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Bisphenol A and Orthodontics: an update of evidence-based measures to mminimize exposure for the orthodontic team and patients

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INTRODUCTION

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 which are the results of false assumption 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 ensuring the implementation of means to shield them from being exposed to BPA. This is because the operatory personnel is exposed repeatedly and for long periods of time to materials and processes, which may 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 skin handling of 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, i.e., more migration with higher temperatures.

Over the past decade, the effects of BPA on a wide array of tissues, organs and systems has been established through in vitro and animal studies, as well as case analyses and observations in humans.[2-4] Therefore, what was initially considered as a topic of dispute among scientists, professional societies and the industry, has reached the status of an unequivocally defined thesis, with organizations, at national with

international legislative level issuing relevant statements.[5-7] These highlight the fact that BPA at levels as low as parts per billion (ppb) 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 biological effects similar to those induced by natural estrogens. The similar chemical structure of BPA to natural estrogen oestradiol 17b is the reason for this deviation of the hormonal homeostasis from the proper pathway.[10]

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

For a given exposure period and BPA quantity, the accumulation of BPA in the body may vary as a function of the developmental stage and the gender of the subject. Exposure of infants to the chemical, leads to higher BPA body levels relative to that during adulthood, because of the absence of enzymes capable of metabolizing BPA to its biologically-inert form.[12] Also, a sexual dimorphism is implied by several studies, which have reported higher plasma BPA levels in male than female foetuses even after correcting for a positive correlation between body weight and BPA concentration.[13] Most importantly, there is extensive evidence that outcomes may not become apparent until long after BPA exposure during development has occurred. The issue of a very long latency for effects *in utero* to be observed is referred to as the developmental origins of adult health and disease (DOHaD) hypothesis.[14] These developmental effects

are irreversible and can occur due to low-dose exposure during brief sensitive periods in development, even though no BPA may be detected when the damage or disease is expressed.

The reader would understand the often contradicting conclusions of studies by considering the objective difficulty in reaching a definitive agreement with regard to levels of BPA released and potential effects; this is due to the fact that the biologic action of BPA sets in at very low concentrations, within the range of the detection threshold of the majority of standard analytical techniques.[15-16] Specifically, substances such as octaphenol, are capable of altering the uptake of dopamine by hypothalamic cells in animals, at levels as low as 10 ppt (part per trillion or pg/l).[17] Therefore, even if a precise and reliable quantitative estimation of BPA is attained, there is still a large window of uncertainty on its potential estrogenicity.

The basic differences between the study of common toxicants or other hazardous materials and BPA, relate to the fact that natural hormones like 17ß-oestradiol educe effects at concentrations far beneath the levels at which all hormone receptors become bound.[18] This observation has given rise to a new perspective of toxicity. Once all receptors are occupied, further increase in natural hormone levels does not result in an increased response. Conventional testing of substances for toxicological impact assessment, involves exposure to levels many times higher than those requiring for complete receptor binding. Thus, the lack of response to excessively high concentrations of effectors may be misinterpreted as lack of effect. Along with that, the effects of BPA on tissues follow a non-monotonic curve pattern, which is characterized by intense reactivity at low levels and no response at very high ones, respectively.[19]

BPA AND ORTHODONTIC POLYMERIC MATERIALS

The broader dental composite polymer materials literature has indicated that a wide range of effects can be induced upon exposure of insufficiently polymerized material to the oral environment. In general, the degree of cure or Carbon double bond conversion of polymers may modulate the physical and mechanical properties of the material especially solubility and degradation.[20] This has pivotal role in altering the

biological performance of the materials because a less densely formed network resulting from a decreased conversion of double bonds, is associated with residual monomer leaching and release of substances which are constituent components of the polymer such as amines, polymerization initiators and inhibitors, among others. Additives such as plasticizers which are used for altering the brittle nature of most polymers include the phthalates, aromatic esters suspected to mimic hormones.[21]

In dental materials, BPA is used as a raw material for formulation of Bis-GMA and polycarbonate products and as a general rule, estrogenic action is confined to molecules with a double benzoic ring. The implication of BPA release from dental biomaterials was first reported in a study, which assessed salivary BPA levels in patients with dental sealants.[22] It may be worth noting that a considerable dispute exists on the actual release of BPA from sealants, since BPA release from sealants has not been confirmed at a large scale.[23-24]

Orthodontic polymers considered in this section include resin adhesives and glass-ionomer modified adhesives (but not glass-ionomer cements) used for bonding brackets and fixed retainers; plastic brackets elastomeric ligatures and chains; protective wire-sleeves; acrylic Hawley appliances; and themo-formed retainers. A critical point in considering the potential implication of these materials in BPA release, relates not only to their composition and manufacturing process but also on their application mode. For example the application of orthodontic adhesives as bonding materials involves a sandwich (between bracket and enamel) material configuration, allowing only the peripheral margins of the material to be exposed to the oral cavity; this is vastly different from the use of adhesives in lingual fixed retainer bonding. In the latter scenario, the material approaches a 2-dimenional structure, with a large surface-to-volume ratio, and therefore exposure of the entire surface of the material to the oral environment takes place. This includes masticatory stresses, temperature variations, pH fluctuation, enzymatic degradation and oral microbiota material challenges, for periods of time many times higher than the duration of a typical orthodontic treatment. It should be stressed that a BPA release assay may not constitute conclusive evidence in

determining the potential of a material to give rise to BPA formation because of the threshold of chromatographic analyses used.[25] This might be a case that the amount released could go undetected by the instrumental analysis.

As an empirical rule, the potential of BPA release is restricted to those materials, which contain BPA as a precursor during manufacturing process. Obviously any polymer without an aromatic ring in its structure is free of this concern and therefore acrylic retainers and other linear carbon chain polymers possess no known risk for BPA release. The materials which in most cases are manufactured with the use of BPA are polycarbonate brackets and Bis-GMA, although recently traces of the molecule have were identified in thermo-formed aligners. Bis-GMA-based orthodontic adhesives were manufactured with a BPA as a precursor, however most manufacturers have reported that they have abandoned this process.

Systematic reviews on the subject identified that the published studies are contradictory with respect to the qualitative and quantitative parameters of BPA release from adhesives and sealants, probably because of the varying methodologies that have been employed.[26-27] Results of one investigation showed no indication of BPA, another study demonstrated that increase of the distance between the light cure tip and the adhesive introduced a decrease in the degree of conversion of the polymer, which led to a greater BPA release, whereas the release of BPA from an orthodontic adhesive used to bond lingual fixed retainers indicated measurable amounts of BPA that were identified for all groups, with the highest found in the immersion media of the thirty-day immersed group. [28-34] In general, the in vivo assessment of BPA release in biological liquids indicates a broad variance along with a rise immediately after bonding of brackets or lingual fixed retainers.

On another class of orthodontic materials, namely the polycarbonate aesthetic brackets, it has been reported that during the synthesis of polycarbonates, non-reacting BPA probably remains inside the materials and is released when these are immersed in water or organic solvents resulting in a rate of BPA

release increased with time and temperature,[35-36] although the issue has not been unequivocally determined with respect to the xenoestrogenicity of the appliances.[37]

Lastly, there has been promising efforts for the development of orthodontic adhesives for use with lingual fixed retainers at first stage, based on monomers without a BPA-derivative or precursor during the synthesis, and with similar performance with respect to bond strength, degree of carbon double bond conversion, hardness, oxygen inhibition polymerization zone and physical properties such as viscosity, with a widely used product.[38-40]

For aligners the evidence is contradictory since BPA's implication in the use of these products has not been conclusive at the cell culture or analytical level, with views, namely their inert profile[41] or BPA release[42], being supported by studies with different methodological approaches.

MANAGING EXPOSURE IN AN ORTHODONTIC SETUP

The important point in addressing this issue is to present the evidence and its potential consequences within the context of everyday life. The materials in question from the body of the literature are Bis-GMA-based adhesives, which additionally are manufactured with BPA as precursor; most of those materials are now claimed to be BPA-free.

Various applications such as bonding materials for fixed retainers, where the adhesive exposes a vast surface relative to its volume to intraoral environment, might constitute a BPA release case scenario only if the adhesive derived from the use of BPA. Also, during the debonding stage where the resin adhesive must be ground with the use of rotary instruments, the particulate matter produced might also have estrogenic action;[43] this is a hazardous situation for the care provider and team, who are exposed to aerosol[44-45] and to a lesser degree for the patient, based on the fact that the orthodontist and staff may be exposed to this factor repeatedly, whereas the patient only once. Access to fresh air, use of surgical mask and glasses, and

surgical suction are strongly advised for this treatment stage, as is the removal of as much material as possible without the use of rotary instruments.

The foregoing discussion excludes most materials from the category or potential BPA releasing polymers and leaves only polycarbonate aesthetic brackets as potential BPA source. Care should be taken not to confuse all plastic aesthetic appliances with polycarbonate brackets because non-polycarbonate brackets may not be implicated in this phenomenon. Therefore from the wide array of orthodontic polymers only one class of materials could be considered as a verified source of concern.

It should be also noted that even if the case of definitive BPA release the levels are within the range found in humans exposed to this agent through dietary habits (canned food), and therefore, although there should be an effort to eliminate all additional sources of BPA release, the amounts of BPA released may not pose a threat for the average patient. Because of lack of evidence however, pregnant patients, and most importantly orthodontists and team who come in contact with grinding products in the form of aerosol during debonding are advised to take extra safety measures, as noted previously.

Caution should be applied in designing effective measures to minimize exposure to patients and staff. Special consideration must be given to the specific conditions of orthodontic practice. Thus, adoption of general guidelines which were intended for professionals in materials industries or other groups of workers by Orthodontists may have futile result and is of unsubstantiated validity. To this end, setting a minimum exposure contact concentration per time interval, i.e., X micrograms per day, for BPA-containing orthodontic materials is a confusing and profoundly unsubstantiated proposal because of the following:

a) There is no direct contact with BOA-containing materials anyway;
b) The proposal is apparently directed to the staff of the practice, with unpredictable impact on the perception of the hazard by patients; and
c) Even if direct contact with resins containing BPA materials took place, the precise estimation of the BPA exposure is impossible because the concentration of BOA in the material is unknown.

Absolute measures of eliminating exposure

Certain ways to prevent patients and most importantly operator and staff from being exposed to BPA include absolute measures to ensure lack of contact of patients and operators with BPA and relative measures to effectively minimize the exposure to this agent. The proposal of these measures take into account the evidence published until June 2017, when about two dozens of studies connecting orthodontic materials with BPA were accessible. Therefore, the evidence cannot be considered as a golden rule as it possesses a validity which might have definitive duration. In as much, whereas the propositions appended below are based on evidence derived primarily from *in vivo* studies, no comparative data is available on the effect of choosing one over the other (i.e., absolute vs. relative measures) as a strategy to minimize exposure of the involved parties in an orthodontic setting.

Materials

The first category (effective elimination of BPA exposure) includes bonding with glass-ionomer cements (not resin-modified glass ionomers), use of metallic or ceramic aesthetic brackets, and Hawley type of retainers. Elastomeric modules are mainly polyurethane-based polymers and possess no known risk of leaching BPA, while for many other categories of polymers such as polypropylene protective sleeves, Teflon- or polyamide-covered wires, a conclusive evidence is lacking.

The second category (relative measures), includes the use of non-BPA derived orthodontic adhesives, mainly non-benzoic ring-containing monomers, to eliminate the case of releasing BPA, or adhesives where BPA is not used as a precursor for the manufacturing of the monomer. Although this is difficult to identify for the public or the trained professionals, it seems not to be of critical importance since a clinical study showed that by having the patients rinse thoroughly after bonding, the levels of BPA in their saliva or rinsing medium returned to the baseline levels.[46] Contrary to previously anecdotal propositions to utilize ethanol solutions in order to induce accelerated ageing thereby increasing the release and somehow inducing a 'BPA drain' of the polymer, this *in vivo* assessment revealed that this remedy had no effect. The

fact that most literature identifies the first time period after bonding as the time span with the highest release, implies that bonding is a critical step in controlling potential release. Multiple rinsing after bonding and a suggestion to continue this for some hours may return the initially higher salivary BPA content to baseline levels.

Along the same line, use ceramic brackets, or polyoxymethylene plastic brackets until the evidence becomes more conclusive on the actual in vivo release of BPA from polycarbonate brackets, is suggested.

Processes (bonding and debonding)

Having established that apart from materials, certain procedures such as thorough rinsing may aid in decreasing exposure to BPA during bonding, it is interesting to identify some factors, which may affect exposure to BPA during debonding.

For debonding, removal as much materials as possible without the use of rotary instruments is suggested. This can be modulated by selecting a bracket mesh and adhesive combination where the application of stresses during debonding would result in a composite cohesive/bracket-resin adhesive type of fracture.[47] In general, optimum mesh grade for increased debonding results in reinforcement of the bracket-adhesive interface shifting the fracture type to the enamel-adhesive complex, thus resulting in leaving a large layer of remnant adhesive onto the enamel, which in turn necessitates longer and more laborious removal process. Remnant adhesive volume is also influenced by the modulus of the adhesive, however the multiplicity of combinations may prevent from providing a clear suggestion, prompting for an empirical selection of the combination which maintain integrity of the bond, while allowing for efficient cleaning and resin grinding stage. In addition, the staff and operator should take extra care with mask, fresh air access, surgical suction to minimize spread of the aerosol in the operatory. This aerosol apart from having estrogenic action as demonstrated in a clinical simulation of the debonding process in vitro, is composed of particles with a size falling within the 2.5 micron range which are considered particularly detrimental to the respiratory system.[45-46]

Therefore, debonding may be facilitated by the use of adhesive removing pliers, with limited use of rotary instruments coupled with measures to avoid dispersion of the aerosol in the operatory. It is worth noting that operatories with multiple dental units within the same area (open bay plan) must allow for sufficient space between chairs and avoid scheduling concurrent debonding appointments in multiple chairs to minimize the production of aerosol.

RESPONSE TO PUBLIC QUERIES

Some years after the saga of amalgam, the dental practitioner is faced again with queries, often aggressive, posed by internet-educated and ill-informed patients and parents on BPA release from dental and more specifically from orthodontic materials. Dealing with these challenges necessitates not only an overview of the issue to the point of understanding doctoral level biological and materials research, but also knowledge of the relevant legislature statutes, which may vary considerably among countries; this is a daunting task, and it is practically impossible for the practicing orthodontist. The objective of this section is to provide the interested clinicians and organizations with the minimum required background in order to efficiently address questions relating to BPA In everyday orthodontic practice. For this purpose the Table provided may be useful to reassure all interested parties that measures taken to eliminate exposure to BPA, include a wide spectrum of means, as noted in the previous section, which effectively limit the exposure to levels below the dietary intake of an average person.

As an introductory remark it might be worth noting that the extent of detrimental effects of BPA described in the relevant literature relate mostly to specific age ranges of animals and humans, which correspond to foetuses, and not to adolescents or developed organisms. Therefore, although exposure to BPA is unwanted, care should be taken to selectively focus in cases where developmental effects can be produced and that means pregnant patients or clinical/staff members.

To this end, it is interesting to consider that the exposure of patients to BPA is much lower than that of the operator and staff who participate in many bonding/debonding procedures daily. Thus, although emphasis should be placed in protecting patients from exposure to BPA, this population should not be the main target of measures aiming at reducing the exposure to BPA.

Going into the analysis of published evidence, it must be emphasized that the literature can be viewed differently depending on the level of expertise of the reader, and therefore, a clinical professional or lay person, without proper background, cannot assess the validity and limitations of experimental procedures and technicalities of testing. The majority of the evidence available on the topic derives mainly from *in vitro* experimental approaches using plethora of variables, conditions, ageing/immersion media, and with analytical techniques of variable thresholds and therefore wide range of sensitivity. The levels of BPA associated with orthodontic materials and procedures such as bonding and debonding vary significantly among studies and in general exceed some of the values reported in the literature to induce effects in animals.

However, this evidence has been derived from studies, which were performed under specific conditions, irrelevant to the actual clinical situation. For example the study of release of BPA from orthodontic adhesives, which involves immersing the adhesive in media immediately after photocuring, or investigating the salivary levels of BPA after bonding orthodontic adhesives or sealants, results in a technical increase of the release of unpolymerized species from the material. This is because unpolymerized layers are allowed to leach compounds in the media, where in reality the patient rinses away whatever would later be released in the media as part of the bonding protocol, which *should* include thorough rinsing after each time a sealant or composite filling material or orthodontic adhesive for bracket or lingual fixed retainer bonding is placed in the oral cavity. Therefore, the result of laborious and technically demanding analyses simply test a condition, which is not taking place in everyday practice.

Supporting evidence on the implication of the conditions of sample collection during bonding in the outcome of BPA release of adhesive is also provided by a recent study, indicating that the levels of BPA, which in this study were much higher than those reported in other publications, returned to baseline or pre-bonding levels, after rinsing with water.[46] This again implies that part of the release relates to the unpolymerized layer of material, which is removed after bonding. A second rinse in this investigation showed BPA levels within the range of those found before bonding. The significance of this finding is two-fold: it provides a first line of means to eliminate BPA release and also suggests that much of the *in vitro* analyses and complicated attempts to simulate the clinical situation are invalid, prompting, once more, for the design of clinical studies to obtain meaningful and clinically relevant data.

Collectively, a critical analysis of the evidence available on the BPA release from orthodontic materials, suggests that it is not only the selection of materials that modulates the release of BPA, rather, the adherence to proper treatment protocols during these stages of treatment can effectively minimize exposure of patients and personnel to this chemical to the levels below what is established as standard dietary intake or associated with everyday life activities.

Table
Sources of BPA release and effects in Orthodontics and suggested measures to minimize exposure for the patient and staff*

ORTHODONTIC MATERIAL/PROCEDURE	MANAGEMENT OF EXPOSURE & SUGGESTED MEASURES	Target group of interest
BONDING Resin-based adhesives (as bracket bonding materials)	Use glass-ionomer cements Request details on BPA use at any stage of production by the manufacturer Optimize polymerization conditions (sufficient light exposure times, close proximity of tip to bracket and adequate light intensity) Have the patient rinse with copious amount of water following bonding	PATIENTS
Resin-based adhesives as lingual fixed retainer bond materials	Sufficient adhesive hardness is essential owing to the exposure of the adhesive to masticatory forces Request details on BPA use at any stage of production by the manufacturer	
Polycarbonate brackets	Ceramic brackets as aesthetic appliances	
Aligners	Inconclusive evidence at this stage	
DEBONDING Resin-based adhesives	Select a bracket base mesh-adhesive filler content combination, which results in a resin cohesive/bracket-adhesive fracture Remove as much material as possible without the use of rotary instruments During resin grinding have access to fresh air, use surgical suction, masks for all staff Pregnant staff and operators must avoid continuous and long-term exposure to the aerosol produced during debonding	STAFF AND PATIENTS

	Operatories with multiple dental units within the same area (open bay plan) must allow for sufficient space between chairs and avoid scheduling concurrent debonding appointments in multiple chairs	

- Table is provided as a demonstration of representative evidence per category of BPA source. It is not supposed to exhaustively cover all published studies on the topic, neither does it endorse *a priori* the validity of the evidence summarized in the second column.

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