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The toxicity of Bis-GMA, a basic monomer of the dental composite's organic matrix – a narrative review

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ABSTRACT
The long history of bisphenol A glycidyl dimethacrylate (Bis GMA) as a major component in resin-based composites is also associated with numerous reports of its toxicity. Since one of the substrates used in the production of BisGMA is bisphenol A (BPA), the question of its release from materials containing this monomer is also raised. Due to the widespread use of BisGMA in modern dentistry, the aim of this narrative review is to provide and summarize information on its toxicity based on the current literature.
It covers the chemical structure and possible synthesis pathways of BisGMA, as well as the toxicity of its substrates. The toxicity of the BisGMA monomer is also discussed, in particular its effect on pulp cells, the release of composite components in the gastrointestinal tract, and its metabolic degradation.
BisGMA and BPA are eluted from resin composites in the oral cavity. Acute toxicity is unlikely due to the small amounts of amounts eluted, but knowledge of chronic exposure is very limited. In addition, the amount of BPA released from dental materials is incomparably low, considering the environmental exposure levels in everyday life. Composite resins provide a highquality treatment that outweighs the potential complications.
Keywords: BisGMA; monomer toxicity; resin-based composite; bisphenol A; dental pulp.

INTRODUCTION

Resin-based composites (RBCs) used in modern dentistry consist of an organic matrix (based on dimethacrylates), inorganic fillers, and a number of additional compounds (silane coupling agents, polymerization initiators and accelerators, pigments, contrast agents, and others). Research on dental materials with aesthetic and mechanical properties similar to modern composites began in the 1940s. Before then, there were no clinically safe ways to use methacrylates as dental fillings. Only the development of a chemical process to cure methacrylates at room temperature led to their immediate popularity in dentistry [1]. However, clinical trials in the 1950s revealed several negative outcomes, such as discoloration, caries growth, and adverse pulp reactions due to high polymerization shrinkage and monomer leaching. In an attempt to reduce polymerization shrinkage, inorganic filler particles were added to the coldcuring methacrylate materials. Raphael Bowen revolutionized resin-based restorative chemistry by exploring the use of diglycidyl ether of bisphenol A (BADGE) mixed with silica [2]. Epoxy resins showed significantly improved strength and adhesiveness, while silica fillers reduced the thermal expansion coefficient and polymerization shrinkage. However, BADGEbased materials did not polymerize well because of the moisture present due to the hydrophilic nature of the resin. In 1963, Bowen solved this problem, adding highly hydrophobic methyl methacrylate groups, converting the epoxy resin to a dimethacrylate – bisphenol A glycidyl dimethacrylate (BisGMA) [3]. Clinical trials confirmed the good properties of the material, also known as Bowen's resin, which was patented shortly after, in 1965. The development of the BisGMA monomer and commercialization of the first resin-based dental composite (Addent, 3M) was considered a revolutionary breakthrough in restorative dentistry [4]. Over the past 60 years, RBCs have significantly improved their mechanical and aesthetic properties, making them the preferred choice for restorative procedures [5]. Despite improvements in composite composition and properties and the development of other basic monomers such as urethane dimethacrylate (UDMA) or ethoxylated bisphenol Adimethacrylate (BisEMA), BisGMA remains a widely used monomer in dental composites. The long history of BisGMA as a major component in RBCs is also associated with numerous reports of its toxicity [6, 7, 8, 9, 10]. Since one of the substrates used in the production of BisGMA is bisphenol A (BPA), the question of its release from materials containing this monomer has also been raised [11, 12, 13, 14].

Due to the widespread use of BisGMA in modern dental composites, the aim of this narrative review is to provide and summarize information on its toxicity based on the current literature. This narrative review focuses on the toxicity of BisGMA substrates, particularly BPA, and the toxicity of the monomer itself. It also presents the release of BisGMA from

dental materials and its toxicity to pulp cells, release into the gastrointestinal tract and its metabolic degradation.

A literature search was performed using a database of PubMed and Google Scholar up to April 2023. In addition, the references from already included articles and relevant reviews were searched manually. The databases were searched using the following keywords: "BisGMA", "monomer toxicity", "resin-based composite", "bisphenol A", and then combining these results using the Boolean "AND". For the keyword: "resin-based composites", the concept identification words: "composite", "dental composite" were used. These concept words were combined using the Boolean "OR". A keyword search was expanded using the growing pearl method. The following words were added: "dental pulp", "metabolic breakdown", and the results were combined using the Boolean "AND".

Eligibility criteria were articles published in English, focusing on papers investigating BisGMA derived from conventional composite materials and examining conditions corresponding to adult patients. Duplicates were screened and removed. A total of 3864 papers were identified using MeSH and keywords from 2 databases, yielding 979 results. The results were prescreened using the title and abstract, yielding a total of 56 articles. The full text of the results was then evaluated based on a quality analysis of the paper. A qualitative analysis of the publications based on checklists recommended for a given type of paper was performed by 2 researchers (MR and KLB). Only relevant papers that met >60% of the quality assessment criteria were included. The narrative review included 5 systematic reviews (quality assessment using the AMSTAR checklist), 7 randomized controlled trials (quality assessment using the Cochrane risk of bias), 7 observational studies (quality assessment using the NewcastleOttawa tool), and 15 other research studies (quality assessment using the SANRA checklist).

CHEMICAL STRUCTURE, POSSIBLE SYNTHESIS PATHWAYS OF BIS-GMA, AND TOXICITY OF REACTION SUBSTRATES

Bisphenol A glycidyl dimethacrylate is a diester derived from methacrylic acid and BADGE (Fig. 1). In his patent, Bowen published 3 distinctive synthesis pathways for BisGMA (Fig. 2) [15]:

1. In the first approach, he proposed attaching methacrylate groups to BADGE using glacial methacrylic acid and a tertiary amine as the catalyst. This method completely eliminates the use of BPA as a reagent. Following this pathway, residual BPA can only originate from the synthesis of BADGE and can thus be minimized to a few parts per million. However, if the product is not thoroughly purified, residual BADGE can cause allergic reactions [16].
2. Second, Bowen proposed condensing the sodium salt of BPA (NaBPA) with 2 equivalents of 3chloro2hydroxypropyl methacrylate – the product of the reaction of glycidyl methacrylate and anhydrous hydrochloric acid. The condensation yields sodium chloride as a byproduct, which can be removed by washing with water. This synthesis method potentially can result in high levels of contamination with BPA, if an excess of NaBPA is added or the reaction is not allowed to complete [17].
3. Finally, Bowen's preferred method was to combine 2 equivalents of glycidyl methacrylate and 1 equivalent BPA with a tertiary amine as the catalyst. The reaction is complete if the product hardens within 10 min of the addition of silicacontaining benzoyl peroxide at 90°C. While this approach was Bowen's preferred approach, he does not specify the efficiency of the synthesis. If the conversion is not complete, large amounts of residual BPA and glycidyl methacrylate remain in BisGMA.

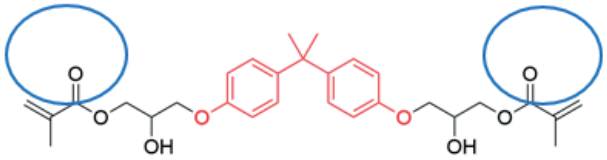

FIGURE 1. The structure of bisphenol A-glycidyl methacrylate (Bis-GMA). Chemical formula C29H36O8; molar mass 512,599 g*mol-1. It is the diester derived from methacrylic acid and bisphenol A diglycidyl ether (red part). The molecule has 2 polymerizable groups that tend to form a cross-linked polymer (reactive ends in blue circles)

One of the suggested toxicity pathways for BisGMAbased material is that it is formed from a BPA molecule [11, 13, 14]. Bisphenol A can trigger estrogenic pathways in the body due to its structural similarity to natural estrogen (17βestradiol) – Figure 3 [17]. Although BPA was tested as a potential artificial estrogen as early as the 1930s, it wasn't until the late 20th century, due to the widespread use of BPA, that the side effects of low doses of BPA on the body began to be studied [18, 19, 20, 21, 22, 23]. Studies have shown a wide repertoire of adverse health effects caused by the xenoestrogenic nature of BPA, such as increased risk of prostate, breast, and mammary cancers, organization of sexually dimorphic circuits in the hypothalamus, early onset of the estrous cycle, early puberty, regulation of body weight and genital malformation [17, 18, 19]. Bisphenol A has been shown to affect the fetus through placental exchange [20, 21]. It is also an endocrine disruptor [22, 23]. Since the contamination of BisGMA produced by the first synthesis route with BPA is negligible, this advantage has led industrial manufacturers to prefer this method. However, since it is unclear exactly which synthesis route is used for the synthesis of specific dental composites, some studies are interested in the possibility that unreacted BPA molecules may be released from the dental composite. One of the first studies describing the release of BPA from composites was the study by Fleisch et al. Bisphenol A was detectable in the saliva of children up to 3 h after insertion of the filling. According to the authors, exposure occurred mainly through contact with the composite

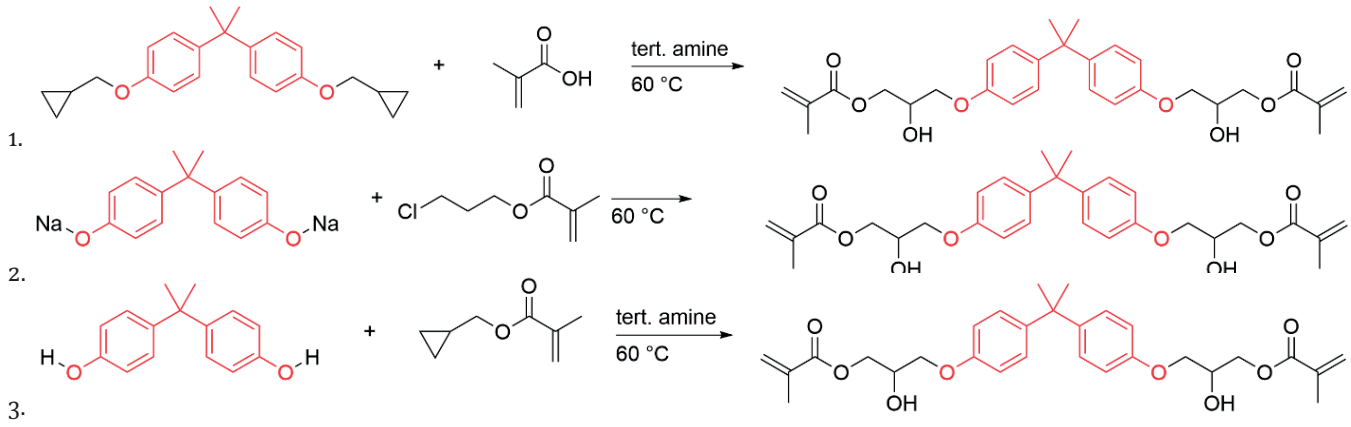

FIGURE 2. Three distinctive synthesis pathways for Bis-GMA according to Bowen's patent (description in text). The part derived from bisphenol A is shown in red

surface and can be minimized by thoroughly cleaning and rinsing the surface of the sealant and filling placement [13]. In contrast, Schmalz et al. observed no BPA release from Bis GMAbased dental materials under the conditions tested [24]. However, the found that 2,2 Bisphenol A dimetacrylate (Bis-DMA) was completely converted to BPA. It should be noted that BisDMA is rarely found in dental materials. Löfroth et al. presented the leaching of BPA from various composites [25]. In the study, all tested materials showed BPA leakage at pH 7, which increased with increasing pH. The greatest leaching of BPA was observed within the first 24 h after treatment and decreased over the next 7 days, but can still be observed after 1 year in ethanol. Most of the data were obtained from *in vitro* studies of dental materials at 37°C in water or ethanol [24, 25]. A recent metaanalysis conducted by De Angelis et al. on the constitutents released from resin-based dental materials found BPA elution in 11 of 23 qualified studies, out of a total of 81 datasets reviewed. Bisphenol A is found as an impurity in RBCs. It is insoluble in water but soluble in organic solvents such as alcohols, ethers and fats. As a result, it is more readily released in organic solvents, with elution values per volume being quite high (the weighted mean of the total cumulative release per volume of the tested specimens was 0.0577 µmol/mm^3) [26]. Considering the importance of purification of BisGMA to avoid adverse health effects, a regulatory guideline for manufacturers is needed. Some commercially available composites show detectable levels of BPA in elution tests, despite the absence of a declaration in the safety data sheet (SDS) [10, 11]. The most likely source is lowquality, insufficiently purified BisGMA used in the polymer matrix. The temporary tolerable daily intake (TDI) for BPA is 4 µg/kg/day according to the European Food Safety Authority (EFSA) [27]. The human body directly and indirectly receives approx. 30.76 ng BPA/kg per body weight per day [28]. Some studies indicate that dental resin-based materials should be considered as one of the sources of oral BPA intake [13, 14, 17, 29].

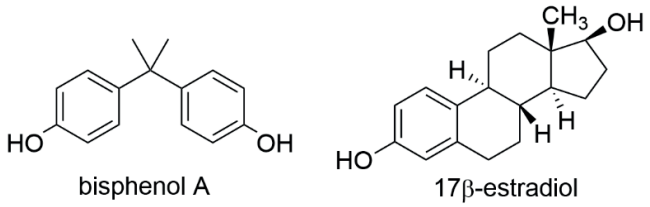

FIGURE 3. The structural pattern of bisphenol A and 17β-estradiol. Bisphenol A may trigger estrogenic pathways in the body due to the similarity of its structure (diphenyl compounds with 2 hydroxy groups in the para position) to natural estrogen (17β-estradiol)

TOXICITY OF BIS-GMA MONOMER

The systemic and local toxicity of BisGMA monomer is well-established [6, 7, 8, 18, 26]. Studies have shown that at high concentrations BisGMA can cause cellular damage and disrupt cell function [30, 31]. This can lead to cytotoxicity, genotoxicity, and even carcinogenicity in some cases [6, 7, 8]. The cytotoxicity of BisGMA has already been demonstrated in mammalian cells [31, 32]. The study by Reichl et al. evaluates the genotoxic effect of BisGMA. A slight improvement in DNA migration was observed, indicating limited genotoxicity of the monomer [33]. The study by Kleinsasser et al. showed that BisGMA is a risk factor for cancer in human salivary glands [31]. A study by Darmani and AlHiyasat found that BisGMA has a negative effect on fertility in female mice. At doses of 0.25 and 100 µg*mL^{1} for 28 days, BisGMA significantly increased the resorption rate of implantations, which increased with the dose administered. The average body weight of mice was drastically reduced and increased ovary weight was observed [34]. In contrast, Moilanen et al. found no such effect at doses of 8, 80, or 800 µg*kg^{1} for 14 days [8]. In addition, Alizadehgharib et al. demonstrated an adverse effect of BisGMA on human neutrophils in an *in vitro* study [35]. It caused an increased release of interleukin8 (IL8), which may lead to an altered inflammatory response and may be related to previously reported negative immune reactions caused by BisGMA.

The toxicity of BisGMA is dosedependent. High concentrations of BisGMA may cause toxicity and adverse effects. The value of toxic doses depends on several factors, such as route of exposure, duration of exposure, and individual susceptibility. Toxic dose estimates are based on animal studies or occupational exposure limits and may not be directly applicable to human exposure. The median lethal dose (LD50) of BisGMA via oral exposure in rats is approx. 7100 mg/kg. This means that a single dose of 7100 mg/kg BisGMA would be lethal to 50% of the rats in the study [18].

Bisphenol A glycidyl dimethacrylate may cause skin irritation and allergic contact dermatitis in some individuals, although the threshold for toxicity is not well established. Allergic skin reactions have been observed in medical staff handling the resin and in patients with BisGMA resin-based sealants [18]. Allergic reactions to BisGMA are relatively rare and typically occur in individuals who are hypersensitive to the monomer [6]. Some of the reported allergic reactions to BisGMA include:

1. contact dermatitis (redness, itching, and swelling);
2. oral lichenoid reactions (white or red lesions on the oral mucosa, tongue, and gums);
3. asthma [6, 36, 37].

The possible exposure pathways for BisGMA monomer released from dental RBCs may be:

1. oral mucosa,
2. diffusion to dental pulp via dentinal tubules, and
3. ingestion of released components in the gastrointestinal tract [18, 38].

BIS-GMA TOXICITY ON PULP CELLS

The toxic effect of monomers on pulp cells may occur during the application of liquid bonding systems as well as during chronic exposure due to the release of residual monomers after polymerization. For methodological reasons, studies on the effect of BisGMA on pulp cells are *in vitro* studies and evaluate acute reactions to the tested monomer [39, 40, 41, 42]. The observed reactions are similar to those in cells in other tissues. The *in vitro* studies by Chang et al. showed that BisGMA (>0.075 nM) induces cytotoxicity in human dental pulp fibroblasts [39]. Bisphenol A glycidyl dimethacrylate monomer may also induce cytotoxicity and prostanoid production by pulp cells, leading to pulp inflammation or necrosis via reactive oxygen species production [40]. The *in vitro* study by Schneider et al. on cultured human dental pulp cells also found monomer toxicity as BisGMA > UDMA > TEGDMA [41]. In the study, BisGMA and UDMA both depleted glutathione and inhibited cystine uptake, leading to oxidative stress and cell death. However, the study by Aranha et al. showed that the toxic effect of the resin on the odontoblastlike MDPC23 cells can be reduced by photopolymerization and shortening the contact time of the unpolymerized material with dentin and pulp cells [42]. To date, no studies have evaluated the chronic effect of released residual monomers on pulp cells.

RELEASE OF BIS-GMA MONOMER INTO THE GASTROINTESTINAL TRACT AND ITS METABOLIC BREAKDOWN

Both BisGMA and BPA are released from dental composites due by elution of free monomers [9, 10, 11, 26, 27, 38]. The amount of monomer leached depends on the degree of monomerto polymer conversion of the material. Incomplete polymerization of dental composites results from the propagation of the crosslinking reaction, which drastically reduces the mobility of the monomers. As a result, solvent molecules penetrate the cured polymer matrix and cause swelling of the micropores, widening them and allowing residual, unbound monomers and other impurities to leach out of the material. According to the metaanalysis by De Angelis et al., BisGMA residual monomer showed the lowest release (per volume and per surface area) of resin matrix monomers, regardless of the solvent used [26]. This is probably related to the high molecular weight of the BisGMA monomer and its limited solubility. The sequence of monomer release from RBCs corresponds to the order of their cytotoxic potential: HEMA < TEGDMA < UDMA < BisGMA [33]. Human gingival fibroblasts showed a 50% reduction in cell viability after exposure to Bis GMA at a concentration of 0.087 mmol/L [33]. According to elution studies, various composite samples immersed in 75% ethanol (recommended by Food and Drug Administration for simulating oral conditions) [43] release a detectable amount of either BisGMA or both BisGMA and BPA. The process mostly takes place shortly after immersion and decreases with time, with 90% of the elution occurring within the first 24 h to 7 days [44]. According to the metaanalysis by De Angelis et al., the weighted means for the BisGMA release measurements collected at 24 h and for the total cumulative release per surface area of RBCs specimens (μmol/mm^2), were 0.0122 and 0.0281, respectively, in water-based incubation solution, and 0.1431 and 0.1544, respectively, in organic incubation solution [26]. The measured concentrations are several times lower than the noobservedadverseeffect level (NOAEL) for BisGMA or BPA (NOAEL = 5 mg/kg body weight/day) [45]. While the acute toxicity of BisGMA has been well studied, the influence of chronic exposure to very low doses of this monomer has not been extensively investigated.

Research on the metabolic degradation of BisGMA is very limited, despite its widespread use in dentistry. Over time, dental composites wear out and the worn products are ingested, raising concerns about their degradation in the body. While most studies focus on the acute toxicity of the wear products, there are much fewer studies on their metabolic pathways [46, 47, 48, 49, 50, 51, 52]. The main concern hereby is the possible degradation of BisGMA to its precursor, BPA.

Nonspecific esterases and human salivaderived esterases (HSDE) can degrade composites by hydrolyzing their ester groups over time. In a study by Munksgaard and Freund, methacrylic acid was found to be a degradation byproduct when various dental resins were incubated with porcine liver esterase [46]. Of the materials tested (HPMA – 2Hydroxyethyl methacrylate, BisGMA, LAMA – Lauryl methacrylate, DECMA – Diethyl fumarate mathacrylate, TEGDMA – Triethylene glycol dimethacrylate,

UEDMA – Urethane dimethacrylate, DEGDMA – Diethylene glycol dimethacrylate) BisGMA samples showed the least amount of methacrylic acid. A possible explanation for this could be steric hindrance at the ester group caused by the nearby hydroxy group, which prevents the enzyme from reaching it well. However, the study did not confirm whether BPA was formed in the process. Similarly, Burmaster et al. found that BisGMA was stable *in vitro* in an aqueous medium, but was rapidly metabolized by rat plasma to bisphenol A bis(2.3dihydroxypropyl) ether (BisHPPP), the tetrahydroxylated metabolite [47]. No degradation products other than the tetrahydroxy metabolite, including BPA, were found after exposure to hepatic S9 fractions [48]. Vervliet et al. investigated the *in vitro* metabolism of BisGMA using human liver microsomes (HLM). When incubated in HLM, BisGMA is rapidly hydrolyzed to BisHPPP – Figure 4. This metabolite was then either oxidized to the corresponding carboxylic acid or further hydroxylated on 1 dihydroxypropyl moiety. Bisphenol A bis(2.3dihydroxypropyl) ether is the major product, followed by bisphenol A (2.3dihydroxypropyl) glycidyl ether and bisphenol A (3chloro2hydroxypropyl; 2.3dihydroxypropyl) ether. All 3 are excreted in urine as free metabolites and as conjugates with sulfate and glucuronide [49]. While BisGMA shows weak antiestrogenic activity, BisHPPP has neither an (anti)estrogenic nor (anti)androgenic activity [50]. Furthermore, Santerre et al. have shown that cholesterol esterase also degrades BisGMA into BisHPPP [51]. This degradation is also observed for other HSDEs [52]. In both cases, polymerized composite material samples were incubated with the respective enzyme. After 180 days in HSDE, the samples showed significantly reduced fracture toughness, suggesting that the degradation process is clinically relevant and compromises the integrity of dental restorations over time. Current research does not indicate that BPA is formed during the metabolism of BisGMA [46, 47, 48, 49, 50, 51, 52]. The major product of enzymatic hydrolysis of BisGMA is BisHPPP. Furthermore, degradation to BPA does not occur under human oral conditions. However, it has been found in samples of other materials. In particular, BisDMA and 2,2Bisphenol A dimethacrylate (BisPMA) have been shown to be susceptible to such degradation. The study by Vervliet et al. study suggests that UDMA in a polymer matrix reduces the susceptibility of polar groups to hydrolysis by formating hydrogenbonded structures. This greatly reduces the availability of the enzyme to the cleavage site [49].

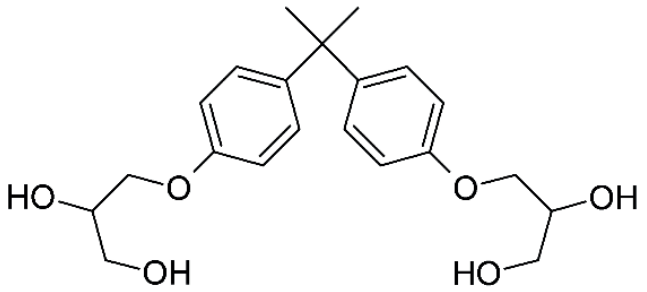

FIGURE 4. The structural pattern of the bisphenol A bis-(2,3-dihydroxypropyl) ether (Bis-HPPP). Structurally, it is a diether of bisphenol A, although no further degradation is observed under *in vivo* conditions

CONCLUSION

Since its introduction, BisGMA has played an important role in dentistry, despite its adverse effects on the human body. The papers included in this narrative review demonstrate that BisGMA and BPA are released from composite materials in the oral cavity. Acute toxicity is unlikely due to the small amounts released, but knowledge of chronic exposure is very limited. In addition, the amount of BPA released from dental materials is very low when compared to environmental exposure levels in everyday life. Composite resins provide a highquality treatment that outweighs any potential complications.

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