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An investigation into bisphenol A leaching from materials used intraorally

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ABSTRACT

Background. In this study, the authors quantitatively determined the bisphenol A (BPA) leached from intraoral materials during simulated intraoral exposure.

Methods. The authors subjected samples of intraoral materials to simulated abrasion, immersion in artificial saliva, thermal shock via temperature cycling, and simulated intraoral exposure. The authors collected sample aliquots for up to 2 weeks after artificial saliva immersion, derivatized, and then analyzed the aliquots for BPA by gas chromatography and mass spectroscopy.

Results. Quantifiable amounts of leached BPA were observed from only 1 of 13 intraoral materials tested: a silicone baby bottle nipple (20 micrograms). BPA leaching was only observed after 3 days of artificial saliva immersion, with no additional leaching thereafter.

Conclusions. Under the test conditions, BPA was observed to leach from a silicone baby bottle nipple.

Practical Implications. Although the quantities of leached BPA were below the reference dose for daily intake, investigators have shown a possible association between low levels of BPA and many medical disorders. BPA exposure, and thus the use of the leaching material identified in this study, should be reduced or eliminated.

Key Words. Bisphenol A; BPA; intraoral materials; leaching.

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Bisphenol A (BPA) is a ubiquitous synthetic compound with an annual production exceeding 3.8 million tons globally.[1] It is one of the highest volume chemicals produced in the world,[2] and its demand is increasing substantially in developing countries.[3] BPA is used in the production of plastics such as polycarbonate and epoxy resins. These plastics are components of electronic equipment, food storage containers, children's toys, and many other everyday household products.[3]

In dentistry, BPA derivatives such as bisphenol A-glycidyl methacrylate, bisphenol A-dimethacrylate, and bisphenol A-ethoxylated dimethacrylate are components of liquid monomers used in dental resins that polymerize via chemical and light curing.[4] BPA is also likely to be present in dental resins as an impurity of the manufacturing process.[5] The degradation or incomplete polymerization of these materials, including pit and fissure sealants,[5-6] composite fillings,[7] bonded orthodontic lingual retainers,[8] polycarbonate orthodontic brackets,[9] orthodontic retainers,[10] and orthodontic bracket adhesives,[10] which are commonly placed in children,[4] have been shown to leach BPA.

Both physical and chemical processes play a role in biomaterial degradation in the oral environment. Chemical degradation can be caused by salivary hydrolysis,[11] pH changes,[12] as well as bacterial[11] and enzymatic activity.[13] Physical breakdown caused by masticatory and particulate wear,[11] as well as temperature,[14] can also increase the release of BPA. Over time, the aging of materials due to the co-action of mechanical water sorption, swelling, and chemical degradation may lead to porosities, which can cause leaching of residual unpolymerized monomers that were formerly trapped in the polymer network.[15]

BPA is thought to exert its biological effects through epigenetic alteration, oxidative stress, inflammatory cytokine release, and interference with the endocrine system.[16] It has been classified as an endocrine disrupting chemical owing to its ability to bind and activate the human estrogen receptor, albeit at an affinity of 1,000 to 5,000 times weaker than that of endogenous estradiol.[17] BPA had been considered to be a weak estrogen, but since 2007, investigators have shown that BPA possesses a

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similar efficacy and potency to estradiol.[2] Moreover, BPA can bind to various other hormone receptors including glucocorticoid receptors,[18] androgen receptors,[19] and thyroid receptors,[20] thus potentially disrupting many different signaling pathways.

Due to the extensive use of BPA, human exposure is widespread worldwide. It has been detected in several human tissues and fluids in children and adults,[2] including the blood[21] and the urine of infants as young as 1 month old.[22] Furthermore, BPA has been shown to collect in human adipose tissue 3 times more than in other tissues, suggesting the possibility of bioaccumulation and the potential to exert ongoing cellular effects.[16] Investigators of epidemiologic studies have measured BPA in the urine of 90% of Canadians aged 3 to 79 years,[23] 90% of Americans 6 years or older,[24] 99% of Germans aged 3 to 14 years,[25] and 94.3% of Asians aged 2 to 84 years from 7 different countries.[26] Considering the high level of BPA measured in various populations, rapid metabolism,[2] and the short half-life of this compound,[4] BPA exposure appears to be from multiple routes and sources on a repeated basis.[27]

Many commercially available intraoral baby products such as baby bottles, bottle nipples, and pacifiers have been marketed and developed to be optimally adapted to the baby's oral cavity; promote proper jaw and tongue positioning, lip closure, and nasal breathing during feeding; and to encourage a healthy oral development.[28,29] These products are commonly used by children from birth to infancy multiple times per day. In the manufacturing process of some of these products, BPA is used as a starting material that can be released into the oral environment under normal conditions of use.

Polycarbonate baby bottles have been shown to account for the greatest source of BPA in children 6 years and under.[30] Furthermore, a 2014 study revealed that bottle-fed infants have higher blood serum BPA levels.[21] However, previous studies failed to distinguish whether the bottle, the nipple, or both were the contributing source of BPA exposure.

Owing to the mounting concern of the adverse effects of BPA, many consumers, companies, and governments have attempted to minimize or eliminate BPA use and exposure. Canada was the first country to declare BPA a "toxic substance"[31] and to ban its use in the production of baby bottles.[1] Several countries followed including the United States[32] and the member states of the European Union.[1] In 2013, the US Food and Drug Administration also banned the use of BPA in baby formula packaging.[1]

It has been shown that the highest level of BPA exposure occurs in the oral cavity, and its rapid absorption through contact with the sublingual oral mucosa provides direct access to the systemic circulation.[33] Furthermore, the aqueous environment of the oral cavity encourages biomaterial chemical degradation and softening.[5] Infants, children, and adults are all exposed to various intraoral materials that may contain BPA as a manufacturing component.

The purpose of this study was to simulate the intense mechanical action and thermal conditions that may occur intraorally to investigate whether these conditions could cause BPA to leach from routinely used intraoral products.

METHODS

Our investigation was an extension of the study by Kotyk and Wiltshire,[10] and we followed the same experimental design and sample analysis.

Sample preparation. We received and used "as-is" several intraoral products (Table 1) for home use that we obtained from the manufacturers in a masked fashion. We thermoformed mouthguard and bleaching tray materials (materials 1A, 2A, and 3A; Table 1) according to the manufacturers' instructions with a vacuum thermoforming system (Model A, Sta-Vac, Buffalo Dental Manufacturing) to produce materials 1B, 2B, and 3B. We subjected materials in contact with incisal or occlusal tooth surfaces (1-8) to initial single surface abrasion with a new high-speed (330) bur. We cut all material samples with scissors into approximately 5 × 5-millimeter squares.

Experimental design. We synthesized unstimulated artificial saliva (AS) based on research by Dawes and Dong.[34] We dissolved the chemical constituents in 1 liter of Milli-Q water (EMD Millipore). We purchased all commercial chemicals from Acros Organics and used them as received. We immersed all material samples (materials 1-10; Table 1) in a medium of 10.0 milliliters of AS in new glass sample vials with polytetrafluoroethylene-lined caps to prevent BPA contamination for each experimental repetition. Then we subjected the samples to thermal shock treatment involving temperature cycling from hot (60°C) to cold (4°C) water baths with shaking for 5 minutes at each temperature; this was repeated for a total of 10 cycles. The samples were then shaken at normal oral temperature (37°C); we removed 1.0 mL aliquots at 24 hours, 3 days, 7 days, and 14 days, and placed them in new glass sample vials with tetrafluoroethylene-lined caps to prevent BPA contamination.

Sample analysis. We conducted the sample analysis as follows: we combined 0.5 mL of a standard BPA-d_{16} solution and 0.5 mL of the aliquot sample solution with 10 mL of a 1.0 molar/liter potassium carbonate solution. We shook the resulting solution, and added 200 microliters of acetic anhydride. After 5 minutes, we added another 200 µL of acetic anhydride while shaking. Then, we added 2.5 mL of iso-octane and checked the pH. If the pH was below 10, we titrated it to 10 with 1.3 mol/L potassium carbonate. If pH was above 10, we added 100 µL of acetic

ABBREVIATION KEY. **AS:** Artificial saliva. **BPA:** Bisphenol A. **GC:** Gas chromatography. **MS:** Mass spectroscopy. **NA:** Not applicable. **ND:** Not detectable.