TRABAJO DE FIN DE GRADO

Grado en Odontología

BISPHENOL A IN DENTAL MATERIALS

Madrid, curso 2020-2021

Número identificativo 169

ABSTRACT

Objective: Through search, the literature and understanding the release of bisphenol-A (BPA) during treatment with the dental material, Further, would like to discuss whether it is possible to manage it to a greater extent to promote patient safety.

Methodology: By searching information in PubMed, Google scholar, and the library of Universidad Europea de Madrid, with a limit placed over the last 10 years, in English, and Spanish.

Keywords: bisphenol a, dentistry, dental restoration materials, orthodontics, endodontics and patient safety.

Results: A total of 16 studies were using. In saliva, the BPA release is increased the initial 5 min to I hour, with dental material placement show in most studies. Then BPA decreases after 24 hours of dental material placement. In urine, BPA release was detected 24 hours after placement. Ultimately, after 30 days, BPA will return to the level prior to placement of the dental material. In Blood before and after treatment in adults, no BPA has been detected in the blood serum.

Conclusion: 1. According to these studies, Bisphenol-A will release: After dental material (orthodontic adhesive; composite resin; endodontic cement) placement in 30 min. Greater light-curing tip distances. Show up of the oxygen inhibited layer of composite. The number of the composite surface to be placed is positively correlated with BPA release. 2. As dentists, protect patients' safety as far as possible without affecting dental treatment. Certain measures can be taken to reduce the release of BPA in the clinical setting, for example, use of rubber dams, immediate polishing of all resins used to avoid uncured layer formulation and rinsing of the mouth after handling. Also, a preventive measure is to use a minimum number of restorers or sealants in each appointment.

RESUMEN

Objetivo: A través de la búsqueda, la literatura y la comprensión de la liberación de bisfenol-A (BPA) durante el tratamiento con el material dental, Además, le gustaría discutir si es posible gestionar en mayor medida para promover la seguridad del paciente.

Metodología: Mediante la búsqueda de información en PubMed, Google scholar, y la biblioteca de la Universidad Europea de Madrid, con un límite puesto en los últimos 10 años, en inglés, y español.

Palabras clave: bisfenol a, odontología, materiales de restauración dental, ortodoncia, endodoncia y seguridad del paciente.

Resultados: Se utilizaron un total de 16 estudios. En la saliva, la liberación de BPA se incrementa la 5 min a I hora inicial, con la colocación de material dental muestran en la mayoría de los estudios. A continuación, el BPA disminuye después de 24 horas de la colocación del material dental. En la orina, la liberación de BPA se detectó 24 horas después de la colocación. Finalmente, después de 30 días, el BPA vuelve al nivel anterior a la colocación del material dental. En la sangre antes y después del tratamiento en adultos, no se ha detectado BPA en el suero sanguíneo.

Conclusión: 1. Según estos estudios, el Bisfenol-A se liberará: Tras la colocación de material dental (adhesivo ortodóntico; resina compuesta; cemento endodóntico) en 30 min. Mayores distancias de la punta de fotopolimerización. Aparición de la capa de composite inhibida por el oxígeno. El número de la superficie de composite a colocar se correlaciona positivamente con la liberación de BPA. 2. Como dentistas, proteger la seguridad de los pacientes en la medida de lo posible sin afectar al tratamiento dental. Se pueden tomar ciertas medidas para reducir la liberación de BPA en el entorno clínico, por ejemplo, el uso de diques de goma, el pulido inmediato de todas las resinas utilizadas para evitar la formulación de capas no curadas y el enjuague de la boca después de la manipulación. Asimismo, una medida preventiva es utilizar un número mínimo de restauradores o selladores en cada cita.

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INTRODUCTION

Bisphenol A (BPA) is an organic synthetic compound that is a derivative of diphenylmethane, and bisphenol industrial chemicals used in the manufacture of polycarbonate plastics. It is widely used in the manufacture of certain plastics and resins, such as water, food and beverage containers, household items, kitchen utensils and medical equipment, that can seep into food and water when we intake food and then into our body (1,2). But also, BPA can be excreted through the urine, blood, and sweat of almost all adults and children. Stephen et al. (2012) collected 20 personals include 10 healthy people and 10 patients with health problems, to study the BPA excretion in blood, urine, sweat. BPA was found to be released in blood, urine and sweat to varying degrees. Among them, BPA was found to be more excreted in sweat (3).

BPA was first synthesized by chemists in 1891. In the late 1930s, scientists discovered that BPA acted as an artificial estrogen. Estrogen impostors would be used as drug hormones, but the invention of a more powerful synthetic estrogen, called DES, precluded the use of BPA. In a warning sign about the potential toxicity of BPA, DES was eliminated because it was linked to reproductive cancer in babies born to mothers who took the drug. As a result, BPA was banned from use in drugs, and subsequently, the use of BPA in plastics would continue for another two decades. In the 1950s, BPA began appearing in plastic consumer products around the world (2,3).

However, as we know, BPA is an endocrine disruptor when absorbed in the body that can decrease or increase the normal hormone level, such as Estrogen, when BPA will replace estrogen with the estrogen receptor to affect the generation of sexual characteristics in

children, the incidence of precocious puberty in young girls is also increased at high BPA exposure levels. Currently, there are limited human data on the association of obesity with environmental chemicals. However, in animal studies, there has been an increase in experimental on environmental chemicals. Obesogens, which are the BPA, affect triacylglycerol accumulation, release insulin, and adipose cellular leads to obesity-associated with insulin and glucose dysregulation, and type 2 diabetes (4,5).

Regarding cancer, there is no positive correlation between BPA and breast, prostate cancer, However, in rodent species, early BPA exposure alters the methylation pattern of several genes expressed in the prostate and mammary gland (6). Juan et al. (1999), based on the consideration that macrophages adhesion is the first step in the phagocytic process, therefore, study the BPA effect capacity of macrophages in Vitro. Shown that the BPA in the composite resin can alter macrophage attachment. Thus, it can inhibit macrophage function in the pulp, and periapical tissues lead to modulate immune and inflammatory responses (7).

In WHO (2010) published estimates, the exposure of adults to BPA was <0.01–0.40 μg/kg body weight (bw) per day at the mean and 0.06–1.5 μg/kg bw per day at the 95th/97.5th percentile. For young children and teenagers, mean exposure was 0.1–0.5 μg/kg bw per day, and exposure at the 95th/97.5th percentile was 0.3–1.1 μg/kg bw per day (8).

In addition, the European Food Safety Authority (EFSA, 2017) has also talked about the risk level of BPA. These organizations limit the use of BPA by introducing tolerable daily intakes (TDI) of BPA based on the results of scientific studies (9).

In 1988, the Environmental Protection Agency (EPA) set the first safety standard at 50 μg/kg body weight (bw)/day. EFSA revised this TDI in January 2015 to a considerably lower and

temporary level of 4 μg/kg bw/day, indicating a major uncertainty regarding the adverse health effects of BPA. EFSA estimates that the combined dietary and non-dietary exposure for adults is 1.449 μg/kg bw/day, which is approximately 3 times lower than the current temporary TDI (10).

in the field of dentistry, Nicolas et al. 1996 are the first to propose questions about the resin-based composite and sealants that BPA release affect estrogen activity (11). Although that not use pure BPA in dental materials, normally use BPA derivatives, are widely used such as BPA glycidyl dimethacrylate(bis-GMA), BPA dimethacrylate (bis-DMA), and BPA ethoxylate dimethacrylate (bis-EMA), at the same time, it reduces the volume shrinkage caused by photopolymerization and enhances resin reactivity, such as obtaining better aesthetic, mechanical and abrasive characteristics of dental materials. But that can be hydrolysis by the saliva or during the procedure of polymerized of the dental material that to break down 2 end hydroxyl groups (12,13, 14).

In pit and fissure sealants are used to prevent caries in those permanent molars, and they have three main materials: glass ionomer cements, compomers and composite resin. Even healthy or with incipient tooth decay by applying composite resin, fundamentally is BPA glycidyl dimethacrylates (bis-GMA) (12,15).

In root canal sealers, more used in resin based endodontic cement like AH plus and AH 26, etc., are the binding agents used to fill the gap between the root canal walls and the obturating materials (15). Of course, these also contain BPA derivatives.

In orthodontic adhesive used for bonding brackets and fixed retainers, such as resin adhesive and glass-ionomer modified adhesive (16,17). For example, the use of orthodontic adhesives

as a bonding material requires a sandwich between the brackets and the enamel so that only the outer edges of the material are exposed to the mouth, but this has the same BPA release concerns.

We can find that BPA in dental products is widespread and I will review, in the scientific literature, whether or not the harmful effects that these materials can produce in the body have been taken into account.

OBJECTIVES

1. The main objective is through search, the literature and understanding the release of bisphenol-A (BPA) during treatment with the dental material.

2. The secondary objective is would like to discuss whether it is possible to manage it to a greater extent to promote patient safety.

METHODOLOGY

According to the correlation of the Bisphenol-A (BPA) and dental materials and combination with composite resins, dental pit and fissure sealants, orthodontic adhesive. Various search engines, such as pubmed, google scholar, and the library of Universidad Europea de Madrid were used to find articles and books. Advanced search limits were placed to find literature published within the last 10 years, to search for articles that match objectives and evaluate and summarize them. More than 30 articles than after analyzing these articles, compared and correlated all the methodologies and results of every article, then discussed the consequences that BPA may influence the efficacy of patient safety use in dental materials.

Inclusion criteria were: 1. Article published from 2010 to 2020. 2. Participants that are adults and children more than 3 years old. 3. Randomized control trials, case report, cohort study and systemic reviews were all included.

Exclusion criteria were: 1. In vitro studies. 2. In vivo studies that BPA release in human salivary, urine and blood.

Keywords: bisphenol a, dentistry, dental restoration materials, orthodontics, endodontics and patient safety.

RESULTS

In Orthodontic materials view

Most orthodontic patients are young people who might be influenced to physical health after exposure to dental material with Bisphenol-A, which affects endocrine disruptors and generation of sexual characteristics.

There are 8 articles that study Bisphenol-A relationship with orthodontic material in removable retainers, adhesives in bracket bonding, and lingual retainer (17, 18, 19, 20, 21, 22, 23, 24) in Table 1. To further study what different uses in light-cured and chemically cured and relationship with time and distance. Analysis of the release of BPA after these treatments which study the BPA level in saliva, urine. The selected BPA assessment methods are high pressure liquid chromatography and gas chromatography; the liquid chromatography uses a liquid mobile phase and the gas chromatography uses a gas as the carrier, and the high-pressure liquid chromatography was most studies. For urine analysis, urinary creatinine is used as a reference analyte against which other urine analytes, such as BPA.

For orthodontic adhesive, BPA release in initial 30 min after placement in saliva and BPA increase release after 1 week in urine. Of course, there are other factors that can trigger the release of BPA. Like:

- When light-curing tip distances of 10mm, the biggest distances, the BPA release is greater than others.
- The water rinse release BPA is higher than the water/ethanol rinse.

- The type of bonding orthodontic lingual retainer, the conventional hybrid, had higher BPA release.
- The type of orthodontic composite, the Enlight, had highest BPA release.

For removable retainers, the Vacuum-formed retainer had a higher BPA release after 1 hour placement.

Table 1. Summary of the included studies in orthodontic materials view					
Authors	Year	Type of treatment	Object of study	BPA evaluation methods	Results
Madhav et al. (17)	2018	Orthodontic adhesive	Analysis of salivary in 40 patients with orthodontic brackets.	High-performance liquid chromatography/ mass spectrometry (LC/MS)	Deviated in 2 group: one light-cured and other chemically cured and analyzes Bisphenol-A release in saliva following in 30 min, 1 day, 1 week, and 1 month. They concluded when the orthodontic adhesive after placement 30 min the BPA release are increase in both group and after that both groups slowly declining over time. The BPA released by the chemically cured (36.2 µg per milliliter) is higher than the light-cured (19 µg per milliliter).
Catherine et al. (18)	2011	Orthodontic adhesive	138 premolar brackets	High-performance liquid chromatography (HPLC) and Fourier transform infrared (FTIR) spectrometer.	Evaluate the BPA release relationship with light-curing tip distance of 0mm, 5mm, and 10mm. BPA release increases when the distance between the light-curing tips increases; therefore, the light-curing tip distance increased the degree of conversion was less to lead the BPA to release more.

Table 1. Cont.					
Deenadayalan et al. (19)	2015	Orthodontic adhesive	598 stainless steel first premolar brackets	High-performance liquid chromatography and Fourier transform infrared spectrometer.	Study the BPA release and difference between light-cured and chemically cured use in orthodontic adhesives. The light-cured used LED (1100 to 1200mW) with different seconds (10, 20, 40seconds) at different distances (0, 5, and 10mm) and divided into 13 groups. They concluded when having greater degrees of conversion then got less BPA release. Therefore, when the light-cured distance tip is bigger, the degrees of conversion will be less. The chemically cured group shows the BPA release less the light-cured group.
Dimitrios et al. (20)	2015	Orthodontic adhesive	20 patients associated with orthodontic bonding in Vivo	Gas chromatography-mass spectrometry (GC-MS)	Divided into 2 groups: Group A using 25ml of tap water mouth rinsing in 60 seconds; Group B using 20ml deionized water with 5ml absolute ethanol mouth rinsing in 60 seconds. Analyze BPA 3 times (before bracket bonding, immediately after bracket bonding first rinse and second rinse). The BPA is released in Both first rinses. However, the water rinse group release BPA is higher than the water-ethanol rinse group thanks to the oxygen-inhibited layer.

Table 1. Cont.					
Akila et al. (21)	2017	Removable retainers	Analysis salivary in 45 patients had retainer treatment.	High-performance liquid chromatography	In 3 groups (Vacuum-formed retainer, heat cure Hawley retainer, chemical cure Hawley retainer). Analysis before placement, after 1 hour, 1 week, and 1-month placement. The Vacuum-formed retainer had a higher BPA release after I hour placement. As well as the heat cure Hawley retainer had the lowest one.
Yoon-Goo et al. (22)	2011	Bond orthodontic lingual retainers	Analysis salivary and urine in 22 patients with lingual retainers	Liquid chromatography/ mass spectrometry (LC/MS)	Resin composite (nanohybrid filled flowable resin and conventional hybrid resin) bonding for orthodontic lingual retainers before placement, after 30 min, 1 day, 1 week, and 1month placement. In immediate placement, the highest level of BPA can be detected in the saliva. The nanohybrid filled flowable resin had a lower BPA release than the conventional hybrid one, and pumice prophylaxis can decrease BPA release in the conventional hybrid group.

Table 1. Cont.					
Theodore et al. (23)	2011	Light-cured orthodontic adhesive	18 patients bonding with orthodontic lingual retainers	Gas chromatography-mass spectrometry (GC-MS)	In 3 groups (immersed in double-distilled water for 10, 20, and 30 days). They were immersed in double-distilled water for 30 days and had the highest level of BPA release than others.
Marilia et al. (24)	2017	Orthodontic adhesive	In Vitro use 5 orthodontic composites (Transbond XT, Mono Lok II, Light bond, Eagle Spectrum, Enlight) for bonding. In Vivo, analysis saliva and urine in 20 patients with bracket bonding.	Gas chromatography-mass spectrometry (GC-MS)	In Vitro use 5 orthodontic composites immersed in water/ethanol solution and analysis after 30 mins, 24 hours, 1 week, 1-month placement. In Vivo only use (Transbond XT) light cure orthodontic adhesive to analysis and 5 times (before bracket bonding, after 30 mins, 24 hours, 1 week, 1-month placement). In vitro, the Enlight had highest BPA release; the Light bond had lowest BPA release in 1-month. In vivo, increase BPA release in saliva placement after 30 mins. For urine, BPA increases after 1 week, then BPA decreases after 1-month, and the level returns before bonding placement.

In Restoration materials view

The restoration including pit and fissure sealants, and filling that material have composite resins, glass ionomer cements, and compomers. The composite resins are the most useful and better property in the restoration areas, however, which use BPA derivatives can release BPA in the oral cavity.

Seven articles study Bisphenol-A relationship with restoration material in pit and fissure sealants and fillings such as composite resins (25, 26, 27, 28, 29, 30, 31) in Table 2. To further investigate BPA release before and after composite resins placement in saliva, urine, and blood. The choice was Liquid Chromatography (LC) and Enzyme Linked ImmunoSorbent Assat (ELISA) for saliva analysis. For urine analysis, check urinary creatinine or liquid chromatography/ mass spectrometry (LC/MS), and for blood, contain BPA in blood serum.

In saliva, the BPA release is increased the initial 5 min to I hour, with dental material placement show in most studies. Then BPA decreases after 24 hours of dental material placement.

In urine, BPA release was detected 24 hours after placement. Ultimately, after 14 to 30 days, BPA will return to the level prior to placement of the dental material.

In Blood before and after treatment in adults, no BPA has been detected in the blood serum.

Of course, there are other factors that can trigger the release of BPA. Like:

- The high-dose group, 4 occlusal sealant placements, had a higher BPA release after 3 hour placement.

- The composite group filled with polymer-based materials, 6 or more tooth surfaces filling, had more BPA can be detected.
- The BPA could be seen in after resin-based composite treatment, like Bisphenol-A Diglycidylmethacrylate (Bis-GMA), Triethylene Glycol Dimethacrylate (TEGDMA), Urethane Dimethacrylate (UDMA) and 2-Hydroxyethyl Methacrylate (HEMA).

Table 2. Summary of the included studies in restoration materials view					
Authors	Year	Type of treatment	Object of study	BPA evaluation methods	Results
Albert et al. (25)	2012	Composite restorations	Analysis saliva and urine in 172 personals	Liquid chromatography / mass spectrometry (LC/MS)	They receive restoration with a composite from before the restoration to the after 1 hour (immediately), 1 to 8 hours, 9 to 30 hours, and then analyze the BPA level in saliva and urine. Divided into two groups, one group is using a rubber dam, and one group is not. The relationship was found that BPA increases after 1 hour (immediately), then after 9 hours will go back to before treatment level. What is of interest is when placing the rubber dam, the BPA level in saliva was lower than other groups. However, rubber dam use does not reduce the BPA level in the urine after 9 to 30 hours of placement.
Joyce et al. (26)	2010	Dental sealant	Analysis blood and saliva in 30 adults	Enzyme Linked Immuno Sorbent Assat (ELISA)	Divided into two groups, one group is a low-dose group (one occlusal sealant placement). Another one is a high-dose group (four occlusal sealant placement). Analyze the BPA in saliva in one-hour prior, one-hour post, three hours post, and 24 hours post. The level of BPA in saliva was higher after placement to three hours in both groups; however, until 24 hours, the level of BPA was going back to prior treatment. Of course, the higher BPA in the high-dose group than in the low-dose group. BPA level was positively correlated with the number of occlusal sealant placement. Analyze the BPA in blood before and after treatment in adults, and then no BPA has been detected in the blood serum.

Table 2. Cont.					
Berge et al. (27)	2017	Dental fillings	Analysis saliva in 40 personals	Liquid chromatography / mass spectrometry (LC/MS)	Divided into 2 groups: 20 individuals with 6 or more tooth surfaces filled with polymer-based materials (composite group) and 20 individuals without polymer-based materials filling (control group). That filling the least placed 7 days. The composite group had 8 of 20 individuals that can be detected with BPA. The more interesting part is the control group without any polymer-based materials filling, which also show-up BPA.
Vibeke et al. (28)	2012	Composite fillings	Analysis saliva in 10 patients in vivo	Liquid chromatography / mass spectrometry (LC/MS)	With a resin-based composite like bisphenol-A diglycidylmethacrylate (Bis-GMA), 2-hydroxyethyl methacrylate (HEMA), triethylene glycol dimethacrylate (TEGDMA), Ethoxylated bisphenol-A dimethacrylate (Bis-EMA) and urethane dimethacrylate (UDMA) analysis before treatment, after treatment 10 min, 24 hours, and 7 days. The BPA could be seen in a short time (10 min) after resin-based composite treatment, like Bis-GMA, TEGDMA, and UDMA. However, the HEMA has been detected BPA after 24 hours of treatment. Only the Bis-EMA can not be detected BPA release in all periods.

Table 2. Cont.					
Jung-Ha et al. (29)	2017	Composite resin restoration	Analysis salivary in 30 patients	Enzyme Linked Immuno Sorbent Assat (ELISA)	Analysis BPA in saliva from before treatment, after treatment 5 min, and 7 days. The BPA has increased after treatment 5 min, but after treatment 7 days has decreased the BPA level. On the other hand, they concluded the number of the restoration surface was not the relationship with BPA level in the saliva.
Nancy et al. (30)	2016	Composite resin restorations	Analysis urine in 91 children and adolescents	Modification of automated online solid-phase extraction-high performance liquid chromatography -isotope dilution tandem mass spectrometry	They are placement composite for restoration treatment and analysis before placement, after 1 day, 14 days, and 6 months. The BPA concentration has increased in placement after one day. However, as time increases, the BPA concentration will not be detectable after 14 days and 6 months of treatment. Also, when the patient had a minor number of restorations of the composite, the BPA was not detectable.

Table 2. Cont.					
Sun-Young et al. (31)	2012	Composite fillings	Analysis urine in 495 children	Examine creatine to know the BPA concentration in urinary	They receive composite resin and fissure sealant treatments divided into 4 groups, which do not have any treatment, have 1 to 5 surfaces, 6 to 10 surfaces, and more than 11 surfaces treated. When the children had more than 11 surfaces that increase BPA concentration in urine, but in those 3 groups, zero, 1 to 5, 6 to 10, the BPA concentration are no differences between them. They concluded the BPA concentration has a relationship with the number of surfaces of the composite used.

In Endodontics material view

The resin cement is most using in endodontic. Therefore, cement sealants can be extruded through the root tip, and such extrusion, if minimal, is not considered a problem for treatment success. However, endodontic materials that may contain BPA in direct contact with the human body may have a negative effect on the patient.

Due to the lack of scientific literature in this area analyzing the release of BPA in the field of endodontics, only one relevant study was found here in Table 3.

Table 3. Summary of the included studies in endodontics material view					
Authors	Year	Type of treatment	Object of study	BPA evaluation methods	Results
Díaz-Flores et al. (15)	2018	Endodontic cements	4 resin cement (Simpliseal®, AH 26®, TopSeal®, and AH Plus®)	liquid-solid extraction procedure and gas chromatography/ mass spectrometry (GC/MS)	The AH Plus had the highest concentration of BPA with 74% by weight that was meaning 100g of the sample had 74g are BPA. and then are 46% (TopSeal®), 22% (AH 26®), 7% (Simpliseal®).

DISCUSSION

In orthodontic view

In orthodontic material view, all studies of light-curing in orthodontic adhesive showed an increase in the level of Bisphenol-A during the initial I hour (17, 18, 19, 20, 21, 22, 24), Not only in orthodontic material will release Bisphenol-A after placement in 30 min to 1 hour, but also in restoration material like composite resin will release BPA when after placement immediately (25, 26, 27, 28, 29). However, even before placement was detected BPA, and after placement, the BPA is not going to zero for a long time (17, 20, 21, 22, 24). That thanks to the BPA is present all around us in the environment and manufactured products.

In the other 2 studies that correlated with the light-curing tip distances of 0mm, 5mm, and10mm, the bisphenol-A release when with a greater light-curing tip distances (10mm), such as a light not complete polymerization with monomers due to lower the degree of conversion and when decreasing curing of the time also decreases the degree of conversion (18, 19). Therefore, the light-curing tip should be as close as possible to the adhesive to reduce the incomplete polymerization monomers formation.

In Deenadayalan et al. (2015), to compare with light-curing and chemically curing, the chemically curing had less Bisphenol-A release related to the greater degree of conversion rate but needs more time to reach a final cure (19). This argument is different from Madhav et al. (2018); they had much higher BPA released in chemically cured than light-cured ones (17).

Also effect Bisphenol-A releases, the oxygen inhibited layer as the uncured resin becomes when the adhesive connects with the air. The oxygen inhibited layer of the composite can be destroyed by saliva or rinsing leading to increased BPA release (20, 22). In Dimitrios et al. (2015), they were using water and water/ethanol to mouth rinsing to analysis that can eliminate oxygen inhibited layer formation also reduce BPA release, although the water rinsing group had a higher level BPA release than the water/ethanol one, that does no statistically significant differences between water and water/ethanol mouth rinsing (20). But in Yoon-Goo et al. (2011) prove that after bonding, pumice prophylaxis in each resin surface can remove uncured resin thereupon to decrease BPA release (22).

Marilia et al. (2017) had done an interesting study in Vivo and in Vitro at the same time and analyzed the BPA release from orthodontic adhesive (24). In vitro study, by different periods of experimental time, we can clearly know which material and quantity will be used when BPA is released, which can be a basis for the In Vivo study. For example:

1. in Vivo group had 20 patients with Transbond XT orthodontic adhesive bonding with bracket, at 30 minutes after bracket bonding start to release BPA; in Vitro group Transbond XT was the same at after 30 minutes release BPA.

2. in Vitro group tightly control quantity of the orthodontic adhesive and physical environment to similar with the oral cavity, use adhesive (5mm diameter x 3mm thick) immersed in 4ml ethanol/water solutions, therefore some uncontrollable factors can be ruled out, different patients have different eating habits, like eating hot food or acidic food, which will interfere with the final release of BPA.

In restoration material view

From the review of the article above, it is clear that when the composite resin releases Bisphenol-A after immediately to 1-hour placement in the saliva and that it can analyze a higher level than other times. After 24 hours it will decline to the baseline (25, 26, 27, 28, 29). In Berge et al. (2017) study 2 groups: with polymer-based material (composite group) and without polymer-based material (control group), The more interesting part is the control group without any polymer-based materials filling, which also show-up BPA. This makes us realize that BPA is not only found in dental materials but also in our daily life, like canned food (27). In the urine, the BPA can be detected after 24 hours to analyze the higher level than the other times (30, 31). The blood serum can not detect BPA (26).

Albert et al. (2012) use a rubber dam to study the impact on BPA level in saliva. The BPA in saliva with rubber dam had a lower level than that without rubber dam one, which means the rubber dam effectively prevents the release of BPA into the saliva (25).

The relationship with Bisphenol-A level and the number of surfaces of the composite used which have 2 studies[26,30]. They concluded the number of the composite surface to be placed is positively correlated with BPA release. From this we can see, in every appointment not to place too many surfaces of composite that can prevent the patient from being excessively exposed to the BPA environment.

The monomer has many types like Bis-GMA, Bis-EMA, HEMA, TEGDMA, and UDMA. Michelsen et al. (2012) study those monomers in composite resin use in filling treatment then analyzed saliva in vivo. Most monomers (Bis-GMA, HEMA, TEGDMA, and UDMA) release BPA in a short time after placement of composite resin. The interesting is, only Bis-EMA can not be detected BPA release in all periods of the treatment as we can say the monomer with Bis-EMA that relatively safe compared to other monomers (28).

In endodontic material view

From the review of the article above, we can try to choose the least BPA material for this field, like Simpliseal® only had 7g BPA in 100g that may be the first choice to use in resin-based cement with the patient safety issues (15). In most cases, resin-based endodontic cement remains in the patient's mouth for a long time. Following the aqueous environment of the oral cavity, chemical degradation and softening are promoted. Thus, erosion and abrasion are key factors in changing the mechanical properties of the resin cement. More research in vivo is needed in this area, in order to avoid future problems that could undermine patient safety if they are applied.

While the retail market may have responded to the safety of BPA, the debate over the validity of current BPA safety standards continues to this day.

The low-dose study of BPA represents part of a larger scientific paradigm shift in environmental health science. This is the result of extensive theoretical development and repeated use of endocrine-disrupting chemicals at low doses.

In Laura et al. (2013) study, Low dose effects of bisphenol A (50 mg/kg/day) produce effects in animals they still consider to impact negatively (32).

Even those studies at Bisphenol-A were far away from the European Food Safety Authority (EFSA) in 2015 and recommended 4 μg/kg/day. However, As dentists, we must avoid exposing our patients to BPA. BPA release should be minimized

We can understand the toxicological potential of BPA and its pathological effects of the medical evidence through the clinical trials that were found in the literature including those studies in Vivo and in Vitro.

From these studies, we know that after the use of composite resins and fissure sealants, it obviously increases a large amount of BPA at the first hour. The increased amount has an exponential relationship with more surfaces and then decreases its levels to base values after 24 hours.

BPA is metabolized from the human body. This metabolic process is a continuous competition between absorption and elimination by the body. A major challenge for future research is to determine the causal relationship between BPA exposure and negative health effects under such dynamic conditions, especially when designing biomonitoring studies.

Such as, what we do not understand is, at the aspect of quantities, how it influences or injures our body and if it has the individual potentiating effect or cumulative effect from different sources. Dental research can greatly contribute to this direction.

Promote patient safety

Based on the analyzed bibliography, the following recommendations are proposed:

1. The composition of the resin used should be considered as some monomers have greater estrogenic effects than others. Bis-EMA is preferable to Bis-GMA (28). However, most composite resins and sealants contain several different monomers in their composition, making selection difficult. The safety data sheet must be as complete as possible so that the percentage of each monomer can be evaluated, and the best choice can be made for the clinician based on this information. For orthodontic retainer, can use heat cure Hawley retainer (21), and for endodontic cement, can use Simpliseal® the resin-based endodontic cement (15).

2. It better be treated with a rubber dam for restoration or sealant to minimize its dissolution in saliva (25).

3. In order to eliminate the formation of an uncured layer, the uncured layer is the last layer of the resin that has not been polymerized by oxygen. Eliminate the formation decreases BPA level in saliva and even eliminates absorption of monomers (20, 22).

    - A glycerin gel barrier must be placed before polymerization.
    - Pumice prophylaxis should also be performed, using pumice for surface polishing.

- At least 30 seconds of air/water spray washing.

4. Patients should rinse their mouths for 30 seconds after treatment, as measures must be taken to dilute it to improve patient safety. After bonding can rinse with water to reduce the presence of BPA to baseline levels (before bonding) (20).

5. Choose light-cured composite resins instead of chemically cured ones, prerequisite the light-curing tip should be placed as close to the adhesive as possible to let the composite reach a great degree of conversion. For example, in the application of orthodontic and restorative devices (19). Of course, it is also necessary to follow the manufacturer's recommendations for the correct distance and time for light curing.

6. Perform as few treatments or reduced surface treatments as possible at one time to minimize the potential increase in BPA release. Up to four treatments per appointment, including restoratives, sealants, and orthodontic (26, 31).

7. Several BPA-free orthodontic adhesives, mainly based on aliphatic dimethacrylate, have been introduced (20). Elisabeth et al. (2016) analyze 160 composite resins made in Europe relationship to BPA, which only had 18 composite resins no contain with BPA derivative (33). We can remember that when need to use composite resin, we can quickly to found it.

8. Because of the high estrogenic and teratogenic levels of BPA, special attention should be given to the treatment of children and adolescents. In these patients, all recommended clinical preventive measures should be taken simultaneously.

9. We found low levels of study compounds (including BPA) in saliva and urine prior to placement of the resin-based composites. However, these background exposure differences are large. Possible BPA from the environment. How to Minimize Your Exposure in a daily lifetime. such as:

    - Avoid packaged foods.
    - Drink from glass bottles.
    - Stay away from BPA products.
    - Be selective with toys made from BPA-free material.
    - Don’t microwave plastic.
    - Buy powdered infant formula: recommend powders.

10. For Bisphenol A excretion in Stephen et al. (2012) study, the excretion of BPA is found to be more in sweat. Therefore, we can also encourage people to exercise more to promote the excretion of BPA from the body (3).

CONCLUSIONS

1. According to these studies, Bisphenol-A will release:

   - After dental material (orthodontic adhesive; composite resin; endodontic cement) placement in 30 min.
   - Greater light-curing tip distances.
   - Show up of the oxygen inhibited layer of composite.
   - The number of the composite surface to be placed is positively correlated with BPA release.

2. Although the BPA released by these studies is lower than the daily limit recommended by the European Food Safety Authority (EFSA), it is still unknown whether BPA can accumulate or multiply in the human body. As dentists, protect patients' safety as far as possible without affecting dental treatment. Certain measures can be taken to reduce the release of BPA in the clinical setting, for example, use of rubber dams, immediate polishing of all resins used to avoid uncured layer formulation and rinsing of the mouth after handling. Also, a preventive measure is to use a minimum number of restorers or sealants in each appointment.

RESPONSIBILITY

Social sustainability

In dentistry, dental materials like orthodontic adhesive, composites resin, endodontic cement, and sealants are mostly used. Some contain the risk of BPA release and can be detected in human saliva and urine after those dental material placements. However, BPA has been shown to have an effect on endocrine disruptors.

As a dentist, we have to strike a balance between those substances that are harmful to the patient and restoring the patient's oral health. Therefore, this article is a consolidation and compilation of when and what can cause BPA release after the placement of dental materials. Finally, what measures can be taken in the clinical setting to avoid patient exposure to BPA and promote patient safety.

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ANNEXES

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Scientific African 5 (2019) e00135

Contents lists available at ScienceDirect

Scientific African

journal homepage: www.elsevier.com/locate/sciaf

Endocrine disrupting effects of bisphenol A exposure and recent advances on its removal by water treatment systems. A review

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ARTICLE INFO

Article history:
Received 10 January 2019
Revised 29 May 2019
Accepted 21 August 2019

Keywords:
Endocrine disruptors
Metabolic disorders
Biodegradation
Advance oxidation
Adsorption

ABSTRACT

Bisphenols (BPA) are phenolic, organic synthetic compounds used as an additive or monomers in the production of polycarbonate plastics and epoxy resins. BPA is a reproductive, developmental, and systemic toxicant, often classified as an endocrine-disrupting compound (EDC). BPA absorption into the body can result in the development of metabolic disorders such as low sex-specific neurodevelopment, immune toxicity, neurotoxicity and interference of cellular pathway. Therefore, the presence of BPA and its analogues in the environment has recently attracted global attention. This review provides evidence of BPA as a harmful compound and summarizes the current state of science on its removal. Several BPA removal techniques that mainly comprised of biological treatment, advanced oxidation and adsorption process were extensively studied. Biological treatment methods involved the use of biological agents such as enzymes (notably, laccase and peroxidase enzyme) to induce a degradation effect on bisphenols, and converting them into relatively harmless and less toxic compounds. Although, the removal efficiencies varied, the efficiencies for BPA by biological techniques was about 84%. Advance oxidation (AO) technique involves the use of highly reactive radical to degrade BPA. Hydroxyl (HO) and sulfate radical (SO_4^-) were the most commonly used radicals for BPA degradation. BPA removal by application of adsorption process were also discussed.

Introduction

Bisphenol A (BPA) is an organic synthetic compound belonging to diphenylmethane derivatives and bisphenols, used as an additive in the production of polycarbonate plastics and epoxy resins. BPA is the most predominant bisphenol, it was first

Abbreviation: EDC, Endocrine Disrupting compound; BPA, Bisphenol A; AO, Advanced Oxidation; WHO, World Health Organisation; FDA, Food and Drug Administration control; CYP, gene-Cytochrome gene; ERR, Estrogen related receptors adrenocortical function-H295R; TNFα, Tumor necrosis factor; ICCs, conversion of islet cell clusters; GLUT, glucose transporter; HRP-1, porphyrin π-cation; HRP, horseradish peroxidase; Hb, haemoglobin; lac-FsNp, Fluorescent silica nanoparticles; WWT, wastewater treatment; PEG, polyethene glycol; UV-C/PMS, ultraviolet/peroxymonosulfate; PES, Polyethersulfone; SMIP, surface molecularly imprinted polymers.

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Reproductive Toxicology 42 (2013) 132–155

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Review

Bisphenol A and human health: A review of the literature

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ARTICLE INFO

Article history:
Received 1 March 2013
Received in revised form 13 June 2013
Accepted 21 August 2013

Keywords:
Bisphenol A
Human
Endocrine-disrupting chemicals
Epidemiology
Reproduction
Development
Metabolic disease
Thyroid

ABSTRACT

There is growing evidence that bisphenol A (BPA) may adversely affect humans. BPA is an endocrine disruptor that has been shown to be harmful in laboratory animal studies. Until recently, there were relatively few epidemiological studies examining the relationship between BPA and health effects in humans. However, in the last year, the number of these studies has more than doubled. A comprehensive literature search found 91 studies linking BPA to human health; 53 published within the last year. This review outlines this body of literature, showing associations between BPA exposure and adverse perinatal, childhood, and adult health outcomes, including reproductive and developmental effects, metabolic disease, and other health effects. These studies encompass both prenatal and postnatal exposures, and include several study designs and population types. While it is difficult to make causal links with epidemiological studies, the growing human literature correlating environmental BPA exposure to adverse effects in humans, along with laboratory studies in many species including primates, provides increasing support that environmental BPA exposure can be harmful to humans, especially in regards to behavioral and other effects in children.

Contents

Abbreviations: 8-OHdG, 8-hydoxydeoxyguanosine; AGD, anogenital distance; ANA, antinuclear antibodies; BADGE, bisphenol A diglycidyl ether; BASC-2, Behavioral Assessment System for Children; bisGMA, bisphenol A-glycidyl methacrylate; BMI, body mass index; BPA, bisphenol A; BRIEF-P, Behavior Rating Inventory of Executive Function-Preschool; CAD, coronary artery disease; CBCL, Child Behavior Checklist; CHAMACOS, The Center for the Health Assessment of Mothers and Children of Salinas, Salina, CA; CHD, coronary heart disease; CMV, cytomegalovirus; CVD, cardiovascular disease; CRP, C-reactive protein; DBP, diastolic blood pressure; DHEAS, dehydroepiandrosterone sulfate; E2, 17-beta estradiol; ECN, embryo cell number; EFS, embryo fragmentation score; EH, endometrial hyperplasia; EPIC-Norfolk Study, The European Prospective Investigation into Cancer and Nutrition Cohort Study, consisting of over 500,000 people (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom); ER, estrogen receptor; FAI, free androgen index (total T divided by SHBG); FDA, Food and Drug Administration; FSH, follicle-stimulating hormone; FT, free testosterone; HbA1c, hemoglobin A1c; hCG, human chorionic gonadotropin; HDL, high-density lipoprotein; HOMES, The Health Outcomes and Measures of the Environment Study (United States); HRV, heart rate variability; InCHIANTI, A European population representative sample (Chianti, Italy); IL-6, interleukin-6; ISCI, intracytoplasmic sperm injection; IVF, in vitro fertilization; LDL, low-density lipoprotein; LH, luteinizing hormone; MaGiCAD, The Metabolomics and Genomics in Coronary Artery Disease Study (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom); MDA, malondialdehyde; MGH, Massachusetts General Hospital (United States); NECAT, The New England Children's Amalgam Trial (United States); NHANES, National Health and Nutrition Examination Survey (United States); NNNS, NICU Network Neurobehavioral Scale; OHAT, Office of Health Assessment and Translation; PCOS, polycystic ovary syndrome; PIVUS, The Vasculature in Uppsala Seniors Study (Uppsala, Sweden); PFOS, perfluorooctane sulfonate; PFOA, perfluorooctanoic acid; rtPCR, reverse transcription polymerase chain reaction; SBP, systolic blood pressure; SCE, sister chromatid exchange; SFF, The Study for Future Families, USA; SHBG, sex hormone binding globulin; SRS, Social Responsiveness Scale; T, total testosterone; T3, triidothyronine; T4, thyroxine; TDI, tolerable daily intake; TSH, thyroid stimulating hormone; UCSF, University of California, San Francisco; USEPA, United Sates Environmental Protection Agency; VCL, curvilinear velocity (μm/s).

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0890-6238/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
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Hindawi Publishing Corporation
Journal of Environmental and Public Health
Volume 2012, Article ID 185731, 10 pages
doi:10.1155/2012/185731

Clinical Study

Human Excretion of Bisphenol A: Blood, Urine, and Sweat (BUS) Study

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Received 16 July 2011; Revised 10 September 2011; Accepted 26 September 2011

Academic Editor: Robin Bernhoft

Background. Bisphenol A (BPA) is an ubiquitous chemical contaminant that has recently been associated with adverse effects on human health. There is incomplete understanding of BPA toxicokinetics, and there are no established interventions to eliminate this compound from the human body. Using 20 study participants, this study was designed to assess the relative concentration of BPA in three body fluids—blood, urine, and sweat—and to determine whether induced sweating may be a therapeutic intervention with potential to facilitate elimination of this compound. *Methods*. Blood, urine, and sweat were collected from 20 individuals (10 healthy participants and 10 participants with assorted health problems) and analyzed for various environmental toxicants including BPA. *Results*. BPA was found to differing degrees in each of blood, urine, and sweat. In 16 of 20 participants, BPA was identified in sweat, even in some individuals with no BPA detected in their serum or urine samples. *Conclusions*. Biomonitoring of BPA through blood and/or urine testing may underestimate the total body burden of this potential toxicant. Sweat analysis should be considered as an additional method for monitoring bioaccumulation of BPA in humans. Induced sweating appears to be a potential method for elimination of BPA.

1. Introduction

First synthesized in 1891 and with current production estimated at 4 billion kilograms each year globally [1], bisphenol A (BPA) is a multipurpose compound that is widely used in the modern industrial world. BPA was initially investigated for its potentially therapeutic estrogenic properties in the 1930s; when diethylstilbestrol (DES) was found to be more potent, however, BPA was temporarily cast aside. Its commercial value was reassessed in the 1950s with the introduction of BPA as a fundamental component in the manufacturing of some plastics. As its primary use currently, BPA is a key monomer in the production of the most common form of clear and shatter-proof polycarbonate plastic, but it has also been incorporated into a variety of everyday goods.

Questions regarding the safety and side effects of BPA began to emerge in the late 1990s when BPA was found to leech out of plastics and into experimental animal subjects, resulting in an increased incidence of chromosomal anomalies in offspring [2]. There has since been ongoing discussion in both scientific and political spheres about the potential for harm resulting from human BPA exposure and potential bioaccumulation. An overview of the literature regarding the effects of BPA on human health is provided, followed by a presentation of data from 20 subjects whose blood, urine, and sweat were tested for BPA. Results and discussion regarding BPA bioaccumulation and elimination are presented for consideration.

2. Background

Currently, BPA is most commonly found as a component in polycarbonates (~74% of total BPA produced) and in the production of epoxy resins (~20%). As well as being found in a myriad of products including plastic food and beverage containers (including baby and water bottles), BPA is also

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Chapter 1
Human Health Effects of Bisphenol A

Thaddeus T. Schug and Linda S. Birnbaum

Abstract Bisphenol A (BPA) is a high production endocrine disrupting chemical found in numerous consumer products. BPA has been used commercially since 1957 to make hard polycarbonate plastics and epoxy resins used in food-can linings, cash-register receipts, and dental resins. The ubiquity of BPA in our environment results in exposure to this chemical daily in human populations. But controversy remains regarding how much BPA humans actually ingest or otherwise encounter. Many laboratory animal and human studies have linked exposures to BPA, a hormone mimicking chemical, to adverse health effects, including altered behavior and obesity in children, reproductive abnormalities, cardiovascular changes, and various cancers. However, there have been considerable inconsistencies in the outcomes from these studies with respect to the nature of the adverse health effects observed, and questions as to whether the BPA dose at which they occur are within the range of non-occupational human exposures. This chapter reviews the latest research on BPA, focusing on human exposure, discussions of biomonitoring studies and toxicokinetic models, human health effects, and research needs. We also include illustrative examples of animal models that address whether BPA-exposure is associated with changes in certain health endpoints.

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S. M. Snedeker (ed.), *Toxicants in Food Packaging and Household Plastics*, Molecular and Integrative Toxicology, DOI: 10.1007/978-1-4471-6500-2_1,

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Published in final edited form as:
Mol Cell Endocrinol. 2012 May 6; 354(1-2): 74–84. doi:10.1016/j.mce.2012.01.001.

THE ESTROGENIC ENDOCRINE DISRUPTING CHEMICAL BISPHENOL A (BPA) AND OBESITY

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Abstract

There is increasing experimental and epidemiological evidence that fetal programming of genetic systems is a contributing factor in the recent increase in adult obesity and other components of metabolic syndrome. In particular, there is evidence that epigenetic changes associated with the use of manmade chemicals may interact with other factors that influence fetal and postnatal growth in contributing to the current obesity epidemic. The focus of this review is on the developmental effects of estrogenic endocrine disrupting chemicals (EDCs), and more specifically on effects of exposure to the estrogenic EDC bisphenol A (BPA), on adipocytes and their function, and the ultimate impact on adult obesity; BPA exposure also results in impaired reproductive capacity. We discuss the interaction of EDCs with other factors that impact growth during fetal and neonatal life, such as placental blood flow and nutrient transport to fetuses, and how these influence fetal growth and abnormalities in homeostatic control systems required to maintain normal body weight throughout life.

Keywords

Endocrine disrupting chemicals; Bisphenol A; Obesity; Metabolic syndrome

1. The importance of life stage

1.1 Effects of exposure to estrogens in adulthood on adipose tissue

Estrogens and other sex hormones regulate the functioning of tissues in addition to those involved in reproduction in adults. The effects that occur when a hormone is present often do not occur after the hormone is withdrawn. These are termed "activational" effects. The typical view is that increased plasma concentrations of estrogens are associated with a reduction in food intake and body weight in adults, and that the loss of ovarian estrogen secretion related to menopause in women results in weight gain [1]. However, evidence is

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Disclosure Statement.
SCN, JAT, BLC and BMA have nothing to disclose. FSvS has been a consultant for attorneys involved in product labeling litigation.

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HHS Public Access
Author manuscript
Reprod Toxicol. Author manuscript; available in PMC 2017 January 01.

Published in final edited form as:
Reprod Toxicol. 2016 January ; 59: 167–182. doi:10.1016/j.reprotox.2015.09.006.

A Review of the Carcinogenic Potential of Bisphenol A

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Abstract

The estrogenic properties of bisphenol A (BPA), a ubiquitous synthetic monomer that can leach into the food and water supply, have prompted considerable research into exposure-associated health risks in humans. Endocrine-disrupting properties of BPA suggest it may impact developmental plasticity during early life, predisposing individuals to disease at doses below the oral reference dose (RfD) established by the Environmental Protection Agency in 1982. Herein, we review the current *in vivo* literature evaluating the carcinogenic properties of BPA. We conclude that there is substantial evidence from rodent studies indicating that early-life BPA exposures below the RfD lead to increased susceptibility to mammary and prostate cancer. Based on the definitions of "carcinogen" put forth by the International Agency for Research on Cancer and the National Toxicology Program, we propose that BPA may be reasonably anticipated to be a human carcinogen in the breast and prostate due to its tumor promoting properties.

Keywords

Bisphenol A; Cancer; Mammary; Prostate; Uterus; Ovary; Estrogen Receptor; Testes

1. Introduction

Incidence and prevalence of cancers of endocrine target organs, including prostate, breast, and testis, as well as other diseases such as infertility and obesity began steadily increasing

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Declaration of Financial Interests: None.

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JOURNAL OF ENDODONTICS
Printed in U.S.A.
VOL. 25, NO. 5, MAY 1999

In Vitro Effect of the Resin Component Bisphenol A on Substrate Adherence Capacity of Macrophages

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This study was design to investigate the "in vitro" effect of bisphenol A (BPA), a component of resin used in dentistry, on viability, and substrate adherence capacity of macrophages. Peritoneal macrophages were obtained from Wistar rats and resuspended in RPMI-1640 medium. Viability was determined by trypan blue exclusion. As a test of macrophage adhesion, the adherence capacity of macrophages to a plastic surface was determined and the adherence index was calculated. Assays were conducted in Eppendorf tubes for 60 min of incubation at 37°C in a humidified atmosphere of 5% CO_2 in air. BPA did not alter significantly macrophage viability at concentrations as high as 10^{-5} *M*, but BPA decreased in a dose-dependent manner the adherence index of rat peritoneal macrophages. Control peritoneal macrophages showed an adherence index = 81.5 ± 7.9%. In the presence of 10^{-8} *M* BPA, the AI of macrophages decreased to 41.4 ± 12.2% ($p < 0.05$). Higher BPA concentrations (10^{-7} to 10^{-5} *M*) also caused a significant inhibition of the adherence index. Half-maximal inhibition (IC_{50}) was obtained at $4.92 \pm 0.39 \times 10^{-6}$ *M* BPA. The in vitro study shows that the resin component BPA can alter macrophage adhesion. Taking into account that adhesion is the first step in the phagocytic process of macrophages and in antigen presentation, BPA could inhibit macrophage function and modulate immune and inflammatory responses in dental pulp and periapical tissues.

Today, the monomer 2,2-bis[4-(2-hydroxy-3-methacrylyloxypropoxy)phenyl]-propane (BisGMA), prepared from bisphenol A (BPA) and glycidyl methacrylate (Fig. 1), is the major ingredient of the resin matrix of most of the resin-based composite restorative materials used in dentistry (1). Furthermore, diglycidyl ether of BPA (BADGE) is also an ingredient of some endodontic sealers used in root canal filling therapy, such as AH26 (2). Polymerization of the monomer BisGMA occurs through the carbon–carbon double bonds of the two methacrylate groups. As polymerization proceeds, diffusion rates of propagating free radicals and unreacted dimethacrylate molecules are drastically reduced, hampering complete conversion of methacrylate double bonds. Thus, as much as 25 to 50% of the methacrylate groups remains unreacted and approximately one-tenth is present as residual monomer. Because of this low degree of polymerization, concerns have been expressed about the leaching of chemicals from material (3). Moreover, cured composites placed in the oral cavity are attacked mechanically and chemically, and the possibility also exists that residual BisGMA may be metabolized to form BPA without prior enzymatic hydrolysis of the ester linkages. Thus, Olea et al. (4) have identified BPA in saliva samples collected during 1 h after placement of a 50 mg fissure sealing in 18 subjects.

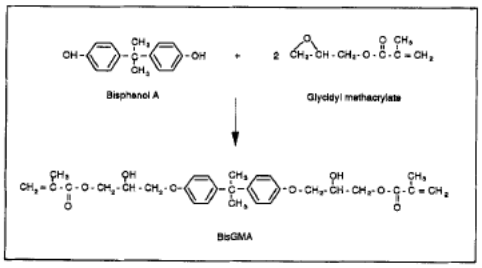
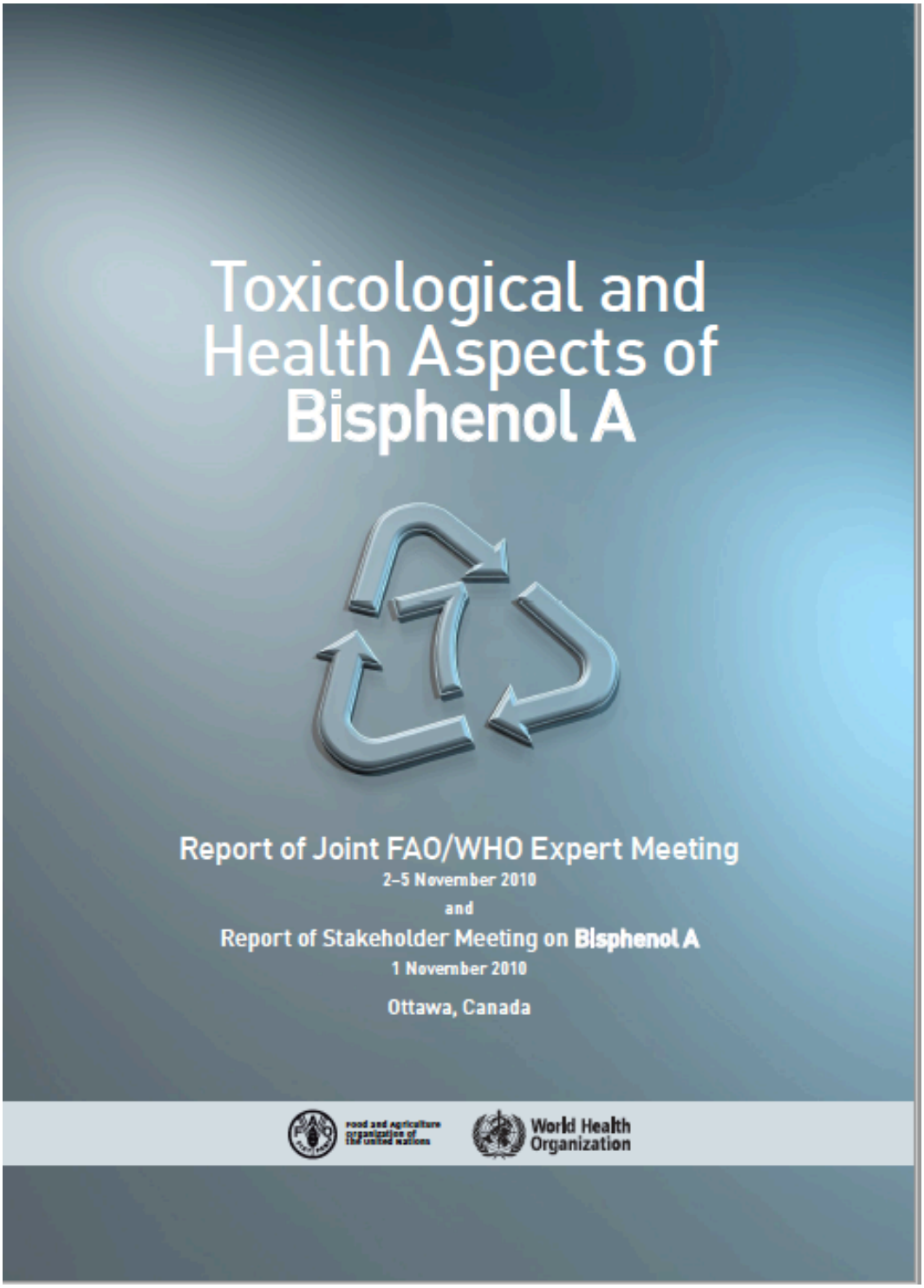


FIG 1. Synthesis of BisGMA from BPA and glycidyl methacrylate.

The potential impact that this material may have on the biocompatibility of the resin composite and endodontic sealers containing BPA with oral tissues has been of great concern. Pulp studies have shown lack of significant pulpal irritation after the placement of properly sealed resin composite filling (5). However, Jontell et al. (6) have demonstrated that BPA, at low concentrations, increased spleen cell proliferation to concanavalin A.

In previous studies, the existence of a variety of immunocompetent cells in the normal and inflamed dental pulp has been documented, with macrophages predominating (7). Moreover, macrophages are the most dominating immunocompetent cells during all stages of experimentally induced periapical lesions (8). They are known to have several mediator and regulatory functions, and are involved in the entire spectrum of defense reactions.

8. Report of Joint FAO/WHO Expert Meeting. *Toxicological and Health Aspects of Bisphenol A.* 2012. (accessed 2-5 November 2010).



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TECHNICAL REPORT

APPROVED: 30 November 2017

doi:10.2903/sp.efsa.2017.EN-1354

Bisphenol A (BPA) hazard assessment protocol

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Abstract

To ensure an efficient, transparent and methodologically rigorous re-assessment of the safety for consumers of bisphenol A (BPA), the European Food Safety Authority (EFSA) has undertaken the task to develop a protocol detailing *a priori* the approach and methodology for performing BPA hazard identification and characterisation. The general aim of this hazard assessment will be to assess whether the new scientific evidence (published from 2013 onwards and not previously appraised by EFSA) still supports the current temporary Tolerable Daily Intake (t-TDI) for BPA of 4 µg/kg bw per day. In line with the principles highlighted in the EFSA project PROmoting METHods for Evidence Use in scientific assessments (PROMETHEUS, https://www.efsa.europa.eu/en/efsajournal/pub/4121), the protocol states upfront and in detail the methods and/or the criteria that will be used in the planned BPA re-evaluation for data collection, study inclusion, evidence appraisal and integration. To pursue the goal of openness, this protocol was subjected to a web-based public consultation and was presented publicly in a stakeholder event. All the relevant comments and feedback received through these procedures were considered in this version of the protocol which will be implemented in the next BPA re-evaluation.

Key words: BPA, Protocol, Hazard assessment methodology, evidence integration, internal validity, external validity, weight of evidence

Requestor: EFSA

Question number: EFSA-Q-2016-00673 and EFSA-Q-2016-00635

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10. Lofroth M., Ghasemimehr M., Falk A., Vult von Steyern P. Bisphenol A in dental materials – existence, leakage and biological effects. *Heliyon* 2019; ():1-9. https://doi.org/10.1016/j.heliyon.2019.e01711 (accessed 8 May 2019).

Heliyon 5 (2019) e01711

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.heliyon.com

Heliyon

Review Article

Bisphenol A in dental materials – existence, leakage and biological effects

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ARTICLE INFO

Keywords:
Public health
Endocrinology
Materials chemistry
Dentistry

ABSTRACT

Objective: Recently, questions have been raised concerning the potential endocrine disrupting effects of bisphenol A (BPA). This substance is a constituent in many different products which we frequently come into contact with, such as food containers and receipts. Resin-based dental filling materials are another source of exposure, although according to previous studies the amount and potential risks are not clear. Thus, the aims of the present study were (1) to identify if direct dental filling materials are liable to leak BPA and (2) to investigate if this leakage could lead to any adverse effects on health.

Materials and methods: A literature search was made with PubMed as the primary source, subsequently complemented with reference tracking.

Results: A total of 26 articles were included, 24 of which were used for the first aim (leakage) and 2 for the second aim (health risks). The majority of studies, including all in vivo studies, showed leakage of BPA from dental materials in various amounts and during different time intervals. The findings showed a contradiction in results regarding the connection between dental materials and adverse health effects.

Conclusions: There is leakage of BPA from some dental materials, but critical levels are not evident. Bis-DMA contents might convert to BPA in the oral cavity. There is a contradiction between in vitro and in vivo studies concerning BPA leakage and finally, there is a lack of studies investigating the association between BPA exposure and its adverse effects on human health.

1. Introduction

Among many endocrine-disrupting chemicals, bisphenol A (BPA) is currently at the forefront of discussion. The substance was synthesized approximately 100 years ago and in the 1930s it was identified as one of the first synthetic estrogens [1, 2, 3, 4]. Since the 1950s, BPA has been used commercially in the manufacture of polycarbonates and epoxy resins, which are used in a variety of commonly used products. Polycarbonates are rigid plastics used in toys, water bottles, eyeglass lenses and compact discs (CDs). Epoxy resins are used in protective linings in cans, as strong adhesives and in dental sealants [4, 5]. BPA is also a constituent in thermal paper, such as receipts and fax machine paper.

The primary cause of exposure to BPA is canned food due to leakage from the protective lining, followed by the second largest source which is thermal paper [6].

Due to its wide range of uses, people are exposed to this substance in their daily lives, possibly without being aware of it. More than 90% of the US population revealed detectable BPA in their urine samples based on the report and updated tables report by the Centre for Disease Control and Prevention [7, 8], which demonstrated frequent and persisting exposure to BPA. In the early 1990s, scientists discovered BPA leakage from polycarbonates, which provided the starting point for further research regarding the possible adverse effects this might have [4]. In 1996, Olea et al. [9] reported a significant leakage of BPA from dental sealants into the saliva of patients which resulted in

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https://doi.org/10.1016/j.heliyon.2019.e01711
Received 19 June 2018; Received in revised form 18 September 2018; Accepted 8 May 2019

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Estrogenicity of Resin-based Composites and Sealants Used in Dentistry

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We tested some resin-based composites used in dentistry for their estrogenic activity. A sealant based on bisphenol-A diglycidylether methacrylate (bis-GMA) increased cell yields, progesterone receptor expression, and pS2 secretion in human estrogen-target, serum-sensitive MCF7 breast cancer cells. Estrogenicity was due to bisphenol-A and bisphenol-A dimethacrylate, monomers found in the base paste of the dental sealant and identified by mass spectrometry. Samples of saliva from 18 subjects treated with 50 mg of a bis-GMA-based sealant applied on their molars were collected 1 hr before and after treatment. Bisphenol-A (range 90–931 μg) was identified only in saliva collected during a 1-hr period after treatment. The use of bis-GMA-based resins in dentistry, and particularly the use of sealants in children, appears to contribute to human exposure to xenoestrogens. *Key words:* bisphenol-A, composite resins and sealants, E-screen bioassay, restorative dentistry, xenoestrogens. *Environ Health Perspect* 104:298–305 (1996)

The impact of certain estrogenic xenobiotics on the development, health, and reproductive systems of wildlife has been clearly documented (*1*). As data accumulate, environmental xenobiotics are also being implicated in human infertility, genital tract malformations, and increased cancer rates in estrogen target tissues (*2,3*). In 1936, Dodds and Lawson reported the estrogenicity of some diphenyl compounds containing two hydroxyl groups in *para* positions (*4*). Reid and Wilson (*5*) subsequently confirmed the estrogenicity of 4,4'-dihyroxydiphenylmethane derivatives. One such derivative, bearing two methyl groups and known as bisphenol-A, is a major component of epoxy resins. Bisphenol-A was found to leach from autoclavable polycarbonate laboratory flasks (*6*). Recently, we demonstrated that food packed in lacquer-coated cans was active in a bioassay for estrogenicity; bisphenol-A released from the epoxy resin lining of the cans was identified as the estrogenic contaminant (*7*).

Bisphenol-A is a common ingredient in restorative materials used in dentistry. Since the 1960s, when bisphenol-A diglycidyl methacrylate (bis-GMA)-based restorative materials were first used in odontology, many studies have assessed the effects of resins on pulpal injury (*8*) and their cytotoxic properties (*9–11*). Little attention was paid, however, to the systemic health effects of these chemicals or their monomers (*12,13*). Some studies focused on the alkylating properties of the glycidaldehyde portion of bisphenol-A diglycidylether (BADGE)(*14*). For example, the formation of glycidaldehyde adducts in adenine residues was demonstrated in mice after cutaneous treatment with BADGE (*15*). Other studies examined the mutagenic and carcinogenic properties of epoxy resin monomers, with contradictory results (*15*).

Resin-based composite restorative materials used in dentistry ("composites") consist of two major components: an organic resin matrix and an inorganic filler. Composites without inorganic fillers are known as "sealants." Tooth-colored restorative materials are increasingly used for preventive purposes, to replace missing tooth structures and to modify tooth color and contour. The resin matrix is initially present as a fluid monomer that is converted into a rigid polymer by a free radical-initiated reaction of addition. The polymerization reaction (curing) can be chemically initiated (autocuring) or photoinitiated using ultraviolet or visible light in the presence of a photoinitiator.

Because of the low degree of polymerization required by the monomers in composites, concerns have been expressed about the leaching of chemicals from unpolymerized material, which is rapidly released after curing (*16*). *In vitro* studies have shown that most of the unpolymerized monomers of bis-GMA had leached 24 hr after setting. In addition, cured composites placed in the oral cavity are attacked mechanically and chemically. Enzymatic hydrolysis of methacrylates, together with mechanical forces, contribute to the breakdown of composite resins (*17*), which are slowly and persistently degraded (*18*).

A significant portion of the uncured or decomposed material that is swallowed can be absorbed by the intestine. Climie et al. (*19,20*) studied the metabolic degradation of ^{14}C-BADGE in mice after the oral administration of a single dose and found that 90% of the radioactivity was eliminated in feces and urine during the first 3 days of the experiment. Interestingly, a small amount of BADGE (~ 5%) underwent oxidative dealkylation to yield glycidaldehyde (which has alkylating properties) and bisphenol-A, among other by-products (*20*). The systemic behavior of the diphenolic derivative is poorly known and needs further investigation.

The purpose of this research was to determine whether bis-GMA-based restorative resins and their components have estrogenic activity in an in culture assay. We demonstrate here that the sealant and resin components bisphenol-A and bisphenol-A dimethacrylate are estrogenic and may represent an additional source of xenoestrogen exposure in humans.

Methods

Cell line and culture conditions. MCF7 human breast cancer cells originally established by Soule and colleagues (*21*) were at passages 100–106 postcloning at the time of study. For routine maintenance, cells were grown in Dulbecco's modification of Eagle's medium (DME) supplemented with 5% fetal bovine serum (FBS; PAA Labor und Forschungs Ges, MBH, Linz, Austria) in an atmosphere of 5% CO_2/95% air under saturating humidity at 37°C.

Plasma-derived human serum and removal of sex steroids. Plasma-derived human serum was prepared from expired plasma by adding calcium chloride to a final concentration of 30 mM to facilitate clot formation. We removed sex steroids from serum by charcoal-dextran stripping (*22*). Briefly, a suspension of 5% charcoal (Norit

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This work was reported in part at the SETAC-Europe meeting held in Copenhagen, Denmark, 25–28 June 1995. We thank Karen Shashok for improving the English of the manuscript. This work was supported by grant 94/1551 from the Fondo de Investigaciones Sanitarias (FIS), the Spanish Ministry of Health and the Consejería de Salud, Junta de Andalucía (to N.O.), National Institutes of Health grant CA13410 (to C.S.), CA 55574, and NSF-DCB-9105594 (to A.M.S.).
Received 9 August 1995; accepted 21 November 1995.

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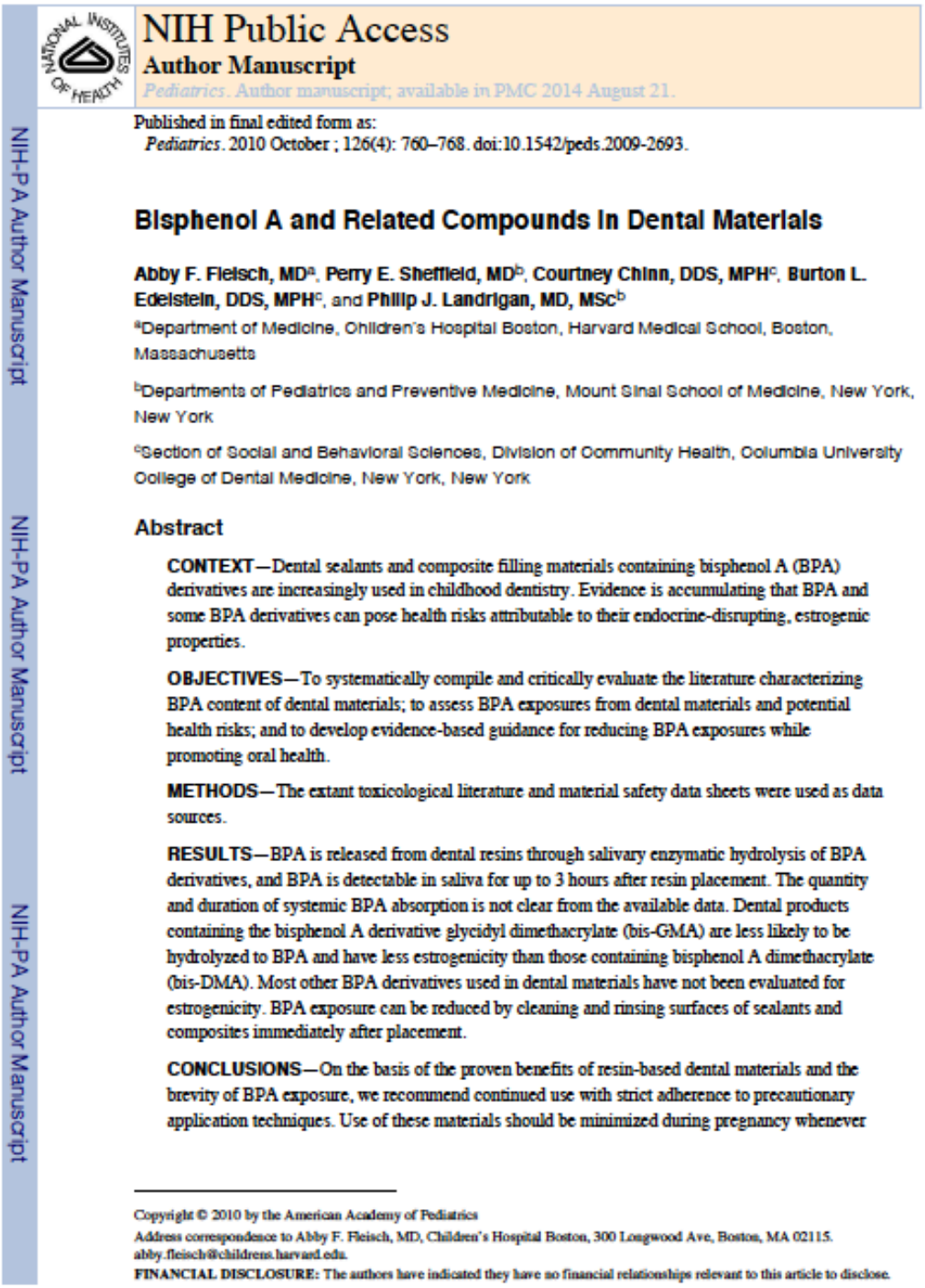

Published in final edited form as:
Pediatrics. 2010 October ; 126(4): 760–768. doi:10.1542/peds.2009-2693.

Bisphenol A and Related Compounds in Dental Materials

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Abstract

CONTEXT—Dental sealants and composite filling materials containing bisphenol A (BPA) derivatives are increasingly used in childhood dentistry. Evidence is accumulating that BPA and some BPA derivatives can pose health risks attributable to their endocrine-disrupting, estrogenic properties.

OBJECTIVES—To systematically compile and critically evaluate the literature characterizing BPA content of dental materials; to assess BPA exposures from dental materials and potential health risks; and to develop evidence-based guidance for reducing BPA exposures while promoting oral health.

METHODS—The extant toxicological literature and material safety data sheets were used as data sources.

RESULTS—BPA is released from dental resins through salivary enzymatic hydrolysis of BPA derivatives, and BPA is detectable in saliva for up to 3 hours after resin placement. The quantity and duration of systemic BPA absorption is not clear from the available data. Dental products containing the bisphenol A derivative glycidyl dimethacrylate (bis-GMA) are less likely to be hydrolyzed to BPA and have less estrogenicity than those containing bisphenol A dimethacrylate (bis-DMA). Most other BPA derivatives used in dental materials have not been evaluated for estrogenicity. BPA exposure can be reduced by cleaning and rinsing surfaces of sealants and composites immediately after placement.

CONCLUSIONS—On the basis of the proven benefits of resin-based dental materials and the brevity of BPA exposure, we recommend continued use with strict adherence to precautionary application techniques. Use of these materials should be minimized during pregnancy whenever

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

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Published in final edited form as:
Dent Mater. 2012 October ; 28(10): 1071–1079. doi:10.1016/j.dental.2012.06.007.

Fabrication and evaluation of Bis-GMA/TEGDMA dental resins/ composites containing halloysite nanotubes

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Abstract

Objective—To investigate the reinforcement of Bis-GMA/TEGDMA dental resins (without conventional glass filler) and the corresponding composites (with conventional glass filler)containing vari ed mass fractions of halloysite nanotubes (HNTs).

Methods—Three dispersion methods were studied to separate the silanized halloysite as individual HNTs and to uniformly distribute them into dental matrices. Photopolymerization induced volumetric shrinkage was measured by using a mercury dilatometer. Real time near infrared spectroscopy was adopted to study the degree of vinyl double bond conversion and the photopolymerization rate. Mechanical properties of the composites were tested by a universal mechanical testing machine. Analysis of Variance (ANOVA) was used for the statistical analysis of the acquired data. Morphologies of halloysite/HNTs and representative fracture surfaces of the reinforced dental resins/composites were examined by SEM and TEM.

Results—Impregnation of small mass fractions (*e.g.*, 1% and 2.5%) of the silanized HNTs in Bis-GMA/TEGDMA dental resins/composites improved mechanical properties significantly; however; large mass fractions (*e.g.*, 5%) of impregnation did not further improve the mechanical properties. The impregnation of HNTs into dental resins/composites could result in two opposite effects: the reinforcing effect due to the highly separated and uniformly distributed HNTs, and the weakening effect due to the formation of HNT agglomerates/particles.

Significance—Uniform distribution of a small amount of well-separated silanized HNTs into Bis-GMA/TEGDMA dental resins/composites could result in substantial improvements on mechanical properties.

Keywords

Dental composites; Bis-GMA; TEGDMA; Halloysite nanotubes

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Impact of various pressures on fracture resistance and microleakage of amalgam and composite restorations

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Key words
Diving; Aviation; Dental; Barotrauma

Abstract
(Shafigh E, Fekrazad R, Beglou A. Impact of various pressures on fracture resistance and microleakage of amalgam and composite restorations. Diving and Hyperbaric Medicine. 2018 September;48(3):168–172. doi: 10.28920/dhm48.3.168-172. PMID: 30199889.)
Background: Pressure changes can influence dental restorations especially among divers. The aim of the current study was to evaluate the fracture resistance and microleakage of mesio-occluso-distal (MOD) amalgam and composite restorations undergoing pressure changes via diving and aviation simulation.
Methods: For the fracture resistance test, 60 sound maxillary premolar teeth were randomly allocated to two groups. Each group was then divided into three subgroups ($n = 10$) for simulating scuba-diving (pressure cycle to 203 kPa, 2 bar), flight (50.6 kPa, 0.5 bar), and control (atmospheric pressure). The teeth underwent pressure cycles for one month and then the fracture resistance test was conducted on them using the Instron testing machine. Microleakage scores were afterwards recorded by using a 2% methylene blue dye for 24 hours.
Results: Composite restorations showed significantly higher fracture resistance values compared to the amalgam group ($P < 0.05$). The control group had significantly higher fracture resistance values compared to the dive group, whereas there was no significant difference between the control group and the flight group ($P = 0.083$). No significant difference in the level of microleakage was observed between restoration materials or pressure cycles ($P > 0.05$).
Conclusions: Composite restorations showed promising fracture resistance compared to the amalgam group. Diving pressure cycles demonstrated adverse effects on the fracture resistance values of the two restorative materials.

Introduction

With the growing number of scuba divers and aircrew members, dentists will increasingly encounter oral conditions relating to pressure changes and these would require careful attention.[1,2] These phenomena are mainly related to the law of Boyle–Mariotte, which states that at a constant temperature the volume and pressure of an ideal gas are inversely proportional.[3,4] Among these oral conditions, barodontalgia is known as the toothache that is related to ambient pressure changes.[5–7] In a diving environment, this pain is commonly called 'tooth squeeze'. Although uncommon, in-diving or in-flight barodontalgia has been recognized as a potential cause of diver or aircrew-member vertigo and sudden incapacitation, jeopardizing the safety of diving or flight, respectively.[8] Odontocrexis is another condition describing tooth or restoration structure destruction associated with pressure changes.[9] Dental barotrauma describes the damage to tooth structure when pressure changes may occur with or without pain. All these conditions potentially may cause incapacitation that could jeopardize the safety of diving or flight.[8]

Defective dental restorations, leakage and secondary caries are assumed to be the most important predisposing factors of dental barotraumas. In-flight bruxism in aircrew members was reported to be the main factor of amalgam restoration failures in World War II.[10] Excessive bite forces were also proposed by the United States Air Force (USAF) symposium of aviation dentistry in 1946 as a predisposing factor for restoration dislodgment.[11] In divers, there is an argument about the effect of clenching on mouthpieces on the deterioration of dental restorations.[12] Based on our literature review, there appear to be no studies examining the effect of pressure changes on the properties of dental restorations.

This study aimed to assess the fracture resistance and microleakage of mesio-occluso-distal (MOD) amalgam and composite restorations undergoing pressure changes. The null hypothesis was that the pressure changes and dental

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ARTÍCULO ORIGINAL

Segundo clasificado, Premio Mejor Artículo Científico Universidades de la CAM 2018

DETECCIÓN MEDIANTE TÉCNICA DE GCMS DE ALTO CONTENIDO DE BISFENOL A EN CEMENTOS DE USO ENDODÓNTICO

Díaz-Flores García, V. Escribano Otero, A. Kayali Sayadi, N. Herreros Ruiz-Valdepeñas, B. Pellicer Castillo, L D. Detección mediante técnica de GCMS de alto contenido de Bisfenol A en cementos de uso endodóntico. Clent Dent 2018; 15; 3; 179-185

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Indexada en / Indexed in:
- IME
- IBECS
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Fecha de recepción: 18 de junio de 2018.
Fecha de aceptación para su publicación: 4 de diciembre de 2018.

RESUMEN

El bisfenol A (BPA, por sus siglas en inglés) es un producto químico utilizado en la producción de policarbonatos y resinas epoxi, cuyo uso está muy extendido en la industria. El BPA puede pasar al organismo por medio de la dieta, ya que sus moléculas tienen migración probable de los recipientes fabricados con este producto a los alimentos contenidos en dichos recipientes.

La presencia de BPA en los materiales de uso odontológico está muy extendida. Una gran cantidad de productos están elaborados con resinas epoxi (procedentes de la reacción entre la epiclorohidrina y el bisfenol A). El presente estudio se analizaron cuatro cementos de uso endodóntico basados en resina (Ah 26®, Ah Plus®, TopSeal® y Simpliseal®) a través de un procedimiento de extracción líquido-sólido y análisis en cromatógrafo de gases acoplado a espectrometría de masas. Los resultados obtenidos muestran valores alarmantemente superiores a los 5x10-6% en peso que permite la Unión Europea para la migración de BPA desde el envase al alimento, obteniéndose unos valores de 7% (Simpliseal®); 22% (AH 26®); 46% (TopSeal®) y 74% (AH Plus®). El presente estudio es pionero en el estudio de la concentración de BPA en materiales endodónticos.

PALABRAS CLAVE

Bisfenol A; Endodoncia; Obturación.

BISPHENOL A DETERMINATION BY GCMS IN RESIN-BASED ROOT CANAL SEALERS

ABSTRACT

Bisphenol A (BPA) is a compound used in the production of polycarbonates and epoxy resins and is widely used in the industry. BPA can be passed into the body through the diet, since its molecules can easily migrate from the containers made with BPA to the food in those containers.

The presence of BPA in dental materials is very common. A large number of products are made with epoxy resins (from the reaction between epichlorohydrin and bisphenol A). This study analyzed four resin-based endodontic cements (Ah 26®, Ah Plus®, TopSeal® and Simpliseal®) using a liquid-solid extraction procedure and gas chromatograph analysis coupled to mass spectrometry. The results obtained show alarmingly higher values than the 5x10-6% by weight that the European Union allows for the migration of BPA from packaging to food, obtaining values of 7% (Simpliseal®), 22% (AH 26®), 46% (TopSeal®) and 74% (AH Plus®). This study is a pioneer in the investigation of the concentration of BPA in endodontic materials.

KEY WORDS

Bisphenol A; Endodontics; Obturation.

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GUEST EDITORIAL

AJO-DO

Bisphenol A and orthodontics: An update of evidence-based measures to minimize exposure for the orthodontic team and patients

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The purpose of this editorial is to present an update of the evidence on bisphenol A (BPA) in orthodontics by critically reviewing the available evidence, which often shows variable validity and derives from in-vitro, animal, simulated in-vivo, and in-vivo experimental configurations; clarify several misconceptions that are the results of false assumptions in the design of studies or limitations of instrumental analyses; and suggest ways to minimize the exposure of operator, staff, and patients to this molecule. The wording of the title implies that the therapeutic team including the clinician and chair-side staff should be given priority with regard to the implementation of means to shield them from BPA. This is because the operatory personnel are exposed repeatedly and for long periods of time to materials and processes that can result in BPA production compared with patients who participate only once in such scenarios.

BPA is a chemical produced in large quantities for use primarily in the production of polycarbonate plastics and epoxy resins, which have many applications in modern material items including food and drink packaging. The primary source of exposure to BPA for most people is through the diet. Whereas air, dust, and water (including through the skin when handling materials, or during bathing and swimming) are other possible sources of exposure, BPA in food and beverages accounts for the majority of daily human exposure. BPA can migrate into food from food and beverage containers with internal epoxy resin coatings and from consumer products made of polycarbonate plastic such as baby bottles, tableware, food containers, and water bottles.[1] Leaching of BPA into packages and food carriers depends more on the temperature of the liquid than the age of the container—ie, more migration with higher temperatures.

Over the past decade, the effects of BPA on a wide array of tissues, organs, and systems have been established through in vitro and animal studies, as well as case analyses and observations in humans.[2-4] Therefore, what was initially considered a topic of dispute among scientists, professional societies, and the industry has reached the status of an unequivocally defined thesis, with organizations at national and international legislative levels issuing relevant statements.[5-7] These highlight the fact that BPA at levels as low as parts per billion are unconjugated, which means that they are not metabolized and thus are biologically active, and are detected in human blood and tissues.[8,9]

BPA as endocrine disruptor

Xenoestrogenicity is a relatively recently described property of certain polymeric molecules such as BPA to express biologic effects similar to those induced by natural estrogens. The similar chemical structure of BPA to natural estrogen (17-beta estradiol) is the reason for this deviation of the hormonal homeostasis from the proper pathway.[10]

The effects of endocrine disrupting compounds were identified in the early 1960s when the nests of bald eagles, which consumed prey contaminated with pesticides, were found to produce 3 to 4 times fewer eaglets than the corresponding numbers recorded in the 1930s.[11] In spite of the early recognition of these effects, it took several decades for a substantial body of literature reporting biologic effects associated with these compounds to be accumulated, demonstrating the phenomena accompanying the exposure of organisms to BPA and including hormonal-related effects.[12]

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The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and none were reported.
Am J Orthod Dentofacial Orthop 2017;152:435-41
0889-5406/$36.00

http://dx.doi.org/10.1016/j.ajodo.2017.08.004

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ORIGINAL ARTICLE CE AJO-DO

High-performance liquid chromatography analysis of salivary bisphenol A levels from light-cured and chemically cured orthodontic adhesives

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Introduction: Our objective was to assess the levels of bisphenol A (BPA) released from light-cured and chemically cured resins used for orthodontic bracket bonding in 1 month. **Methods:** Saliva specimens were obtained at 5 time periods from 40 healthy patients treated with orthodontic mechanotherapeutics. The periods of collections were just before bonding orthodontic brackets, followed by 30 minutes, 1 day, 1 week, and 1 month after orthodontic bonding. The specimens were analyzed with the high-performance liquid chromatography/mass spectrometry method for quantitative evaluation of BPA levels. **Results:** We observed a large increase in BPA levels 30 minutes after orthodontic bonding in the 2 groups. Thereafter, there was sudden decline in BPA levels as time passed, and the levels reached a statistically significant level at 1 month after orthodontic bonding. Interestingly, the amount of BPA released from chemically cured resin was much higher; this was also significant statistically compared with light-cured resins. **Conclusions:** The results of this in-vivo approach with high-performance liquid chromatography on salivary specimens confirmed continued release of BPA after bonding brackets for 1 month, although in smaller quantities. The release during the initial 30 minutes is high, making it essential to introduce measures to dilute it for better patient safety. (Am J Orthod Dentofacial Orthop 2018;154:803-8)

Bisphenol A (BPA), an important component of many manufactured products, including polycarbonate plastics, the inner coating of food cans, and cosmetics, is a basic material in dental resins as a precursor for the generation of BPA glycidyldimethacrylate (Bis GMA) and BPA dimethacrylate. Researchers have removed the smoke screen regarding the deleterious effects of BPA on almost all organs and systems in the human body, and concerned authorities have issued appropriate statements at national and international levels.[1-3] There is evidence that BPA mimics 17β-estradiol and aims at all estrogen target organs in the body. BPA also mimics synthetic estrogens such as diethylstilbestrol, and experiments have shown that its dimethacrylate derivative Bis-DMA, BADGE, and related diphenylalkanes are estrogenic in different bioassays and systems.[4] Recently, reports demonstrating BPA's effect on thyroid hormones as well as reduction in testosterone levels in boys have also been published.[5] All hormone-mimicking effects can lead to obesity, widespread fertility problems, feminization of boys, accelerated maturational changes in girls, and increased diabetes risks and breast cancer incidences.[4,5]

Orthodontic resin-based adhesives consist of 2 main components: an organic monomer matrix based on functional dimethacrylate such as Bis GMA, urethane dimethacrylates, or triethyleneglycol-dimethacrylate; and inorganic filler components such as silica, glass, and ceramic. These are used for bonding various attachments because of their better mechanical and esthetic properties as well as lower failure rates. The risk associated from the systemic intake of BPA is due to the orthodontic brackets bonded to the dentition that stay for approximately 2 years as well as bonded lingual retainers that stay longer than that. The literature abounds with documented evidence of leaching BPA components from

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Submitted, July 2017; revised and accepted, February 2018.
0889-5406/$36.00

https://doi.org/10.1016/j.ajodo.2018.02.008

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ORIGINAL ARTICLE AJO-DO

Bisphenol A release from an orthodontic adhesive and its correlation with the degree of conversion on varying light-curing tip distances

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Introduction: The aims of this research were to use high-performance liquid chromatography to assess the bisphenol A (BPA) released from an orthodontic adhesive (Transbond XT; 3M Unitek, Monrovia, Calif) with various light-curing tip distances and to correlate the release to the degree of conversion. **Methods:** One hundred thirty-eight premolar brackets were divided into 3 groups of 40 each for the high-performance liquid chromatography analysis and 3 groups of 6 each for assessing the degree of conversion. Fourier transform infrared spectroscopy was used for this purpose. Each group was studied at light-curing tip distances of 0, 5, and 10 mm. Statistical analyses were performed by using 2-way analysis of variance (ANOVA), post-hoc multiple comparisons Tukey HSD tests, and paired *t* tests. Pearson correlation was used to assess the correlation between the degree of conversion and BPA release. **Results:** BPA release was greater in specimens cured with a greater light-curing tip distance. The degree of conversion decreased with increased light-curing tip distances. A negative correlation was found between BPA release and degree of conversion. **Conclusions:** Clinicians should ensure that the adhesive is completely cured by keeping the light-curing tip as close to the adhesive as clinically possible. (Am J Orthod Dentofacial Orthop 2011;140:239-44)

Orthodontic bonding resins are exposed to oral fluids and are in contact with tissues throughout treatment. Leaching from resin can occur at 2 times: during the setting period of the resin and later when the resin is degraded. Leaching during the first process is related to the degree of conversion (DC).[1] The DC of adhesives is of particular importance, since it modulates the physical and mechanical properties of the material, especially solubility and degradation.[2]

Leaching results in the release of monomers such as bisphenol A (BPA). The implications of BPA released from dental biomaterials was first reported in a study that assessed dental sealants.[3] BPA causes skin allergies,[4] adverse effects on the reproductive systems of animals,[5] cell death via necrosis,[6] and high hemolytic activity.[7] Terhune et al[8] have suggested clinicians should be cautious in preventing extended contact of any of these materials with a patient's skin, mucosa, and gingiva.

The depth of cure of resin-based composite decreases with increasing irradiation distance.[9] The light-curing unit tip should ideally be in direct contact with the resin composite; however, this is not always clinically possible.[10] Inability to place thelight tip near the bonding material might reduce intensity and provide a lower degree of polymerization.[10,11]

Hence, the purposes of this study were to quantitatively assess the BPA released from the Transbond XT (3M Unitek, Monrovia, Calif) when varying the light-curing tip distances by 0, 5, and 10 mm with high performance liquid chromatography (HPLC) after accelerated chemical aging on days 1, 7, 21, and 35 and to evaluate the DC by using Fourier transform infrared (FTIR) spectroscopy on day 1. BPA release was also correlated to the DC.

MATERIAL AND METHODS

A visible light-cured adhesive, Transbond XT, was used. From 138 premolar stainless steel brackets (3M Unitek), 120 were used to assess BPA release with HPLC, and 18 were used for estimating the DC with the FTIR spectrometer (Perkin-Elmer, Norwalk, Conn).

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The authors report no commercial, proprietary, or financial interest in the products or companies described in this article.
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Submitted, December 2009; revised and accepted, February 2010.
0889-5406/$36.00

doi:10.1016/j.ajodo.2010.02.037

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ORIGINAL ARTICLE CE AJO-DO

Bisphenol A release from orthodontic adhesives and its correlation with the degree of conversion

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Introduction: Our objective was to quantitatively assess and compare the bisphenol A (BPA) released from an orthodontic adhesive using a light-emitting diode device (LED) or a halogen light-curing unit (HLC) at 3 tip-to-bracket distances (0, 5, and 10 mm) and varying curing times using high-performance liquid chromatography. BPA release with self-etching and moisture-insensitive primers with light-cured and chemically cured composites was also evaluated. BPA release was correlated to the corresponding degree of conversion. **Methods:** Our sample consisted of 598 stainless steel first premolar brackets. Of these, 520 were used for assessing BPA release and divided into 13 groups of 40 each. In groups I, II, and III, the composite was cured with the LED for 20 seconds at distances of 0, 5, and 10 mm, respectively. Groups IV, V, and VI were cured with the HLC for 40 seconds at the same 3 distances. Groups VII and VIII were cured for 5 and 10 seconds with the LED, and groups IX and X were cured for 10 and 20 seconds with the HLC at 0-mm distance. Groups XI, XII, and XIII consisted of brackets bonded with a self-etching primer and Transbond (3M Unitek, Monrovia, Calif), with a moisture-insensitive primer and Transbond, and with a chemically cured composite. The remaining 78 brackets were also divided into 13 groups and used for assessing the degree of conversion. **Results:** The LED devices demonstrated significantly less BPA release and greater degrees of conversion ($P < 0.05$). For both units, BPA release increased and the degree of conversion decreased as the tip distance increased and curing time decreased. The chemically cured group showed significantly less BPA release ($P < 0.05$). Among the light-cured composites, those cured according to the manufacturers' recommendations (40 seconds and 0-mm distance for the HLC unit) released less BPA than did the self-etching primer and the moisture-insensitive primer. The degree of conversion was greatest for the chemically cured composite, whereas it was similar for the conventional, self-etching primer, and moisture-insensitive primer groups. However, correlations ranged from strongly negative to weakly positive between BPA release and degree of conversion. **Conclusions:** Clinicians should consider using LEDs in clinical practice and should keep the light-cure tip as close to the bracket as clinically possible. Curing time should be according to the manufacturer's recommendations. These steps will ensure less BPA release and a greater degree of conversion. Since chemically cured composites had less BPA release and a greater degree of conversion, they can be considered superior to light-cured composites in this aspect. (Am J Orthod Dentofacial Orthop 2015;147:29-36)

One of the most dramatic changes in the orthodontic specialty in the 1970s was the use of composite resin as a bonding material.[1] Both light-cured and chemically cured composites have been shown to be clinically acceptable and effective.[2] However, curing lights are required for light-cured resins. To obtain the correct irradiance using a halogen lamp, the initial power must be considerably high, producing heat that can cause pulpal damage.[3] As an alternative to halogen light curing units (HLC), light emitting diode (LED) technology has been proposed for curing dental composites. The curing time recommended is between 5 and 20 seconds.

Bisphenol A (BPA) is used as a raw material for the formulation of Bisphenol A diglycidyl dimethacrylate (Bis-GMA). Although bond strength has been evaluated, BPA release has not been extensively studied especially in self-etching primers (SEP) and moisture-insensitive primers (MIP); Eliades et al[4] reported no traces, whereas Gioka et al[5] found that the leachable components involved exclusively the TEGDMA monomer.

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Submitted, April 2012; revised and accepted, September 2014.
0889-5406/$36.00

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DENTAL MATERIALS XXX (2015) XXX–XXX

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.intl.elsevierhealth.com/journals/dema

BPA qualtitative and quantitative assessment associated with orthodontic bonding *in vivo*

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ARTICLE INFO

Article history:
Received 5 February 2015
Received in revised form
17 April 2015
Accepted 28 April 2015
Available online xxx

Keywords:
Orthodontic bracket bonding
Bisphenol-A (BPA)

ABSTRACT

Objective. To assess the *in vivo* amount of BPA released from a visible light-cured orthodontic adhesive, immediately after bracket bonding.

Methods. 20 orthodontic patients were recruited after obtaining informed consent. All patients received 24 orthodontic brackets in both dental arches. In Group A (11 patients), 25 ml of tap water were used for mouth rinsing, whereas in Group B (9 patients) a simulated mouth rinse formulation was used: a mixture of 20 ml de-ionized water plus 5 ml absolute ethanol. Rinsing solutions were collected before, immediately after placing the orthodontic appliances and after washing out the oral cavity and were then stored in glass tubes. Rinsing was performed in a single phase for 60 s with the entire volume of each liquid. The BPA analysis was performed by gas chromatography–mass spectrometry.

Results. An increase in BPA concentration immediately after the 1st post-bonding rinse was observed, for both rinsing media, which was reduced after the 2nd post-bonding rinse. Water exhibited higher levels of BPA concentration than water/ethanol after 1st and 2nd post-bonding rinses. Two-way mixed Repeated Measures ANOVA showed that the primary null hypothesis declaring mean BPA concentration to be equal across rinsing medium and rinsing status was rejected (p-value <0.001). The main effects of the rinsing medium and status, as well as their interaction were found to be statistically significant (p-values 0.048, <0.001 and 0.011 respectively).

Significance. A significant pattern of increase of BPA concentration, followed by a decrease that reached the initial values was observed. The amount of BPA was relatively low and far below the reference limits of tolerable daily intake.

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http://dx.doi.org/10.1016/j.dental.2015.04.020

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ORIGINAL ARTICLE CE AJO-DO

Comparative evaluation of salivary bisphenol A levels in patients wearing vacuum-formed and Hawley retainers: An in-vivo study

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Introduction: The aims of the study were to evaluate and compare the bisphenol A (BPA) levels in saliva in patients using vacuum-formed retainers or Hawley retainers. **Methods:** Forty-five patients who had completed their fixed orthodontic treatment and were entering the retention phase were randomly allocated into 1 of 3 groups: vacuum-formed retainer, Hawley retainer fabricated by heat cure, and Hawley retainer fabricated by chemical cure. Saliva samples were collected immediately before placement, within 1 hour after placement, 1 week and 1 month after placement. Statistical analyses were performed by using 2-way analysis of variance and post-hoc multiple-comparisons Tukey HSD tests. **Results:** Statistically significant BPA levels in saliva were found for all groups ($P \leq 0.05$). The highest levels were noted in the vacuum-formed retainer group, followed by Hawley retainers fabricated by chemical cure; the lowest levels were found with Hawley retainers fabricated by heat cure. **Conclusions:** With many options available for removable retainers, clinicians should consider the BPA release from these retainers; a Hawley retainer fabricated by heat cure is a favorable choice. (Am J Orthod Dentofacial Orthop 2017;151:471-6)

Retention, described as "secondary orthodontic treatment," is a key step to successful treatment.[1,2] To prevent relapse, almost every person who has orthodontic treatment will require some type of retention.[3] Commonly used removable retainers are vacuum-formed retainers (VFRs) and Hawley retainers; they differ from each other in composition and fabrication.[4,5] Although Hawley retainers can be fabricated using either heat cure or chemical cure acrylic and are composed of polymethyl methacrylate, VFRs, introduced in the 1970s by Ponitz,[5] are composed of polypropylene/polyethylene. Hawley retainers have an inherent disadvantage of unaesthetic display of wires on the labial surface of teeth, but VFRs have certain advantages such as durability, esthetics, ease of maintenance, reduced fabrication time and cost, ability to produce minor tooth movement, and ability to serve as carriers for bleaching solutions.[6-9]

The unease about the release of chemicals from various appliances has grown over recent decades. The World Health Organization in 2011 listed endocrine disruptive chemicals; one of them was bisphenol A (BPA), a synthetic compound that has gained medical attention because of its estrogenic action.[10]

The increased emphasis on BPA release can be attributed to the fact that it affects various organs, has teratogenic effects even at a low dose, results in early onset of puberty, causes feminization in males, and also has carcinogenic effects. Animal studies have shown the presence of BPA in body fluids including urine, adult and fetal blood, amniotic fluid, placental tissues, breast milk, and saliva.[11,12]

Chemicals such as hydroquinone, present in the liquid component of the Hawley retainer's base-plate material,[13] are BPA-related products.[14] BPA is added to polymers to make them clear and tough. Therefore, VFRs fabricated of clear thermoplastic material could release BPA.[10] The possible BPA release from these materials would be into the saliva; hence, saliva was chosen as a medium for the analysis of BPA. The added

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Submitted, March 2016; revised and accepted, July 2016.
0889-5406/$36.00

http://dx.doi.org/10.1016/j.ajodo.2016.07.022

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ORIGINAL ARTICLE AJO-DO

Release of bisphenol A from resin composite used to bond orthodontic lingual retainers

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Introduction: In this study, we assessed the changes in bisphenol A (BPA) levels in saliva and urine after placing lingual bonded retainers. **Methods:** Liquid chromatography/mass spectrometry was used to examine the BPA levels in the saliva and urine samples collected from 22 volunteers who received a lingual bonded retainer on their mandibular dentition. Samples were collected immediately before placement and 30 minutes, 1 day, 1 week, and 1 month after placement. The time elapsed after placement, type of resin composite (nanohybrid filled flowable resin or conventional hybrid resin), surface prophylaxis, age, and sex were evaluated for their effects on the BPA levels. **Results:** The only significant high level of BPA was observed in the saliva collected just after placement of the lingual bonded retainer. Age and sex did not affect the BPA levels. Subjects in the flowable resin group had lower BPA levels than those in the conventional hybrid resin group; pumice prophylaxis decreased the level of BPA released from the conventional hybrid resin at the immediate time point. The salivary BPA level (maximum, 20.889 ng/mL) detected in the samples collected just after placement was far lower than the reference daily intake dose. **Conclusions:** Accordingly, the potential toxicity of BPA from placing lingual bonded retainer might be negligible. On the other hand, because the health-effective amount of BPA is controversial, BPA release should be minimized. (Am J Orthod Dentofacial Orthop 2011;140:779-89)

Bisphenol A (BPA) is a well-known potent endocrine disruptor with a weak estrogenic effect. It is one of many commercial chemicals found in daily life, with more than 6.4 billion pounds produced worldwide in 2003 and growing at 6% to 10% per year.[1] BPA has many applications in manufactured products, such as polycarbonate plastics, inner coating of food cans, antioxidants in cosmetics and food, and so on. In dentistry, BPA is a basic material for dental resins that is a precursor for BPA glycidyl dimethacrylate (Bis-GMA) and BPA dimethacrylate (Bis-DMA). On the other hand, the degradation of dental resins can leach BPA, and this reverse process is accelerated with heat, mechanical wear, and bacterial or salivary enzymatic action.

Articles on the possible hazardous effects of BPA have been published. BPA has an estrogenic effect, and the intake of BPA was reported to have a hazardous effect on living bodies. These effects involve increased growth rate,[2] precocious puberty,[3] decreased sperm count and infertility,[4,5] increased risks of breast and prostate cancers,[6] behavioral effects,[7,8] and altered immune functions.[9] Animal studies provided evidence of these effects, but the hazardous effects on human health are uncertain. Moreover, its risk assessment is unclear because the research design for humans is difficult. There is an extrapolated potential risk from animal study results, and it appears logical to err on the side of caution in this matter.

In dentistry, BPA is a source material used for manufacturing dental resins including dental sealants. Incomplete polymerization can result in the release of resin monomers into the oral cavity, and Bis-DMA–based resins have been shown to release BPA through biodegradation.[10,11] Although Bis-GMA–based resins are reported not to release BPA from biodegradation, there is still the possibility that BPA and Bis-DMA, as impurities in the resins, might be released during biodegradation.[11] Many studies have evaluated the amounts of BPA released from dental resins and attempted to assess

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The authors report no commercial, proprietary, or financial interest in the products or companies described in this article.
Based on a thesis by Ji-Young Kim submitted to the graduate faculty, Kyung Hee University, in partial fulfillment of the requirements for the PhD degree.
Supported by a grant from Kyung Hee University in 2009 (KHU-20091425).
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Submitted, December 2010; revised and accepted, April 2011.
0889-5406/$36.00

doi:10.1016/j.ajodo.2011.04.022

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ORIGINAL ARTICLE AJO-DO

Release of bisphenol-A from a light-cured adhesive bonded to lingual fixed retainers

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Introduction: Our aim was to quantitatively determine the bisphenol-A (BPA) released from a light-cured orthodontic adhesive used to bond lingual fixed retainers. **Methods:** Eighteen recently extracted premolars, divided into 3 groups of 6 teeth each, were embedded in plaster in an arch shape. A light-cured adhesive (Transbond XT, 3M Unitek, Monrovia, Calif) was bonded to a .0195-in, 3-strand heat-treated twist flex wire (Wildcat, GAC International, Bohemia, NY) adjusted to the lingual surface of the teeth, and the arches were immersed in doubled-distilled water for 10, 20, and 30 days. The concentration of BPA in the 3 eluents was investigated with gas chromatography-mass spectroscopy; all assays were performed in triplicate, and the results were averaged. **Results:** Measurable amounts of BPA were identified for all groups, with the highest found in the immersion media of the 1-month groups (2.9 μg/L), whereas the control (tooth storage solution) had 0.16 μg/L. **Conclusions:** The BPA released from a light-cured adhesive used to bond lingual fixed retainers might be assigned to the application mode of the material that differs from conventional use. Further testing including estrogenicity assays will assess the potential estrogenic action of this application. Composite restorative resins should replace orthodontic adhesives that were not intended to function with their surfaces in the oral cavity; alternatively, canine-bonded fixed retainers might reduce the amount of adhesive used. (Am J Orthod Dentofacial Orthop 2011;139:192-5)

The issue of bisphenol-A (BPA) release, which is a precursor of Bis-GMA and polycarbonate materials manufacturing, from orthodontic polymers has received wide interest from academic groups, legislatures, and international organizations. BPA's reported action covers a wide spectrum of effects at the tissue, organ, and system levels.[1-4]

Recent evidence has indicated that chemically cured and light-cured orthodontic adhesives do not show measurable release of BPA and lack estrogenic action.[5,6] BPA release is associated with both the composition and the application mode of materials, since Bis-GMA–containing adhesives can release BPA depending on the state of the material. A recent study demonstrated that adhesives that did not show estrogenicity in the bulk form exhibited this property in the form of powder produced during simulated debonding and cleanup with rotary instruments.[7]

Fixed retainers have been used in orthodontics for many years. Especially in the mandibular arch, they are commonly used for an extended period of time or permanently, because they have proven to be efficient in preventing relapse in most patients.[8] Two main types of mandibular retainers are used: large-diameter wires bonded only to the lingual surfaces of the canines, and small-diameter ones bonded to the lingual surfaces of all 6 mandibular teeth. From the latter type, the flexible spiral wire retainer is the most common,[9] even though in a few patients it can produce unwanted tooth movements during retention.[10] For bonding both retainer types, specific orthodontic adhesives (mainly light-cured) are used. The adhesive in this case is used in a mode that involves exposure of its surface to the oral environment and an extremely large surface-to-volume ratio, which increases its reactivity with the surrounding environment and favors aging and degradation, with unpredictable BPA release.

The purposes of this study were to quantitatively determine the BPA released from light-cured adhesive used

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The authors report no commercial, proprietary, or financial interest in the products or companies described in this article.
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Submitted, September 2009; revised and accepted, December 2009.
0889-5406/$36.00

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ORIGINAL ARTICLE

AJO-DO

Bisphenol A release from orthodontic adhesives measured in vitro and in vivo with gas chromatography

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Introduction: The objectives of this study were to quantify in vitro the Bisphenol A (BPA) release from 5 orthodontic composites and to assess in vivo the BPA level in patients' saliva and urine after bracket bonding with an orthodontic adhesive system. **Methods:** For the in-vitro portion of this study, 5 orthodontic composites were evaluated: Eagle Spectrum (American Orthodontics, Sheboygan, Wis), Enlight (Ormco, Orange, Calif), Light Bond (Reliance Orthodontic Products, Itasca, Ill), Mono Lok II (Rocky Mountain Orthodontics, Denver, Colo), and Transbond XT (3M Unitek, Monrovia, Calif). Simulating intraoral conditions, the specimens were immersed in a water/ethanol solution, and the BPA ($ng.g^{-1}$) liberation was measured after 30 minutes, 24 hours, 1 day, 1 week, and 1 month by the gas chromatography system coupled with mass spectrometry. Twenty patients indicated for fixed orthodontic treatment participated in the in-vivo study. Saliva samples were collected before bracket bonding and then 30 minutes, 24 hours, 1 day, 1 week, and 1 month after bonding the brackets. Urine samples were collected before bonding and then at 1 day, 1 week, and 1 month after bonding. The results were analyzed statistically using analysis of variance and Tukey posttest, with a significance level of 5%. **Results:** All composites evaluated in vitro released small amounts of BPA. Enlight composite showed the greatest release, at 1 month. Regarding the in-vivo study, the mean BPA level in saliva increased significantly only at 30 minutes after bonding in comparison with measurements recorded before bonding. **Conclusions:** All orthodontic composites released BPA in vitro. Enlight and Light Bond had, respectively, the highest and lowest BPA releases in vitro. The in-vivo experiment showed that bracket bonding with the Transbond XT orthodontic adhesive system resulted in increased BPA levels in saliva and urine. The levels were significant but still lower than the reference dose for daily ingestion. (Am J Orthod Dentofacial Orthop 2017;151:477-83)

During orthodontic treatment with fixed appliances, bracket bonding with composite materials based on bisphenol A glycidyl methacrylate is of great importance for treatment outcome.[1,2] It is the main monomer used in resins and orthodontic adhesives,[3] and bisphenol A (2,2'-bis [4-hydroxyphenyl] propane; BPA) is the main component of this monomer.[4]

BPA is a synthetic chemical substance widely used for production of epoxy resin and polycarbonate plastic used to manufacture various products, including bottles, food packaging, baby bottles, toys, detergents, pesticides, cars, and dental resinous materials, such as composites and pit-and-fissure sealants.[5,6] Due to the increase in the number of products based on epoxy resins and polycarbonate plastics, human exposure to BPA has increased rapidly.[7,8]

BPA has been extensively studied as one of the most common environmental endocrine disruptors, having an estrogenic action from competitive binding of estrogen-like polymer molecules to natural hormone receptors.[9] The environment—water, air, and soil—can be a route of exposure to BPA, but foods are the primary source

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Submitted, March 2016; revised and accepted, July 2016.
0889-5406/$36.00

http://dx.doi.org/10.1016/j.ajodo.2016.07.019

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COVER STORY

Bisphenol A and other compounds in human saliva and urine associated with the placement of composite restorations

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Bisphenol A (BPA) is a widely used organic compound shown to mimic estrogen activity, primarily as an endocrine disruptor.[1,2] BPA is used in the production of epoxy resins and polycarbonate plastics, which are used to make many drinking bottles, food storage containers, dental polymers, adhesives, flame retardants and water supply pipes.[1,3] The primary source of BPA exposure for the general population is thought to be food that contains BPA that leaches from food containers or drinking bottles.[4] Other environmental sources, including air, dust and water, also may contribute to total BPA exposure in the general population.[2,5] However, data are lacking regarding the relative contributions of these different sources to human exposure to BPA.

Authors of literature reviews have documented several types of endocrine-disruptive effects associated with BPA, which display variation among species, animal strain and source of exposure.[3,6,7] Investigators in cross-

ABSTRACT

JADA CE CONTINUING EDUCATION ARTICLE 1

Background. Bisphenol A (BPA) and other related chemical compounds may be components used in the manufacturing process of resin-based composite dental restorative material. The purpose of the authors' study was to assess salivary and urinary concentrations of BPA and other compounds before and after placement of resin-based composite dental restorations.

Methods. The authors collected saliva and urine from 172 participants receiving composite restorations before and as long as 30 hours after placement of composite restorations. The authors analyzed saliva specimens from 151 participants and urine specimens from 171 participants for concentrations of BPA and five related compounds by using liquid chromatography/mass spectrometry (LC/MS).

Results. Salivary concentrations of BPA and some related compounds increased immediately (within one hour) after composite placement. Salivary concentrations of BPA and most study compounds returned to prerestoration levels within eight hours after composite placement. With the exception of a 43 percent increase in BPA, concentrations of the study compounds in urine returned to prerestoration levels nine to 30 hours after restoration placement. Concentrations in saliva were lower when a rubber dam was used; however, rubber dam use appeared to have no effect on urinary concentrations of the measured compounds during the study period. The authors observed similar changes in study compound levels in both saliva and urine between participants who received anterior restorations and those who received posterior restorations.

Conclusions. Placement of resin-based composite restorations was associated with detectable increases in saliva of BPA and other study compounds within one hour after restoration placement and an increased concentration of BPA in urine nine to 30 hours after restoration placement. Rubber dam use did not reduce the absorption of BPA (measured as BPA level in urine) during the study.

Clinical Implications. Additional studies are needed to address how long BPA levels in urine associated with composite placement remain elevated to aid in better understanding of the clearance rates of BPA and other study compounds.

Key Words. Bisphenol A; dental composites; liquid chromatography/mass spectrometry; urine; saliva.

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Research

Bisphenol A Blood and Saliva Levels Prior To and After Dental Sealant Placement In Adults

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Abstract

Purpose: This study examined the effects of a widely used (Delton® Pit & Fissure Sealant – Light Cure Opaque, DENTSPLY Professional, York, PA) pit and fissure sealant material on bisphenol A (BPA) levels in blood and saliva, among both low and high–dose groups over time.
Methods: A convenience sample of 30 adults from the Old Dominion University population were randomly and evenly divided into 2 independent variable groups: a low–dose group (1 occlusal sealant application) and high–dose group (4 occlusal sealant applications). A 2 group, time series design was used to examine the presence and concentration of BPA in serum and saliva after sealant placement. Differences comparing low–dose and high–dose groups were examined 1 hour prior (baseline), 1 hour post, 3 hours post and 24 hours after sealant placement, as measured by a direct–competitive BPA Enzyme Linked ImmunoSorbent Assay (ELISA). Hypothesized outcomes were evaluated by applying a parametric, 2 way ANOVA for repeated measures technique to data on the 30 participants ranging in age from 18 to 40 years, and were of mixed gender and ethnicity.
Results: BPA was detected in the saliva of all participants prior to sealant placement and ranged from 0.07 to 6.00 ng/ml at baseline. Salivary BPA concentration levels peaked over a 3 hour period following sealant placement and returned to baseline levels within 24 hours. BPA was significantly elevated at all post–sealant placement time periods for both the low–dose (1 occlusal sealant application) and high–dose (4 occlusal sealant applications) groups with peak levels of 3.98 ng/ml and 9.08 ng/ml, respectively. The blood serum did not contain BPA at any point in this investigation.
Conclusions: Exposure to BPA from sources other than dental resins contributes to salivary baseline concentration levels and indicates environmental exposure and use of products containing BPA. Use of specific molecular formulations of dental sealant material determines the release of BPA, therefore, dental sealant materials should be reviewed independently when questioning the release of BPA from dental sealants. In addition, dosage amounts of the dental sealant material used in this study do not influence the serum concentration levels of BPA. Further research is needed to examine the cumulative estrogenic effects of BPA from dental sealants.

Keywords: sealants, dental, bisphenol A, estrogenic

This study supports the NDHRA priority area, Occupational Health and Safety: Investigate methods to decrease errors, risks and or hazards in health care and their harmful impact on patients.

Introduction

Occlusal sealants in permanent molars demonstrate caries–preventive effects, lasting 15 to 20 years.[1,2] Dental sealants differ from restorative composite fillings. Unfilled pit and fissure dental sealants contain only the dimethacrylate resin component of composite dental materials made of an organic monomer, bisphenol A–diglycidyl methacrylate (bis–GMA). This is the most commonly used resin matrix which is formed by reacting glycidyl methacrylate with bisphenol A (BPA).[3] Additional monomers, including acrylates and methacrylates, may be added to bis–GMA to dilute the resin and make the sealant material more flowable.[4] One of the most common monomers added to bis–GMA is BPA, which is a hormonally active, synthetic chemical and part of a broad group of chemicals known as endocrine disrupting compounds.[4] More specifically, BPA is a xenoestrogen, which mimics the relative bioactivity of estrogen.[5]

Among all xenoestrogens, BPA has received increased attention due to its pervasive presence in the environment and ubiquitous human exposure. BPA is used in the manufacture of polycarbonate plastics and epoxy resins and leaches from food and beverage containers, baby bottles, children's toys and dental sealants.[6–8] BPA leaches from some formulations of dental sealants, if not completely polymerized, may be released into the oral cavity as a result of enzymatic activity within saliva, and may be systemically absorbed by the patient.[9–11]

Perinatal low–dose exposure to BPA results in functional and morphological alterations of the rodent

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Clin Oral Invest
DOI 10.1007/s00784-017-2055-9

ORIGINAL ARTICLE

Bisphenol A concentration in human saliva related to dental polymer-based fillings

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Received: 20 March 2016 / Accepted: 9 January 2017

Abstract
Objectives The aims of this study were to quantify salivary concentrations of bisphenol A (BPA) and to assess if presence of dental composite fillings is associated with higher BPA levels in saliva.
Materials and methods Twenty individuals with six or more tooth surfaces filled with polymer-based dental materials (composite group) and 20 individuals without any polymer-based materials (control group) were included in the study. Saliva was collected in polypropylene tubes and stored at −80 °C before analysis. Concentration of free (unconjugated) and total bisphenol A was determined by liquid chromatography/mass spectrometry (LC/MS). Values below limit of detection (0.1 ng/mL) were set to one-half of the limit of detection. Mann-Whitney *U* test (one sided; the Exact Tests Option in IBM-SPSS version 21) was used for the statistical analyses.
Results The concentration of BPA in saliva was very low. In the composite group, 8 of 20 samples had detectable concentrations of BPA. In the control group, 3 of 20 samples had detectable concentrations of BPA. Statistical analysis indicated that the concentration of unconjugated BPA was slightly higher in the composite group ($p = 0.044$) than in the control group.
Conclusions Presence of dental composites may be associated with slightly higher concentration of unconjugated BPA in saliva. However, additional studies using sensitive analytical methods are needed before firm conclusions can be drawn. Influence from other factors, like food intake and time of the day for saliva sampling, must be considered.
Clinical relevance The relative contribution of existing polymer-based dental fillings to total BPA exposure seems to be low.

Keywords Bisphenol A · Human saliva · Dental polymer-based fillings · Composite resins

Introduction

The health concerns regarding bisphenol A (BPA), a chemical that is widely used in the production of polycarbonate plastic and epoxy resins, have received increased attention during the last years. BPA is known to be an endocrine-disrupting chemical, which mimics oestrogen [1–3].

Exposure to low doses of BPA has been associated with adverse health effects such as diabetes, heart disease, coronary artery disease, obesity, disorders of the immune system and reproductive disorders [4, 5]. However, the risk assessment of low-dose effects from BPA is controversial [6] and represents a challenge for the traditional regulatory health risk assessment [7]. In January 2015, The European Food Safety Authority (EFSA) reduced the recommended limit of tolerable daily intake (TDI) of BPA from 50 to 4 μg per kg body weight per day [8].

B. A. G. Jönsson passed away on 24 November 2016

Electronic supplementary material The online version of this article (doi:10.1007/s00784-017-2055-9) contains supplementary material, which is available to authorized users.

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Published online: 09 February 2017

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European Journal of Oral Sciences

Eur J Oral Sci 2012; 120: 89–95
DOI: 10.1111/j.1600-0722.2011.00897.x
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European Journal of Oral Sciences

Detection and quantification of monomers in unstimulated whole saliva after treatment with resin-based composite fillings *in vivo*

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Michelsen VB, Kopperud HBM, Lygre GB, Björkman L, Jensen E, Kleven IS, Svahn J, Lygre H. Detection and quantification of monomers in unstimulated whole saliva after treatment with resin-based composite fillings in vivo.
Eur J Oral Sci 2012; 120: 89–95. © 2012 Eur J Oral Sci

Resin-based dental restorative materials contain allergenic methacrylate monomers, which may be released into saliva after restorative treatment. Monomers from resin-based composite materials have been demonstrated in saliva *in vitro*; however, studies analyzing saliva after restorative therapy are scarce. The aim of this study was to quantify methacrylate monomers in saliva after treatment with a resin-based composite filling material. Saliva was collected from 10 patients at four start points – before treatment, and 10 min, 24 h, and 7 d after treatment – and analysed by combined chromatography/mass spectrometry. The monomers bisphenol-A diglycidyl methacrylate (Bis-GMA), 2-hydroxyethyl methacrylate (HEMA), and urethane dimethacrylate (UDMA) were detected and quantified in the samples collected shortly (10 min) after treatment. The amounts detected ranged from 0.028 to 9.65 $\mu g\ ml^{-1}$ for Bis-GMA, from 0.015 to 0.19 $\mu g\ ml^{-1}$ for HEMA, and from 0.004 to 1.2 $\mu g\ ml^{-1}$ for UDMA. Triethyleneglycol dimethacrylate (TEGDMA) was detected in four of the samples. Ethoxylated bisphenol-A dimethacrylate (Bis-EMA) was not detected. Monomers were not detected in saliva samples collected before treatment, or 24 h or 7 d after treatment, with the exception of one sample, 24 h after treatment, in which HEMA was detected. In conclusion, monomers from the investigated resin-based composite and adhesive system were present in saliva shortly after treatment. One week after treatment, no monomers could be detected in patients' saliva samples.

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Key words: chromatography; eluates; monomers; resin-based composites; saliva

Accepted for publication September 2011

Dental materials are among the most extensively used artificial materials in humans. Among restorative materials, resin-based materials are most commonly applied. Resin-based dental restorative materials are complex materials consisting of inorganic or organic filler particles embedded in an organic, resin-based matrix. This matrix is a cross-linked polymer network formed by the polymerization of various types of monomers. The degree of conversion is never complete, and therefore residual monomers are left unbound and initially trapped in the cured material. These substances may elute from the material, and compounds like bisphenol A diglycidylmethacrylate (Bis-GMA), 2-hydroxyethyl methacylate (HEMA), triethylene glycol dimethacrylate (TEGDMA), and urethane dimethacrylate (UDMA) have been demonstrated to be released in several types of liquid, such as ethanol, methanol, water, and saliva (1–7).

Several studies have shown that methacrylate-based monomers from dental resin-based materials have the potential to cause adverse effects in mammalian *in vitro* systems. Cytotoxic (8, 9), genotoxic (10–16), and estrogenic (17, 18) effects have been discussed and demonstrated. Numerous studies on *in vitro* adverse reactions, but few studies on clinical side effects, have recently resulted in a recommendation of the re-evaluation of biological properties of dental materials in current use (19).

Although resin-based filling materials and adhesives contain several substances with well known allergenic potential (20–22), there are few reports in the literature on local side effects in the oral mucosa from these materials. The clinical picture of reactions reported in association with resin-based filling materials and adhesives is heterogeneous (20). An asthmatic reaction and urticaria have been described in association with the use of a fissure sealant (22, 23), and contact reactions in the oral mucosa,

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Chemosphere 172 (2017) 46–51

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

Salivary bisphenol A levels and their association with composite resin restoration

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HIGHLIGHTS

- The level of BPA in saliva collected 5 min after filling procedure was 3.64 μg/L.
- The level of BPA in saliva 7 d after filling procedure was 0.59 μg/L, which was lower compared to level 5 min after procedure.
- On the basis of the EFSA criterion, level of BPA after filling procedure was assessed as safe and found not harmful to health.

ARTICLE INFO

Article history:
Received 2 September 2016
Received in revised form
24 November 2016
Accepted 24 December 2016
Available online 27 December 2016

Handling Editor: Andreas Sjodin

Keywords:
Bisphenol A
Dental composites
Endocrine disruptor
Pit and fissure sealant
Saliva

ABSTRACT

Composite resin has been increasingly used in an effort to remove minimal amount of tooth structure and are used for restoring not just carious cavities but also cervical abrasion. To synthesize composite resin, bisphenol A (BPA) is used. The aim of the study was to measure the changes in salivary BPA level related with composite resin restoration. ELISA was used to examine the BPA levels in the saliva collected from 30 volunteers whose teeth were filled with composite resin. Salivary samples were collected immediately before filling and 5 min and 7 d after filling. Wilcoxon signed-ranks test and linear regression were performed to test the significant differences of the changes in BPA levels in saliva. Before a new composite resin filling, there was no significant difference between with and without existing filling of composite resin and BPA level in the saliva was not correlated to the number of filled surfaces with composite resin. However, BPA level in the saliva increased to average 3.64 μg/L from average 0.15 μg/L after filling 5 min. BPA level increased in proportion with the number of filled surfaces. BPA level decreased to average 0.59 after filling 7 d. However it was higher than the BPA level before a new composite resin filling. Considering 50 μg/kg/day as the Tolerable Daily Intake of BPA suggested by European Food Safety Authority, the amount of BPA eluted in saliva after the composite resin filling is considered a safe level that is not a hazard to health at all.

1. Introduction

Mastication is a fundamental function to sustain survival behavior of eating and drinking. It is difficult to conduct everyday activities if teeth are lost (Kim et al., 2009a, 2009b). Dental caries, also known as tooth decay, cavities, or caries, is a breakdown of teeth due to activities of bacteria (Silk, 2014). Dental caries and periodontitis have been reported as leading causes of tooth loss both in and outside Korea (Richards et al., 2005; Aida et al., 2006; Ro et al., 1998; Lee et al., 2002). To prevent tooth loss, the primary strategy is to prevent dental caries and periodontitis, but if the disease is already present, secondary prevention in the form of

Abbreviations: BPA, Bisphenol A; Bis-GMA, Bisphenol A-glycidyl dimethacrylate; Bis-DMA, Bisphenol A-dimethacrylate; BADGE, Bisphenol A-diglycidyl ether; Bis-EMA, Bisphenol A-ethoxylate dimethacrylate; TEGDMA, Triethylene glycol dimethacrylate; UDMA, Urethane dimethacrylate; MFDS, The Korean Ministry of Food and Drug Safety; TDI, Tolerable daily intake; EFSA, European Food Safety Authority.

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ARTICLE IN PRESS
ORIGINAL CONTRIBUTIONS

Changes in urinary bisphenol A concentrations associated with placement of dental composite restorations in children and adolescents

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Bisphenol A (BPA) is a chemical used in the manufacturing of polycarbonate plastics and epoxy resins, which are used by nearly every industry, including dentistry. Concern about human BPA exposure exists because BPA is an endocrine-disrupting chemical and because the results of animal studies have shown that BPA has reproductive, developmental, and systemic toxic effects even at low doses (for example, less than 50 milligrams per kilogram per day).[1-3] A causal role for BPA in human health problems remains to be determined, and most studies to date have been cross-sectional.[4,5] However, evidence from prospective human studies suggests that prenatal or postnatal exposure to BPA is associated with reproductive health measures (for example, ovarian toxicity in women[6] and delayed puberty in boys[7]), immune function,[8,9] and neurodevelopment in children.[4]

The possibility of adverse effects related to BPA exposure in humans has driven research efforts to identify BPA exposure sources, improve BPA exposure characterization in humans, and produce BPA-free substitute products.[10,11] The predominant exposure route in the

ABSTRACT

Background. Bisphenol A-glycidyl methacrylate (bis-GMA)–based dental composite restorations may release bisphenol A (BPA). The authors assessed changes in urinary BPA concentrations over a 6-month follow-up period in children and adolescents who received bis-GMA–based restorations.

Methods. The authors collected data from 91 study participants aged 3 to 17 years who needed composite restorations. Participants provided urine samples and information on BPA-related exposures before and at approximately 1 day, 14 days, and 6 months after treatment. The authors used multivariable linear regression models to test associations between the number of surface restorations placed and the changes in urinary BPA concentrations.

Results. Participants had a mean (standard deviation [SD]) of 1.4 (1.0) for surfaces restored with composite at the first treatment visit and 2.3 (1.6) for surfaces restored during the entire study period. Mean (SD) change in urinary BPA concentrations between pretreatment and day 1 was 1.71 (9.94) nanograms per milliliter overall and 0.87 (5.98) after excluding 1 participant who had 8 surfaces restored at the visit. Overall, the authors observed an association between a greater number of composite surface restorations placed and higher urinary BPA concentrations in the 1-day sample (posterior-occlusal exponentiated coefficients [e^{β}] = 1.47; 95% confidence interval [CI], 1.18-1.83; $P < .001$), but the association was attenuated after the authors restricted the sample to the 88 participants who had up to 4 restorations ($e^{\beta} = 1.19$; 95% CI, 0.86-1.64), and they did not observe any association using 14-day ($e^{\beta} = 0.94$; 95% CI, 0.75-1.18) or 6-month ($e^{\beta} = 0.88$; 95% CI, 0.74-1.04) samples.

Conclusions. Placement of bis-GMA–based restorations in children and adolescents may produce transient increases in urinary BPA concentrations that are no longer detectable in urine samples taken approximately 14 days or 6 months after treatment. After placement of a few restorations, increases in urinary BPA concentrations may not be detectable, owing to a high level of variation in background BPA exposure.

Practical Implications. These results suggest that leaching of BPA from newly placed composite restorations ceases to be detectable in urine within 2 weeks after restoration placement. The potential human health impact of such short-term exposure remains uncertain.

Key Words. Dental restoration; dental care for children; composites; pediatric dentistry; polymers; bisphenol A.

JADA 2016:■(■):■-■. ClinicalTrials.gov identifier NCT01484132.

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ORIGINAL ARTICLE

International Dental Journal 2012; 62: 65–69

doi: 10.1111/j.1875-595X.2011.00089.x

Dental composite fillings and bisphenol A among children: a survey in South Korea

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Aims: Bisphenol A (BPA)-based dental composites have commonly been used to fill dental cavities or seal pits and fissures on teeth. However, epidemiological evidence with regard to the BPA exposure from dental composites among children has rarely been reported. This study investigated whether there is a relationship between the BPA concentration in urine and the presence of composite restorations and sealants among South Korean children. **Methods:** Oral examinations and urine sample analyses were conducted on a total of 495 children aged 8–9 years. We classified the participants into four groups by the number of resin composites and sealant surfaces (0, 1–5, 6–10 and 11+). **Results:** BPA concentrations in urine were higher in children with 11 or more surfaces restored with sealants and resin composites than in those with zero restored surfaces, although no difference was seen in the group with 1–10 surfaces. After adjusting for gender and age, the urinary BPA concentration in children with 11 or more resin composite surfaces was 2.67 μg/g creatinine, which was higher than the concentration found in those with no filling surfaces ($P < 0.01$). **Conclusions:** Having many dental composite filling surfaces on teeth may increase the urinary BPA concentration in children.

Key words: *Bisphenol A, children, dental composites, sealant, urine*

Resin composites are being used as restorative materials with increasing frequency in dentistry because of the demand for aesthetic restorations and concerns about the adverse effects of mercury from amalgam[1]. Resin-based composite restorative materials consist of two major components: a resin matrix and a filler. Composites without fillers are known as sealants[2]. The resin matrix commonly contains monomers, such as 2, 2-bis[4-(2-hydroxy-3-methacryloxy-propoxy)-phenyl] propane (Bis-GMA), urethane dimethacrylate (UDMA) and/or triethylene glycol dimethacrylate (TEGDMA)[3,4]. After a curing process, unpolymerised monomers can be leached from the resin-based composites and may be absorbed systemically[5].

Bis-GMA, the most commonly used matrix material for dental polymers[6], is a methacrylate ester based on bisphenol A (BPA)[7], which is known to disrupt endocrine function by mimicking oestrogen[8], and has the potential to interfere with natural hormones in the human body[9]. As a result of the metabolism of BPA by androgens[10], it has been reported that serum BPA levels are strongly associated with higher androgen concentrations. It has also been hypothesised that BPAs bind to oestrogen receptors in the pituitary gland, leading directly to the suppression of follicle-stimulating hormone secretion[11]. However, although many studies evaluating the effects of BPA exposure from various sources have been performed[12,13], there is little epidemiological evidence describing the amount of BPA leached from resin composites or sealants and its health effects in humans[5,8,14].

As newborn children do not have fully developed metabolic mechanisms[12], they are more susceptible than adults to possible adverse effects[15] of the same levels of external BPA exposure. Therefore, it is important to determine the BPA levels derived from exposure to resin composites in children because of the age-dependent differences in metabolic clearance[10]. However, few studies have demonstrated the BPA concentrations in the body brought about by resin-based dental materials in children. For this reason, this study investigates the relationship between the number of sealant and/or composite filling surfaces and BPA concentration in urine among South Korean children.

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REVIEW

Endocrine Disruptors 1:1, e25078; October-December 2013; © 2013 Landes Bioscience

Low dose effects of bisphenol A

An integrated review of in vitro, laboratory animal, and epidemiology studies

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Keywords: cell culture, endocrine disruptor, epidemiology, LOAEL, non-monotonic dose response, aquatic animal, xenoestrogen

Abbreviations: BPA, bisphenol A; CNS, central nervous system; EDC, endocrine disrupting chemical; EPA, US Environmental Protection Agency; ER, estrogen receptor; IVF, in vitro fertilization; LOAEL, lowest observed adverse effect level; NIEHS, National Institute of Environmental Health Sciences; NMDRC, non-monotonic dose response curve; NTP, US National Toxicology Program; OECD, Organization for Economic Cooperation and Development; T4, thyroxine; TSH, thyroid stimulating hormone

In 2007, a group of experts critically analyzed hundreds of publications on bisphenol A (BPA), including the evidence for low dose effects. Here, we have updated these evaluations to determine the strength of the evidence for low dose effects of BPA. Based on the cut-offs for "low doses" established previously (i.e., the lowest observed adverse effect level [LOAEL], or 50 mg/kg/day for mammalian studies), we identified more than 450 low dose studies. Using an integrative approach, we examined five endpoints in depth that had evidence from two or more study types (in vitro, in vivo laboratory animal, and human). Based on all available studies, we are confident that consistent, reproducible, low dose effects have been demonstrated for BPA. We conclude that the doses that reliably produce effects in animals are 1–4 magnitudes of order lower than the current LOAEL of 50 mg/kg/day and many should be considered adverse.

Introduction

Bisphenol A (BPA; CAS# 80-05-7) is a high-volume chemical that is widely used in the production of consumer products.[1] BPA has estrogenic properties in vitro and in vivo, binds the membrane-associated estrogen receptor (ER), and may also act via the androgen receptor, thyroid hormone receptor, peroxisome proliferator-activated receptor-γ, and other endocrine-relevant signaling pathways.[2] A recent study by the US Environmental Protection Agency (EPA) and US National Toxicology Program (NTP) assigned BPA the third highest Toxicological Priority Index (ToxPi) score of the 309 chemicals examined based on its ability to interact with a number of signaling pathways.[3]

This review focuses on examining one aspect of the action of BPA, effects at low doses. We provide a brief overview of previous assessments of low dose effects and an updated review of low dose studies published since 2007. Further, we use an integrative biology approach to identify endpoints consistently affected by BPA exposures, examining five endpoints that have been observed in multiple studies from several laboratories, assessing the effects of low doses on multiple levels of biological organization (cells, animals, and human populations).

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Submitted: 09/08/2013; Accepted: 09/13/2013
http://dx.doi.org/10.4161/endo.26490

Defining "Low Dose"

In 2001, an NTP panel of experts assessing low dose effects for a number of endocrine-disrupting chemicals (EDCs) defined "low dose" as any biological change occurring in the range of typical human exposures or at doses lower than those tested in traditional toxicology assessments.[4] At that time, the NTP panel concluded that there were low dose effects for a number of EDCs. It should be noted that the NTP's definitions for low dose (human exposure levels vs. doses used in traditional toxicology assays) produce very different cut-offs for many EDCs, including BPA.[5]

Defining "low dose" cut-offs for BPA studies

Using the NTP's definition of doses lower than those tested in traditional toxicology assessments,[4] a cut-off for low dose BPA

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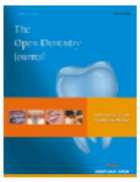
DOI: 10.2174/1874210601610010446



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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1874-2106/16