

Monomer release from orthodontic retentions: An in vitro study

Chloé Pelourde,^a Raoul Bationo,^b Marie-José Boileau,^a Jacques Colat-Parros,^a and Fabienne Jordana^c

Nantes and Bordeaux, France, and Ouagadougou, Burkina Faso

Introduction: The adhesives used to bond orthodontic retentions are low-loaded composite resins with a resinous matrix containing bisphenol A diglycidyl ether dimethacrylate synthesized from bisphenol A (BPA), fluidizers such as triethylene glycol dimethacrylate (TEGDMA) and hydrophilic polymers such as hydroxyethylmethacrylate. BPA disrupts the endocrine balance, and TEGDMA has high risks for human health: eg, allergies and cytotoxicity. The aim of this study was to evaluate in vitro the release of monomers from orthodontic bonded retentions. **Methods:** A reproducible model of bonded retentions was carried out using calibrated molds. We analyzed the release of monomers by gas phase chromatography coupled with mass spectrometry. **Results:** This model allowed us to qualitatively and quantitatively evaluate the in-vitro release of monomers from orthodontic adhesives. The quantitative and qualitative analyses showed no BPA release above the 0.02 ppm detection limit. A greater release of TEGDMA was observed with Transbond LR (31.7 µg/mL) than with Transbond XT (13.12 µg/mL) (both, 3M Unitek, Monrovia, Calif). Other toxic components (iodobenzene, iodobiphenyl, triphenyl stibine, and so on) were also identified. **Conclusions:** Toxic and carcinogenic molecules not mentioned in the material safety data sheets were identified. (Am J Orthod Dentofacial Orthop 2018;153:248-54)

Bonded systems occupy a prominent place in orthodontics, including fixed retainers that can remain in the mouth for several decades.

Fixed lingual retainers, which have been used in orthodontics since the 1970s,¹ are bonded to the anterior mandibular teeth to prevent relapse or secondary crowding of the incisors.² These retainers are composed of braided or metallic wires bonded to enamel with a restorative resin composite or flowable orthodontic adhesives.^{3,4} Depending on the protocol, all 6 anterior teeth or only the canines are involved.⁴

The composite resins used in orthodontics consist of mineral fillers, resin matrix—generally bisphenol A diglycidyl ether dimethacrylate (Bis-GMA) synthesized from bisphenol A (BPA) and urethane—fluidifiers belonging

to the triethylene glycol family, catalysts (eg, camphorquinone), and various other additives. The self-etch bonding systems have introduced acid polymers and hydrophilic polymers such as hydroxyethyl-methacrylate.⁵

The increasing presence of polymers in the oral cavity has raised questions for several years about the safety of the components of the resinous matrix. Orthodontic adhesives induce cytotoxicity, disturbing cell metabolism and inducing cell death, even up to 2 years after polymerization⁶⁻¹⁵ and may cause inflammatory response in test animals.¹⁶⁻¹⁹ Eliades et al²⁰ indicated the absence of estrogenicity in orthodontic adhesive eluents. Gioka et al²¹ noted that a moderate reduction in DNA synthesis was obtained by adhesive eluents, implying a minor cytostatic effect.

Among the leached compounds, BPA is the most studied. Qualified as an endocrine disruptor due to its ability to bind and activate the estrogen receptor in humans, its effects are proven in animals and suspected in humans.²²⁻²⁶ In July 2012, the United States Food and Drug Administration²⁷ amended its regulations to disallow the use of BPA-based epoxy resins as coatings in packaging for infant formula.²⁸ The no observable adverse effect level is 5 mg per kg body weight per day of BPA in the United States.²⁷ In January 2015, the tolerable daily intake of BPA was reduced from 50 to 4 µg per kg body weight per day. BPA is banned for food contact in some European countries.^{29,30}

^aPôle d'Odontologie et de Santé buccale, Hôpital Pellegrin, Bordeaux, France; UFR d'Odontologie, Université de Bordeaux, Bordeaux, France.

^bClinique Bucco-dentaire, Centre Médical des Armées, Ouagadougou, Burkina Faso.

^cFaculty of Dentistry Nantes, France; Service d'Odontologie, Nantes, France.

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and none were reported.

Address correspondence to: Fabienne Jordana, Université de Nantes, 1 Place Alexis Ricordeau, BP 84215, Nantes cedex 1 44042, France; e-mail, fabienne.jordana@univ-nantes.fr.

Submitted, January 2017; revised and accepted, June 2017.

0889-5406/\$36.00

© 2017 by the American Association of Orthodontists. All rights reserved.

<https://doi.org/10.1016/j.ajodo.2017.06.021>

Other products less investigated than BPA but with potential toxicity, including some diluents such as triethylene glycol dimethacrylate (TEGDMA) and Bis-GMA, are released from restorative or bonding composites.^{22,23,31-37}

A protocol for the bonding of orthodontic retention wires has been developed to investigate the possible release of monomers (BPA and TEGDMA in particular) and to quantify this release by expressing it per unit area of exposed bond using gas phase chromatography coupled with mass spectrometry.

MATERIAL AND METHODS

To better simulate the quantity of adhesive applied to an orthodontic retainer, a sample of each composite (Transbond XT, Transbond LR; 3M Unitek, Monrovia, Calif) was prepared using calibrated molds by Mini-Mold Wire Bonder LG (diameter, 4 mm; height, 1.5 mm; G & H Wire Company, Franklin, Indiana). For each sample, 6 dots of composite representing the 6 anterior teeth were placed. The composition of the adhesives used is detailed in Table I.

Each dot was cured using a curing light (ScanWave Mini LED; Acteon; France) with a power of $1500 \pm 10\%$ mW per square centimeter and a wavelength of radiant energy between 390 and 510 nm for 20 seconds.

In accordance with recommendations, the distance between the light and the composite was reduced to a minimum of 1 mm to prevent contact and therefore the mobilization of the Mini-Mold while remaining as close as possible to the bond.³⁵

The total surface area of each adhesive dot was 32.16 mm^2 according to the geometry calculation. Following the International Organization for Standardization (ISO) 10993-12:2012 standard for medical-device testing in biologic systems,³⁸ each cured sample was immediately immersed in 0.66 mL (surface area/volume ratio, $3 \text{ cm}^2/\text{mL} \pm 10\%$) of Milli-Q water (Merck Millipore, Billerica, Mass) in a glass tube for 24 hours at 37°C .^{35,39} The immersion liquid was then lyophilized, and 100 μL of dichloromethane was added.

The composition of the eluates was analyzed using gas phase chromatography and mass spectrometry (TRACE Ultra Gas Chromatograph and ISQ Thermo; Thermo Finnigan Electron, Waltham, Mass). A capillary column 15 m in length with an internal diameter of 0.25 mm and a film thickness of 0.25 mm was used with helium carrier gas at a flow rate of 1.5 mL per minute. The splitless mode was used to identify a maximum of molecules. The column temperature program was set as follows: initially, 50°C for 1 minute, increasing to 300°C at a rate of 15°C per minute. The injector temperature was 230°C , and the transfer line was 250°C . Mass spectra were obtained using

Table I. Composition of resins used

Product	Batch	Composition from chemical safety data sheet
Transbond LR	GF9RC	Silane treated quartz: 75%-85% (C.A.S. No. 100402-78-6) Triethylene glycol dimethacrylate (TEGDMA): 5%-15% (C.A.S. No. 109-16-0) Bisphenol A diglycidyl ether dimethacrylate (Bis-GMA): 5%-15% (C.A.S. No. 1565-94-2) Dichloromethylsilane reaction product with silica: <2% (C.A.S. No. 68611-44-9) N,N-dimethylbenzocaine: <0.3% (C.A.S. No. 10287-53-3) Diphenyliodonium hexafluorophosphate: <0.1% (C.A.S. No. 58109-40-3)
Transbond XT	N592900	Silane treated quartz: 70%-80% (C.A.S. No. 100402-78-6) Bisphenol A diglycidyl ether dimethacrylate (Bis-GMA): 10%-20% (C.A.S. No. 1565-94-2) Bisphenol A Bis(2-hydroxyethyl ether) dimethacrylate: 5%-10% (C.A.S. No. 24448-20-2) Silane treated silica: <2% (C.A.S. No. 68611-44-9) Diphenyliodonium hexafluorophosphate: <0.2% (C.A.S. No. 58109-40-3)

electron impact ionization (70 eV, 150 μA , 200°C). The compounds primarily sought were BPA, TEGDMA, and hydroxyethyl-methacrylate. Data were processed with the software Thermo Scientific Xcalibur (Thermo Fisher Scientific, Waltham, MA).

After identification of the released compounds, the molecules of interest were quantified. The exact concentration was calculated by comparison between the standard and the sample compound. To increase the sensitivity, the acquisition was performed by single ion monitoring.

RESULTS

The Figure shows the chromatograms of each sample; peaks correspond to chemical compounds according to their retention time.

The identified chemical molecules in the tested samples are presented in Table II.

Both samples released iodobenzene, camphoric anhydride, iodobiphenyl, dimethyl benzocaine, TEGDMA, triphenyl stibine, and alkanes. Camphorquinone, lauric acid, and hydroxydiphenyl were only detected in Transbond XT. Butylhydroxytoluene was identified in Transbond LR (Table II).

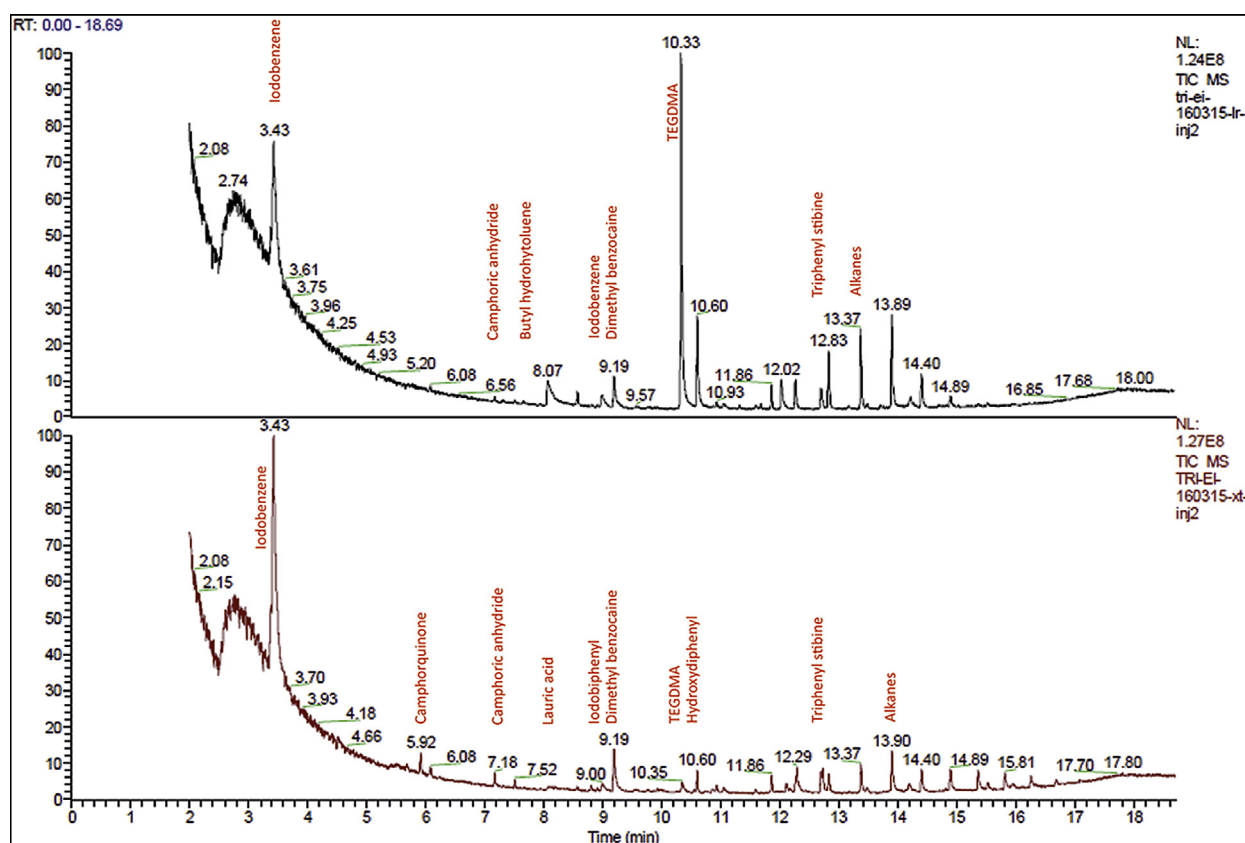


Fig. Chromatograms for Transbond LR (*top*) and Transbond XT (*bottom*).

Table II. Compounds found and their chemical formulae

Retention time (min)	Compounds	Molecular weight	Transbond LR	Transbond XT
3.43	Iodobenzene C ₆ H ₅ I	204	X	X
5.92	Camphorquinone C ₁₀ H ₁₄ O ₂	166		X
7.18	Camphoric anhydride C ₁₀ H ₁₄ O ₃	182	X	X
7.68	Butylhydroxytoluene C ₁₅ H ₂₄ O	220	X	
8.11	Lauric acid C ₁₂ H ₂₄ O ₂	200		X
8.9	Iodobiphenyl C ₁₂ H ₉ I	280	X	X
9.19	Dimethyl benzocaine C ₁₁ H ₁₅ NO ₂	193	X	X
10.34	TEGDMA C ₁₄ H ₂₂ O ₆	286	X	X
10.54	Hydroxydiphenyl C ₁₂ H ₁₀ O	170		X
12.73	Triphenyl stibine Sb (C ₆ H ₅) ₃	352	X	X
12.83–14.89	Alkanes	–	X	X

Of all the compounds, only TEGDMA and dimethylbenzocaine were indicated on the Transbond LR safety data sheet (Table I).

The release of TEGDMA, as indicated by the heights of the retention peaks characteristic of this molecule, was lower for Transbond XT. This result was confirmed by the quantitative analysis, which yielded TEGDMA concentrations of 31.7 µg/mL for Transbond LR vs

13.12 µg/mL for Transbond XT. No trace of BPA was detected above the detection threshold of 0.02 ppm.

DISCUSSION

We followed the same ISO 10993-12:2012 38 standards as did Bationo et al⁵ for sample preparation and reference material selection for medical-device testing in biologic systems. We used glass bottles, free from

Table III. Protocols for the in-vitro study of the release of monomers from orthodontic adhesives in the literature (1 ppm = 1 mg/l = 1 µg/mL)

	Monomer	Studied adhesives	Immersion medium and time	Analysis	Results
Eliades et al ⁵⁶ 1995	TEGDMA Bis-GMA	Transbond Concise	Ethanol + water 15 days	HPLC	Maximum values: - TEGDMA: 17.4 ppm (Concise) - Bis-GMA: 6.16 ppm (Transbond)
Gioka et al ²¹ 2005	TEGDMA Bis-GMA	Rely-a-bond Reliance	Saline solution 2 months	HPLC	TEGDMA: 11.5 and 13.2 ppm Bis-GMA: unmeasurable
Eliades et al ⁵¹ 2007	BPA	Rely-a-bond Reliance	Pure alcohol 1, 7, 21, 35 days	HPLC	No release above the detection limit (0.1 ppm)
Eliades et al ⁵⁵ 2011	BPA	Transbond XT	Double-distilled water 10, 20, and 30 days	GC-MS	BPA detected in all samples Highest amount: 1-month group (2.9 µg/L) Control (tooth storage solution): 0.16 µg/L.
Sunitha et al ⁵² 2011	BPA	Transbond XT	Pure alcohol 1, 7, 21, 35 days	HPLC	The release increases: - with the lamp-adhesive distance - depending on the immersion time: from 1 to 21 days (maximum: 65.67 ppm)
Kotyk and Wiltshire ⁵³ 2014	BPA	Transbond XT	Artificial saliva 1, 3, 7, 14 days	GC-MS	Release at 3 days of 0.34 ppm
Malkiewicz et al ⁵⁴ 2015	BPA Poly-BPA Bis-GMA	Transbond XT Light Bond Resilience Aspire GrænGloo ConTec LC	Water + antibiotic antimicrobial preparation 1 hour, 1, 7, 31 days	HPLC	Resilience: release of BPA, maximal at 1 hour (32.10 ppm) ConTec LC, Light Bond and Resilience: release of poly-BPA (maximal with ConTec LC 1 hour (371.90 ppm)) Aspire: release of Bis-GMA, maximal 1 hour (425.07 ppm)
Purushothaman et al ⁵⁷ 2015	BPA	Transbond XT	Alcohol 1, 7, 21, and 35 days	HPLC	BPA release increased as distance increased and time decreased. Chemically cured composites had less BPA release (0.18 ± 0.00 at day 1)
Bationo et al ⁵ 2016	BPA TEGDMA	Transbond XT Transbond Supreme LV Blugloo MonoLok 2	Milli-Q water 1 day	GC-MS	BPA detected in Blugloo TEGDMA detected in all samples

SPME, Solid phase microextraction; HPLC, high performance liquid chromatography; LC-MS, liquid chromatography-mass spectrometry; GC-MS, gas chromatography-mass spectrometry.

interfering compounds, during sampling, sample storage, and extraction, as recommended.⁴⁰ The 24-hour period, recommended in the standard 38, was also retained because salivary BPA concentrations are higher immediately after material placement and decrease during the next hours.^{41,42}

Gas phase chromatography and mass spectrometry allows detection of a variety of elutable and toxicologic relevant substances.⁴³ This method after derivatization was also used to determine the low levels of BPA because it provides high sensitivity and selectivity.⁴⁰ An analytic procedure to detect low volatile monomers such as bisEMA is now available.⁴³

On the material safety data sheets, only TEGDMA and dimethylbenzocaine were indicated for Transbond LR (Table I).

As in the study of Bationo et al,⁵ most of the compounds found in this study were monomers or their derivatives and additives. Camphorquinone is a photoinitiator, dimethyl benzocaine is a coinitiator, dihydroxybenzophenone is a photostabilizer, and butyl-hydroxytoluene is a setting inhibitor. Some compounds are synthesis residues of the raw material (stabilizers, catalysts, and so on).⁴⁴

TEGDMA was detected in both samples, although a more significant quantity was detected in Transbond LR. According to the manufacturer, the proportion of TEGDMA in Transbond LR is approximately 5% to 15%. Since Transbond LR is intended to bond retention wires, its composition requires this diluent to reduce the adhesive viscosity and therefore facilitate its handling and shaping.

Triphenyl stibine is a contaminant that can be genotoxic.⁴⁵ The photoinitiator camphorquinone and butylhydroxytoluene, a preservative and anti-oxidant used in food, cosmetics, and medications, are allergens.^{46,47} Butylhydroxytoluene is toxic in mice and rats at high doses after long-term exposure. It may mimic estrogen.³² According to Williams and et al,⁴⁸ at current levels of use as a food additive, butylhydroxytoluene poses no cancer hazard and, to the contrary, may be anticarcinogenic. Iodobenzene is comparable to T4 hormone and may act as a thyroid stimulant in rats.⁴⁹ o-phenylphenol, listed in the Toxic Substances Control Act, is an experimental teratogen and a human mutagenic. It can have reproductive effects. p-phenylphenol, also listed in the Act, is a possible carcinogen and an experimental tumorigenic, with the blood as its target organ.⁵⁰

A comparison of published results was limited because there are few studies on orthodontic adhesives and the inhomogeneity of protocols.

Our study did not show the release of BPA above the detection threshold of 0.02 ppm. Bationo et al⁵ also followed the ISO 10993-12:2012 38 standards and used gas phase chromatography and mass spectrometry analysis. They highlighted the release of BPA from the Blugloo adhesive (Ormco, Orange, Calif) but not from Transbond XT, Transbond Supreme LV, or MonoLok 2 (Rocky Mountain Orthodontics, Denver, Colo). Their detection threshold was also 0.02 ppm.⁵

Eliades et al⁵¹ in 2007 did not observe release above a detection threshold of 0.1 ppm regardless of the duration of immersion and despite the aging caused by alcohol. However, they studied different adhesives (Rely-a-Bond; Reliance Orthodontic Products, Itasca, Ill) with a model for the bonding of orthodontic brackets and an analysis of leached monomers by high performance liquid chromatography. In contrast, in 2011, Sunitha et al⁵² used a protocol similar to that of Eliades et al that focused on Transbond XT and detected measurable amounts of BPA in all samples (at 1, 7, 21, and 35 days); the maximum amount found reached 65.67 ppm at 21 days.

In 2014, Kotyk and Wiltshire⁵³ observed BPA release from Transbond XT composite discs (2 mm thickness, 6 mm diameter) of 0.34 ppm at 3 days. However, they did not detect BPA above the detection threshold of 0.17 ppm at 24 hours (similar to the results of our study) at 7 and 14 days.

Finally, Malkiewicz et al⁵⁴ did not detect BPA in their Transbond XT samples, but the detection threshold was not indicated and could therefore have been quite high; the lowest concentration of BPA found among the various adhesives tested was 1.71 ppm.

The results of in-vitro studies are thus highly variable because of the diversity of protocols and methods of analysis. The fact that some authors have observed the release of BPA above our detection threshold but we have not can be explained by the differences in the immersion media (pure alcohol^{51,52} or artificial saliva⁵³) and the immersion time.⁵⁵

The release of TEGDMA by Transbond XT observed in vitro at 24 hours was similar to the gas phase chromatography and mass spectrometry results of Bationo et al,⁵ who analyzed the release of monomers from adhesive discs.

On the other hand, the quantities recorded by Eliades et al⁵⁶ and Gioka et al²¹ for other composite resins for bonding brackets were similar to the results obtained in our study, although the protocols were different (Table III): 17.4 ppm (Concise, 3M Unitek) according to Eliades et al; from 11.5 (Reliance, Reliance Orthodontic Products) to 13.2 ppm (Rely-a-bond) according to Gioka et al; and 13.12 ppm (Transbond XT) in our study.

However, the release of TEGDMA from composites intended for bonding retention wires, which must be more fluid, has not yet been studied. It is therefore not possible to compare the results obtained in this study for Transbond LR.

CONCLUSIONS

The analysis of the bonded retention model developed in this study allows us to highlight the following results.

1. The absence of BPA above the detection threshold of 0.02 ppm, which does not exclude the possibility that this molecule is released in lower quantities.
2. The release of monomers and particularly TEGDMA at 24 hours from Transbond XT and Transbond LR, 2 composites used for bonding orthodontic retention wires.
3. Greater release of TEGDMA from Transbond LR than from Transbond XT.
4. The release of potentially toxic compounds (iodobenzene, iodobiphenyl, dimethyl benzocaine, triphenyl stibine, hydroxydiphenyl and butylhydroxytoluene).

Although in-vivo phenomena are more complex (accelerated biodegradation by salivary enzymes and mechanical stresses applied by masticatory forces and contact with food as well as dilution of harmful agents in saliva), the results of this in-vitro study allowed us to validate a model of monomer release from an orthodontic bonded retainer.

REFERENCES

- Knierim RW. Invisible lower cuspid to cuspid retainer. *Angle Orthod* 1973;43:218-20.
- Little RM, Riedel RA, Årtun J. An evaluation of changes in mandibular anterior alignment from 10 to 20 years post-retention. *Am J Orthod Dentofacial Orthop* 1988;93:423-8.
- Pandis N, Vlahopoulos K, Madianos P, Eliades T. Long term periodontal status of patients with mandibular lingual fixed retention. *Eur J Orthod* 2007;29:471-6.
- Iliadi A, Kloukos D, Gkantidis N, Katsaros C, Pandis N. Failure of fixed orthodontic retainers: a systematic review. *J Dent* 2015;43:876-96.
- Bationo R, Jordana F, Boileau MJ, Colat-Parros J. Release of monomers from orthodontic adhesives. *Am J Orthod Dentofacial Orthop* 2016;150:491-8.
- Jonke E, Franz A, Freudenthaler J, König F, Bantleon HP, Schedle A. Cytotoxicity and shear bond strength of four orthodontic adhesive systems. *Eur J Orthod* 2008;30:495-502.
- Jagdish N, Padmanabhan S, Chitharanjan AB, Revathi J, Palani G, Sambasivam M, et al. Cytotoxicity and degree of conversion of orthodontic adhesives. *Angle Orthod* 2009;79:1133-8.
- D'Antò V, Spagnuolo G, Polito I, Paduano S, Ambrosio L, Valletta R. In vitro cytotoxicity of orthodontic primers. *Prog Orthod* 2009;10:4-11.
- Tang AT, Liu Y, Björkman L, Ekstrand J. In vitro cytotoxicity of orthodontic bonding resins on human oral fibroblasts. *Am J Orthod Dentofacial Orthop* 1999;116:132-8.
- Vande Vannet BM, Hanssens JL. Cytotoxicity of two bonding adhesives assessed by three-dimensional cell culture. *Angle Orthod* 2007;77:716-22.
- Huang TH, Tsai CY, Chen SL, Kao CT. An evaluation of the cytotoxic effects of orthodontic bonding adhesives upon a primary human oral gingival fibroblast culture and a permanent, human oral cancer-cell line. *J Biomed Mater Res* 2002;63:814-21.
- Huang TH, Liao PH, Li HY, Ding SJ, Yen M, Kao CT. Orthodontic adhesives induce human gingival fibroblast toxicity and inflammation. *Angle Orthod* 2008;78:510-6.
- Tell RT, Sydiskis RJ, Isaacs RD, Davidson WM. Long-term cytotoxicity of orthodontic direct-bonding adhesives. *Am J Orthod Dentofacial Orthop* 1998;93:419-22.
- Angiero F, Farronato G, Dessy E, Magistro S, Seramondi R, Farronato D, et al. Evaluation of the cytotoxic and genotoxic effects of orthodontic bonding adhesives upon human gingival papillae through immunohistochemical expression of p53, p63 and p16. *Anticancer Res* 2009;29:3983-7.
- Ahrari F, Tavakkol Afshari J, Poosti M, Brook A. Cytotoxicity of orthodontic bonding adhesive resins on human oral fibroblasts. *Eur J Orthod* 2010;32:688-92.
- Malkoc S, Corekci B, Botsali HE, Yalçın M, Sengün A. Cytotoxic effects of resin-modified orthodontic band adhesives. Are they safe? *Angle Orthod* 2010;80:890-5.
- Malkoc S, Corekci B, Ulker HE, Yalçın M, Sengün A. Cytotoxic effects of orthodontic composites. *Angle Orthod* 2010;80:759-64.
- Davidson WM, Sheinis EM, Shepherd SR. Tissue reaction to orthodontic adhesives. *Am J Orthod* 1982;82:502-7.
- Santos RL, Pithon MM, Fernandes AB, Cabral MG, Ruellas AC. Biocompatibility of orthodontic adhesives in rat subcutaneous tissue. *J Appl Oral Sci* 2010;18:503-8.
- Eliades T, Gioni V, Kletsas D, Athanasiou A, Eliades G. Oestrogenicity of orthodontic adhesive resins. *Eur J Orthod* 2007;29:404-7.
- Gioka C, Eliades T, Zinelis S, Pratsinis H, Athanasiou AE, Eliades G, et al. Characterization and in vitro estrogenicity of orthodontic adhesive particulates produced by simulated debonding. *Dent Mater* 2009;25:376-82.
- Al-Hiyasat AS, Darmani H, Elbetieha AM. Effects of bisphenol A on adult male mouse fertility. *Eur J Oral Sci* 2002;110:163-7.
- Al-Hiyasat AS, Darmani H, Elbetieha AM. Leached components from dental composites and their effects on fertility of female mice. *Eur J Oral Sci* 2004;112:267-72.
- Goldberg M. In vitro and in vivo studies on the toxicity of dental resin components: a review. *Clin Oral Investig* 2008;12:1-8.
- Hashimoto Y, Nakamura M. Estrogenic activity of dental materials and bisphenol A related chemicals in vitro. *Dent Mater J* 2000;19:245-62.
- Hashimoto Y, Moriguchi Y, Oshima H, Nishikawa J, Nishihara T, Nakamura M. Estrogenic activity of chemicals for dental and similar use in vitro. *J Mater Sci Mater Med* 2000;11:465-8.
- Bisphenol A Joint Emerging Science Working Group to Food and Drug Administration Chemical and Environmental Science Council; memoranda dated 5/24/2011, 8/22/2013, and 6/9/2014: updated review of the "low-dose" literature (data) on bisphenol A (CAS RN 80-05-7) and response to charge questions regarding the risk assessment on bisphenol A; 2012 updated review of literature and data on bisphenol A (CAS RN 80-05-7); 2014 updated review of literature and data on bisphenol A (CAS RN 80-05-7). Silver Spring, Md: Food and Drug Administration.
- U.S. Food and Drug Administration, U.S. Department of Health and Human Services. Bisphenol A (BPA): use in food contact application: Available at: <http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm064437.htm>; 2016. Accessed December 11, 2016.
- European Information Centre on bisphenol A. Food Contact Regulation: Available at: http://www.bisphenol-a-europe.org/en_GB/legislation/food-contact. Accessed December 11, 2016.
- European Food Safety Authority. Opinion of the scientific panel on food additives, flavourings, processing aids and materials in contact with food on a request from the commission related to 2,2-bis(4-hydroxyphenyl) propane (bisphenol A). Question number EFSA-Q-2005-100. *EFSA J* 2006;4:28:1-75.
- Gioka C, Bourauel C, Hiskia A, Kletsas D, Eliades T, Eliades G. Light-cured or chemically cured orthodontic adhesive resins? A selection based on the degree of cure, monomer leaching, and cytotoxicity. *Am J Orthod Dentofacial Orthop* 2005;127:413-9.
- Wada H, Tarumi H, Imazato S, Narimatsu M, Ebisu S. In vitro estrogenicity of resin composites. *J Dent Res* 2004;83:222-6.
- Nathanson D, Lertpitayakun P, Lamkin MS, Edalatpour M, Chou LL. In vitro elution of leachable components from dental sealants. *J Am Dent Assoc* 1997;128:1517-23.
- Volk J, Leyhausen G, Geurtsen W. Glutathione level and genotoxicity in human oral keratinocytes exposed to TEGDMA. *J Biomed Mater Res B Appl Biomater* 2012;100:391-9.
- Kloukos D, Pandis N, Eliades T. Bisphenol-A and residual monomer leaching from orthodontic adhesive resins and polycarbonate brackets: a systematic review. *Am J Orthod Dentofacial Orthop* 2013;143(Suppl 4):S104-12.
- Wisniewska-Jarosinska M, Poplawski T, Chojnacki CJ, Pawlowska E, Krupa R, Szczepanska J, et al. Independent and combined cytotoxicity and genotoxicity of triethylene glycol dimethacrylate and urethane dimethacrylate. *Mol Biol Rep* 2011;38:4603-11.
- Schmalz G, Preiss A, Arenholt-Bindslev D. Bisphenol-A content of resin monomers and related degradation products. *Clin Oral Investig* 1999;3:114-9.
- International Organization for Standardization. 10993-12:2012. Biological evaluations of medical devices. Part 12: sample preparation and reference materials. Geneva, Switzerland: International Organization for Standardization; 2012.

39. Van Landuyt KL, Nawrot T, Geebelen B, De Munck J, Snauwaert J, Yoshihara K, et al. How much do resin-based dental materials release? A meta-analytical approach. *Dent Mater* 2011;27:723-47.
40. Voutsas D. Analytical methods for determination of bisphenol A. In: Eliades T, Eliades G, editors. *Plastics in dentistry and oestrogenicity*. Berlin, Germany: Springer; 2014. p. 51-79.
41. Fung EY, Ewoldsen NO, St Germain HA Jr, Marx DB, Miaw CL, Siew C, et al. Pharmacokinetics of bisphenol A released from a dental sealant. *J Am Dent Assoc* 2000;131:51-8.
42. Joskow R, Boyd Barr D, Barr JR, Calafat AM, Needham LL, Rubin C. Exposure to bisphenol A from bis-glycidyl dimethacrylate-based dental sealants. *J Am Dent Assoc* 2006;137:353-62.
43. Durner J, Schrickel K, Watts DC, Ilie N. Determination of homologous distributions of bisEMA dimethacrylates in bulk-fill resin-composites by GC-MS. *Dent Mater* 2015;31:473-80.
44. Spahl W, Budzikiewicz H, Geurtsen W. Determination of leachable components from four commercial dental composites by gas and liquid chromatography/mass spectrometry. *J Dent* 1998;26:137-45.
45. Heil G, Reifferscheid J, Waldmann P, Leyhausen G, Geurtsen G, Geurtsen W. Genotoxicity of dental materials. *Mutat Res* 1996;386:181-94.
46. Bruzell Roll EM, Jacobsen N, Hensten-Pettersen A. Health hazards associated with curing light in the dental clinic. *Clin Oral Investig* 2004;8:113-7.
47. U.S. National Library of Medicine. Occupational health database Haz-Map®: Available at: <https://hazmap.nlm.nih.gov>. Accessed December 11, 2016.
48. Williams GM, Iatropoulos MJ, Whysner J. Safety assessment of butylated hydroxyanisole and butylated hydroxytoluene as antioxidant food additives. *Food Chem Toxicol* 1999;37:1027-38.
49. Visvanathan A, Narayanan U, Shanmugasundaram KR. Effect of iodobenzene therapy on mitochondrial activity in 2-thiouracil-induced hypothyroidism in weanling rats. *Res Commun Chem Pathol Pharmacol* 1983;42:339-42.
50. Ash M, Ash I. *Handbook of preservatives*. Endicott, NY: Synapse Information Resources; 2004.
51. Eliades T, Hiskia A, Eliades G, Athanasiou AE. Assessment of bisphenol-A release from orthodontic adhesives. *Am J Orthod Dentofacial Orthop* 2007;131:72-5.
52. Sunitha C, Kailasam V, Padmanabhan S, Chitharanjan AB. Bisphenol A release from an orthodontic adhesive and its correlation with the degree of conversion on varying light-curing tip distances. *Am J Orthod Dentofacial Orthop* 2011;140:239-44.
53. Kotyk M, Wiltshire WA. An investigation into bisphenol-A leaching from orthodontic materials. *Angle Orthod* 2014;84:516-20.
54. Malkiewicz K, Turlo J, Marciniuk-Kluska A, Grzech-Leśniak K, Gąsior M, Kluska M. Release of bisphenol A and its derivatives from orthodontic adhesive systems available on the European market as a potential health risk factor. *Ann Agric Environ Med* 2015;22:172-7.
55. Eliades T, Voutsas D, Sifakakis I, Makou M, Katsaros C. Release of bisphenol-A from a light-cured adhesive bonded to lingual fixed retainers. *Am J Orthod Dentofacial Orthop* 2011;139:192-5.
56. Eliades T, Eliades G, Brantley WA, Johnston WM. Residual monomer leaching from chemically cured and visible light-cured orthodontic adhesives. *Am J Orthod Dentofacial Orthop* 1995;108:316-21.
57. Purushothaman D, Kailasam V, Chitharanjan AB. Bisphenol A release from orthodontic adhesives and its correlation with the degree of conversion. *Am J Orthod Dentofacial Orthop* 2015;147:29-36.