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Assessing Toxicological Safety of EverX Posterior and Filtek Ultimate: An In-Depth Extractable and Leachable Study Under ISO 10993-17 and 10993-18 Standards

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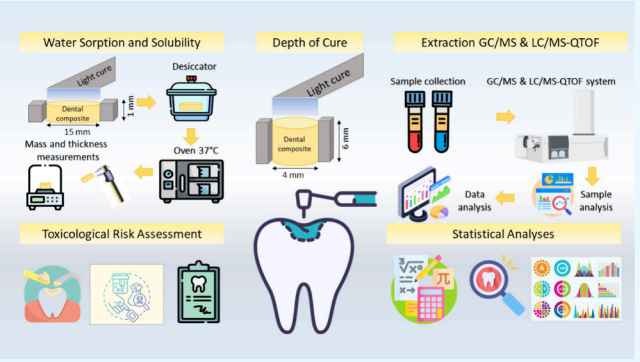
ABSTRACT: This study critically evaluates the biocompatibility and toxicological safety of EverX Posterior (eXP) and Filtek Ultimate (FU) dental composites following the International Standardization Organization (ISO) 10993-17:2023 and 10993-18:2020 guidelines. Our research highlights important findings on the depth of cure, water absorption, solubility, and release profiles of organic compounds in these composites using advanced chromatographic techniques. The analysis revealed that both eXP and FU composites are safe for patients regarding extractable and leachable (E&L) compounds, indicating a low risk of adverse biological effects. It was found that eXP and FU had solubilities of 6.062 ± 0.576 and 0.864 ± 0.436 $\mu g/mm^3$, respectively, revealing their stability and reliability for clinical use. Our results suggest that there is no significant difference in the release profiles of the uncured (dough) and cured forms of these materials. Also, the likelihood of systemic toxicological effects caused by the identified E and L compounds is considered to be low. This research emphasizes the compliance of these materials with strict ISO standards and highlights the importance of conducting extraction studies on both dough and cured forms for comprehensive toxicological safety assessments in dental practice.



INTRODUCTION

Resin-composite materials have revolutionized the field of dentistry, offering a promising blend of durability, aesthetic appeal, and ease of application.[1] These composites are intrinsically complex, encompassing both organic and inorganic components. The organic component typically consists of a polymerizable resin matrix laden with base monomers, notably bisphenol A-glycidyl methacrylate (BisG-MA) and urethane dimethacrylate (UDMA). This matrix is further enhanced by diluent comonomers and supplemented by various additives which influence the polymerization and stability of the composite.[2]

Conventional resin composites like Filtek Ultimate (FU) are widely used in restorative dentistry due to their aesthetic appeal and safety. However, they present challenges such as polymerization shrinkage, wear, technique sensitivity in back tooth restorations, and discoloration. These issues spark debate about the effectiveness of composite restorations. Moreover, conventional resin composites are cured in 2 mm layers, but this depth of cure is often inadequate for posterior restorations.[3] Therefore, innovations in the field have given rise to bulk fill composites, notable for their ability to be applied in thicker layers without compromising quality.[4] Among them, microfill composites, with low filler content, mimic the appearance of enamel but have weaker mechanical properties. In contrast, hybrid composites containing higher amounts of filler offer better mechanical strength and acceptable esthetic qualities. Studies have shown that nano-hybrid composites exhibit significantly better mechanical properties compared to microhybrid composites. Another noteworthy entrant in this category is short-fiber bulk materials such as EverX Posterior (eXP). Its formulation incorporates familiar elements but is further distinguished by a semi-interpenetrating polymer network (semi-IPN) matrix, resulting in a composite that offers superior bonding capabilities and enhanced resilience.[5−7]

In dental restoration applications, bulk fill composites such as eXP are used up to a thickness of 4 mm in place of dentin. Subsequently, traditional resin composites like FU are applied as a replacement for enamel.[8] The mechanical advantages and

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Table 1. Composite Materials Tested

material	sample code	composition	type	filler loading (wt %)	manufacturer
EverX Posterior Glass Fiber-Reinforced Composite	eXP	bisGMA, TEGDMA, PMMA barium borosilicate glass filler, E-glass fiber	fiber-reinforced composite	74.2	GC, Tokyo, Japan
Filtek Ultimate Universal Restorative Composite	FU	BisGMA, TEGDMA, BisEMA, UDMA, silica/zirconia cluster filler (0.6−10 μm), zirconia particles (4−11 nm)	hybrid	74.2	3M ESPE, St. Paul, MN, USA

clinical applications of eXP, particularly when used in conjunction with traditional dental composites, such as FU, have been comprehensively documented in the literature. This documentation covers a range of scenarios showcasing the efficacy and benefits of integrating eXP with these established materials in dental restorations.[9−16] On the other hand, there is no research on how these two materials, when used synergistically, will impact toxicological risks within the scope of the toxicological risk assessment established before the market release of each medical device, which is based on ISO 10993-18:2020 and ISO 10993-17:2023. This paucity of research is surprising, given the importance of understanding the leaching behaviors of dental composites.[17]

In general, the leaching or release of compounds from dental materials has been a topic of keen interest.[18] The comprehensive understanding of which components migrate from dental materials and potentially enter the human body is paramount for ensuring the safety of such applications.[19] Monomers like BisGMA and TEGDMA often draw attention due to their potential health implications, but it is also essential to recognize the role of additives in this context.[20−28] To accurately discern which compounds are being released and in what quantities, sophisticated methodologies are employed. High-performance liquid chromatography (HPLC) stands as a prime example of the techniques used to assess the quality and quantity of these eluted monomers. Other techniques used include gas−liquid chromatography, gas and liquid chromatography/mass spectrometry, and very recently, electrospray ionization/mass spectrometry and micellar electrokinetic chromatography. Analysis is usually performed with liquid chromatography−mass spectrometry (LC/MS).[20] In this case, the pure components are used as external standards for the identification and quantification of the eluted components.[29] Different extraction strategies such as simulated-use extraction, exaggerated extraction, and exhaustive extraction are evaluated depending on the nature and duration of body contact. ISO 10993-18:2020 recommends the use of exhaustive or exaggerated extractions for medical devices used for prolonged exposure, defined as 24 h to 30 days, and for medical devices used for more than 30 days.

As dentistry, like all medical fields, is increasingly governed by standardized practices, the importance of extractable and leachable (E&L) studies, in compliance with ISO 10993--12:2021, ISO 10993-18:2020, and ISO 10993-17:2023 guidelines, cannot be overstated. According to ISO 10993-18:2020, leachables are the substances that are released from a medical device and to a potentially affected individual during its clinical use and extractables are the substances that are released from a medical device or material of construction when the medical device or material is extracted using laboratory extraction conditions and vehicles. The aim of ISO 10993-18:2020 is to provide guidance on the determination of the amount of organic components and elements (E&L) released from medical devices, including dental materials, and their potential toxicological effects.[30] ISO 10993-17:2023, on the other hand, outlines the process for evaluating the biocompatibility of medical devices based on the risk management process. It specifically addresses the assessment of the toxicological risks associated with the chemical characterization of materials used in medical devices.[31] ISO 10993-12:2021 provides guidance on sample preparation and reference materials for biological testing, which is relevant for conducting the tests outlined in ISO 10993-18:2020 and ISO 10993-17:2023.[32] Therefore, these standards are interrelated, as they collectively contribute to ensuring the biocompatibility and safety of medical devices, including dental materials, through comprehensive testing and risk assessment processes. Given the vastness of compounds typically identified in E&L studies, it is pragmatic to establish a threshold, known as the analytical evaluation threshold (AET), to prioritize which compounds warrant further toxicological scrutiny.[30]

In practical terms, while resin-composites such as eXP often undergo rigorous individual assessments, they are seldom used alone. Their combination with other dental materials such as FU can potentially modify the overall elution profiles, necessitating a holistic examination.[4] The biocompatibility of composite resins is not merely an academic concern but has profound real-world implications. These materials, upon interaction with the unique environment of the oral cavity, can release various compounds. These constituents have the potential to induce a plethora of adverse effects, ranging from allergies to more severe teratogenic, mutagenic, and estrogenic outcomes.[33−37] As such, the safety profile of a dental material is pivotal.

This study is poised to bridge a critical knowledge gap by delving deep into the E&L profiles of both eXP and FU, not just as separate entities but, more crucially, in their combined form (cc-eXP-FU). Utilizing the benchmarks outlined in ISO 10993-18:2020, this research aims to establish a comprehensive safety profile for the combination of these materials by replicating their application in real-world usage, thus ensuring alignment with the highest standards of patient safety and clinical efficacy.

EXPERIMENTAL METHODS

Fiber-reinforced bulk fill composite eXP (GC, Europe) and resin-composite FU (3 M ESPE, USA) were used. The material details are listed in Table 1. A blue LED(Elipar S10, 3 M ESPE) was used for curing the light-cured resin composites. The light intensity of this unit was 500 mW/cm^2.

Depth of Cure (DOC) Determination. ISO 4049:2019 specifies requirements and test methods for polymer-based restorative materials used in dentistry. It covers materials such as dental composites and dental cements, providing guidance on their physical properties, biocompatibility, and clinical performance. Compliance with ISO 4049:2019 ensures that dental restorative materials meet established quality and safety standards, contributing to their effectiveness and reliability in

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dental practice.[38] The depth of cure test (DOC) is conducted to determine the maximum thickness of a dental composite material that can be adequately cured or polymerized. This test is crucial, as insufficient curing can result in much more elution from the restoration. In this study, DOC was performed according to ISO 4049:2019 using a cylindrical Teflon mold (4 mm in diameter and 6 mm in height). Three different groups were tested in terms of DOC. For the first and second groups, molds were filled with eXP and FU, separately. For the third group (cc-eXP-FU), clinical practice was simulated. Briefly, half of the mold was filled with eXP and cured. Then the top of the eXP was filled with FU. For all samples, the mold was placed on a glass slide, and the topside of the mold was covered with a second glass slide and compressed with clamps. The specimens (n = 5) were polymerized from the top of the cylinder mold with a hand-light curing unit for 20 s using the light source. After curing, the samples were removed from the mold immediately. Uncured parts of the samples on the bottom side were scrubbed using a plastic spatula. Finally, the remaining cured part was measured three times with a digital caliber with an accuracy of ±0.1 mm, and the given value was divided by 2. The mean value of the measurements was recorded as the DOC for each specimen.

Water Sorption and Solubility Determination. Water sorption (W_{sp}) and solubility (W_{sl}) are important properties evaluated for dental materials, including resin-based composites, cements, and other restorative materials. Water sorption refers to the ability of a material to absorb water molecules from its surroundings, while solubility refers to the tendency of a material to dissolve in water.[38] Both water sorption and solubility testing were conducted according to ISO 4049:2019. These tests are essential for assessing the durability, biocompatibility, and performance of dental materials and ensure their suitability for clinical use and patient safety. In this study, the samples were prepared with the same protocol as the depth of cure, but the mold was different. Samples (n = 5) were prepared using a Teflon mold (15 mm in height and 1 mm in diameter) according to ISO 4049:2019. All of the samples were cured from both sides for 20 s. After curing, samples were taken out from the mold, and excess materials were removed from the surface using P320 grit abrasive paper. The dried samples were placed in a desiccator with freshly dried silica gels for 24 h at 37 °C. At the end of this process, samples were placed in a second desiccator at 23 ± 1 °C for 1 h. Then the mass of each sample was measured using an analytical balance with an accuracy of 0.0001 g until the mass of the samples reached the constant mass (m_1). Then, samples were immersed in distilled water for 7 days at 37 °C. After that, the second mass measurement was conducted (m_2). Finally, the samples were placed again into a desiccator until reaching a constant mass value (m_3). The diameter and thickness of the samples were also measured with a digital caliper (500-151-30 Mitutoyo, 0.01 mm resolution). Finally, water sorption (W_{sp}) and solubility (W_{sl}) values were calculated using eqs 1 and 2, respectively, in accordance with the ISO4049:2019 standard:

$$W_{sp} = \frac{m_2 - m_3}{V} \quad (1)$$

$$W_{sl} = \frac{m_1 - m_3}{V} \quad (2)$$

- W_{sp}: water sorption in $\mu g/mm^3$
- W_{sl}: water solubility in $\mu g/mm^3$
- m_1: the conditioned mass, in μg, prior to immersion in water
- m_2: the mass of the specimen, in μg, after immersion in water for 7 days
- m_3: the mass of the reconditioned specimen, in μg
- **V:** the volume of the specimen, mm^3

Extraction Protocol. eXP, FU, and cc-eXP-FU were analyzed according to "ISO 10993-18:2020 Biological evaluation of medical devices: Chemical Characterization of Medical Device Materials within a Risk Management Process" and "ISO 10993-12:2021 Biological Evaluation of Medical Devices: Sample Preparation and Reference Materials". Extraction studies include two actions: generation of the extract and testing of the extract. ISO 10993-18:2020 recommends identifying extractables and leachables (E&L) using polar (water), semipolar (IPA), and nonpolar (hexane) solvent media under the extraction protocol defined in 10993-12:2021. Organic extractables can be qualitatively placed into three classes based on their volatility: volatile organic compounds (VOCs), semivolatile organic compounds (SVOCs), and nonvolatile organic compounds (NVOCs). The analytical techniques used to screen for these classes of organic extractables are different, though one chemical may often be detected using a variety of techniques; for example, gas chromatography with headspace sampling (HS-GC) is typically used to analyze VOCs, gas chromatography (ALS-GC) is typically used to analyze SVOCs, and liquid chromatography (LC) is used to analyze NVOCs. Since IPA and hexane dissolve uncured (dough form) materials, these samples were extracted using only water. The cured samples were placed separately in solvent media containing water and IPA. Hexane was not used as extraction media, as it compromised the cured samples.[30] Briefly, blank samples were inserted into an inert container and incubated at 50 ± 2 °C for 72 ± 2 h. Then, sample extraction was performed in the same vessel using the same conditions.[32] Additionally, an internal standard (IS) mixed in AET limit, including naphthalene, DPA, and EP, was spiked to the flasks before extraction to verify the effectiveness of the extraction protocol. Cured samples were prepared with the same protocol as that of DOC. The only exception was that the bottom side was not scrubbed before the samples were inserted into the extraction media.

The application of the AET requires that a dose-based threshold (DBT) be converted to a concentration-based threshold, as such a conversion would facilitate extractable identification decisions based on the concentration of the extractable in an extract. Such an analytical threshold has been termed the AET. AET establishes a threshold for identification. Extractables whose concentrations are above the AET should be identified as a prerequisite for their toxicological risk assessment, as there is a sufficient possibility that the extractables could be unsafe. On the other hand, extractables whose concentrations are below the AET do not need to be identified for toxicological risk assessment. The AET in $\mu g/mL$ was calculated as given in eq 3:[30]

$$\mathrm{AET} = \frac{\mathrm{DBT} \times \frac{A}{B \times C}}{\mathrm{UF}} \quad (3)$$

- A: the number of medical devices that were extracted to generate the extract; 0.35 g
- B: the volume of the extract (measured in mL); 14 mL[32]

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- C: the clinical exposure to the medical device (number of devices a user would be exposed to in a day under normal clinical practice); 0.75 g
- DBT: the dose-based threshold in μg/day (a toxicologist should be consulted in selecting a specific threshold that can support risk assessment); 1.5 μg/day[31]
- UF: an uncertainty factor that could be applied to account for the analytical uncertainty of the screening methods used to estimate extractables' concentrations in an extract[2]

$$\text{AET}\ (\mu\text{g/mL}) = \{1.5\ \mu\text{g/day} \times [0.35\text{device} / (0.75\text{device/day} \times 14\ \text{mL})]\}/2 \quad (4)$$

$$\text{AET}\ (\mu\text{g/mL}) = 0.025\ \mu\text{g/mL} = 25\ \text{ppb} \quad (5)$$

The AET limit of the samples was calculated as 25 ppb according to eq 3.

Instrumentation. Quality controls and the internal standards of naphthalene, diphenylamine (DPA), and ethyl paraben (EP) were purchased from Sigma-Aldrich (Table 2).

Table 2. Quality Control Standards Used in the Study for System Suitability Determination[a]

QC	abbreviation	CAS no.	MW (g/mol)	mode
styrene		100-42-5	104.1	HS-GC/MS
butylated hydroxytoluene	BHT	128-37-0	220.35	GC/MS
diphenylamine	DPA	122-39-4	169.1	GC/MS
diethyl phthalate	DEP	84-66-2	223.1	LC/MS-PM
caprolactam		105-60-2	114.09	LC/MS-PM
bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate	Tinuvin	52829-07-9	481.40	LC/MS-PM
2,2′-methylenebis(6-*tert*-butyl-4-methylphenol)	BKF	119-47-1	339.23	LC/MS-NM

[a]Abbreviations: HS-GC/MS, headspace-gas chromatography/mass spectrometry; GC/MS, gas chromatography/mass spectrometry (ALS); LC/MS, liquid chromatography/mass spectrometry; PM, positive mode for compounds that ionized positively; NM, negative mode for compounds that ionized negatively; HS-GC/MS, headspace gas chromatography/mass spectrometry.

Acetonitrile, formic acid, ammonium acetate, ultrapure water, isopropanol (IPA), and hexane were purchased from Merck. All materials' purity was ≥98%, except for acetonitrile, which was ≥99.9% LC/MS grade. The stock solution was prepared separately with water and IPA at a concentration of 1000 ppm. GC/MS and LC/MS-QTOF were performed to determine VOCs, SVOCs, and NVOCs that were eluted to the extraction media from materials. A quality control mix solution (Table 2) was prepared at an AET value of 25 ppb to ensure system suitability and identification procedures for HS-GC/MS, GC/MS (ALS), and LC/MS-QTOF (positive and negative modes) methods. QC-mix was analyzed at the end of the sequence to show that mass spectrometry can detect a wider range of compounds and helps identify potential unknown peaks.

GC/MS Analysis. VOCs and SVOCs from cured and uncured composites were analyzed by an Agilent 8890 GC system with an Agilent 5977B GC/MSD mass selective detector. The capillary column, Agilent 19091S-433UI, 30 m, 0.25 mm i.d., 0.25 lm film thickness, was placed in a chromatographic oven that was temperature-programmed as follows: 70 °C for 2 min; temperature increase at 4 °C/min) to 150 °C; temperature increase at 8 °C/min) 1 to 300 °C; hold time of 2 min. The carrier gas was ultrahigh-purity helium, and the injector was set to 250 °C. HS oven temperature was set to 80 °C for 15 min, and the transfer line temperature was 120 °C for 1 min injection duration. 5 mL Agilent headspace vials filled with 2.5 mL of the sample and other conditions were similar to GC/MS.

Standard Preparation. Naphthalene was used as the internal standard at the 25 ppb AET limit to establish an approximate identification limit to identify unknown chemical species above the AET limit. Naphthalene was prepared with hexane for a final concentration of 1000 ug/mL (ppm). Further dilution to 10 ppm and 25 ppb AET limit were prepared in IPA.

Sample Preparation. A calibration curve was used to quantify IS in the extracted samples. 3-point, including 12, 25, and 50 ppb were used to obtain the calibration curve. The ALS method was used in the analysis of the IPA sample extracts. The HS method was used in the analysis of aqueous sample extracts. 2.5 mL of water extract and blank were placed in a 5 mL HS vial.

LC/MS-QTOF Analysis. For qualitative screening, the LC system consisting of an Agilent 1260 binary pump, an Agilent 1260 autosampler, and an Agilent iFunnel G6530C Accurate-Mass QTOF instrument (Agilent, SEM, Türkiye) was used. Chromatographic separation was achieved using an Agilent Poroshell 120 EC-C18 (150 × 3.0 mm, 2.7 μm) column (Agilent, SEM, Türkiye). The injection volume was 8 μL, and the flow rate was set at 0.5 mL/min based on backpressure during the chromatographic run.

Mobile phases consisted of ultrapure water with 0.1% formic acid (A) and acetonitrile (Ac) (B). The chromatographic run started at 0.5 min isocratic at 10%B, followed by a first gradient to increase the percentage of B to 100% at 11 min. This was held for 19.5 min before a second gradient increased the percentage of B to 90% after 20 min. Next, the column was rinsed with 95% B for 5 min and re-equilibrated at 10% B for 5 min before the next injection for positive mode. Mobile phases consisting of 10 mM ammonium acetate/water (A) and acetonitrile (B) were used for the negative mode, with the same gradient flow as the positive mode. The chromatographic run started at 0.5 min isocratic at 10% B, followed by a first gradient to increase the percentage of B to 100% at 11 min. This was held for 19.5 min before a second gradient increased the percentage of B to 90% at 20 min. Next, the column was rinsed with 95% B for 5 min and re-equilibrated at 10% B for 5 min before the next injection for positive mode. The column temperature was kept constant at 40 °C. The mass spectrometer was operated in extended dynamic range (2 GHz) mode providing a full width at half maximum (fwhm) resolution of approximately 5100 at m/z 118.0862 and 10000 at m/z 922.0098. The ions m/z 112.0508 and 922.0097 for positive mode and m/z 112.9855 and 940.0009 for negative mode were selected for a constant recalibration throughout the chromatographic run to ensure good mass accuracy. The eluted compounds were ionized with a jet stream electrospray ionization source (AJS ESI source) operating in positive and negative ionization mode. The drying gas temperature and flow were 325 °C and 5 L/min, respectively. The nebulizer pressure

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Table 3. Depth of Cure (DOC), Water Sorption, and Water Solubility of the Samples

	sample group	minimum	maximum	mean	std deviation	p value
depth of cure (mm)	eXP	3.12	3.14	3.13	0.01	>0.05
	FU	3.06	3.14	3.09	0.04	
	cc-eXP-FU	3.02	3.09	3.06	0.04	
W_{sp} (μg/mm^3)	eXP	20.40	37.50	29.48	8.13	>0.05
	FU	21.60	31.20	28.04	3.81	
	cc-eXP-FU	23.30	27.90	24.78	1.79	
W_{sl} (μg/mm^3)	FU	0.41	1.33	0.86	0.43	<0.001
	eXP	5.47	6.84	6.06	0.57	
	cc-eXP-FU	1.69	3.76	2.81	0.81	

was set at 20 psig. Capillary and fragmentor voltages were 3500 and 145 V, respectively. The acquisition parameters were set in an m/z range from 80 to 1000 at a scan rate of 2.5 and 6.67 scans/s for the MS and MS/MS spectra, respectively. Collision energies of 20 and 40 V were applied. Signals were detected by using a data-dependent analysis method (Auto-MS/MS), selecting the three most abundant ions. Active exclusion of 0.2 min was applied to prevent repetitive acquisition of spectra for the same ion.

Standard Preparation. DPA and EP were used as the internal standards at the 25 ppb AET limit to establish an approximate identification limit to identify unknown chemical species above the AET limit. DPA and EP were prepared with IPA for a final concentration of 1000 ug/mL (ppm). Further dilution to 10 ppm was also performed in IPA.

Sample Preparation. A calibration curve was used to quantify IS in the samples. Three points, including 12.5, 25, and 50 ppb, were used to obtain the calibration curve. 1000 μL of each sample extract and a blank extract containing 25 ppb of the internal standard were placed in an autosampler vial.

Data Analysis. VOCs and SVOCs were analyzed using an automated data analysis workflow using Agilent MassHunter Unknowns Analysis software (version 10, Agilent Technologies, Santa Clara, USA) for mass spectral deconvolution, peak detection, and library searching (METLIN) and reporting. The automated process ensured data integrity and consistency of compound identification with known compounds (Table 2).

NVOCs were analyzed by using LC/MS-QTOF. Agilent MassHunter Profinder software (version B.10, Agilent Technologies, Santa Clara, USA) and Agilent MassHunter Profiler software (version B.10, Agilent Technologies, Santa Clara, USA) were subsequently used for the identification of the compounds. In short, the Batch Molecular Feature Extraction algorithm of Profinder software was used to extract chromatographic peaks. Then results were identified using Agilent Profiler Software using the E&L PCDL library of Agilent.

Semiquantification of the samples was conducted using calibration curves of ISs, including 12, 25, 50, 100, 200, 400, 800, 1600, and 3200 ppb. Quant software from Agilent was used for the quantifications of the compounds.

Toxicological Risk Assessment. The exposures were based on the potential chemical release of the test articles under extremely conservative conditions. The extracted amounts were based on the highly conservative assumption that they were released daily over the entire lifetime of the device. The toxicological risk assessment of the compounds was conducted in two steps. In the first step, a screening threshold, toxicological screening limit (TSL), was applied to identify chemicals of potential concern.[31] TSL is the cumulative exposure dose to an identified constituent over a specified time period that will be without appreciable harm to health expressed in μg. The TSL value is calculated using the mutagenic threshold of toxicological concern (TTC) values from ISO/TS 21726.[39] TSL values were compared with the worst-case exposure of the identified compounds (μg/device) by multiplying,[32] maximum number of clinical use of the device (considered 32 devices for the 32 teeth in the mouth). TSLs of 120 and 600 μg were applied for short-term exposure (i.e., $\leq$ 30 days) and long-term exposure (i.e., >30 days up to lifetime), respectively.[31] The compounds with worst-case exposures below a TSL were excluded from further evaluation, as they could be considered a negligible toxicological hazard. In the second step, a quantitative risk evaluation was carried out using compound-specific toxicity data to assess the worst-case estimated exposure dose (EED) of a potential concern. To derive a compound-specific tolerable intake (TI), experimental or observational data corresponding to a no observed adverse effect level (NOAEL) or a lowest observed adverse effect level (LOAEL) were taken into account. Thereafter, the modifying factor (MF) approach was applied, which is made up of several uncertainty factors (UFs). The TI is calculated as follows:

$$\text{TI} = \text{NOAEL or LOAEL}/\text{MF(UF1, UF2, UF3)}$$

The worst-case EED was calculated by dividing the worst-case exposure level to the lowest body weight of a child (10 kg) and assumed (worst-case) a release duration of 1 day. The EED is calculated as follows:

$$\text{EED } (\mu\text{g}/(\text{kg bw}/\text{day})) = \text{worst-case exposure } (\mu\text{g})/10 \text{ kg}/1 \text{ day}$$

Then the proposed TI of the compound was compared to the EED to be represented as a margin of safety (MOS), as given in the formula

$$\text{MOS} = \text{TI } (\mu\text{g}/(\text{kg bw}/\text{day}))/\text{EED } (\mu\text{g}/(\text{kg bw}/\text{day}))$$

A MOS greater than 1.0 indicates that the daily potential exposure for an E&L compound is considered safe from a regulatory standpoint.[31]

Statistical Analyses. Statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). The normality of the data was examined using the Kolmogorov–Smirnov test. To determine+ the differences between the

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groups, mean values were analyzed using a one-way ANOVA and Tukey HSD at a significance level of $p < 0.05$.

RESULTS AND DISCUSSION

Determination of the chemical characteristics of dental filling materials is crucial to the treatment's success. As a result, the chemical characteristics of the two commercial goods and their combinations in practice, such as their depth of cure, water sorption and solubility, and their E&L profiles, were established in the study's scope in accordance with the most recent laws. The filler content of these components, as reported by the makers, is 74.2% by weight. Our findings cannot be explained by the filler loading similarities between the materials. It is more plausible that our findings could have been influenced by the different chemistry of the materials, the filler size, and the distribution of the filler particles.

The DOC test is pivotal in the realm of dental restoration, as it gauges the polymerization effectiveness of the dental material used. This assessment is essential, since it informs how efficiently the dental filling material cures in areas devoid of direct exposure to the curing apparatus. This factor is fundamental for ensuring the durability of dental restoration. The results highlighted in Table 3 display the mean DOC values for eXP, FU, and cc-eXP-FU. Across all groups, there was no statistically significant difference in the DOC values ($p > 0.05$). A consistent and thorough polymerization process is crucial for ensuring the stability and biocompatibility of dental restorations. When a material is not fully polymerized, it may contain residual monomers or other components. Therefore, the absence of significant differences in DOC values suggests that all tested materials achieved adequate polymerization, minimizing the likelihood of leachable substances being released into the oral cavity. The comparative analysis of water sorption also did not indicate any significant disparities among the tested materials ($p > 0.05$). This observation underlines a consistent behavior among the materials in the context of water sorption.

In contrast, when it comes to the solubility properties, differences emerge. The solubility values differed notably, as detailed in Table 4. Specifically, eXP exhibited the highest solubility at 6.062 ± 0.576 $\mu g/mm^3$, while FU registered the lowest solubility at 0.864 ± 0.436 $\mu g/mm^3$. cc-eXP-FU, falling between the two extremes, had a solubility of 2.8120 ± 0.8173 $\mu g/mm^3$, which was anticipated ($p < 0.05$). The solubility of FU was observably higher than those of eXP and cc-eXP-FU, a finding corroborated by both GC/MS and LC/MS studies. As a result of this enhanced solubility in FU, when combined with eXP, there's a potential increase in the elute concentration compared to using FU alone. Furthermore, eXP displayed the highest monomer elution, succeeded by cc-eXP-FU. It is also worth noting that factors such as the extraction medium and immersion duration influenced the release dynamics of the monomers or additives.

Table 4. Comparison of the Statistical Differences (p) of W_{sl} Values between Groups

	Sample	p
W_{sl} ($\mu g/mm^3$)	eXP and FU	<0.001
	eXP and cc-eXP	<0.005
	FU and cc-eXP-	<0.001

To assess the extraction protocol's aptness, internal standards (ISs) were examined for recovery (RC%) and relative standard deviations in both retention times (RSD_{RT}%) and concentrations (RSD_{conc}%) using multiple analysis methods: HS-GC/MS, GC/MS, and LC/MS-QTOF. The evaluation was based on Appendix F: Guidelines for Standard Method Performance Requirements of the Association of Official Agricultural Chemists (AOAC). As per these guidelines, the RSD% for 25 ppb should be under 22%, and recovery rates should range from 60 to 115%. The specific values for compounds such as naphthalene, DPA, and EP are provided in Tables S1−S3. These metrics confirm the system's suitability aligns with AOAC's expectations. Additionally, a QC-mix analysis was performed to demonstrate mass spectrometry's capability to detect a broader compound spectrum and identify unknown peaks. The QC-mix findings are detailed in Table 5, showing that the established protocol effectively identified all standards with a high accuracy rate.

Table 5. System Quality Control Compound Results of HS-GC/MS, GC/MS, and LC/MS-QTOF

compound	CAS no.	RT (min)	match factor	mode
Styrene	100-42-5	3.04	96.8	HS-GC/MS
BHT	128-3700	9.20	83.5	GC/MS
DPA	122-39-4	10.31	99.5	GC/MS
DEP	84-66-2	9.84	99.5	LC/MS-PM
caprolactam	105-60-2	3.87	84.2	LC/MS-PM
Tinuvin	52829-07-9	6.67	91.7	LC/MS-PM
BKF	119-47-1	13.81	89.8	LC/MS-NM

In the comprehensive elution profiles, dental composites were systematically distinguished between dough (uncured) and cured (polymerized) materials. Using HS-GC/MS and GC/MS, VOCs and SVOCs were identified in the extraction media. To begin, any peaks that had a response greater than that of the internal standard (IS) underwent tentative identification, followed by semiquantification. Concurrently, NVOCs were earmarked by using LC/MS-QTOF, with compounds of significant abundance in both positive and negative modes. All peak lists identified as a result of extraction studies are given in Table 6.

Through the utilization of HS-GC/MS and GC/MS techniques, we identified monomers and additives in different extraction solutions, which included components like 6-*tert*-butyl-2,4-dimethylphenol (topanol A), camphourquinone (CQ), phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl- (BHT), ethyl 4-dimethylaminobenzoate (4-EDMAB) and triethylene glycol dimethacrylate (TEGDMA) (Figure 1).

As can be seen in Figure 1, the substance released in the highest amount was triethylene glycol dimethacrylate (TEGDMA), which is used as a diluent agent in restorative composites.[40] According to the manufacturer's statements eXP and FU contain TEGDMA in their compositions. In this study, TEGDMA was only extracted in IPA. The results indicated that the elution of TEGDMA followed the order eXP > cc-eXP-FU > FU. Using eXP with FU significantly decreased the TEGDMA elution compared to eXP ($p < 0.05$). However, the combination group showed an increase in TEGDMA elution compared to FU ($p < 0.05$). Additionally, TEGDMA is recognized as the hydrolytic product of TEG and methacrylic acid.[41] Therefore, the detection of TEG in LC/MS was linked to TEGDMA. The elution of TEG was assessed only for eXP

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Table 6. Organic Components Released in Water and IPA from the Dough and/or Cured eXP, FU, and cc-eXP-FU Sample Groups

compound name	CAS n.o	RT (min)	instrument	mode	mass	m/z	ion	match factor (%)
Topanol A	1879-09-0	8.11	GC/MS	HS/ALS				82−98
phenol	108-95-2	4.15	GC/MS	ALS				72−86
CQ	595-30-2	8.75	GC/MS	ALS				91−92
BHT	128-37-0	9.2	GC/MS	ALS				84−89
4-EDMAB	10287-53-3	10.78	GC/MS	ALS				85−94
TEGDMA	109-16-0	11.88	GC/MS	ALS				74−97
2-HPA	999-61-1	10.80	LC/MS	positive	130.06	131.07	$(M + H)^+$	74−97
3,4-DBAL	5973-71-7	7.45	LC/MS	positive	134.07	135.08	$(M + H)^+$	70−97
TEG	112-27-6	1.76	LC/MS	positive	150.09	173.08	$(M + Na)^+$	72−91
4-MABA	1204-86-0	11.91	LC/MS	positive	191.09	192.10	$(M + H)^+$	93−88
4-EDMAB	10287-53-3	10.34	LC/MS	positive	193.11	194.12	$(M + H)^+$	79−99
DEAP	6175-45-7	7.46	LC/MS	positive	208.11	209.12	$(M + H)^+$	84−98
TPO	75980-60-8	11.37	LC/MS	positive	348.13	349.13	$(M + H)^+$	88−99
BPAHPE	5581-32-8	7.46	LC/MS	positive	376.19	394.22	$(M + NH_4)^+$	74−96
BisGMA	1565-94-2	11.28	LC/MS	positive	512.24	535.23	$(M + H/NH_4/Na)^+$	75−98
DBHBA	14035-33-7	11.12	LC/MS	negative	248.18	293.17	$(M + HCOO)^-$	71−88
Irgafos 128	1809-14-9	14.53	LC/MS	negative	306.23	351.23	$(M + HCOO)^-$	72−86
Irganox 1520	110553-27-0	12.45	LC/MS	negative	424.28	469.28	$(M+HCOO)^-$	81−86
stearic acid	57-11-4	16.62	LC/MS	negative	284.27	283.27	$(M - H)^-$	71−94
tridecyl acrylate	3076-04-8	13.25	LC/MS	negative	254.22	253.22	$(M - H)^-$	74−87

and FU, excluding the cc-eXP-FU samples. Thus, a significant reduction in the elution of TEG could offer a notable benefit from a toxicological perspective[40] when eXP and FU are used in combination. It is also significant to highlight that TEGDMA, which was the compound released in the greatest quantity, exhibited a higher extraction rate in an IPA medium. Conversely, TEG, a compound closely related in structure to TEGDMA, was more effectively extracted in water. This observation underscores the influence of solvent polarity on the solubility and extraction efficiency of these compounds, suggesting differential solvent interactions based on the chemical characteristics of each compound.

Topanol A[42] and BHT[43] are used as stabilizers and antioxidants in dental composites. As shown in Figure 1, Topanol A was identified in the eXP and cc-eXP-FU samples, but it was not present in the FU samples. On the contrary, BHT elution was only observed for FU. Our findings suggest that the elution of both Topanol A and BHT is highly dependent on extraction conditions. For eXP used individually, the elution of Topanol A was significantly higher when in its doughy form and extracted in water ($p < 0.05$). Additionally, the cured-eXP in IPA exhibited a higher elution profile for Topanol A compared to water extraction. This discrepancy can be attributed to its solubility properties. Its solubility in water is notably low, usually less than 0.01 g/L at room temperature. In contrast, it is soluble in organic solvents like ethanol, methanol, and IPA. BHT, on the other hand, was detected only in the cured-FU samples extracted in IPA. The release of BHT was lower compared to that of Topanol A. For combination groups, its release was significantly reduced compared to FU alone ($p < 0.05$). However, it is worth noting that this might be disadvantageous for the FU sample since it does not contain Topanol A. Another key observation is the absence of BHT elution in combination groups, which might be seen as a benefit in terms of toxicological impact.

Camphourquinone (CQ) is known to be used as a photoinitiator in dental composites.[44] CQ elution was only observed in eXP and remained below the AET limit in FU and cc-eXP-FU samples.

When employing LC/MS-QTOF in the positive mode (Figure 2), compounds such as bisphenol A-glycidyl methacrylate (BisGMA), ethyl 4-dimethylaminobenzoate (4-EDMAB), 3,4-dimethylbenzaldehyde (3,4-DBAL), triethylene glycol (TEG), 2,2-diethoxyacetophenone (DEAP), diphenyl-(2,4,6-trimethylbenzoyl)phosphine oxide (TPO), 2-hydroxypropyl acrylate (2-HPA), 4-morpholinobenzaldehyde (4-MBAD), and bisphenol A bis(2,3-dihydroxypropyl) ether (BisDPE) were detected in both dough and cured states. Additionally, when the LC was operated in negative MS mode, it revealed the presence of DBHBA, Irgafos 128, Irganox 1520, stearic acid (STA), and tridecyl acrylate (TDA). It is worth noting that these constituents are commonly found in dental composites. No matter the extraction method or substance, more BisGMA, 4-EDMAB, and stearic acid were liberated than other monomers or additives. Due to their high solubility in IPA, BisGMA and TEGDMA eluted more readily in IPA extracts than in water extracts.

BisGMA is widely used as a base monomer in polymeric dental materials, e.g., restorative composites, adhesives, and prophylactic sealants.[45] BisGMA elution from dental materials has been widely investigated because it is designated as cytotoxic. However, compared to other materials eluted from dental materials, its elution was lower than those of additives such as 4-EDMAB and stearic acid in this study. For eXP, BisGMA elution was significantly higher in cured samples, and BisGMA elution was just identified for the eXP itself. This can be explained by higher cross-linking and monomer conversion in cc-eXP-FU samples because of a large number of photoinitiators in combination groups. BisDPE was assessed as the side product of BisGMA, and its elution in cc-eXP-FU was lower than those in eXP and FU. Phenol and its derivatives are used in the synthesis of phenolic monomers such as BisGMA and BHT. In the present study, phenol was only found to be eluted by polymerized composite samples of eXP in IPA above the AET limit. This contrasts with previous

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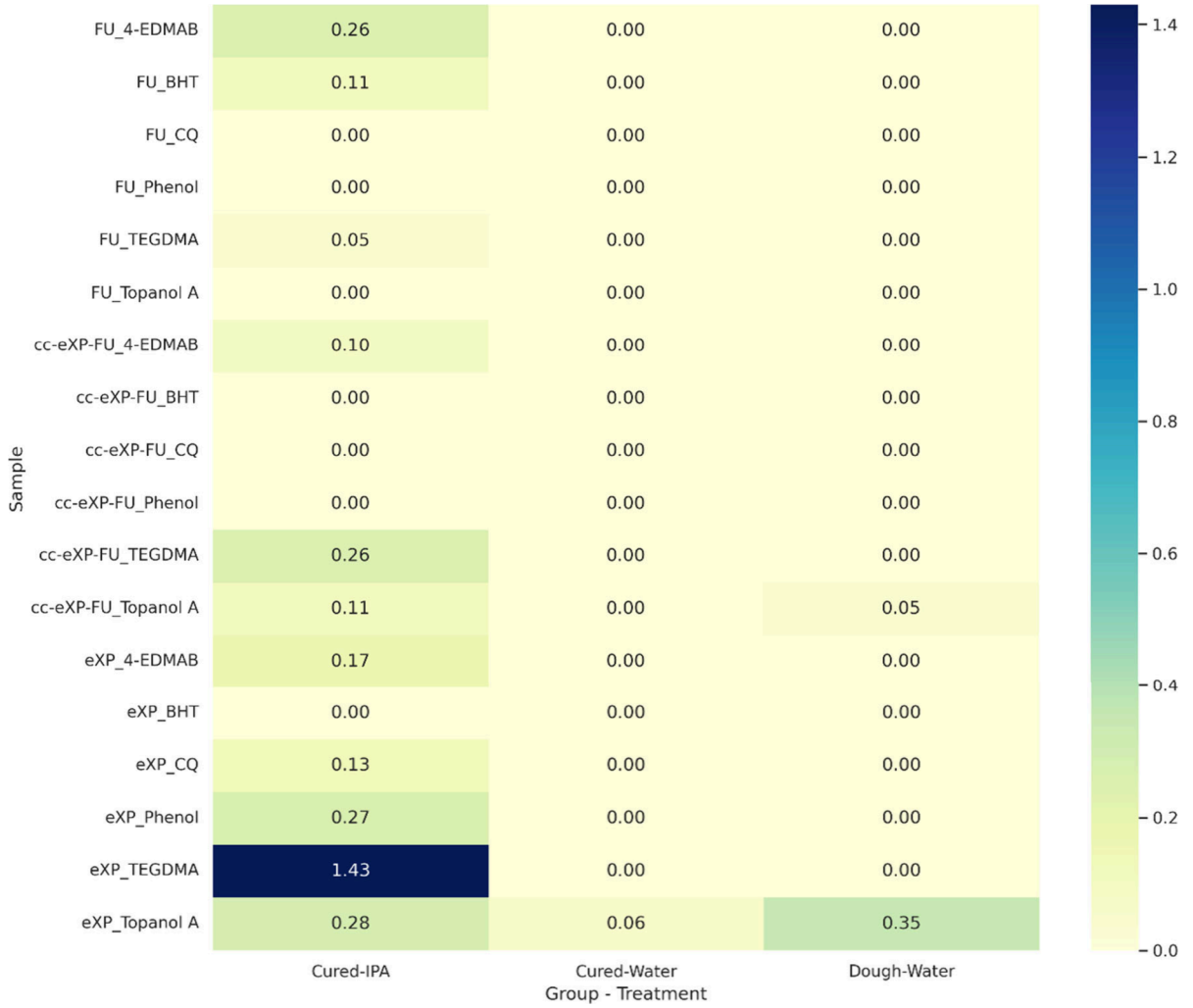

Figure 1. Quantitative distribution of tentatively identified compounds across different sample treatments as determined by HS-GC/MS and GC/MS. Abbreviations: 4-EDMAB, ethyl 4-dimethylaminobenzoate; BHT, phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl; CQ, camphorquinone; TEGDMA, triethylene glycol dimethacrylate; Topanol A, 6-*tert*-butyl-2,4-dimethylphenol.

studies where no phenolic compounds were detected.[46−48] However, detectable amounts of phenol have also been mentioned by other authors[49] to be extracted from composite materials. As is known, dental composites typically contain monomers (such as BisGMA and bisphenol A dimethacrylate [BisDMA]) that are derived from bisphenol A (BPA) or other phenolic compounds, but there is no known use for phenol or BisDPE itself in dental composites. As these monomers may leach from dental composites, their stability has been studied under a variety of conditions to determine whether they may hydrolyze to form phenol. BisGMA, the base monomer for many resin composites, has been found to be stable under various hydrolytic conditions.[47] However, two researchers have reported that BisDPE is hydrolyzed to phenol, which probably accounts for the phenol detected in extracts from certain composites.[40] According to literature findings, the phenol compound was considered as a side product from BisGMA or other phenolic additives such as BHT.

4-EDMAB is an aromatic amine used as a coinitiator, and it donates hydrogen. It is reported to be unable to polymerize with monomers.[50,51] 4-EDMAB elution was observed in both GC/MS and LC/MS analyzes. However, the elution of 4-EDMAB in LC/MS was quite different from that in the GC/MS results. Since 4-EDMAB concentration observed in LC/MS analysis was higher than that in GC/MS, chemical evaluation and toxicological risk assessment were conducted according to LC/MS results. Considering the elution values observed for the doughy samples, it was determined that eXP had a higher release than FU. 4-EDMAB elution was more in FU than in cc-eXP-FU. Therefore, the significant decrease in the elution of 4-EDMAB provides a great advantage for the application in doughy samples.[40] On the other hand, in terms of cured samples, water and IPA extracts were evaluated in the same manner. According to the findings 4-EDMAB elution was determined in the order cc-eXP-FU > FU > eXP. This result indicates that cocuring of cc-eXP-FU and FU significantly increases the elution of 4-EDMAB ($p < 0.05$).

4-MBAD is used as an amine donor compound in radical polymerization reactions. It is preferred as a component of photoinitiator systems.[52] Therefore, 4-MBAD was considered a side product that was eluted from initiators or other products containing amine structures, such as 4-EDMAB. The elution of 4-MBAD was significantly higher in cc-eXP-FU than in FU itself, as was in the elution of 4-EDMAB ($p < 0.05$).

2-DEAP and TPO are also used as photoinitiators in dental composites.[53] In dough forms, 2-DEAP was only detected in

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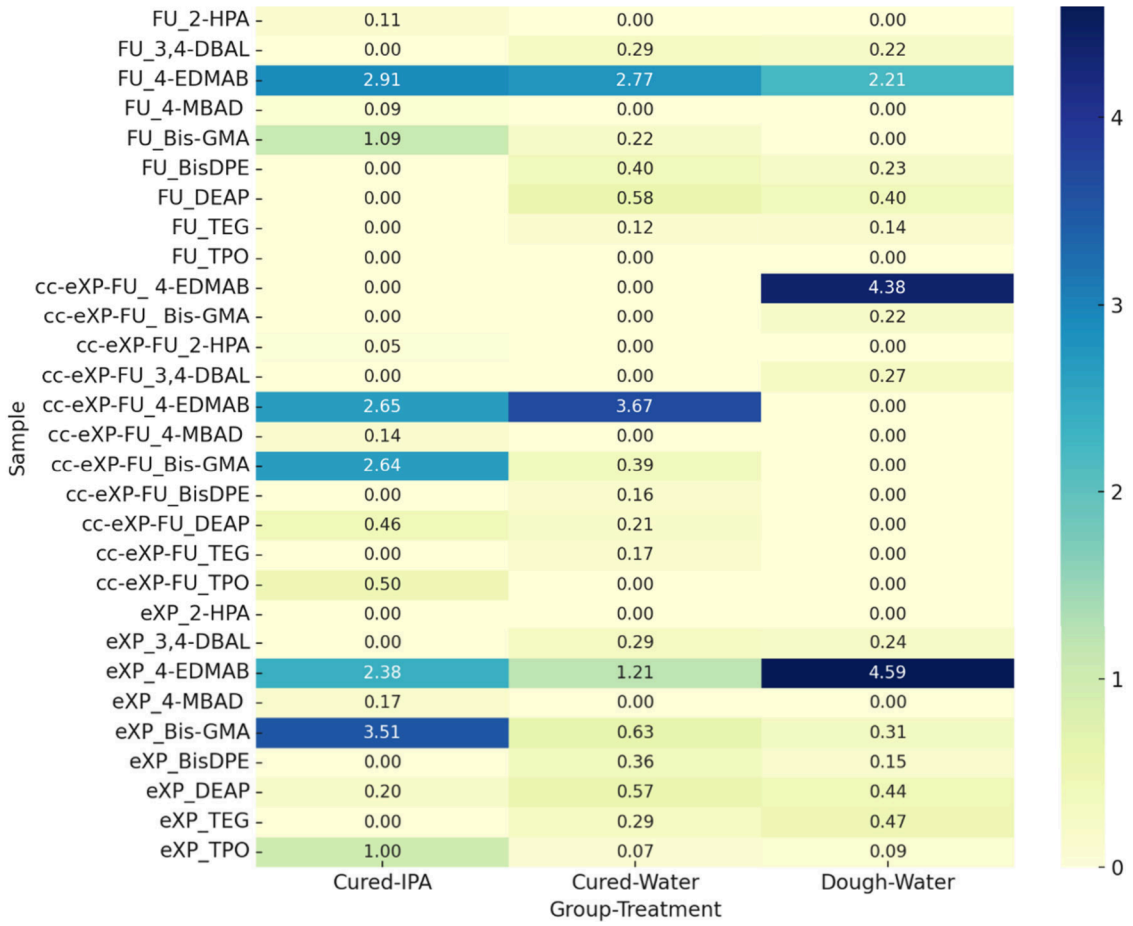

Figure 2. Quantitative distribution of tentatively identified compounds across different sample treatments as determined by LC/MS-QTOF in positive mode. Abbreviations: 2-HPA, 2-hydroxypropyl acrylate; 3,4-DBAL, 3,4-dimethylbenzaldehyde; 4-EDMAB, ethyl 4-dimethylaminobenzoate; 4-MBAD, 4-morpholinobenzaldehyde; BisDPE, bisphenol A, bis(2,3-dihydroxypropyl) ether; BisGMA, bisphenol A glycerolate dimethacrylate; DEAP, 2,2-diethoxyacetophenone; TEG, triethylene glycol; TPO, diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide.

eXP and FU. In cured samples, the elution of 2-DEAP was lowest in cc-eXP-FU ($p < 0.05$). TPO was identified for the eXP but not for FU. It was also eluted in cured samples of cc-eXP-FU.

Aldehydes may be used as the polymerization accelerator in the chemical polymerization initiator, including terphthalaldehyde and benzaldehyde derivatives. One of the examples of the benzaldehyde derivatives is 3,4-DBAL.[54] 3,4-DBAL was detected in water extracts of doughy and cured samples by LC/MS (Figure 2). The 3,4-DBAL elution profile was not similar in dough and cured samples. Its elution was significantly higher in cc-eXP-FU than in FU in doughy samples ($p < 0.05$). On the other hand, it was not released in cured samples of cc-eXP-FU.

3-DTBBDA is used as an inhibitor in dental restoratives.[55] Its elution profile was different in dough and cured samples (Figure 3.). In dough samples, its elution was higher in FU than in cc-eXP-FU. On the other hand, in cured samples, 3-DTBBDA elution was higher in cc-eXP-FU than in FU.

Irgafos phosphites and Irganox were evaluated as side products that may be contained in the synthesis of monomers, oligomers, or other substances. Irgafos is a hydrolytically stable phosphite processing stabilizer. It also acts as a secondary antioxidant, which induces degradation and extends the performance of primary antioxidants. It has a low volatility and is particularly resistant to hydrolysis. It provides storage stability and gives the polymer long-term protection against thermo-oxidative degradation during the processing steps (compounding/pelletizing, fabrication, and recycling) from molecular weight change (by chain scission or cross-linking) and prevents discoloration.[56] Irganox 1520 is an efficient antioxidant for both nonaqueous and water-dispersible formulations. The Irganox antioxidants work to scrub away peroxyl radicals and minimize the formation of hydroperoxides (which are key contributors to yellowing, etc.). The Irganox and Irgafos products often work synergistically as thermal stabilizers.[57] In doughy samples, Irgafos elution is greater in cc-eXP-FU than in FU ($p > 0.05$). On the other hand, in cured samples, Irgafos 128 elution was not statistically different among eXP, FU, and cc-eXP-FU ($p > 0.05$). Irganox 1520 was only detected in cured samples of FU and cc-eXP-FU, and elution in cc-eXP-FU was significantly lower than in FU ($p < 0.05$).

Stearic acid (STA) and generally fatty acids can perform numerous functions: they can behave as dispersing agents,[58] activators,[59] surfactants,[59] softening agents,[60] lubricants,[61] and surface modifiers.[62] Essentially by referring to the world of composite materials and suspensions, these components have been added in the formulations, mainly in the role of processing aids[63] to improve the workability behavior of filled plastics, rubbery or binder, by lowering the mixture viscosity, and increasing the overall flowability.[64] In this study, the

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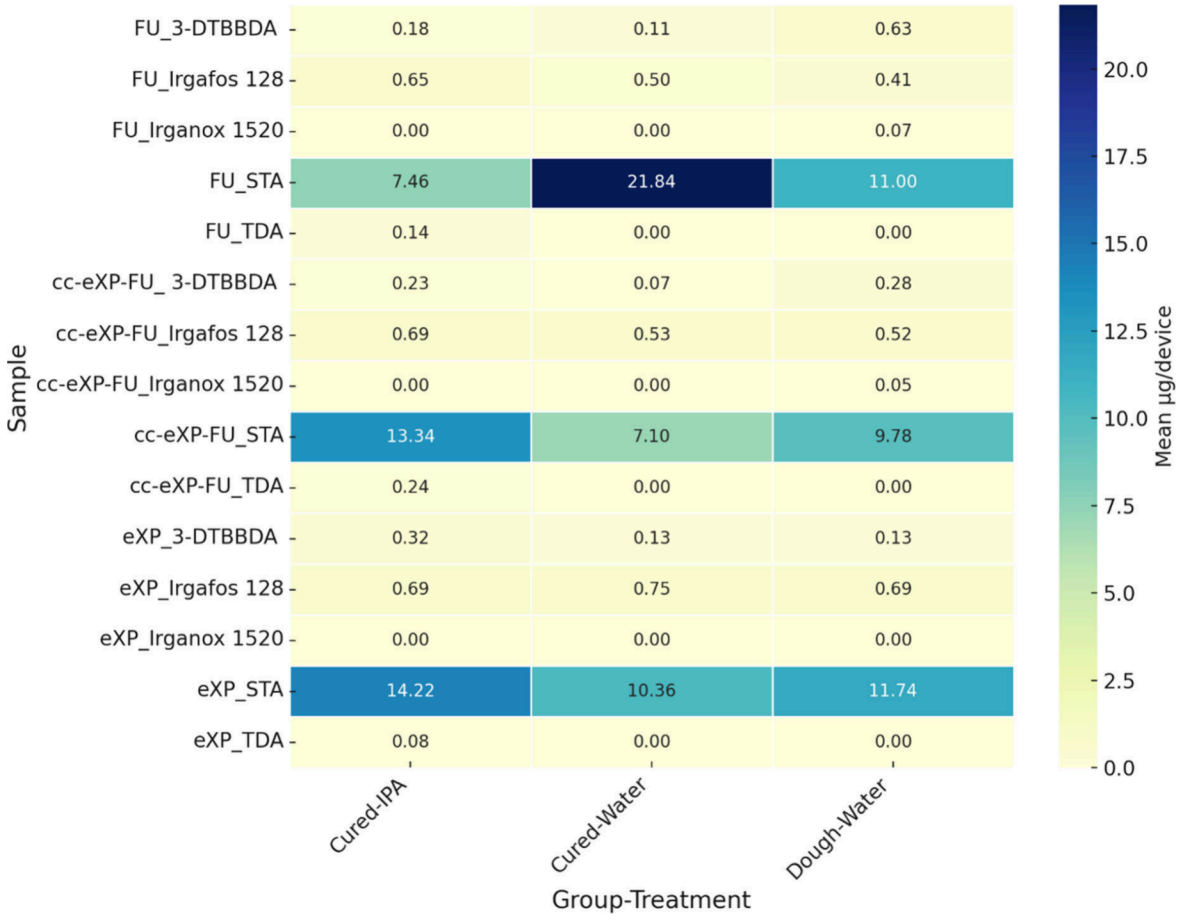

Figure 3. Quantitative distribution of tentatively identified compounds across different sample treatments as determined by LC/MS-QTOF in negative mode. Abbreviations: 3-DTBBDA, 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde; STA, stearic acid; TDA, tridecyl acrylate.

elution amount of stearic acid was statistically similar in all groups for doughy samples ($p > 0.05$). On the other hand, in cured samples, stearic acid elution was higher in cc-eXP-FU than in FU ($p < 0.05$).

Tridecyl acrylate (TDA) and other methacrylates are used as polymerizable plasticizers in dental composites. Those materials are generally modified other acrylates, such as *n*-butyl/ethyl methacrylate or ethoxyethyl methacrylate.[65] In this study the elution of TDA was found to be higher in cc-eXP-FU compared to FU itself ($p < 0.05$).

The toxicological risk characterization of the E&L compounds from the dough and cured forms of ePX, FU, and cc-ePX-FU is given in Tables 7−9. The worst-case exposures of the compounds were based on the maximum value (µg/device) when the same compound was detected in different extracts. Based on the characterization study, no compound belonged to the CoC substances or excluding compounds per ISO/TS 21726. Through the TSL approach, all identified compounds in the test extracts except ethyl 4-EDMAB and STA were considered as a negligible toxicological hazard under a worst-case assumption. 4-EDMAB and STA in the dough form of ePX, STA in the cured form of ePX, STA in the dough and cured forms of FU, 4-EDMAB and STA in the dough form, and STA in the cured form of cc-ePX-FU were found above a TSL value.

For 4-EDMAB and STA, the TIs were established per ISO 10993-17:2023.[31] The derived no effect level (DNEL) of 4-EDMAB for the general population via oral exposure was reported to be 0.08 mg/((kg bw)/day) based on testicular atrophy and anemia on rats.[66] The DNEL of 0.08 mg/((kg bw)/day) (80 µg/((kg bw)/day)) was used as the TI for 4-EDMAB.

STA is a saturated long-chain (>C12) fatty acid. Fatty acids are found in all living organisms, fulfilling fundamental physiological functions within the body. The short (≤C6), medium (C6−12), or long-chain aliphatic acids serve as a fuel for muscular contraction and general metabolism, in addition, stored in adipose tissue as lipids.[67] In a combined repeated dose toxicity study with the reproduction and developmental toxicity screening test, STA was administered at doses of 100, 300, and 1000 mg/((kg bw)/day) via oral gavage to male rats for 42 days and female rats from 14 days prior to mating to day 3 of lactation. It was reported that no deaths or clinical signs related to STA occurred at any of the administered dosages. The study revealed that all mating and fertility parameters and all litter and fetal data were unaffected and there were no gross or histopathological tissue changes. The NOAEL of STA was reported to be 1000 mg/((kg bw)/day), the highest dose tested.[68] The TI was calculated by dividing the NOAEL of 1000 mg/((kg bw)/day) to a composite UF of 1000 (10 for mice-to-human extrapolation, 10 for interspecies differences, and 10 for short-term study to longer-term exposure), resulting in 1 mg/kg bw/day (1000 µg/((kg bw)/day)).

In Tables 7−9, the all EEDs for 4-EMBAD and STA were found to be below the proposed TIs, as indicated by a MOS above 1.0.

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Table 7. Risk Characterization of Extractables and Leachables from eXP Dough and the Cured Form[a]

Type	Compound	μg/device	Worst-case exposure* (μg)	Is worst-case exposure less than TSL≤30 d of 120 μg (Y/N)	Is worst-case exposure less than TSL>30 d of 600 μg (Y/N)	Comments
Dough	3-DTBBDA	0.13	4.27	Y	Y	Considered safe.
	Irgafos 128	0.69	22.19	Y	Y	
	STA	11.74	375.79	N	Y	EED= 375.79 μg ÷ 10 kg ÷ 1 d = 37.6 μg/kg bw/d MOS= 1000 μg/kg bw/d ÷ 37.6 μg/kg bw/d = 27 Because the MoS is above 1.0, exposure is considered safe.
	3.4-DBAL	0.24	7.57	Y	Y	Considered safe.
	4-EDMAB	4.59	146.88	N	Y	EED= 146.88 μg ÷ 10 kg ÷ 1 d = 14.7 μg/kg bw/d MOS= 80 μg/kg bw/day ÷ 14.7 μg/kg bw/d = 5.4 Because the MoS is above 1.0, exposure is considered safe.
	BisDPE	0.15	4.69	Y	Y	
	BisGMA	0.31	9.81	Y	Y	
	DEAP	0.44	13.97	Y	Y	
	TEG	0.47	15.15	Y	Y	Considered safe.
	TPO	0.09	2.88	Y	Y	
	Topanol A	0.35	11.20	Y	Y	
Cured	4-EDMAB	2.38	76.16	Y	Y	
	4-MBAD	0.17	5.55	Y	Y	
	BisDPE	0.36	11.41	Y	Y	
	BisGMA	3.51	112.43	Y	Y	
	CQ	0.13	4.26	Y	Y	Considered safe.
	DEAP	0.57	18.13	Y	Y	
	Irgafos 128	0.75	24.11	Y	Y	
	Phenol	0.27	8.54	Y	Y	
	STA	14.22	455.04	N	Y	EED= 455.04 μg ÷ 10 kg ÷ 1 d = 45.5 μg/kg bw/d MOS= 1000 μg/kg bw/day ÷ 45.5 μg/kg bw/d = 27 Because the MoS is above 1.0, exposure is considered safe.
	TDA	0.08	2.56	Y	Y	
	TEG	0.29	9.17	Y	Y	
	TEGDMA	1.43	45.76	Y	Y	Considered safe.
	Topanol A	0.28	9.06	Y	Y	
	TPO	1.00	31.89	Y	Y	

[a]Abbreviations: TSL, toxicity screening level; Y, yes; N, no; MOS, margin of safety; EDD, worst-case estimated exposure dose; 3,4-DBAL, 3,4-dimethylbenzaldehyde; 3-DTBBDA, 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde; 4-EDMAB, ethyl 4-dimethylaminobenzoate; 4-MBAD, 4-morpholinobenzaldehyde; BisDPE, bisphenol A, bis(2,3-dihydroxypropyl) ether; BisGMA, bisphenol A glycerolate dimethacrylate; CQ, camphorquinone; DEAP, 2,2-diethoxyacetophenone; STA, stearic acid; TEGDMA, triethylene glycol dimethacrylate; TDA, tridecyl acrylate; TEG, triethylene glycol; Topanol A, 6-*tert*-butyl-2,4-dimethylphenol; TPO, diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide. The asterisk indicates consideration of maximum number of devices clinically used (n = 32).

Elution of compounds from dental resin composites is generally completed within a couple of hours or days after polymerization. However, leachables may also formed by erosion and degradation due to mechanical, chemical, photo,

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Table 8. Risk Characterization of Extractables and Leachables from FU Dough and Cured Form[a]

Type	Compound	μg/device	Worst-case exposure* (μg)	Is worst-case exposure less than TSL≤30 d of 120 μg (Y/N)	Is worst-case exposure less than TSL>30 d of 600 μg (Y/N)	Comments
Dough	3-DTBBDA	0.63	20.05	Y	Y	Considered safe.
	Irgafos 128	0.41	13.01	Y	Y	
	Irganox 1520	0.07	2.13	Y	Y	
	STA	11.00	351.89	N	Y	EED= 351.89 μg ÷ 10 kg ÷ 1 d = 35.2 μg/kg bw/d MOS= 1000 μg/kg bw/day ÷ 35.2 μg/kg bw/d = 28 Because the MoS is above 1.0, exposure is considered safe.
	3,4-DBAL	0.22	6.93	Y	Y	
	4-EDMAB	2.21	70.61	Y	Y	
	BisDPE	0.23	7.36	Y	Y	Considered safe.
	DEAP	0.40	12.80	Y	Y	
	TEG	0.14	4.37	Y	Y	
Cured	3-DTBBDA	0.18	5.76	Y	Y	
	2-HPA	0.11	3.52	Y	Y	
	3,4-DBAL	0.29	9.39	Y	Y	
	4-EDMAB	2.91	93.23	Y	Y	
	4-MBAD	0.09	2.88	Y	Y	Considered safe.
	BHT	0.11	3.52	Y	Y	
	BisDPE	0.40	12.80	Y	Y	
	BisGMA	1.09	34.77	Y	Y	
	DEAP	0.58	18.67	Y	Y	
	Irgafos 128	0.65	20.69	Y	Y	
	STA	21.84	698.88	N	N	EED= 698.88 μg ÷ 10 kg ÷ 1 d = 69.9 μg/kg bw/d MOS= 1000 μg/kg bw/day ÷ 69.9 μg/kg bw/d = 14 Because the MoS is above 1.0, exposure is considered safe.
	TDA	0.14	4.37	Y	Y	
	TEG	0.12	3.73	Y	Y	Considered safe.
	TEGDMA	0.05	1.50	Y	Y	

[a]Abbreviations: TSL, toxicity screening level; Y, yes; N, no; MOS, margin of safety; EDD, worst-case estimated exposure dose; 2-HPA, 2-hydroxypropyl acrylate; 3,4-DBAL, 3,4-dimethylbenzaldehyde; 3-DTBBDA, 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde; 4-EDMAB, ethyl 4-dimethylaminobenzoate; BisDPE, bisphenol A, bis(2,3-dihydroxypropyl) ether; BisGMA, bisphenol A glycerolate dimethacrylate; DEAP, 2,2-diethoxyacetophenone; STA, stearic acid; TDA, tridecyl acrylate; TEGDMA, triethylene glycol dimethacrylate; TEG, triethylene glycol. The asterisk indicates consideration of maximum number of devices clinically used (n = 32).

or thermal effects over the service life of the material.[69] The compounds may also be released into the oral cavity due to incomplete polymerization.[70] The assumption that maximum E&L compounds are released daily over the entire lifetime of each dental composite is extremely conservative, as it is overestimating the potential risks from exposure to E&Ls following initial application. The chemical characterization of ePX, FU, and cc-ePX-FU showed that the identified E&L compounds were generally similar but with some quantitative differences. However, the toxicological risk assessment (Tables 7−9) indicates that the likelihood of toxicological effects from these E&Ls was considered low. It should be noted that the combined toxicological effects of E&Ls may be additive or synergistic, and the TSL approach or calculated MOS values may not be applicable to sensitive subgroups such as patients with renal/liver failure or pregnant or lactating women.

Conducting the present study according to ISO standards is important for comparing the monomer release of restorative materials under the same conditions. Semiquantitative studies of dental materials are still in progress. The E&L studies of the composites can be enough to make a toxicological risk assessment. We concluded that the medical use of eXP and FU separately or with cc-eXP-FU is not expected to pose any additional risk or concern for patient safety.

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Table 9. Risk Characterization of Extractables and Leachables from cc-eXP-FU Dough and Cured Form[a]

Type	Compound	μg/device	Worst-case exposure* (μg)	Is worst-case exposure less than TSL≤30 d of 120 μg (Y/N)	Is worst-case exposure less than TSL>30 d of 600 μg (Y/N)	Comments
Dough	3,4-DBAL	0.27	8.53	Y	Y	Considered safe.
	4-EDMAB	4.38	140.05	N	Y	EED= 140.05 μg ÷ 10 kg ÷ 1 d = 14.0 μg/kg bw/d MOS= 80 μg/kg bw/day ÷ 14.0 μg/kg bw/d = 5.7 Because the MoS is above 1.0, exposure is considered safe.
	BisGMA	0.22	7.15	Y	Y	
	Topanol A	0.05	1.50	Y	Y	
	3-DTBBDA	0.28	9.07	Y	Y	Considered safe.
	Irgafos 128	0.52	16.53	Y	Y	
	Irganox 1520	0.05	1.71	Y	Y	
	STA	9.78	313.07	N	Y	EED= 313.07 μg ÷ 10 kg ÷ 1 d = 31.3 μg/kg bw/d MOS= 1000 μg/kg bw/day ÷ 31.3 μg/kg bw/d = 32 Because the MoS is above 1.0, exposure is considered safe.
Cured	3-DTBBDA	0.23	7.47	Y	Y	
	2-HPA	0.05	1.60	Y	Y	
	4-EDMAB	3.67	117.44	Y	Y	Considered safe.
	4-MBAD	0.14	4.48	Y	Y	
	BisDPE	0.16	5.23	Y	Y	
	BisGMA	2.64	84.48	Y	Y	
	DEAP	0.46	14.72	Y	Y	
	Irgafos 128	0.69	21.97	Y	Y	
	STA	13.34	426.77	N	Y	EED= 426.77 μg ÷ 10 kg ÷ 1 d = 42.7 μg/kg bw/d MOS= 1000 μg/kg bw/day ÷ 42.7 μg/kg bw/d = 23 Because the MoS is above 1.0, exposure is considered safe.
	TDA	0.24	7.79	Y	Y	
	TEG	0.17	5.55	Y	Y	
	TEGDMA	0.26	8.32	Y	Y	Considered safe.
	Topanol A	0.11	3.52	Y	Y	
	TPO	0.50	16.00	Y	Y	

[a]Abbreviations: TSL, toxicity screening level; Y, yes; n, No; MOS, margin of safety; EDD, worst-case estimated exposure dose; 2-HPA, 2-hydroxypropyl acrylate; 3,4-DBAL, 3,4-dimethylbenzaldehyde; 3-DTBBDA, 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde; 4-EDMAB, ethyl 4-dimethylaminobenzoate; 4-MBAD, 4-morpholinobenzaldehyde; BisDPE, bisphenol A bis(2,3-dihydroxypropyl) ether; BisGMA, bisphenol A glycerolate dimethacrylate; DEAP, 2,2-diethoxyacetophenone; STA, stearic acid; TDA, tridecyl acrylate; TEGDMA, triethylene glycol dimethacrylate; TEG, triethylene glycol; Topanol A, 6-*tert*-butyl-2,4-dimethylphenol; TPO, diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide. The asterisk indicates consideration of maximum number of devices clinically used (n = 32).

CONCLUSION

The comprehensive evaluation of eXP and FU dental composites has confirmed their biocompatibility and adherence to the ISO 10993-17:2023 and 10993-18:2020 standards. Both materials demonstrated a consistent depth of cure, with eXP and FU achieving average depths of 3.13 and 3.09 mm, respectively. This consistency ensures that both materials cure properly under clinical conditions, minimizing the risk of incomplete curing, which could lead to higher solubility and potential toxicity. Our results highlighted a distinct difference in solubility between the two materials. eXP exhibited a higher solubility (6.062 ± 0.576 $\mu g/mm^3$) compared to FU (0.864 ± 0.436 $\mu g/mm^3$), which suggests that eXP may be more susceptible to degradation in moist environments. However, both composites fell within safe limits, which affirms their

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suitability for long-term dental applications. The toxicological assessment revealed low levels of E and L compounds for both materials, indicating a minimal risk of adverse effects from chemical exposure. The release profile varied between the cured and uncured forms, emphasizing the importance of understanding how different states of these materials interact with the biological environment. The safe use of eXP and FU in dental restorations is supported by their robust chemical and physical properties. However, the variation in solubility and organic compound release between their cured and uncured forms suggests that handling and curing protocols are critical to maximizing patient safety and material performance. Further studies are recommended to explore the long-term effects of environmental exposure on the stability and toxicity of these materials. Additionally, investigating the interaction effects when these composites are used in conjunction with other dental materials could provide deeper insights into their comprehensive safety profiles. By bridging critical knowledge gaps, this study not only reinforces the safety and efficacy of eXP and FU but also underscores the importance of rigorous standards compliance in developing dental materials that ensure patient safety and clinical success.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c01432.

Detailed data and analysis on the toxicological safety of EverX Posterior and Filtek Ultimate, comprehensive extractable and leachable studies conducted in accordance with ISO 10993-18 standard, data covering the various compounds detected, their match factors, modes, retention times, abundance, concentrations, and recovery percentages for multiple sample injections analyzed by HS-GC/MS, GC/MS, and LC/MS-QTOF methods, with specific focus given to compounds such as naphthalene, DPA, EP, and others across different sample conditions (e.g., cured with IPA or water, dough with water) (PDF)

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