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Changes in Urinary Bisphenol A Concentrations Associated with Placement of Dental Composite Restorations in Children and Adolescents

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Abstract

Background—BisGMA-based dental composites may release bisphenol A (BPA). Our purpose was to assess changes in urinary BPA concentrations over 6-months follow-up in children and adolescents receiving bisGMA-based restorations.

Methods—We collected urine and interviewed parents/guardians for BPA-related exposure information before and approximately one-day, 14-days, and 6-months post-treatment among 91 participants aged 3–17 years needing composite restorations. We used multivariable linear regression models to test associations between number of surface-restorations placed and changes in urinary BPA concentrations.

Results—Participants had on average 1.4 (sd=1.0) surfaces filled with composite at the first treatment visit and a cumulative 2.3 (sd=1.6) surfaces filled during the study. Mean change in BPA between pretreatment and next-day was 1.71 ng/mL (sd=9.94) overall and 0.87 (sd=5.98) after excluding one participant with 8 surfaces filled at the visit. Overall, a greater number of composite surface-restorations placed was associated with higher BPA in the next-day sample (posterior-occlusal $e^{\beta}=1.47$, 95% CI 1.18–1.83; $P<0.001$), but this was attenuated after restricting to the 88

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participants with 4 fillings ($e^{\beta}=1.19$, 95% CI 0.86, 1.64), and no association was observed 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 bisGMA-based restorations in children and adolescents may produce transient increases in urinary BPA concentration, which are no longer detectable approximately 14-days or 6-months post-treatment in urine samples. When few restorations are placed, increases in urinary BPA concentrations may not be detectable owing to high inter-individual variation in BPA exposure.

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

Keywords

Dental restoration; Dental care for children; Composites; Pediatric dentistry; Polymers; Bisphenol A

INTRODUCTION

Bisphenol A (BPA) is a chemical used in the manufacturing of polycarbonate plastics and epoxy resins that are used by nearly every industry, including dentistry. Concern over human BPA exposure exists because BPA is an endocrine disrupting chemical, and animal studies show that BPA has reproductive, developmental, and systemic toxic effects even at low doses (e.g., <50 mg/kg/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 (e.g. ovarian toxicity in women,⁶ delayed puberty in boys⁷), and immune function^{8,9} and neurodevelopment in children.⁴

The possibility of adverse effects of 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 general population appears to be through foods and beverages manufactured and stored using BPA-containing materials.^{12–17} However, such products account for only ~20% of the BPA produced worldwide each year,¹¹ and human biomonitoring studies suggest that non-dietary exposure sources also exist.^{18,19}

In dentistry, BPA is used to synthesize matrix monomers, such as bisphenol A glycidyl dimethacrylate (bisGMA), that are commonly used in composite restorative and sealant materials.²⁰ The BPA structure has benefits of bulk, rigidity and strength.²¹ An unfavorable feature of such composite materials is incomplete polymerization, which results in shrinkage, marginal leakage, and degradation over time.^{21,22} Numerous studies have shown that composite materials release various chemicals, including BPA, while in the oral environment.^{23–25} The largest human biomonitoring study of this issue to date included 172 adults followed for a maximum of 30 h after receiving composite restorations. The study reported increases in BPA and other related compounds in saliva within 1 h after restoration placement, and an increased concentration of BPA in urine 9–30 h after placement.²⁶

However, the time window of chemical release from composite restorations may extend past this initial placement period, throughout the life of the restoration, as the composite degrades over time.²⁴ *In vitro* studies indicate that storage time, as well as mechanical stress such as chewing, and acidic food/beverage, are associated with release of chemical components of composite.^{24,27,28} The extent to which BPA continues to be released over the long-term remains unexamined in human biomonitoring studies. Even if very low dose (<no-observed-adverse-effect-level) as suggested by *in vitro* studies,²² the possible chronic exposure may have an impact on health outcomes, as low levels of endocrine disrupting chemicals are sufficient for adverse effects in animal studies.^{2,29}

The possibility of adverse health effects of composites was suggested in the New England Children's Amalgam Trial (NECAT), a 5-year clinical trial designed to test the safety of dental amalgam for restorations: Children who were randomly assigned treatment with composite had worse psychosocial health outcomes after 4–5 years compared to children randomized to amalgam.³⁰ Further analysis showed that greater treatment level of composite restorations containing bisGMA was associated with increased behavioral problems, certain neuropsychological measures, and, possibly, certain immune function markers.^{31–33} However, randomization to composite was not associated with altered physical development,³⁴ and there was no association between preventive sealants or other flowable composite materials and psychosocial or neuropsychological health.³⁵ While the dental materials used in the trial have been shown to release BPA, bisGMA and related materials,^{36–39} the trial did not measure changes in children's urinary concentrations of BPA or other compounds that may leach from composite. Thus, it remains uncertain the extent to which composite restorations lead to BPA exposure in children.

The aim of this study was to examine changes in urinary BPA concentrations in children and adolescents before and after placement of dental composite restorations, up to 6 months post-treatment.

METHODS

The Composites and Urinary Bisphenol-a Study (CUBS) was a clinical study designed to examine changes in urinary BPA concentration in pediatric dental patients after placement of dental composite restorations over approximately 6 months follow-up. Figure 1 outlines the enrollment eligibility criteria and data collection visits. Study participants were recruited from 8 participating clinical sites in the greater Boston area: two academic hospital settings (Tufts University School of Dental Medicine; Franciscan Hospital for Children), three community health centers (Cambridge Health Alliance; Lynn Community Health Center; Edward M. Kennedy Community Health Center), two private practices, and one oral health research institute (The Forsyth Institute). The study was approved by a central institutional review board (IRB) and each participating institutional IRB, including the IRB of the independent research organization, New England Research Institutes, Inc. The analysis of blinded specimens by the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subjects research. Written informed consent was obtained from the parent or legal guardian of participants, and signed assent was obtained from participants of appropriate age. Recruitment occurred February 2012

through December 2013, and follow-up visits were completed in June 2014. A total of 113 patients were enrolled, of which 91 had at least one pre-treatment and one post-treatment urine sample and were therefore included in statistical analyses.

Urine Sample Data Collection and Laboratory Methods

After enrollment, each parent/guardian completed a baseline interview with a data collector, who then provided a polypropylene urine cup and instructions on collecting a first morning urine sample. The instructions stated that parents should try to avoid having the participant eat canned foods or drinks the day before collecting urine and provided step-by-step directions for collecting, handling, and refrigerating urine samples if the first morning void occurred prior to the arrival of the data collector. Two data collectors scheduled and conducted all urine sample collection visits, generally at the participant's home. Data collectors obtained urine samples at two pretreatment visits and at three post-treatment visits, scheduled to occur next morning, 14 days and 6 months approximately after restoration placement (Figure 1). Of the two pretreatment samples, one was collected on the morning of the restoration placement, and the other was collected in the morning one to seven days prior to the treatment to ensure availability of at least one pretreatment sample and to allow analysis of the within-person variability of BPA pretreatment. For participants who needed more than one treatment visit to have all composite restorations placed, we requested additional urine sample collections the next morning and approximately 14 days after each additional treatment visit, with up to 7 post-treatment urine samples collected per participant.

Data collectors transported each urine sample in a cooler to the processing area, where they brought the sample to room temperature, aliquotted it into Nalgene® cryovials using a sterile polypropylene pipette, and measured specific gravity using a calibrated refractometer (Atago 4410 PAL-10S). Samples were then stored at -86 °C until shipment to the CDC (Atlanta, GA). Staff members at the CDC performed laboratory assays to quantify the concentration of total (free plus conjugated) species of urinary BPA using a modification of the automated online solid-phase extraction-high performance liquid chromatography-isotope-dilution tandem mass spectrometry approach previously described.⁴⁰ The limit of detection (LOD) was 0.1 ng/mL.

At each urine collection visit, the data collector conducted a brief interview, which included a 24 h food recall with probes for canned foods and use of plastic containers to gather information on recent possible BPA exposure sources. The final urine sample collection visit, which occurred approximately 6 months after the last treatment visit, marked the end of active study participation.

Dental Materials and Data Collection

We aimed to standardize the dental materials and restoration placement procedures for study participants across clinical sites. To be consistent with NECAT, the standard treatment materials were Z100 restorative (3M ESPE, St. Paul, MN) with Optibond bonding agent (Kerr, Orange, CA). Both materials contain bisGMA among other compounds. Similar to many other bisGMA-containing composite restoratives, the composite restorative has been

previously shown to release BPA and bisGMA.^{24,36–39} If patients needed sealants placed while enrolled in the study, the standard sealant was Embrace (Pulpdent, Watertown, MA), which contains no bisGMA or related compounds. All treatments and materials were used according to manufacturers' indications. For each dental visit that occurred between the first study-related composite restoration until the patient's final 6-month urine sample collection, we collected data on the type of treatments received, tooth surfaces treated, rubber dam usage, and manufacturers/brands of materials used. Because participants may have had composites and sealants already in place prior to the first study-related treatment, the dentist recorded the number of existing restored or sealed surfaces and material types present at baseline.

Statistical Analysis

We calculated descriptive statistics for BPA concentrations at each visit. BPA concentrations were log-normally distributed, therefore, we log_e transformed concentrations prior to further analysis. One sample had a BPA concentration below LOD; for this sample, we used LOD/2.⁴¹ We corrected BPA concentrations (ng/mL) for specific gravity to account for variations in urine dilution.⁴² The primary dependent variable was change from baseline in log-transformed BPA concentration corrected for specific-gravity. For patients who provided two pre-treatment urine samples, we used the geometric mean of the two samples, each corrected for specific gravity, to obtain the baseline BPA concentration.⁴³ We calculated the intraclass correlation coefficient (ICC) to examine the temporal reproducibility of the two measures, by dividing the estimate of between subject variance by the estimated total variance. For patients who provided just one pre-treatment sample, the BPA concentration corrected for specific gravity was used as the baseline BPA concentration.

The analysis included 91 participants who provided at least one pretreatment urine sample, had at least one composite restoration newly placed, and provided at least one post-treatment urine sample. Preliminary analyses included descriptive statistics on the change in urinary BPA concentration from pretreatment to each post-treatment visit. In the main analyses, the primary independent variable was the total number of surfaces restored with composite while on-study. A secondary measure was the number of posterior occlusal surfaces restored on-study. We used multivariable linear regression models to estimate the association between composite treatment levels and change in BPA concentration from baseline to each follow-up time point (next-day, 14-day, and 6-months post-treatment) separately. We assessed several sociodemographic, dietary and other factors as potential predictors of BPA concentration based on the published literature.^{13,14,44–46} Potential predictors of BPA exposure considered as covariates in the models included: age, race/ethnicity, sex, body mass index, parent/guardian education, household income, presence of orthodontic dental materials, presence of dental sealants or composites at baseline, urine collection time, location of urine sample storage prior to processing, and consumption of canned food, foods microwaved in plastic, or foods and beverages in plastic containers within 24h of the urine sample. Participants missing data on a potential confounder were included using an indicator category for missing in that variable. We ran regression models for change in BPA with each potential covariate; variables for which $P < 0.2$ were entered into a single multivariable model, which we then reduced to retain only variables for which P remained < 0.2 . The final

models adjusted for baseline BPA concentration and household income as fixed variables, and canned food consumption in the day prior to urine sample collection and the season of urine sample collection as time-varying variables. The exponentiated beta coefficients represent the percent change in urinary-BPA concentration from the pretreatment geometric mean associated with each composite surface placed.

The sample size had 80% power to detect a difference of 0.3 standard deviations using paired t-tests to compare urinary BPA values before and at various time points after the first dental treatment. As few participants had additional treatment visits and provided additional next-day or 14-day urine samples, analyses of pre/post changes in next day or 14 days after additional treatments were exploratory. For example, 26 participants in the analysis provided 80% power to detect a difference of 0.6 standard deviations. In the regression models, statistical significance was tested at level 0.05. All analyses were conducted using SAS v9.3 (Cary, NC).

RESULTS

Figure 1 provides a flow chart of the number of patients enrolled and urine sample collections pre-treatment and during follow-up. Approximately half (N=49/91, 53.8%) of participants had a single visit with composite placement. Of the participants who had additional composite placement visits and provided additional urine samples, the median time between the first and second treatment was 21 days, and between the first and third treatment was 37 days. The final urine sample collection occurred at a median of 162 days and mean 170 (sd=32) days, or approximately 5.7 months after treatment.

At baseline, study participants were on average 9.5 years old (sd=3.7) and represented a diverse patient population in race/ethnicity, body size, and parental education level (Table 1). Use of plastic containers for drinking was common, with over two-thirds reporting use on some or most days. Few participants (n=14) reported canned food consumption in the day prior to the pretreatment urine collection. Data on the number of restorations and sealants present at baseline were available for 63 (69.2%) of participants, of which 39 (42.9%) had composite restorations and 35 (38.5%) had sealants present.

Dental Treatment

At the first treatment visit, most participants (68.5% of the 89 with treatment 1) had only one surface filled, while 23.6% had two surfaces, 6.7% had 3 or 4 surfaces, and one patient (1.1%) had 8 surfaces filled, resulting in a mean 1.4 (sd 1.0) surfaces filled at this visit (Table 2). Over the course of the study, including participants who required additional treatment visits, the mean number of surfaces filled was 2.3 (sd=1.6, N=91). Overall, 43.9% of participants had one surface filled with composite, 25.3% had two surfaces, 17.6% had three surfaces, 8.8% had four surfaces, 2.2% (n=2) had six surfaces, and 2.2% (n=2) had eight composite surface-restorations placed. Most filled surfaces were posterior occlusal surfaces; both the mean and median number of posterior-occlusal surfaces filled during the study were 2.0 (sd 1.4). Z100 restorative was used in 93.4% of participants (n=85/91). A rubber dam was used for at least one filling in 51.6% of participants. Twenty participants

had sealants placed during the course of the study, of which 16 (80%) used Embrace material.

Urinary BPA Concentration

Pretreatment, the median BPA concentration unadjusted for specific gravity was 1.98 ng/mL, with 75th percentile 3.80 ng/mL and 95th percentile 8.28 ng/mL. Corrected for specific gravity, the geometric mean (sd) pretreatment BPA concentration was 3.32 ng/mL (sd=3.80, min=0.43, max=23.41 ng/mL, N=91 participants). Among participants who had two pre-treatment samples (N=84), there was a statistically significant correlation between the two measures of BPA ($P=0.02$), with an intraclass correlation coefficient of 0.25. There was no association between the number of pre-existing composite restorations and changes in BPA concentration over follow-up (data not shown).

Table 2 provides the mean change in BPA from baseline to each follow-up visit. Compared to baseline, the mean BPA concentration was increased next-day post-treatment 1 (mean change 1.71 ng/mL, sd=9.94, $P=0.11$, n=89 participants) and treatment 3 (mean change 1.97 ng/mL, sd=2.91, $P=0.36$, n=3 participants), but not treatment 2 (mean change -0.59 ng/mL, sd=3.62, $P=0.41$, n=26 participants). The next-day group mean BPA concentration of 5.04 ng/mL [sd=10.11, min=0.56, max=81.8] corresponds to a 51.4% increase in the baseline group mean of 3.33 ng/mL.

In the multivariable linear regression model (Table 3), a greater number of surfaces filled with composite at treatment 1 was associated with a greater change in urinary BPA concentration the next day ($P=0.002$ for all surfaces, $P<0.001$ for posterior occlusal surfaces), but not in the 14-day or 6-month samples. For each surface placed, a 37% increase in geometric mean BPA concentration would be expected, controlling for other predictors of BPA change.

In sensitivity analysis, we explored the impact of participants with the highest number of surfaces restored. The participant with 8 surfaces restored in a single visit had a considerably higher BPA concentration the day after treatment (81.8 ng/mL) compared to other participants (mean 4.17 ng/mL, range 0.56–35.1 ng/mL). Seven of the 8 surfaces were poster-occlusal surfaces. The participant reported no canned food consumption within the day prior to the urine sample collections and was not missing data on any covariates included in the models. Excluding this participant, the mean change in BPA was 0.87 ng/mL (sd=5.98), and the association between number of composite-restored surfaces and next-day change was attenuated (multivariable-adjusted $e^{\beta}=1.19$, $P=0.29$ for posterior occlusal surfaces, $e^{\beta}=1.08$, $P=0.57$ for all surfaces). Another participant accumulated 8 surface fillings across three visits, at the last of which two surfaces were filled, and the next-day BPA concentration was increased by 0.71 ng/mL from baseline. At the final visit approximately 6 months later, both of these participants had BPA concentrations (1.52 ng/mL and 1.30 ng/mL) close to the median pretreatment value (2.12 ng/mL).

DISCUSSION

This study found that placement of a higher number of composites in children and adolescents was associated with a greater increase in urinary BPA concentrations one day after treatment, but there was no detectable increase at approximately 14 days or 6 months after treatment, or when few restorations were placed. Adjusting for other predictors of urinary-BPA concentration, each posterior-occlusal composite-surface restoration was associated with a 47% increase next-day in the geometric mean baseline value, but the association was attenuated to 19% when we excluded the only participant to have a considerably higher number of 8 surfaces filled in a single visit. Given that an increase in mean BPA concentration was no longer detectable approximately 14 days or 6 months later, the findings of this study do not support the hypothesis that dental composites remain a measurable BPA exposure source after a brief period post-placement in children and adolescents.

CUBS is the first study designed to examine BPA exposure from dental composites over the longer term. It is also the first longitudinal study including a sufficient sample size of children and adolescents. Prior studies focused on the first 24–30 h after placement in adults. We focused on children and adolescents for multiple reasons, including (a) findings from the NECAT that children randomized to composites (vs. amalgam) and with higher numbers of composite restorations performed worse on certain neuropsychosocial outcome measures after 4–5 years follow-up;^{30–33} (b) data from numerous countries that children and adolescents had higher urinary BPA concentrations compared to adults, with little understanding as to the exposure sources or metabolic differences that may account for age-related differences;^{46–48} and (c) knowledge that dental restorations are most frequently placed at younger ages.⁴⁹ In the US, more than 60% of 5–19 year olds have dental caries or restorations present.⁴⁹

The finding of a 51% increase in the overall mean BPA concentration the day after restoration placement is consistent with results in adults from a prior study, which showed a 43% increase in the overall mean urinary BPA concentration 9 to 30 hours after composite restoration placement.²⁶ Also, despite the different ages, the pretreatment BPA concentrations were similar in the two studies. Data from the US National Health and Nutrition Examination Survey (NHANES) show that in recent years, BPA concentrations have declined more among the population aged 6–19 y than among adults, bringing reference values closer for the different age groups.^{44,48,50} Our observed distribution of pretreatment BPA concentrations was within the range for reference values reported for 6–11 year olds and 12–18 year olds in the 2011–2012 NHANES.⁴⁸ In NHANES, children with 7 restorations had 20% higher mean urinary BPA concentration compared to children with no restorations (95% CI: –6, 53; $P=0.13$).⁵¹ However, NHANES did not have data on restorative material type, hence combined amalgam, glass ionomer and other materials with bisGMA-based composites, and other limitations in the cross-sectional design weakened the ability to detect an association with bisGMA-based materials.^{51,52} In a meta-analysis of *in vitro* studies of dental materials, it was estimated that one full crown molar restoration may release an average 57.4 nmol of BPA per surface after 24 h, which implicated composites alongside contaminated food (~43.8 nmol) as a relevant BPA source.²⁴ Thus, the observation

of a mean 43–51% increase in pretreatment BPA concentration within approximately one day post-treatment supports the notion that placement of composite dental materials may expose the patient, albeit transiently, to BPA.

Our lack of finding a longer-term association between composite placement and BPA concentrations supports the American Dental Association (ADA) 2014 statement that most residual BPA in bisGMA-based materials is probably locked inside the polymer matrix after polymerization.²² The ADA's *in vitro* analyses of various bisGMA-based composite restoratives using artificial saliva highlighted the importance of polymerization in the first 48 h.²² Although composites are cured during placement, polymerization remains incomplete. Thus, the mechanism of BPA exposure during and shortly after placement is thought to involve leaching of non-polymerized components. In an *in vitro* study using dynamic mechanical analysis to experiment with various mechanical and environmental stressors on three different composite restoration material over 90 days, the researchers found that storage in water or artificial saliva for 1 to 7 days caused post-curing reactions, but storage for 30 or 90 days had no further effect for two of the three materials.⁵³ Together, these results support the notion that leaching of non-polymerized components of newly-placed composite materials terminates after a few days to a few weeks from the start of polymerization during treatment.²⁸

The question remains whether degradation of composite restorations, typically occurring over a course of many years after placement, results in chronic, low levels of BPA exposure. The CUBS follow-up time of approximately 6 months post-treatment was too short to include the typical life span of restorations including degradation, which may extend well over 10–20 years for current materials.⁵⁴ In addition, few participants had more than one treatment visit during follow-up, and the sample sizes were not sufficient for hypothesis testing after each additional treatment visit. As such, changes in BPA concentration next-day or 14-days after treatment 2 or treatment 3 were analyzed as exploratory analysis, and results were presented for completeness rather than to draw conclusions.

The consistency in dental materials used in CUBS and NECAT was intended to help explore changes in urinary BPA as a possible source for health outcomes observed in NECAT. However, the ability to generalize from CUBS participants to NECAT participants, or to patients receiving multiple surface fillings in one visit, was limited by the low treatment needs in CUBS participants. In NECAT, children had an average of 9.3 surfaces with caries at the first dental examination, whereas the average was only 2.3 surfaces in CUBS.³¹ The results of both studies point to the possibility of dose-response relationships, but the CUBS data were insufficient to thoroughly examine high treatment levels, as few participants had more than 3 surfaces filled. Given that the most striking increase in next-day urinary BPA concentration was in a patient with 8 surfaces filled in a single visit, it is possible that for the majority of patients who received just one or two surface fillings, changes in BPA concentrations were not measurable in the context of high inter-individual variation. That is, large variation in BPA may decrease the power to detect very small changes associated with dental treatment. Furthermore, while only two CUBS participants had more than 7 surfaces restored on-study (2.2%), 21.3% of the children in a published NHANES analysis⁵¹ had 7 or more restorations (maximum=42). As such, the patient sample in CUBS was not suitable to

examine associations with the high levels of composite treatment that may often occur in the general population. It remains uncertain if children receiving more than three fillings in one visit have a greater increase and/or extended release over time in BPA concentration.

High within-person variability in urinary BPA concentration and BPA's short half-life (~6 h through oral route)⁵⁵ are problematic in long-term studies, as single spot samples may be dramatically affected by acute exposures, such as food consumption.⁵⁶ Given this knowledge, we took numerous steps to in both our design and analysis to strengthen our ability to detect an association with composite placement. First, we considered non-dental BPA exposure sources. For example, we requested participants refrain from consuming canned foods and collected detailed data on foods/beverages consumed and preparation methods in the day prior to each urine collection. In the analysis, canned food consumption and season of urine collection were indeed time-varying predictors of urinary BPA changes. Second, we collected two pretreatment urine samples, which allowed us to evaluate baseline variability. The ICC of 0.25 was consistent with results of other studies of urinary BPA concentration in children⁵⁷ or adults.^{58,59} A study of Australian children found that a single sample provided moderately reliable assessment of BPA exposure in children, with 68% of individuals correctly classified by a single sample, and 76% correctly classified by 2 samples.⁶⁰ Third, we followed recommendations from prior studies to request standardized timing (first morning) of collections, record the time of day and handling of samples, and measure urine dilution using specific gravity.^{42,58}

In conclusion, placement of composite restorations in children and adolescents was associated with transient increases in urinary BPA concentration, which were no longer detectable at approximately 2 weeks or 6 months post-placement or after excluding study participants receiving high number of fillings in a single visit. The magnitude of change in BPA may depend on the number of surfaces restored, and additional research would be needed to precisely estimate such changes among children with more than 3 surfaces filled in one visit. It is unlikely that pre-existing composite restorations or sealants are measurable BPA exposure sources, but further research would be necessary particularly for failed restorations or degradation of restorations over their lifespan. Given that the human health effects of BPA remain to be determined, this study was not designed to directly affect clinical practice. Nonetheless, dentists should be aware of possible concerns regarding BPA exposure and take steps to prevent exposure during and shortly after treatment, such as improved methods for curing.⁶¹ Alternatives to bisGMA-based materials are increasing available, in part owing to concerns over BPA.²¹ For comprehensive safety and benefit-risk assessments, more information would be needed on human health effects of BPA and alternatives, as the benefits of composite restorations are well-established.

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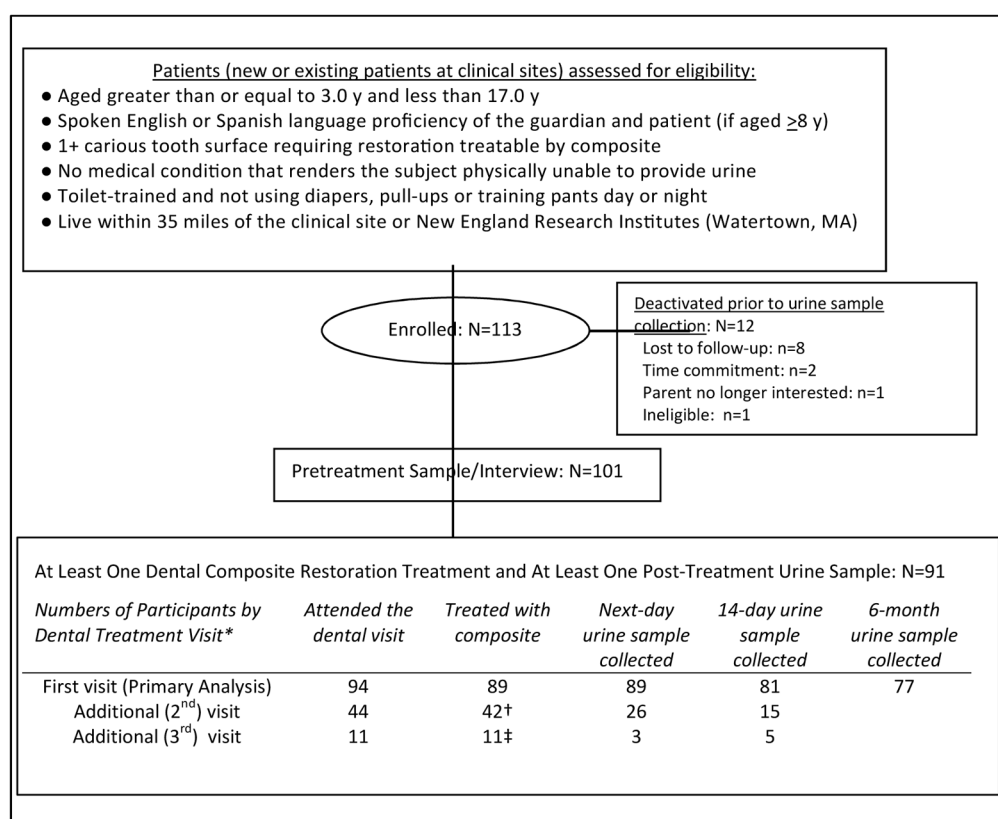
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**Figure 1.****Patient Eligibility Criteria and Flow through Study Visits**

*Additional visits were not required by the study protocol, but some participants had additional treatment visits to complete their composite treatment needs. Such participants were asked, but not required, to provide additional next-day and 14-day urine samples after each additional treatment visit (scheduled to occur approximately 2–3 weeks apart). For participants with multiple visits, the final urine sample collection was scheduled to occur approximately 6 months after the final restoration treatment visit.

[†]Includes 40 participants who received composite at the first treatment, and 2 participants who attended the first visit but did not receive composite restorations until the 2nd visit.

[‡]Includes 9 children who received composite at all 3 visits, and the 2 participants who received composite restorations only at visits 2 and 3.

Table 1

Baseline Characteristics of CUBS Participants in the Analysis (N=91) *

Age, years, mean (sd)	9.5 (\pm 3.7)
Sex	
Male	47 (53.4%)
Female	41 (46.6%)
Race/Ethnicity	
Hispanic	35 (38.5%)
White	24 (26.4%)
Black	16 (17.6%)
Other/missing	16 (17.6%)
Body mass index, kg/m ² , mean (sd)	19.6 (\pm 6.0)
Education level of parent/guardian	
No high school diploma	18 (20.7%)
High school graduate	30 (34.5%)
College graduate or above	39 (44.8%)
Household income	
< \$20,000	21 (23.1%)
\$20,000-\$50,000	21 (23.1%)
\$50,000+	22 (24.2%)
Missing	27 (29.7%)
Frequency of drinking from plastic containers	
Almost every day	37 (42.0%)
Some days	23 (26.1%)
Never	28 (31.8%)
Consumed canned food in the previous 24 h	
No	77 (84.6%)
Yes	14 (15.4%)
Composite restorations present	
Missing data	28 (30.8%)
No	24 (26.4%)
Yes	39 (42.9%)
Mean (SD)	3.4 (4.2)
Median (Q1, Q3)	2 (1, 4)
Sealants (preventive pit and fissure) present	
Missing data	28 (30.8%)
No	28 (30.8%)
Yes	35 (38.5%)
Mean (SD)	3.8 (2.4)

Median (Q1, Q3)	4 (2, 6)
Plastic space maintainers present	
No	86 (95.6%)
Yes	4 (4.4%)
BPA concentration specific-gravity adjusted (ng/mL)	
Mean (SD)	3.32 (3.80)
Median (min, max)	2.12 (0.43, 23.41)

* Percentages are calculated excluding participants missing data from the denominator, except for race/ethnicity, household income, composite restorations present, and sealants present. Missing data at baseline for other variables were as follows: sex n= 3; education level n=4, drinking from plastic containers n=3, plastic space maintainers present, n=1. The total sample size (N=91) is comprised of 89 participants treated with composite at the first visit and 2 participants who had no composite treatment at that visit but received composite at visits 2 and 3.

Table 2
Number of Composite Restorations Placed and Change in Urinary BPA Concentrations between Baseline and Each Follow-up Visit

Change from Baseline to:	N	No. Surfaces Restored Cumulatively			Baseline Urinary BPA (ng/mL)			Change in Urinary BPA (ng/mL)			Percent Change in Group Mean
		Median	(Min, Max)	Mean (sd)	Median	Mean (sd)	Median	Mean (sd)	Median	Mean (sd)	
Next day post-treatment visit 1 [*]	89	1	(1, 8)	1.4 (1.0)	1.97	3.33 (3.84)	0.28	1.71 (9.94)	0.28	1.71 (9.94)	51.4%
14 days post-treatment visit 1	81	1	(1, 8)	1.4 (1.0)	2.13	3.45 (3.97)	-0.15	-0.50 (4.09)	-0.15	-0.50 (4.09)	-14.5%
Next day post-treatment visit 2	26	3	(2, 6)	3.1 (1.3)	2.10	3.45 (3.35)	-0.50	-0.59 (3.62)	-0.50	-0.59 (3.62)	-17.1%
14-day post-treatment visit 2	15	3	(2, 6)	2.9 (1.2)	1.79	3.21 (2.36)	-0.34	-0.28 (3.55)	-0.34	-0.28 (3.55)	-0.4%
Next day post-treatment visit 3 [‡]	3	5	(3, 8)	5.3 (2.5)	1.10	1.03 (0.53)	0.71	1.97 (2.91)	0.71	1.97 (2.91)	191.3%
14-day post-treatment visit 3	5	5	(3, 8)	5.0 (1.9)	1.53	1.91 (1.38)	-0.02	-0.27 (1.28)	-0.02	-0.27 (1.28)	-14.1%
Final visit (approximately 6 mo)	77	2	(1, 8)	2.3 (1.6)	2.12	3.07 (3.01)	-0.17	0.29 (4.66)	-0.17	0.29 (4.66)	9.4%

^{*} Results in table included all participants. Excluding the participant with 8 surfaces restored at visit 1 and with high next-day BPA concentration of 81.8 ng/mL, results were: median baseline 1.90 ng/mL; mean baseline 3.30 (sd 3.86) ng/mL; median change 0.25 ng/mL; mean change 0.87 (sd 5.98) ng/mL, percent change in group mean 26.4%.

[‡] Of the 3 participants with a visit 3, the number of surfaces filled at visits 1, 2 and 3, respectively, were as follows: 1, 1, 1 (total 3 surfaces); 2, 1 (total 3 surfaces); and 3, 3, 2 (total 8 surfaces).

Table 3

Association between Number of Surfaces Restored with Composite and Change from Baseline in BPA from Regression Models *

	Type of Composite Surface Restored							
	All Surfaces				Posterior Occlusal Surfaces			
	N	eβ	95% CI	P-value	N	eβ	95% CI	P-value
Change from Baseline to Visit:								
Next day after composite placement [†]	89	1.37	1.13, 1.67	0.002	89	1.47	1.18, 1.83	<0.001
14 days after composite placement	81	0.93	0.78, 1.16	0.64	81	0.94	0.75, 1.18	0.60
6 months after composite placement	77	0.93	0.81, 1.08	0.35	77	0.88	0.74, 1.04	0.13

* The regression models analyzed the outcome of log-transformed BPA corrected for specific gravity. Values presented as e β are the back-transformed coefficients. Models adjusted for baseline BPA concentration and household income as fixed covariates, and level of canned food consumption in the day prior to urine sample collection and season of urine sample collection as time-varying covariates. The available sample sizes for BPA concentration measured after treatment visits 2 and 3 were insufficient for modeling analyses.

[†] Results in table included all participants. Excluding the participant with 8 surfaces restored at visit 1 and with high next-day BPA concentration of 81.8 ng/mL, results for next day were: all surfaces e β = 1.08 (95% CI 0.81, 1.47), $P=0.57$; posterior-occlusal surfaces e β = 1.19 (95% CI 0.86, 1.64), $P=0.29$.