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Literature Review

Dental Materials and Bisphenol-A Exposures

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ABSTRACT

The utility of dental materials to posing oral diseases have impact in the risk of Bisphenol A (BPA) exposure which can be harmful to human organs. BPA used in dentistry is related to the production of polycarbonate plastics and epoxy resins. For instance, composite filling materials and dental sealant are containing BPA that can promote risk to endocrine-disrupting, estrogenic effect, and renal exposure. The current study reviews the BPA exposures of dental materials and its impact risk to the systemic health. This systematic review critically evaluates data and gathers information from several literatures. The source of these articles was Pub Med and Web of Science, and the search was done by the following terms: BPA of dental materials, BPA exposure, BPA and health risks, BPA and oral health. BPA exposure was found in oral mucosa and saliva after the application of BPA-containing dental materials. BPA derivatives used in dental products have not been evaluated for the endocrine disruptor, and estrogenicity. BPA exposures can be absorbed through the oral mucosa and may lead to internal exposures by the absorption of BPA from the gastrointestinal tract. Manufacturers should be required to report complete information of the dental materials' chemical composition and strict precaution application techniques must be considered by the practitioner.

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INTRODUCTION

Bisphenol-A (BPA), is one of the chemicals known as the endocrine disruptor that can affect various biological processes in the body.[1] Several studies have shown the negative impact of BPA which has an impact on health problems, such as, reproductions, cancer, diabetes, and other metabolic problems.[1-7]

Frequent BPA exposure may increase contribution to the health problems of the people who often interact with BPA-releasing materials. Currently, the use of materials containing BPA and BPA derivatives is increasing in dental practice, especially in preventive oral health care and dental restoration treatments. In addition, the use of composite resin filling as the replacement of amalgam filling (due to the toxic effect of amalgam) and higher demand of aesthetic restoration in dental fillings are the enhancement factors of the popularity of resin-based materials.

Meanwhile, dental practitioners believe that resin composite is better than amalgam and provide better esthetical results than other filling materials[8], yet the possible negative effects should not be denied as the main concern is its contribution of BPA exposure to the human body. The BPA content in dental materials is mainly BPA-derivatives.[1] However, there is still presence possibility of BPA exposure to the human body. Therefore, studies about the possibility of side effects that can be generated from BPA-containing dental materials to human health are needed. This systematic review will give an idea of the contribution of dental materials on BPA exposure to human body.

METHODS

This systematic review critically evaluates and gathers information from several literatures. The source of these articles was Pub Med and Web of Science, the search was done by the following terms: BPA of dental materials, BPA exposure, BPA and health risks, BPA and oral health.

BISPHENOL-A

Bisphenol-A (4.4'-isopropylidene-2-diphenol) is known as plasticizer materials in the manufacturing process of polycarbonate plastics and epoxy resins (Figure 1). BPA is composed of carbon bridging which has two unsaturated phenolic rings.[9] BPA is a synthetic chemical formed by the condensation of the phenol group and one molecule of acetone. BPA was first synthesized in 1891, and its estrogenic effect was known since 1938. Since 1940 BPA was used in the polymer manufacturing companies as monomers such as polycarbonate, epoxy resin, polysulfone or polyacrylate.[10]

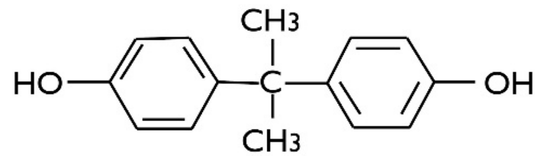

Figure 1. Chemical structure of Bisphenol-A

STATE OF THE ART: CURRENT DENTAL MATERIALS AND BISPHENOL-A

In dentistry, the commonly used BPA is BPA-derivatives that are used as monomers in dental materials manufacturing. A variety of dental materials containing BPA components have been collected from various literatures as illustrated in Table 1.

Table 1. BPA components in dental materials

Dental Materials	BPA Component
Composite Dental Filling	diglycidyl ether methacrylate (bis-GMA)[11]
	triethylene glycol dimethacrylate (TEGDMA)[1] ethoxylated bisphenol-A dimethacrylate (bis-EMA)[1] dimethacrylate (bis-DMA)[1]
Orthodontic Adhesives	diglycidyl ether methacrylate (bis-GMA)[12] hydroxyethyl-methacrylate (HEMA)[12]
Fissure Sealant	diglycidyl ether methacrylate (bis-GMA)[1] urethane-modified bis-GMA dimethacrylate[1]

BPA derivatives in dental resins are solid materials from liquid monomers that is maximally polymerized by using light curing or chemically. The most frequently used BPA-derivative as resin base is glycidyl dimethacrylate (bis-GMA). The hydroxyl groups of BPA are bonded to the methyl methacrylate groups by using a glycidyl spacer.[1]

Other monomer used in resin-based dental materials include BPA dimethacrylate (bis-DMA), BPA diglycidylether (BADGE), BPA ethoxylate dimethacrylate (bis-EMA) and urethane-modified bis-GMA. (Figure 2) Other monomers are used to increase viscosity of the resin include triethylene glycol dimethacrylate (TEGDMA) and urethane dimethacrylate (UDMA).[13]

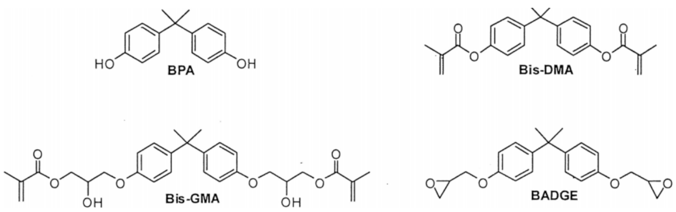

Figure 2. Chemical structures of BPA and BPA derivatives

The selling composites and sealants (Tables 2 and 3) did not include the specific monomer compositions of their resins in the material safety data sheets (MSDS). Some manufacturers that provide product composition data often use unexamined unique monomers of their estrogenic effects, e.g., urethane modified or merely listing generic names of monomers used.[1]

METABOLISM OF BISPHENOL-A

Metabolism of BPA begins after oral phase; the first metabolic phase in the gastrointestinal tract and liver. Once absorbed completely in the gastrointestinal tract, BPA will be conjugated with glucuronic acid in the liver to become an inactive form. A small percentage of BPA reacts with sulphate to form BPA-sulphate. Conjugated BPA will undergo a process of detoxification, and the BPA-free form indicates estrogenic properties. The conjugated BPA forms into the circulation, reaches the kidneys and is excreted in the urine.[35,36,37]

Inhaled BPA, through mucosa or dermal contacts will not pass metabolism in gastrointestinal tract and liver, will be eliminated slowly, so that it will produce concentrations in the blood greater than the hepatic BPA.[38]

BPA exhibits estrogenic properties in many studies and is described as Endocrine Distrupting Chemicals (EDC).[39] This compound specifically binds and activates estrogen receptors with an affinity capacity 1000-5000 times weaker than endogenous estradiol.[40] In vitro BPA shows an effect of about 1000-10,000 times weaker than estradiol.[41] However, in vivo experiments show that BPA has an equally strong effect over estradiol, presumably due to non-genomic activation.[42,43]

Sakurai, *et al*.[44], exhibits that BPA not only works through endoplasmic reticulum (ER) membrane alone but is also suspected through nuclear receptors. BPA is also suspected to work through non-classical membrane ER (ncmER).[45,46] In addition, BPA interacts with thyroid hormone receptors, and Peroxysome Proliferator-Activated Receptor Gamma (PPARγ).[41]

WHO WILL BE AFFECTED?

The U.S. Environmental Protection Agency (U.S. EPA) provides safe BPA levels within the body of 50µg/kg/day. This range is used as a reference because it is the minimum amount of BPA exposure that does not cause any impact to the body.[47]

In dental practice, the use of a substance (e.g., composite) containing BPA or BPA derivatives may have an adverse effect on the person exposed to the substance, including (i) the patients, dental materials applied directly to the human tissue may release the BPA compound; (ii) dental practitioners (dentists, nurses, and dental technicians), may be exposed to residual monomers containing BPA during dental care and dental manufacturing process.[48-49] Nevertheless, there have been no studies that directly calculate the amount of BPA exposure associated with the use of BPA-contained dental materials, such as composite resin and sealant.

PROBLEM CAUSED BY BISPHENOL-A

BPA as an Endocrine Disrupting Compounds/ Chemicals (EDC) is a substance present in dental materials that can interfere with biosynthesis, metabolism, and hormonal action, which may lead to homeostatic or reproductive disorders.[41] An estrogenic toxin from BPA has a potential to cause disease (Table 4).

Table 4. Potential disorders caused by BPA

Potential Disorders	Effect	Cause
Reproduction[1,2]	Growth, functioning, and differentiation of the reproductive systems in male/female	Xenoestrogen mimics the structure and function of estrogen hormone
Cancer[2,3]	Increase the risk of protein mutations	Higher rate of mRNA leads overproduction of protein
Obesity[2,4]	Unmetabolized BPA remains attached to plasma proteins interact with biological process	Unconjugated BPA converted to BPA-Sulfate
Heart Disease[5]	Diabetes and dyslipidemia as risk factors of heart disease	Lipid accumulation (adipocytes, hepatoma cell)
Hypertension[6,7]	Obesity and diabetic	Insulin resistance, thyroid, and endothelial dysfunction
Diabetes[1,3]	Hyperinsulinemia, worsening glucose tolerance, and decreased insulin sensitivity	Insulin resistance caused by BPA inductions

Table 2. The monomer compositions in MSDS data of dental sealants

Manufacturer	Dental Selant	Clinical Application	MSDS Monomer Composition	Hazard statements	Reference No.
Ultradent	UltraSeal XT™ plus	Pit and fissure sealant	Bis-GMA (CAS No. 1565-94-2); diurethane dimethacrylate (CAS No. 41137-60-4);	Allergic skin reaction, rash/ skin irritation, if the dust inhaled lead unconsciousness	14
Ultradent	Permaseal®	Composite sealant	Bis-GMA (CAS No. 1565-94-2); Triethylene Glycol Dimethacrylate (CAS No. 109-16-0); 2-dimethylaminoethyl Methacrylate (CAS No. 2867-47-2)	Irritating, eyes, respiratory system, ingestion, and skin	15
Ultradent	Opal™ Seal™	Orthodontic Primer & Sealant	Hydroxypropyl Methacrylate (CAS No. 27813-02-1); Methacrylic Acid (CAS No. 79-41-4)	Severe skin burns and eye damage, respiratory irritation	16
3M ESPE	Clinpro Sealant	Dental sealant	Bis-GMA (CAS No. 1565-94-2); TEGDMA (CAS No. 109-16-0)	Eye irritation, allergic skin reaction, toxicological effects	17
Dentsply Preventive Care	Delton	Pit and fissure sealant	Aromatic and aliphatic dimethacrylate monomers; ethyl 4-dimethylaminobenzoate (CAS No. 10287-53-3)	Skin, eyes, and respiratory irritation, causing genetic defects	18
Dentsply Milford	FluroShield®	Pit and fissure sealant	Urethane-modified bis-GMA dimethacrylate (CAS No. 126646-17-1); Bis-GMA (CAS No. 1565-94-2)	Mucosa, skin, and eyes irritation	19
Pulpdent Corporation	Embrace™	Pit and fissure sealant	Uncured acrylate ester monomers (Proprietary)	Eyes, respiratory system, skin irritation or skin sensitization	20
Pulpdent Corporation	Seal-Rite™ Pit and Fissure Sealant	Pit and fissure sealant	Uncured acrylate ester monomers (Proprietary)	Eyes, respiratory system, skin irritation or skin sensitization	21
Kerr Corporation	OptiGuard	Surface sealant	2,2'-ethylenedioxydiethyl dimethacrylate (CAS No. 109-16-0)	Eyes, skin, respiratory irritation	22
Ivoclar	Helioseal F	Fissure sealant	Bis-GMA (CAS No. 1565-94-2); TEGDMA (CAS No. 109-16-0); urethane dimethacrylate CAS No. 72869-86-4)	Skin, eyes, respiratory irritation, allergic skin reaction, carcinogenic.	23

*CAS: Chemical Abstracts Service

Table 3. The monomer compositions in MSDS data of dental composites

Manufacturer	Dental Composite	Clinical Application	MSDS Monomer Composition	Hazard statements	Reference No.
3M ESPE	3M™ Filtek™ Supreme Ultra Universal Restorative	Nanocomposite esthetics and strength universal restoration	BPA ethoxylate dimethacrylate (CAS No. 41637-38-1); diurethane dimethacrylate (CAS No. 72869-86-4); bis-GMA (CAS No. 1565-94-2); TEGDMA (CAS No. 109-16-0)	Allergic skin reaction	24
3M ESPE	3M™ Filtek™ Supreme Flowable Restorative	Composite restorative material	Bis-GMA (CAS No. 1565-94-2); TEGDMA (CAS No. 109-16-0); BPA ethoxylate dimethacrylate (CAS No. 41637-38-1)	Allergic skin reaction, damage fertility or the unborn child	25
3M ESPE	Filtek™ Z250	Microhybrid universal composite restoration	BPA ethoxylate dimethacrylate (CAS No. 41637-38-1); diurethane dimethacrylate (CAS No. 72869-86-4); bis-GMA (CAS No. 1565-94-2); TEGDMA (CAS No. 109-16-0)	Allergic skin reaction, reproductive toxicity	26
3M ESPE	Filtek™ Z100	Microhybrid universal composite restoration	Bis-GMA (CAS No. 1565-94-2); TEGDMA (CAS No. 109-16-0)	Eye irritation, allergic skin reaction	27
3M ESPE	Filtek™ One Bulk Fill	Nanocomposite bulk fill posterior restoration	Aromatic Urethane Dimethacrylate (CAS No. 1431303-59-1); UDMA (CAS No. 72869-86-4)	Allergic skin reaction, reproductive toxicity	28
Dentsply Sirona Pty Ltd	TPH 3Spectra	Universal composite restoration	Urethane-modified bis-GMA dimethacrylate (CAS No. 126646-17-1); polymerizable dimethacrylate resin (CAS-109-16-0 and 24448-20-2)	Allergic skin reaction	
Dentsply Sirona Pty Ltd	Esthet-X® HD	Micro matrix universal restoration	Urethane-modified bis-GMA dimethacrylate (CAS No. 126646-17-1)	Skin irritation	29
Kerr Corporation	Premise Indirect	Low shrinkage flowable composite	Uncured methacrylate ester monomers (CAS No. 109-16-0)	Eyes, skin, respiratory irritation	30
Kerr Corporation	Herculite XR	Microhybrid universal restoration	Uncured methacrylate ester monomers (CAS No. 109-16-0)	Eyes, skin, respiratory irritation	31
Ultradent	Vit-l-escence™	Esthetic restorative material	Tetramethylene Dimethacrylate (CAS No. 2082-81-7)	Allergic skin reaction	32
Ultradent	Composite wetting resin	Dental liquid resin	Triethylene Glycol Dimethacrylate (CAS No. 109-16-0); Diurethane Dimethacrylate (CAS No. 72869-86-4)	Allergic skin reaction	33

*CAS: Chemical Abstracts Service

BISPHENOL-A EXPOSURES IN HUMAN SALIVA

However, the component of resin-based dental materials is not pure BPA, De Nys, et al.[48] and Lopes-Rocha, et al.[49] found that after dental resin placement, BPA were detected in saliva due to the hydrolysis of bis-DMA.

Over the years, various studies have shown mixed results on the evaluation of BPA, bis-GMA, and bis-DMA content in saliva after the application of dental composites and sealants. In vitro studies showed BPA and BPA derivatives were detected in saliva.[49,50] These results in line with numerous in vivo studies that tested the BPA and BPA derivatives content in saliva.[48,51,52] Nevertheless, some studies detect the BPA decreased in saliva after placement of dental sealants during several weeks observation period.[53,54]

Study conducted by Joskow, *et al.*[52] showed that mean BPA level in the saliva after sealants application which contained bis-DMA 26.5 ng/mL immediately after treatment and decreased 1 hour after treatment with 5.12 ng/mL mean BPA level. BPA exposure found in oral mucosa and saliva after the application of BPA-containing dental materials. BPA derivatives used in dental products have not been evaluated for the endocrine disruptor, estrogenicity.

RECOMMENDED APPLICATION TECHNIQUES

According to the results of various studies showing the amount of BPA contained in saliva after dental material application are significantly below from the maximum tolerance level of acceptable BPA exposure in the human body. Nevertheless, prevention to a minimum BPA exposure should still be an essential concern. The best way to solve this problem as a user is to put more concern in how the safe application techniques that recommended for BPA-related dental materials.

Product Choice

Product selection is necessary, especially related to monomer content of dental materials. Users should pay attention to the data provided by the manufacturer regarding the estrogenicity effects of monomers that are corresponding to the various studies conducted.

The current limitation of this point is the combination of bis-GMA with other monomers which used by manufacturers that potentially have estrogenicity effect, such as urethane-modified bis-GMA. The combination of these monomers is still in question, regarding the effect of BPA exposure that can be affected due to it has not been well tested by toxicological testing.[1] The manufacturer is mandatory to provide appropriate information in the material safety data sheets (MSDS) for each manufactured product, so that dentists and other users can easily determine the type of considerably safe dental materials.

Resin Application

Fleisch, et al.[1] recommended the application technique as a precaution to the BPA exposure. This technique basically refers to the residual monomer removal, including (i) using cotton roll with pumice to rub the monomer layer, (ii) gargling for 30 seconds and spitting after resin-based dental materials application, (iii) rinsing with water syringe on the operative field, and (iv) using rubber dam to limit the potential exposure of BPA to the other area. Regarding the sensitivity effect of foetus to BPA and other developmental prenatal effect due to BPA exposure, it is recommended to minimize and control the use of resin-based dental materials during pregnancy.[55,56]

Additional Study

Preliminary requirement of the research is to assess the estrogenicity and BPA absorption to body fluids (e.g., saliva, urine, blood) of the all-current resin-based dental products. Additional studies are also demanding for the further observation on the concentration of BPA exposure to the saliva through clinical procedures.

Product Development

The development of BPA-free-based dental materials should be the priority in the product manufacturing. Furthermore, the alternatives of BPA-used should be guaranteed to be safe and biocompatible by toxicological testing during the dental materials development.

CONCLUSION

The contribution of dental materials to the BPA exposure seems uncertain, yet it potentially can be controlled. Several findings have shown the adverse effects of BPA exposure to humans, yet these can be used as reference to the safe application on BPA-related dental materials to minimize BPA exposure as the effect precaution on the human health. The described precaution techniques should be a primary consideration to reduce BPA exposures during resin-based dental materials applications.

Manufacturers have to report complete information on the chemical composition of dental materials and strict precaution application techniques must be considered by the practitioner.

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