylic monomers to cause contact sensitivity in guinea pigs. Twenty-one different acrylic monomers were scanned for their ability to induce contact sensitivity, using five different sensitization protocols. Contact reactions of various intensities were produced to all the mono-, di-, and tri-acrylates tested. However, they did not succeed in sensitizing guinea pigs to any methacrylates and concluded that guinea pigs cannot be contact sensitized to acrylic monomers that are substituted on carbon 2. Cross-reactivity was not studied.

Björkner (14) and van der Walle & Bensink (15) were the first to study experimentally the cross-reactivity of di(meth)acrylates. Björkner (11) (Table 4) studied the

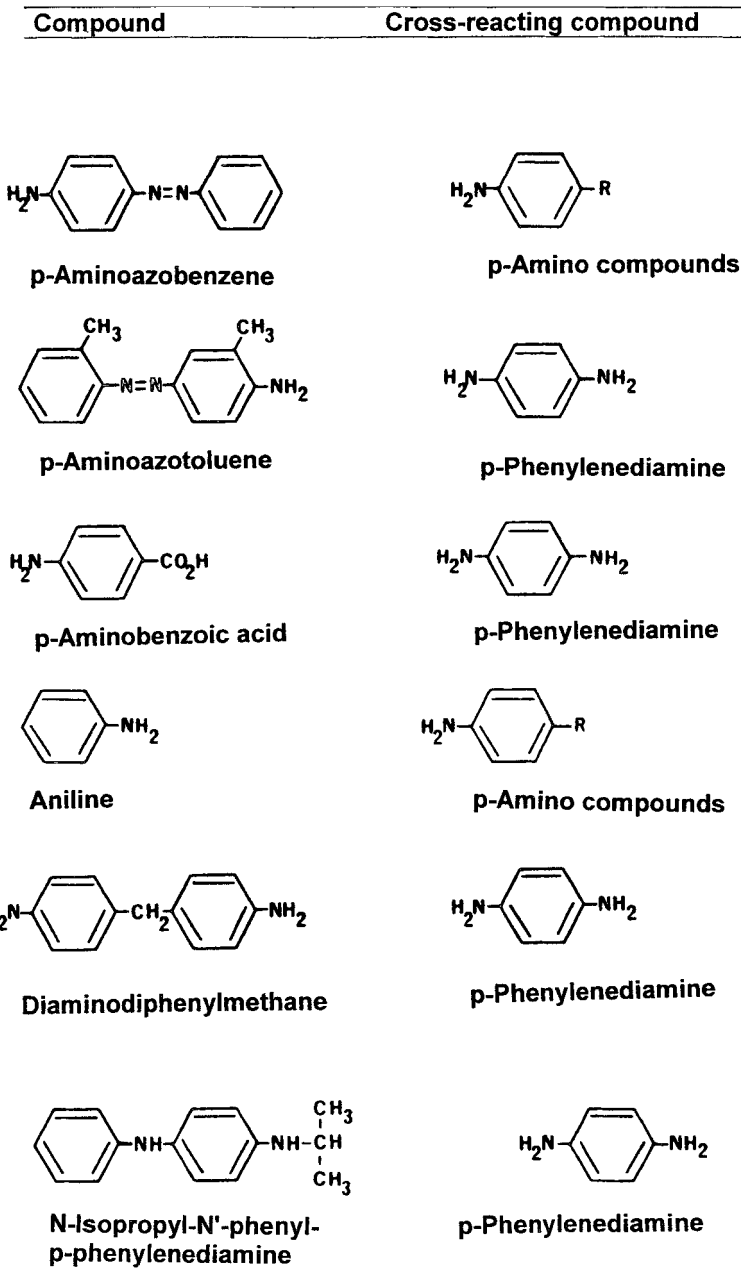

Fig. 1. Cross-reactivity between some *para*-amino compounds (see Ref. 2).

sensitizing capacity of various multifunctional acrylates, such as diacrylates and dimethacrylates, and their cross-reactivity pattern, using the guinea pig maximization test. The multifunctional acrylates are usually based on di(meth)acrylate esters of dialcohols or tri- and tetra-acrylate esters of polyalcohols. TEGDMA and EGDMA are most commonly used in dental composite resin materials. Björkner's studies (14) indicated that BUDA (1,4-butanediol diacrylate) and 1,6-hexanediol diacrylate (HDDA) were moderate to strong sensitizers and that they probably cross-react with each other (Table 4). The *n*-ethylene glycol diacrylates and dimethacrylates tested were weak or non-sensitizers. Tripropylene glycol diacrylate (TPGDA) was a moderate, and neopentyl glycol diacrylate (NPGDA) a strong, sensitizer, whereas neopentyl glycol dimethacrylate was a non-sensitizer. Of the multifunctional acrylates tested, the di- and tri-acrylic compounds were classified as potent sensitizers. The methacrylated multifunctional acrylic compounds were considered weak or non-sensitizers. Cross-reac-

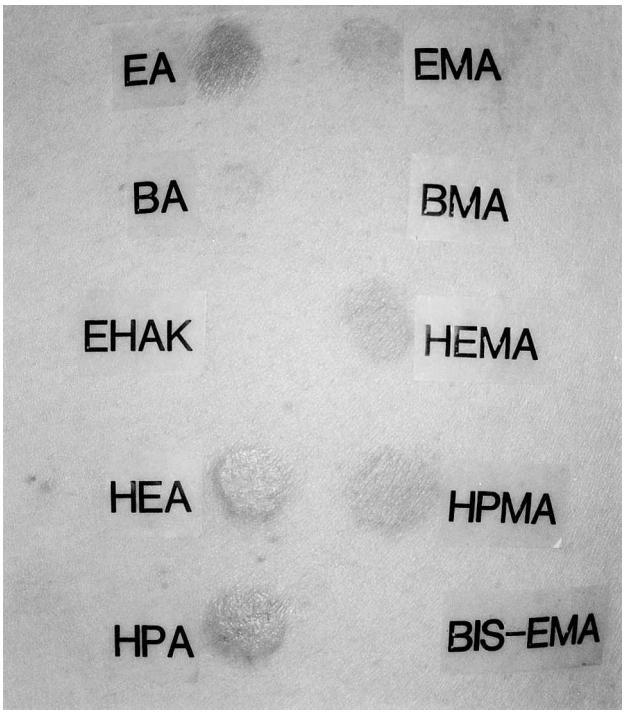

Fig. 2. Allergic patch test reactions to several (meth)acrylates: ethyl acrylate (EA), 2-hydroxyethyl acrylate (HEA), 2-hydroxypropyl acrylate (HPA), ethyl methacrylate (EMA), 2-hydroxyethyl methacrylate (HEMA), and 2-hydroxypropyl methacrylate (HPMA) show distinct allergic reactions. Butyl acrylate (BA) shows a weak (barely visible in the figure) reaction, whereas 2-ethylhexyl acrylate (EHAK), butyl methacrylate (BMA), and BIS-EMA are negative.

tions between diacrylates and dimethacrylates or between different dimethacrylates were not observed (Table 4).

Van der Walle & Bensink (15) studied the cross-reaction pattern of acrylic monomers. Animals sensitized to one monoacrylate reacted to other monoacrylates. Reactions to corresponding monomethacrylates (same alcohol group in the ester) or other monomethacrylates did not occur. Several animals sensitized to one monomethacrylate reacted to some other monomethacrylates and to monoacrylates. Very few cross-reactions between di(meth)acrylates were observed (Table 5).

Rustemeyer et al. (16, 17) used inbred guinea pigs to study sensitizing capacities and cross-reactivity patterns between four widely used acrylics: MMA, 2-HEMA, 2-hydroxypropyl methacrylate (2-HPMA), and EGDMA. Strongly positive skin tests for methacrylates could be induced in almost all guinea pigs (MMA, 26 of 26; 2-HEMA, 16 of 18; 2-HPMA, 15 of 16; and EGDMA, 11 of 11), indicating the strong sensitizing capacity of these acrylic monomers. EGDMA induced only weak or infrequent cross-reactivities, whereas 2-HEMA sensitization led to strong cross-reactions to all of the other methacrylates mentioned above. Both MMA and 2-HPMA induced strong cross-reactivity to EGDMA but only weak to moderate reactivities to the other methacrylates. The absence of strong cross-reactions with monomethacrylates in EGDMA-sensitized animals may be explained by the predominance of highly EGDMA-specific T cells in these animals. On the other hand, Rustemeyer et al. believed that sensitization to MMA, 2-HEMA, and 2-HPMA leads to recruitment of T cells cross-reactive to the other monomethacrylates, depending on molecular similarities. The strong skin hypersensitivities observed for EGDMA in these latter groups were ascribed to in vivo degradation of EGDMA into monomethacrylate compounds, notably 2-HEMA. The studies of Rustemeyer et al (16, 17) could explain many of the cross-reactions seen in humans.

It has been difficult to sensitize mice with (meth)acrylates (16). Recently, however, Hayes & Meade (18) reported that they could sensitize female B6C3F1 mice to *n*-butyl acrylate (BA), ethyl acrylate (EA), and trimethylol propane triacrylate (TMPTA), using the murine local lymph node assay (LLNA) and the mouse ear swelling test (MEST). Cross reactivity was only seen when mice were sensitized with TMPTA and challenged with BA. In these studies the LLNA was a more sensitive indicator of the allergic potential of these three acrylates than the MEST.

Human studies of cross-reactivity between epoxy diacrylates

Epoxy diacrylates, such as BIS-GMA, BIS-EMA, and urethane acrylates are widely used in dental acrylic monomers. Very little is known about the cross-reactivity of acrylic monomers, including epoxy diacrylates, in humans. We have recently reported on cross-reactivity between various epoxy diacrylates and between epoxy diacrylates and the diglycidyl ether of bisphenol A epoxy resin (DGEBA, standard epoxy) (19, 20), respectively. Thirteen patients with an allergic patch test reaction to BIS-GMA also reacted to DGEBA (Table 6). Seven of 10 patients with an allergic patch test reaction to DGEBA reacted to BIS-GMA. Four of 13 patients developed BIS-GMA allergy from dental composite resins. Six of 13 patients had apparently been sensitized to DGEBA, and no exposure to BIS-GMA was known. One patient (1 of 13) had been sensitized to 2,2-bis[4-(2-hydroxy-3-acryloyloxypropoxy)phenyl]-propane (BIS-GA). Three of 13 patients had first been sensitized to DGEBA and then concomitantly to BIS-GMA or BIS-GA. Some practical conclusions can be drawn from the above studies: to find the causative agent of ACD in patients with allergic patch test reactions to BIS-GMA and/or DGEBA, patients with an allergic patch test reaction to DGEBA should also be tested against BIS-GMA and other epoxy diacrylates, and patients with an allergic patch test reaction to epoxy diacrylates should be tested against DGEBA.

Table 2. Patch test reactions to (meth)acrylates in six patients (Pt1–Pt6). The table also shows allergic patch test reactions with the series of (meth)acrylates during a 5-year period at the Section of Dermatology, Finnish Institute of Occupational, Helsinki (6, 8). The results have been compared with the sensitizing capacity of (meth)acrylates based on animal studies (25)

(Meth)acrylate series	Abbreviation	Patch test conc. (%) (w/w)	Allergic/ tested	Allergic (%)	Ranking	Pt1	Pt2	Pt3	Pt4	Pt5	Pt6	Sensitizing capacity
Ethyl acrylate	EA	0.1–0.5	9/124	7.3	8	–	1+	–	–	3+	–	NG
Butyl acrylate	BA	0.1–0.5	6/124	4.8	10	–	2+	–	–	3+	?+	NG
2-Ethylhexyl acrylate	2-EHA	0.1–0.5	0/124	0		–	–	–	–	–	–	V
2-Hydroxyethyl acrylate	2-HEA	0.1–0.5	14/124	11.3	2	–	3+	–	–	3+	?+	NG
2-Hydroxypropyl acrylate	2-HPA	0.1–0.5	12/124	9.7	4	–	2+	–	–	3+	–	NG
Methyl methacrylate	MMA	2	8/124	6.5	9	3+	–	–	–	2+	–	NG
Ethyl methacrylate	EMA	2	6/124	4.8	10	–	–	–	–	3+	–	NG
n-Butyl methacrylate	BMA	2	2/124	1.6	17	–	–	–	–	2+	–	NG
2-Hydroxyethyl methacrylate	2-HEMA	2	13/124	10.5	3	–	1+	–	2+	3+	–	I
2-Hydroxypropyl methacrylate	2-HPMA	2	15/124	12.1	1	–	2+	–	2+	3+	–	I
Ethyleneglycol dimethacrylate	EGDMA	2	11/124	8.9	6	–	–	–	3+	2+	–	I
Triethyleneglycol dimethacrylate	TEGDMA	2	11/124	8.9	6	–	3+	–	4+	2+	3+	I
1,4-Butanediol dimethacrylate	BUDMA	2	4/124	3.2	14	–	–	–	–	1+	–	I
Urethane dimethacrylate	UEDMA	2	0/124	0		–	–	–	–	–	–	II
2,2-Bis[4-[2-methacryloyloxyethoxy)phenyl]propane	BIS-EMA	1	2/124	1.6	17	–	3+	–	–	–	–	IV
2,2-Bis[4-(methacryloyloxy)phenyl]propane	BIS-MA	2	0/124	0		–	–	–	–	–	–	V
2,2-Bis[4-(2-hydroxy-3-methacryloyloxypropoxy)phenyl]propane	BIS-GMA	2	4/124	3.2	14	4+	3+	2+	2+	–	–	I
1,4-Butanediol diacrylate	BUDA	0.1	6/124	4.8	10	–	2+	–	–	2+	2+	III–V
1,6-Hexanediol diacrylate	HDDA	0.1	5/124	4.0	13	–	2+	–	–	–	–	III–V
Diethyleneglycol diacrylate	DEGDA	0.1	6/124	4.8	10	–	3+	–	–	2+	2+	II
Tripropyleneglycol diacrylate	TPGDA	0.1	0/124	0		–	–	–	–	–	–	IV
Pentaerythritol triacrylate	PETA	0.1	2/124	1.6	17	–	–	–	–	–	–	V
Oligotriacrylate 480	OTA 480	0.1	0/124	0		–	–	–	–	–	?+	III
Epoxy diacrylate (2,2-bis[4-(2-hydroxy-3-acryloyloxypropoxy)phenyl]propane	BIS-GA	0.5	4/124	3.2	14	4+	2+	2+	2+	–	–	III–V
Urethane diacrylate (aliphatic)	al-UDA	0.1	0/124	0		–	–	–	–	–	–	V
Urethane diacrylate (aromatic)	ar-UDA	0.05	2/124	1.6	17	–	–	–	–	–	–	II
Triethyleneglycol diacrylate	TEGDA	0.1	12/124	9.7	4	–	3+	–	2+	3+	3+	I
N,N-Methylenebisacrylamide	MBAA	1	0/83	0		ND	ND	ND	ND	ND	–	NG
Tetrahydrofurfuryl methacrylate	THFMA	2	2/16	1.6	17	ND	ND	ND	MD	ND	–	NG

NG = not given; I = weak; II = mild; III = moderate; IV = strong; V = extreme sensitizing capacity according to Björkner (25).

Table 3. Identified chemicals in dental plastics according to gas chromatographic analysis. The data have been compared with the information given in the material safety data sheets (MSDS). NG = not given (see Refs. 9, 10).

Dental composite resins and bonding materials	Conc. (%)	MSDS (%)
Product 1 (adhesive of dental composite resin)		
2,2-bis[4-(2-hydroxy-3-methacryloyloxypropoxy)phenyl]propane (BIS-GMA)	7.6	NG
Triethyleneglycol dimethacrylate	24	NG
2-Hydroxyethyl methacrylate	6.8	5–9
Decamethylene dimethacrylate	1.5	NG
Diethyleneglycol dimethacrylate	0.5	NG
Ethyleneglycol dimethacrylate	0.3	NG
Ethyl ester of dimethylaminobenzoic acid	0.3	NG
Product 2 (dental filling material)		
Tricyclodecanediyldimethyl bisacrylate, two isomers	18	11–17
Methyl methacrylate	0.3	NG
Product 3 (light-cured microfiller composite resin)		
BIS-GMA	7.9	15–20
Triethyleneglycol dimethacrylate	8.3	15–20
Diethyleneglycol dimethacrylate	0.15	NG
Methyl methacrylate	0.1	NG
Tinuvin P (= 2(2-hydroxy-5-methylphenyl)benzotriazol)	0.1	NG
Product 4 (light-cured dental filling material)		
BIS-GMA	5.1	5–10
Triethyleneglycol dimethacrylate	5.5	5–10
Diethyleneglycol dimethacrylate	0.07	NG
Methyl methacrylate	0.07	NG
Dimethylaminophenethylalcohol	0.05	NG
Product 5 (light-cured adhesive)		
BIS-GMA	32	50–60
2-Hydroxyethyl methacrylate	29	40–50
Ethyleneglycol dimethacrylate	13	NG
Di- and tri-ethyleneglycol dimethacrylate	0.06	NG
Dimethylaminophenethylalcohol	0.2	<1
Product 6 (light-cured adhesive)		
BIS-GMA	57	55–65
Triethyleneglycol dimethacrylate	37	NG
Diethyleneglycol dimethacrylate	1.5	NG
Ethyleneglycol dimethacrylate	0.13	NG
Product 7 (radiopaque filling)		
BIS-GMA	14	22?
Decamethylene dimethacrylate	5.9	NG
2-Hydroxyethyl methacrylate	0.8	NG
Urethane dimethacrylate		35?
Product 8 (adhesive)		
Methyl methacrylate	0.03	NG
Product 9a (dentin primer)		
2-Hydroxyethyl methacrylate	48	30–65
Methacrylic acid	~9	<18
Ethyleneglycol dimethacrylate	0.8	NG
Methyl methacrylate	0.2	NG
Product 9b (bonding agent for composite resin)		
N-methacryloyloxyethyl-*N*-methylformamide	~20	20–30
BIS-GMA	5.5	5–10
Methacrylic compound	0.4	NG

NG = not given.

Hypothesis of cross-reactivity of methacrylates based on chemical structure

Koppula et al. (21) hypothesized that cross-reactions occur between (meth)acrylates with a carboxy ethyl side group (Fig. 3). Accordingly, they believed that diethylene glycol dimethacrylate (DGDMA), EGDMA, ethyl methacrylate (EMA), EA, TEGDMA, 2-hydroxyethyl acrylate (2-HEA), 2-HPA, 2-HEMA, 2-HPMA, triethyleneglycol diacrylate (TREGDA), tetraethylene glycol dimethacrylate (TTEGDMA), and ethyl cyanoacrylate (EACA) would cross-react. They believed that the functional group in some other acrylics, such as 1,4-butanedioldimethacrylate (N-BUDMA), I-BUDMA, BIS-GMA, BIS-EMA, BA, BUDA, and HDDA, is too hydrophobic and bulky and that it is concealed from the antigen-presenting cells, rendering these acrylics less frequently positive. MMA, trimethylol propane trimethacrylate (TMPTMA), tetrahydrofurfuryl methacrylate

Table 4. Challenge reactions and simultaneous reaction pattern in animals sensitized with di(meth)acrylates (see Ref. 14). The figures indicate the positive animals tested. For abbreviations, see Table 2

Challenged with/ sensitized to	No. of animals tested	Diacrylate (DA)							Dimethacrylate (DMA)					
		BUDA	HDDA	DEGDA	TREG-DA	TEGDA	TPGDA	NPGDA	BUDMA	HD-DMA	EGDMA	TREG-DMA	TEG-DMA	NPG-DMA
Diacrylate														
BUDA	15	10	7	3	–	0	1	0	0	–	0	–	0	–
HDDA	15	1	9	4	–	4	0	0	0	0	–	–	–	–
DEGDA	15	3	0	2	–	3	0	0	–	–	0	–	0	–
TREG-DA	19	–	–	0	0	0	0	–	–	–	–	0	–	–
TEGDA	15	0	0	0	–	0	–	0	–	–	–	–	0	–
TPGDA	14	7	0	10	–	10	11	4	–	–	0	–	0	–
NPGDA	14	8	0	11	–	10	3	14	–	–	0	–	0	0
Dimethacrylate														
BU-DMA	10	0	0	–	–	0	–	–	0	–	0	–	0	–
HD-DMA	15	0	0	0	–	0	0	–	0	0	–	–	0	–
EGDMA	13	0	0	–	–	0	–	–	0	–	0	–	0	–
TREG-DMA	15	0	0	–	0	-	–	–	0	–	0	1	–	–
TEG-DMA	15	–	–	–	–	0	–	–	–	–	0	0	0	–
NPG-DMA	15	–	–	–	–	0	–	0	–	–	–	–	0	0

Table 5. Cross-reaction pattern of acrylic monomers modified from van der Walle & Bensink (15). For abbreviations, see Table 2

Animals sensitized to	No. of animals	Diacrylates (DA)						Dimethacrylates (DMA)					
		1,2-Ethanediol-DA	1,4-Butanediol-DA	1,5-Pentanediol-DA	Neopentanediol-DA	1,6-Hexanediol-DA	Diethylene glycol DA	1,2-Ethanediol-DMA	1,4-Butanediol-DMA	1,5-Pentanediol-DMA	Neopentanediol-DMA	1,6-Hexanediol-DMA	diethylene glycol-DMA
DA													
1,2-Ethanediol-DA	2	*	–	–	–	–	–	–	–		–	–	–
1,6-Hexanediol-DA	4	–	–	++	–	*	–	+	+	–	–	+	–
DMA													
1,2-Ethanediol-DMA	2	–	–	–	–	–	–	*	–		–	–	–
1,4-Butanediol-DMA	5	–	–	–	–	–	–	–	*		–	–	–
1,5-Pentanediol-DMA	6	–	–	+	–	–	–	–	–	*	++	++	++
1,6-Hexanediol-DMA	4	–	–	–	–	–	–	–	–		+	*	–
Diethylene glycol-DMA	4	–	–	–	–	–	–	–	–	–	–	–	*

Table 6. Patch test results to epoxy di(meth)acrylates and DGEBA in 13 patients with an allergic patch test reaction from BIS-GMA (see Ref. 21).

Patient	Occupation	Patch test concentration (PET) and results				
		BIS-GMA, 2%	BIS-GA, 0.5%	BIS-EMA, 1%	BIS-MA, 2%	DGEBA, 1%
1	Dental nurse	4+*	4+*	–	–	3+*
2	Dental nurse	3+*	4+*	3+*	–	3+*
3	Dental nurse	2+*	2+*	–	–	3+*
4	Dental nurse	2+*	2+*	–	–	3+*
5	Cleaner	3+	3+	3+	–	3+
6	Mechanic	1+	2+	ND	ND	3+
7	Sales manager	2+	2+	ND	–	3+
8	Floor layer	2+	2+	2+	–	3+
9	Sales person	2+	?+	–	–	2+
10	Industrial painter	1+	1+	ND	ND	3+
11	Worker in vacuum impregnation plant	2+	2+	ND	–	3+
12	Building technician	2+	2+	ND	–	3+
13	Silk screen printer	?+	2+	–	–	3+

BIS-GMA = 2,2-bis[4-(2-hydroxy-3-methacryloyloxypropoxy)phenyl]-propane; BIS-GA = 2,2-bis[4-(2-hydroxy-3-acryloyloxypropoxy)phenyl]-propane = epoxy diacrylate; BIS-MA = 2,2-bis[4-(methacryloyloxy)phenyl]-propane; BIS-EMA = 2,2-bis[4-(2-methacryloyloxyethoxy)-phenyl]-propane; DGEBA = diglycidyl ether of bisphenol A; DCR = dental composite resin; ND = not done; PET = position emission tomography.

(THFMA), urethane dimethacrylate (UEDMA), al-urethane diacylate (al-UDA), and ar-UDA are the acrylates that do not show the functional group and would therefore not cross-react with the first-mentioned group. Our own results with regard to, for example, cross-reactivity between cyanoacrylates (EACA) and acrylic monomers (methacrylates and acrylates) were not in accordance with the above hypothesis (22). That is, in our material there is no evidence of cross-reactivity between EACA and (meth)-acrylates. It also seems feasible to assume that acrylic monomers cannot be separated into only two or three groups on the basis of their cross-reactivity.

Purity of patch test (meth)acrylates and cross-reactivity

The presence of impurities may lead to errors when

Table 7. Purity of some di- and trifunctional patch test acrylates and methacrylates determined by gas chromatography (24).

Patch test substance	Identified impurities	Relative concentration	Identification
EGDMA	1,4-Butanediol diacrylate	99	MS-EI, -CI
(ethyleneglycoldimetacrylate)		1	RS
TEGDMA	Ethyleneglycoldimethacrylate	98	MS-EI, -CI
(triethyleneglycoldimethacrylate)		2	MS-EI, -CI
BUDMA	Butanediol methacrylate-based impurity	97	MS-EI, -CI
(1,4-butanediol dimethacrylate)		1	MS-EI, -CI
BUDA	Butanediol acrylate-based impurities	89	MS-EI, -CI
(1,4-butanedioldiacrylate)	Butanediolmonoacrylate	7	MS-EI, -CI
		3	MS-EI, -CI
DEGDA	Ethyleneglycol acrylate-based impurities	91	MS-EI, -CI
(diethyleneglycoldiacrylate)	Diethyleneglycolmonoacrylate	7	MS-EI, -CI
		2	MS-EI, -CI
TRPGDA	Tripropyleneglycolmonoacrylate	81	MS-EI, -CI
(tripropyleneglycoldiacrylate)	Propyleneglycol acrylate-based impurity	13	MS-EI, -CI
		2	MS-EI, CI
TMPTA	Trimethylolpropane triacrylate adduct	86	MS-EI, -CI
(trimethylolpropane triacrylates, two peaks)	Trimethylolpropane diacrylate	3	MS-EI, -CI
		1	MS-EI, -CI
PETA-3	Pentaerythritol diacrylate	82	MS-EI, -CI
(pentaerythritol triacrylates, two peaks)	Pentaerythritol tetra-acrylates (two peaks)	8	MS-EI, -CI
	Trimethylolpropane triacrylate	5	MS-CI
		2	RS, MS-EI, CI
OTA 480	Propylene glycol acrylates (four peaks)	99	MS-EI, -CI
(oligotriacrylate)			

RS = reference substance; MS = mass spectrometry; EI = electron impact mode; CI = chemical ionization mode.

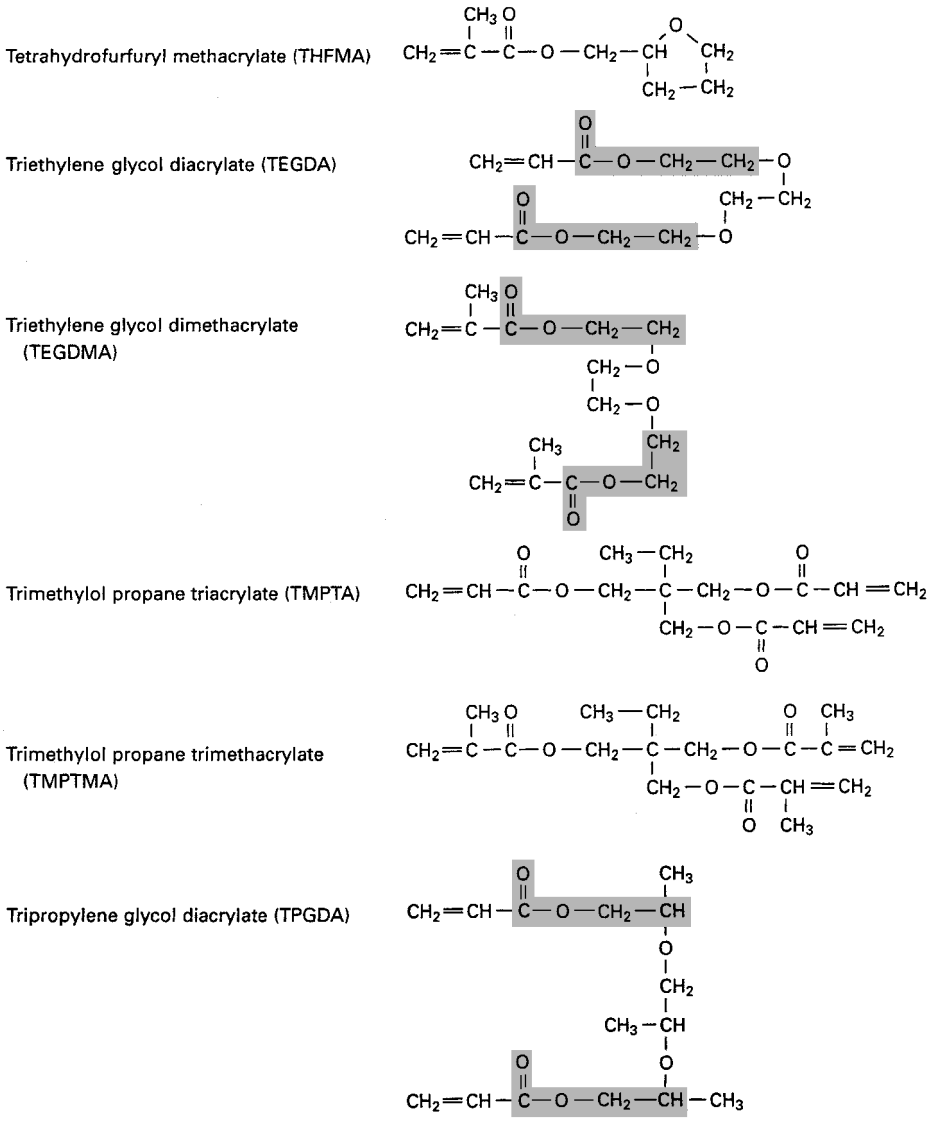

Fig. 3. According to the hypothesis of Koppula et al. (22), cross-reactions occur between (meth)acrylates with a carboxy ethyl side group, such as TEGDA, TEGDMA, and TPGDA, whereas, for example, THFMA and TMPTA do not show the functional group and therefore do not cross-react with the first-mentioned group.

drawing conclusions on cross-reactivity. The primary allergen may be an impurity of a putative allergen, or impurities that are present in patch test materials may cause chemicals to be wrongly classified as allergens.

In our studies (24) the analyzed patch test dimethacrylates were very pure (97%–99%) (Table 7). The purity of three studied diacrylates was 81%–91%, but tripropyleneglycol diacrylate (81% pure) contained as much as 13% tripropyleneglycol monoacrylate. The purities of the triacrylates were 82%–86%. All di- and tri-acrylates contained 1%–13% of the corresponding hydroxyacrylates.

Impurities may result in false interpretation of patch test results and, accordingly, incorrect diagnosis. If the patch test substance is impure, then, at the very least, the chemical impurities that can be detected by gas chromatography should be measured and reported by the manufacturer in a certificate of analysis, preferably for each batch.

Why is cross-reactivity between acrylic monomers important in dentistry?

Tens of acrylic monomers are used in dentistry (Table 2).

There is poor correlation between the frequency of patch test reactions and the sensitizing capacity of acrylic monomers in animal studies (Table 2) (8, 24). This could be caused by a much longer exposure of patients to acrylic monomers of low sensitizing capacity (for example, such as 2-HEMA (on the other hand, Rustemeyer et al. (16) considered 2-HEMA to be a strong allergen). It could also be that animal tests do not accurately predict sensitivity to acrylic monomers. When a dental patient or dental personnel become sensitized, it would be of great importance to know the dental acrylic preparations that the sensitized individual could use. Currently, there is not enough knowledge about the cross-reactivity of acrylic monomers used in dentistry to select an appropriate compound for the sensitized individual. Another important aspect is that product declarations of dental acrylic materials should show all acrylic compounds present in the products—even impurities with concentrations lower than 1%, which are currently not declared (25). If all sensitizers in a product, and their cross-reactivity, were known, then a sensitized individual could select an appropriate product. Because this is not the case, some dental workers are forced to avoid employment in the dentistry sector because of occupational ACD (6, 26). Another problem is occupational asthma from dental acrylic monomers (7). There is no information about the role of cross-reactivity in bronchial asthma caused by acrylic monomers.

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