



The Open Dentistry Journal

Content list available at: www.benthamopen.com/TODENTJ/

DOI: 10.2174/1874210601610010446



CASE REPORT

Bisphenol A Release: Survey of the Composition of Dental Composite Resins

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Received: April 6, 2016

Revised: June 15, 2016

Accepted: July 27, 2016

Abstract:

Background:

Bisphenol A (BPA) is an endocrine disruptor with potential toxicity. Composite resins may not contain pure BPA, but its derivatives are widely used. Several studies found doses of BPA or its derivatives in saliva or urine of patients after composite resin placement.

Objective:

The aims of this study were to establish an exhaustive list of composite resins marketed in Europe and their composition, and to assess the extent of BPA derivatives used.

Methods:

A research on manufacturers' websites was performed to reference all composite resins marketed in Europe, then their composition was determined from both material safety data sheets and a standardized questionnaire sent to manufacturers. Manufacturers had to indicate whether their product contained the monomers listed, add other monomers if necessary, or indicate "not disclosed".

Results:

160 composite resins were identified from 31 manufacturers and 23 manufacturers (74.2%) responded to the survey. From the survey and websites, the composition of 130 composite resins (81.2%) was: 112 (86.2%) based on BPA derivatives, 97 (74.7%) on bis-GMA, 17 (13.1%) without monomer derived from BPA (UDMA, sometimes with TEGDMA) and 6 (4.6%) with UDMA (only); 1 (0.8%) did not contain a BPA derivative or UDMA or TEGDMA. Pure BPA was never reported.

Conclusion:

This work has established a list of 18 composite resins that contain no BPA derivative. Manufacturers should be required to report the exact composition of their products as it often remains unclear or incomplete.

Keywords: Biocompatibility, Bisphenol A, Composite resin, Monomer.

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INTRODUCTION

Bisphenol A (BPA) is an organic compound used in the industrial production of polycarbonates and epoxy resins [1]. However, BPA is an endocrine disruptor, with potential toxicity *in vitro* [2] and *in vivo* [3]. Among other effects, it can cause changes in the structure of the unborn child's mammary glands - promoting further tumor development - and has effects on the brain and behavior, the female reproductive system, and metabolism and obesity [4]. Infants, young children and pregnant or lactating women are the most sensitive [5]. Thus, the manufacturing of baby bottles containing BPA has been banned by the European Union since 2011. From January 1, 2015, France has banned BPA in all food packaging. In its latest comprehensive re-evaluation of BPA exposure and toxicity, the European Food Safety Authorities has concluded no risks at actual exposure levels [6]. However, a lower Tolerable Daily Intake (TDI) has been set at 4µg/kg bw/day (ie 12.5 times less than the last TDI). Besides, its possible "low-dose effect" [7 - 9], defined as "any biological changes occurring in the range of typical human exposures, or biological changes that occur at doses below those used in traditional toxicology studies" was suspected.

Pure BPA is not a component of dental composite resins. However, derivatives of BPA - from pure BPA - are widely used: bisphenol A diglycidyl methacrylate (bis-GMA) especially, but also bisphenol A dimethacrylate (bis-DMA), polycarbonate-modified bis-GMA (PC bis-GMA), ethoxylated bisphenol A glycol dimethacrylate (bis-EMA) and 2,2-bis[4-(4-methacryloxy polyethoxy)phenyl]propane (bis-MPEPP).

Several studies have investigated the levels of BPA and its derivatives in the saliva or urine after polymerization of a restoration made of a composite resin containing at least one of these monomers. The results vary: some studies *in vitro* [10] and *in vivo* [11] have detected some levels (in very low doses) and others do not detect any [12]. This BPA elution would result from impurities in the synthesis of resins or their degradation [13]. These variations can be explained by the different susceptibility of BPA derivatives to hydrolysis by salivary esterases. Bis-GMA does not undergo this reaction, because its chemical structure with stable ether bonds prevents hydrolysis. However, bis-DMA hydrolyzes at its ester bonds, releasing an amount of BPA that is not negligible. These differences could also be related to the detection technique [14]. Furthermore, a recent study showed absorption of BPA by the sublingual area in dogs, allowing its direct entry into the bloodstream, by passing the digestive system and liver and multiplying its bioavailability by a factor of 80 [15].

Yet, the exact composition of the composite resins on the market and the potential composite resins without BPA derivatives are not known. No study has sought to identify all monomers contained in the marketed composite resins.

The objectives of this study were first, to provide an exhaustive list of the composite resins sold in Europe and detail their composition and second, to estimate the number of composite resins using BPA or BPA derivatives (bis-GMA, bis-DMA, bis-EMA, bis-MPEPP, PC bis-GMA) in their manufacturing.

MATERIALS AND METHODOLOGY

To reference all composite resins sold in Europe, a search was conducted of the manufacturers' websites. Next, the composition of the composite resins was searched on the materials' safety data sheet (MSDS) and using a standardized questionnaire sent to manufacturers. This questionnaire listed 13 monomers found in the MSDS and in the various studies of these materials; the manufacturer had to indicate, for each product, if the material contained these monomers or not, or else write "not disclosed" (ND). The manufacturer could also add monomers to the proposed list (Table 1). Manufacturers were contacted by email and/or telephone and the details were transmitted by email; they had 4 months to answer and an extra 2 months after a reminder email. When the manufacturer had not answered or the information was not available (MSDS, internet), the result was noted as "ND". All results were recorded and analyzed by using Microsoft Excel 2008, v12.3.6.

Table 1. List of the surveyed monomers (found in materials' safety data sheet and various studies of these resin composites and proposed to manufacturers) that resin composites can contain.

Monomer (abbreviation)	Monomer (detailed chemical name)
Bisphenol A	2,2-bis(4-hydroxyphényl)propane
Bis-GMA	2,2-bis[4-(3-methacryloxy-2-hydroxypropoxy)phényl]propane
PC Bis-GMA	Polycarbonate-modified bis-GMA
Bis-DMA	2,2-bis-(4-(méthacryloxy) phényl) propane
Bis-EMA or EBPADMA	Ethoxylated bisphenol-A glycol dimethacrylate

(Table 1) contd....

Monomer (abbreviation)	Monomer (detailed chemical name)
Bis-MPEPP or BPEDMA	Bisphenol A polyethoxy dimethacrylate or 2,2-bis(4-methacryloxy poly-ethoxyphenyl)propane
UDMA	Urethane dimethacrylate or 1,6-di(methacryloyloxyethylcarbamoyl)-3,3,5-trimethylhexan
TEGDMA	Triethylene glycol dimethacrylate
HEMA	Hydroxyethyl methacrylate
HEDMA	Hexane diol dimethacrylate or 2-hydroxyethyl dimethacrylate
TMPTMA	Trimethylolpropane trimethacrylate
4-MET	4-methacryloxyethyl trimellitic acid
IBMA	Isobutyl methacrylate

RESULTS

A total of 160 composite resins were identified from 31 companies (Table 2); 23 companies (74.2%) responded to the survey, with complete responses for 119/135 composite resins they marketed (88%). For the 8 manufacturers who did not respond (25.8%), the search of the internet and especially the MSDS provided responses for 11 of the 25 composite resins marketed (44%).

Table 2. List of the 160 composite resins marketed in Europe by 31 manufacturers and type of response (R) from the manufacturer (1: response; 2: partial response; 0: no response).

Fabricant	R	Composite Resins
3M ESPE	1	Filtek Bulk Fill Fluide, Filtek P60, Filtek Silorane, Filtek Supreme XTE, Filtek Supreme XTE fluide, Filtek Z250, Filtek Z500, Z100 MP
Alpha Dent	0	Alpha II AP, Alpha Flow, Alpha-Dent Light Cure, Alpha-Dent Self Cure
Apol	1	Ivoa, Ivoa flow, Xtrem nano, Sharkcomp, Sharkflow
Bisco	1	Aelite Aesthetic Enamel, Aelite All Purpose Body, Aelite LS Posterior, Aelite LS Packable, Aelite Flo, Aelite Flo LV
Cavex	1	Quadrant Anterior Shine, Quadrant Universal LC, Quadrant Flow
Centrix	1	C-R Hybrid, VersaFlo, VersaLite
Coltene Whaledent	1	Miris 2, Synergy D6, Synergy D6 Flow, Synergy Nano formula Duo Shades
Cosmedent	0	Renamel Flowable Microhybrid, Renamel Flowable Microfill, Renamel Microfill (+ superBrite), Renamel Posterior, Renamel Microhybrid (+ SuperBrite), Renamel Nano
DenMat	2	Virtuoso Flowable, Virtuoso Universal, Nuance, Nuance Flow
Dentoria	0	Flexfil
Dentsply	2	Ceram.X Duo, Ceram.X Mono +, Esthet.X HD, Esthet.X Flow, Quixfil TM, Spectrum TPH3, SDR, Surefill
Elsodent	1	Cirus, Must Flow
GC	1	EverX posterior, G-Aenial Anterior, G-Aenial posterior, G-Aenial Flow, G-Aenial Universal Flo, Kalore, Gradia Direct (X), Gradia Direct Flo, Gradia Direct LoFlo
Henry Schein	0	Natural Elegance, 20/20, Natural Elegance Flowable
Heraeus Kulzer	1	Charisma, Charisma Classic, Durafill VS, Charisma Flow, Solitaire 2, Venus, Venus Diamond, Venus Pearl, Venus Diamond flow, Venus Bulk Fill, Venus Flow
Itena	1	Reflectys, Reflectys Flow, Perfect Feel Flow
Ivoclar Vivadent	1	IPS Empress Direct, IPS Empress Direct Flow, Tetric, Tetric Ceram HB, Tetric EvoCeram, Tetric EvoCeram Bulk Fill, Tetric EvoFlow
Jeneric Pentron	1	Alert, Artiste, Flow-It ALC, Fusio Self-adhesive, Simile
Kent Dental	0	Kentfil Anterior, Kentflow, Kentfil Posterior, Microhybrid + Kent, Nanohybrid Kent Dental
Kerr Hawe	2	Herculite XRV Ultra, Herculite XRV, Point 4, Premise, Premise Flowable, Revolution 2, SonicFill, Vertise Flow (autoadhésif)
Kuraray	1	Clearfil AP-X, Clearfil Majesty ES-2, Clearfil Majesty Esthetic, Clearfil Majesty Flow, Clearfil Majesty ES Flow, Clearfil Majesty Posterior, Clearfil Photo Bright, Clearfil Photo Posterior, Clearfil Posterior 3, Clearfil F II
Micerium	1	Enamel Plus HFO, Enamel Plus HFO Flow, Enamel Plus HRi, Enamel Plus HRi Flow
Pulpdent	0	Flows-Rite
R&S	0	Nanofil, Suprafil
Saremco	1	Saremco microhybrid composite, els (extra low shrinkage)
Shofu	0	Beautifil II, Beautifil Flow, Beautifil Flow Plus
Southern Dental Industries (SDI)	2	Glacier, Ice, Rok, Wave (3 viscosities)
Sun Medical	1	Fantasia, Metafil CX, Metafil Flo
Tokuyama	1	Estelite Sigma Quick, Estelite Posterior, Estelite Asteria, Estelite Color, Estelite Flow Quick, Estelite Flow Quick High Flow, Palfique Estelite LV

(Table 2) contd....

Fabricant	R	Composite Resins
Ultradent	1	Amelogen Plus, Permaflo, Permaflo DC
Voco	2	Admira, Admira Flow, Alfacom LC, Amaris, Amaris Flow, Arabesk Flow, Arabesk, Arabesk Top, Grandio, Grandio Flow, Grandio SO, Grandio SO Flow, Grandio SO Heavy Flow, X-tra Base, X-tra fil

In total, 12 monomers were found in these 130 (119+11) composite resins; pure BPA was never reported. Table 3 reports their frequency of use.

Table 3. List of the 12 monomers contained in the surveyed composite resins (CR) and their frequency of use (among the 130 CR whose composition was established).

Monomers	Number of CR (%)
Bis-GMA	97 (74,6)
TEGDMA	79 (60, 8)
UDMA	68 (52,3)
Bis-EMA ou EBPADMA	28 (21,5)
Bis-MPEPP ou BPEDMA	10 (7,7)
HEDMA	4 (3,1)
PC Bis-GMA	3 (2,3)
TPPTMA	3 (2,3)
HEMA	2 (1,5)
Bis-DMA	1 (0,8)
4-MET	1 (0,8)
IBMA	1 (0,8)

Table 4. List of the composite resins that contain no bis-GMA, no BPA-derivative (with UDMA), or neither BPA-derivative nor UDMA.

Composite resins	Manufacturers		
Aelite Flo	Bisco	Without bis-GMA	Without bis-GMA or BPA-derivative: resin composite with UDMA * with also TEGDMA
Aelite Flo LV	Bisco		
Alert*	Jeneric Pentron		
Quixfil TM	Dentsply		
SDR	Dentsply		
Venus Bulk Fill	Heraeus Kulzer		
Venus Diamond flow	Heraeus Kulzer		
Estelite Flow Quick	Tokuyama		
G-Aenial Anterior	GC		
G-Aenial Flow	GC		
G-Aenial posterior	GC		
G-Aenial Universal Flo	GC		
Kalore	GC		
Aelite LS Packable	Bisco		
Clearfil Majesty ES Flow*	Kuraray		
Clearfil Majesty Flow*	Kuraray		
Fantasisista*	Sun Medical		
Fusio*	Jeneric Pentron		
Gradia Direct (X)	GC		
Gradia Direct Flo*	GC		
Gradia Direct LoFlo*	GC		
Metafil CX*	Sun Medical		
Perfect Feel	Itena		
Perfect Feel Flow*	Itena		
Renamel Microfill (+ superBrite)	Cosmedent		
Tetric*	Ivoclar Vivadent		
Venus Diamond	Heraeus Kulzer		
Venus Pearl	Heraeus Kulzer		
Wave (3 viscosités)	Southern Dental		
Xtrem nano	Apol		
Filtek Silorane	3M		Without BPA-derivative or UDMA

Among the 130 composite resins: 112 (86.2%) contained BPA derivatives, 97 (74.7%) bis-GMA and 43 (33.1%) bis-GMA and urethane dimethacrylate (UDMA); 17 (13.1%) contained no monomer derived from BPA (UDMA, sometimes with TEGDMA) and 6 (4.6%) with UDMA (only); 1 (0.8%) did not contain a BPA derivative or UDMA or TEGDMA (Table 4). 18 (13.8%) composite resins without any BPA derivative were identified. Among the 33 composite resins (25.4%) that did not contain bis-GMA, 24 (18.5%) did not contain bis-EMA and 18 (13.8%) did not contain bis-MPEPP. A single composite resin contained bis-DMA.

DISCUSSION

The adverse estrogenic effects of BPA are well established, which explains the new regulations banning this molecule, especially in food containers [4]. The elution of BPA sometimes detected after the making of a composite resin restoration remains far below toxic levels and at a certain time after placement, unpolymerized monomers would be completely absorbed into saliva, posing little risk of chronic low-dose BPA exposure, so some authors still encourage the use of molecules made from BPA [14, 16].

However, two factors seem to follow the recommendations against BPA content in composite resins. The first is related to the 2008 results of Bellinger *et al.* [17], who demonstrated that in children 6 to 10 years' old, the presence of composite resins was associated with a psychosocial behavior that was worse than with amalgams. These results were confirmed and clarified by Maserejian *et al.* in 2012 [18], who indicated that the psychosocial behavior was worse for children with bis-GMA than UDMA composite resin restorations. Fortunately, the last studies of this team are more reassuring concerning sealants and fluid composite resin [19] and concerning the renal function of the children [20] or their immunity markers [21]. Recently, Maserejian *et al.* [22] in 2016 showed that placement of bis-GMA-based restorations in children and adolescents may temporarily increase BPA concentration in urine, but no longer detectable 14 days or 6 months after treatment. Second, BPA may have greater effects at low than high doses. Wozniack *et al.* [23] registered effects at doses of 1 pmol. The American National Toxicology Program [24] states that these low-dose effects can occur from 0.23 mg/L. This theory remains controversial [25]. However, the European Food Safety Authority decided last year recently to divide by 10 the maximum daily dose allowed (or 5 mg/kg/day).

Moreover, exposure to BPA during gestation could induce increased spontaneous abortion, abnormal gestation time, reduced birth weight, increased male genital abnormalities, childhood obesity, but also altered behavior, disrupted neurodevelopment in children and increased asthma risk [26]. Because of these potential adverse developmental effects after prenatal exposure to BPA, it would be cautious to limit exposure to unpolymerized dental resin materials during pregnancy. Thus, it could be relevant to select composite resins that do not contain these derivatives for at-risk populations, such pregnant women [27] and as children [28].

Moreover, patients may ask about the possible bis-GMA content of composite resins. Whatever the opinion of the practitioner, he or she must know the composition of the composite resins used. In this study, 160 composite resins currently marketed by 31 manufacturers in Europe were identified. The composition of 130 (marketed by 23 manufacturers) was established: 112 (86.2%) contain BPA derivatives. Although we had a good response rate (74.2%), we could not obtain the composition of all the products because of strategic reasons, lack of reliable representatives or trade secrets.

In total, 25.8% of the manufacturers did not agree to communicate the composition of their composite resins. They are not required to indicate the exact composition of the materials, which should be required as for drugs. MSDS forms indicate the product's composition only partially, often mentioning only the family of the molecules.

However, we should be cautioned against choosing one of the 18 composite resins without BPA derivatives: the latter contain other monomers that are not necessarily more biocompatible. Indeed, BPA is not the only potentially toxic monomer in composite resins; others may be toxic [29]. In particular, the structure of TEGDMA and HEMA can be degraded by salivary esterases and result in liposoluble metabolites that could accumulate in fatty tissues [30]. Even UDMA, deemed less risky, may present some cytotoxicity beyond a certain concentration [31]. Whatever the composite resin, a certain rate of unpolymerized monomers is released, which is associated with their characteristics, the degree of polymerization and the release medium [32].

Indirect and CAD-CAM composite restorations maximize the conversion rate and thus minimize the release. Certain procedures reduce exposure to free monomers due to direct composite restorations: rubber dam use, prolonged curing (up to double the recommended time) or a second curing step after covering the restoration with glycerin. In addition, these free monomers are mostly present on the surface of the material, where the exposure to oxygen inhibits

polymerization. Hence, Rueggeberg *et al.* [33] and Komurcuoglu *et al.* [34] showed that brushing the restoration's surface with pumice allowed for removal of the inhibition layer and eliminated more than 90% of the residual monomers. Applying a dry or wet cotton roll and, to a lesser extent, water/air spray also enables their withdrawal up to 70%. Sasaki *et al.* [35] showed that gargling with warm water for 30 sec after placement of the composite resin may reduce salivary levels of BPA.

Finally, using alternative materials without resin would be ideal; some high-viscosity glass ionomers or inorganic biomaterials, carbomers (albeit with lower mechanical and aesthetic properties) or ceramic (for extended restorations) may be considered.

CONCLUSION

This study has established a list of 18 BPA derivative-free products that can be used on a daily basis by the general practitioner. The respective long-term effects on human health of the different monomers remain unclear and deserve to be the subject of cohort studies.

Manufacturers should be required to report the exact composition of their products, as is required in the pharmaceutical industry, so that practitioners are able to communicate it to patients and to meet the traceability requirements.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

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