



**CESPU**  
INSTITUTO UNIVERSITÁRIO  
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# The Impact of Bisphenol-A on Universal Adhesive systems and BPA-Free Alternatives

## A Systematic Review

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Dissertação conducente ao **Grau de Mestre em Medicina Dentária (Ciclo Integrado)**

—

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**A Systematic Review**

Trabalho realizado sob a Orientação de

**Professora Doutora Lígia Lopes Da Rocha**

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## ABSTRACT

Introduction: Universal adhesives revolutionise restorative dentistry by combining versatility and simplicity. However, the use of Bisphenol A (BPA), valued for enhancing mechanical properties, raises health concerns due to its endocrine-disrupting potential. This review examines BPA's impact on adhesive performance, health implications, and recent advancements in BPA-free alternatives for safer dental practices.

Objectives: This systematic review aims to determine the actual impact of bisphenol A and its derivatives on universal adhesives, focusing on benefits, risks, and new alternatives.

Material and Methods: The literature search was performed in the PubMed database for articles published from 2015 to March 2025, using keyword combinations. The PICO strategy was used, and inclusion and exclusion criteria were determined to choose the most valuable articles for the present study.

Results: Eight articles were selected, all of which are in-vitro studies.

Discussion: The cytotoxicity of the tested adhesives varied according to their composition; however, no clear correlation could be established, as some adhesives without BPA derivatives exhibited greater cytotoxicity. Nevertheless, the bonding performance of BPA-free universal adhesive systems appeared to be at least comparable, and in some cases superior, to that of commonly used universal adhesives. While some of the evaluated adhesives were experimental, others were commercially available products.

Conclusion: BPA-derivative-free adhesive systems demonstrate promising bonding performance; however, the absence of BPA cannot be directly linked to a decrease in cytotoxicity.

**Keywords:** "Universal adhesives"; "Dental adhesives"; "Bonding"; "Bisphenol A"; "BPA"; "BPA derivatives"; "Performance"; "Adhesion"; "Bond strength"; "Impact"; "Risks".



## RESUMO

**Introdução:** Os adesivos universais revolucionam a odontologia restauradora combinando versatilidade e simplicidade. No entanto, o uso do Bisfenol A (BPA), valorizado por melhorar as propriedades mecânicas, levanta preocupações de saúde devido ao seu potencial disruptor endócrino. Esta revisão examina o impacto do BPA no papel da adesão, suas implicações para a saúde e os avanços recentes em alternativas livres de BPA para práticas odontológicas mais seguras.

**Objetivos:** Esta revisão sistemática tem como objetivo determinar o impacto real do Bisfenol A e seus derivados nos adesivos universais, com foco nos benefícios, nos riscos e nas novas alternativas.

**Material e Métodos:** Utilizando combinações de palavras-chave, a pesquisa bibliográfica foi realizada na base de dados PubMed para artigos publicados entre 2015 e março de 2025. A estratégia PICO foi utilizada, e critérios de inclusão e exclusão foram determinados para selecionar os artigos mais relevantes para o presente estudo.

**Resultados:** Foram selecionados oito artigos, todos estudos in-vitro.

**Discussão:** A citotoxicidade dos adesivos testados variou de acordo com a composição; no entanto, não foi possível estabelecer uma correlação clara, pois alguns adesivos sem derivados de BPA apresentaram maior citotoxicidade. No entanto, o desempenho de adesão dos sistemas adesivos universais sem BPA parecia ser pelo menos comparável, e em alguns casos superior, ao dos adesivos universais comumente utilizados. Alguns dos adesivos avaliados eram experimentais, enquanto outros eram produtos comerciais.

**Conclusão:** Os sistemas adesivos sem derivados de BPA demonstram um potencial de adesão promissor, no entanto, a ausência de BPA não pode ser diretamente associada a uma redução na citotoxicidade.

**Palavras-chaves:** "Universal adhesives"; "Dental adhesives"; "Bonding"; "Bisphenol A"; "BPA"; "BPA derivatives"; "Performance"; "Adhesion"; "Bond strength"; "Impact"; "Risks".



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**List of abbreviations and acronyms:**

**BPA:** Bisphenol-A

**Bis-GMA:** Bisphenol A Glycidyl Methacrylate

**Bis-EMA:** Bisphenol A Ethoxylated Dimethacrylate

**HEMA:** Hydroxyethyl-Methacrylate

**TEG DVBE:** Triethylene Glycol Divinylbenzyl Ether

**PMGDMA:** Pyromellitic Glycerol Dimethacrylate

**UDMA:** Urethane Dimethacrylate

**TEGDMA:** Triethylene Glycol Dimethacrylate

**SEM:** Scanning Electron Microscope

**EFSA:** European Food Safety Authority

**TDI:** Tolerable Daily Intake



## 1. Introduction

Universal adhesive systems represent a significant advancement in restorative dentistry, offering versatility by adapting to different adhesion techniques such as self-etch, total-etch, or selective-etch. Their advanced formulations ensure excellent adhesion to enamel and dentin while simplifying clinical protocols. These modern systems typically consist of a combination of functional monomers, solvents, and other chemical additives used to optimize performance, durability, and practicality (1).

One key compound historically used in these adhesives is Bisphenol A (BPA), a crucial precursor in the synthesis of monomers such as Bis-GMA and Bis-EMA. These derivatives provide adhesives with remarkable mechanical properties, including increased rigidity, and high resistance to chemical and thermal degradation. Moreover, they enhance viscosity and handling, making adhesives systems more efficient and reliable for clinicians (1).

However, BPA is also recognised for its endocrine-disrupting properties (2). Studies have indicated that small amounts of BPA can be released from dental materials after polymerization, which raises concerns about its potential health repercussions (3).

In this context, modern dentistry faces a critical challenge: how to maintain the performance of universal adhesives while eliminating the risks associated with BPA. Recent studies have focused on developing BPA-free formulations using alternatives, although these materials do not always provide the same advantages.

This systematic review explores the impact of BPA on universal systems, examining its role in adhesive performance and health implications. It also aims to highlight recent advancements and potential alternatives for safer and more sustainable dentistry.



## 2. Objectives and hypotheses

### 2.1 Objectives

This systematic review aims to investigate the influence of BPA and its derivatives on universal adhesive systems, examining their effects on adhesion quality and potential health risks. It also explores recent developments and emerging alternatives for a safer and more sustainable approach in dentistry.

### 2.2 Hypotheses

Null hypothesis: The BPA derivatives in adhesive systems have no significant impact on adhesion strength or patient health.

Positive hypothesis: The BPA derivatives in adhesive systems improve adhesion strength but may have potential negative effects on patient health.



### 3. Materials and Methods

#### 3.1 Research Protocol

A bibliographic search was performed in the PubMed database for articles published in English from 2015 to March 2025.

The following keywords were used: "Universal adhesives" [Mesh], "Dental adhesives" [Mesh], "Bonding" [Mesh], "Bisphenol A" [Mesh], "BPA" [Mesh], "BPA derivatives" [Mesh], «Performance" [Mesh], "Adhesion" [Mesh], "Bond strength" [Mesh], "Impact" [Mesh], "Risks" [Mesh], combined with "AND" and "OR".

**Table 1:** Article research methodology.

N°Research	KEYWORDS	ARTICLES
#1	<i>("Bisphenol A"[All Fields] OR "BPA"[All Fields] OR "Bis-GMA"[All Fields]) AND ("Universal adhesives"[All Fields] OR "Dental adhesives"[All Fields])</i>	150
#2	<i>("Universal Adhesives"[All Fields]) AND ("HEMA-free"[All Fields] OR "BPA-free"[All Fields])</i>	14
#3	<i>(Toxicity) AND (Universal dental adhesives)</i>	24
<b>TOTAL ARTICLES: 188</b>		

### 3.2 PICOS Strategy

The studies included in this systematic review were selected according to the PICOS strategy.

➤ **Population:**

Human recently extracted teeth, in-vitro cell cultures.

➤ **Intervention:**

Use of universal adhesives containing BPA and its derivatives.

➤ **Comparison:**

BPA-free adhesive systems.

➤ **Outcome:**

Effects of BPA regarding biocompatibility or cytotoxicity and adhesion performances.

➤ **Study design:**

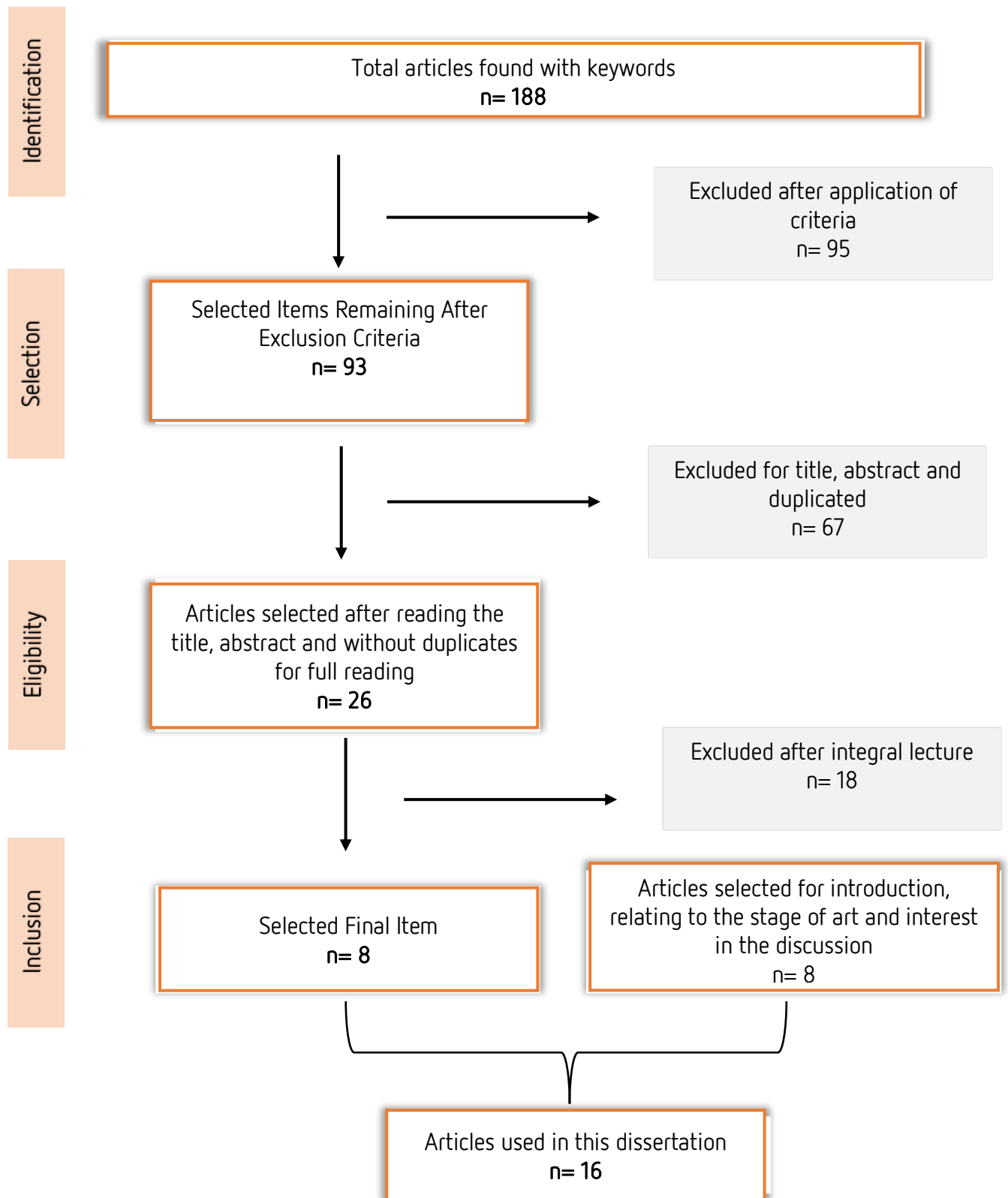
Systematic review of original studies published in the last 10 years.

### 3.3 Inclusion and Exclusion Criteria

**Table 2:** Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Articles published in the last 10 years (from 2015)	Articles older than 10 years (before 2015)
Original articles	Non-original articles (Systematic review, meta-analyses, literature review)
Articles must cover, among other aspects, universal adhesive systems	Studies not focused on universal adhesives systems
Free and fully available articles	Articles that are not fully accessible or behind paywalls

## 4. Results



**Figure 1:** PRISMA flowchart 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

## Presence or absence of BPA

In this study, we will focus on 19 universal adhesive systems. Some are well known, others are less, and there are also 5 experimental adhesives that are not commercial like the others (orange in the table). Among these adhesive systems that we will compare, some contain BPA derivatives, and others don't. This table shows the distribution.

**Table 3:** Distribution of all adhesives systems used in this review and their composition.

Adhesive system designation	Presence of BPA-derivatives	occurrence in the articles
Clearfil SE Bond® (Kuraray Noritake Dental Inc., Tokyo, Japan)	YES	3
Scotchbond Universal® (3M ESPE, St. Paul, Minnesota, United States)	YES	5
Single bond Universal® (3M ESPE, St. Paul, Minnesota, United States)	YES	1
TEG DVBE with TEGDMA	NO	1
TEG DVBE with PMGDMA	NO	1
exp. Bis-GMA/HEMA	YES	1
Optibond Universal® (Kerr Corporation, Orange, California, United states)	YES	2
Prime&Bond Universal® (Dentsply Sirona, Konstanz, Germany)	YES	2
Adhese Universal® (Ivoclar Vivadent, Schaan, Liechtenstein)	YES	1
All bond Universal® (BISCO Inc., Schaumburg, Illinois, United States)	YES	1
Clearfil Universal Bond Quick® (Kuraray Noritake Dental Inc., Tokyo, Japan)	YES	2

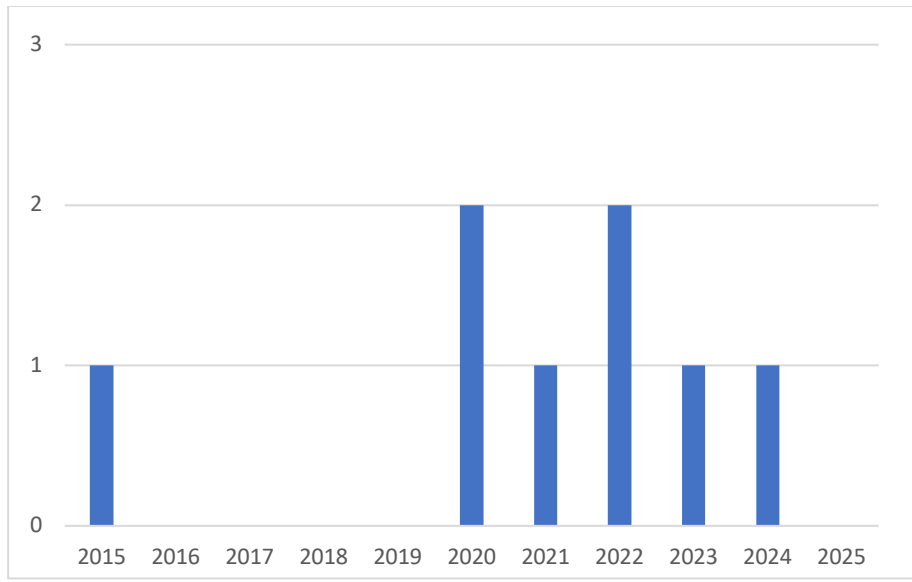
G-Premio bond® (GC Corporation, Tokyo, Japan)	NO	1
Zip bond Universal® (SDI Limited, Melbourne, Australia)	YES	1
Futurabond U® (VOCO, Cuxhaven, Germany)	YES	1
EM1	YES	1
EM2	NO	1
G2-bond Universal® (GC Corporation, Tokyo, Japan)	NO	1
Healbond Max® (ELSODENT, Cergy-Pontoise, France)	NO	1
Healbond MP® (ELSODENT, Cergy-Pontoise, France)	NO	1

**Table 4:** Table of Results

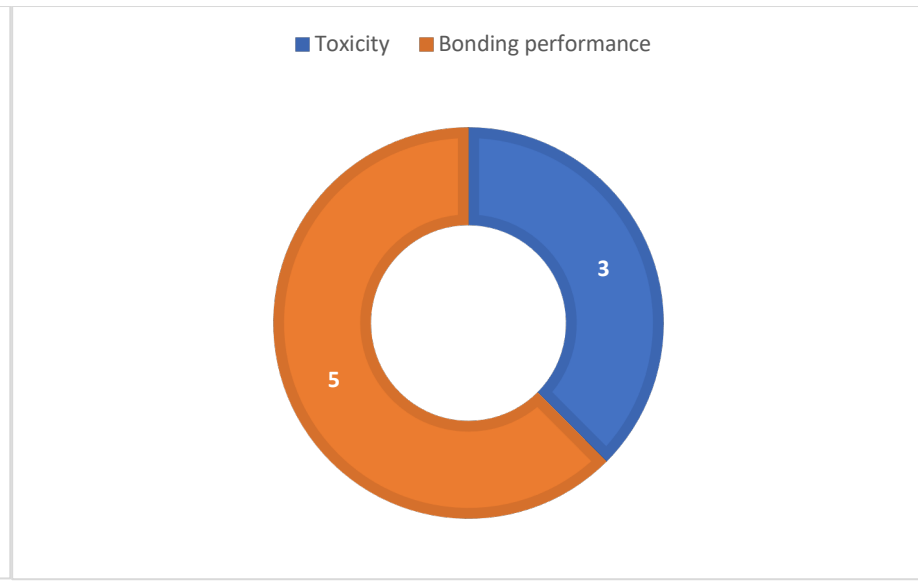
ARTICLE REFERENCE	STUDY DESIGN	PURPOSE	MATERIAL AND METHODS			RESULTS	CONCLUSIONS
			SAMPLE	MATERIAL	METHODS		
<p>Cytotoxicity of universal, self-etching and etch-and-rinse adhesive systems according to the polymerization time.</p> <p>(Elias ST et al., 2015)</p>	Comparative in-vitro study	To evaluate the direct cytotoxicity of several adhesives system including universal	Fibroblasts cell line L929	-Single Bond -Scotchbond -Clearfil SE Bond -Scotchbond Universal	Discs impregnated with adhesive systems stored with fibroblasts for 24h and 7 days	-24h: percentage of viable cells 40 to 50% all adhesives were similar (p>0.05) -7 days: percentage of viable cells 33 to 51% all adhesives were similar (p>0.05)	-All the adhesive systems reduced cellular metabolism, caused morphological alterations and damaged the cell membrane -They are all cytotoxic, with minor variations possibly related to their composition
<p>High-Performance Dental Adhesives Containing an Ether-Based Monomer</p> <p>(Yamauchi S et al., 2020)</p>	Comparative in-vitro study	To compare adhesive systems containing Bis-GMA or HEMA with adhesives containing an ether-based monomer (TEG DVBE)	n=35 molars (5 for SBS test, 15 for $\mu$ TBS test without thermal cycling and 15 for $\mu$ TBS test with thermal cycling)	-TEG DVBE with UDMA -TEG DVBE with PMGDMA -BisGMA/HEMA -Scotchbond	Shear Bond Strength (SBS) and Micro tensile Bond Strength ( $\mu$ TBS) were tested.  Thermal cycling (10 000 cycles from 5°C to 55°C)	-SBS test shows similar Bond strength between the two experimental adhesives and Scotchbond, and better strength than the Bis-GMA/HEMA adhesive.  -After thermal cycling, the Bis-GMA/HEMA adhesive and Scotchbond suffered a drop of their $\mu$ TBS, whereas the two experimental adhesives didn't.	- The bonding strength of the TEG DVBE-containing adhesives to dentin and resin composites was equivalent to the experimental and commercial controls.  -The bonding stability of these Bis-GMA/HEMA-free adhesives exceeded stability of controls under extended challenges by thermocycling.
<p>The Cytotoxicity and Genotoxicity of Three Dental Universal Adhesives, an In-Vitro Study.</p> <p>Wawrzynkiewicz A et al., 2020)</p>	Comparative in-vitro study	To evaluate the cytotoxicity and genotoxicity of 3 universal dental adhesive systems	monocyte/macrophage cell line SC (ATCC CRL-9855)  n=96-well plates for XTT assay	-OptiBond Universal -Prime&Bond Universal -Adhese Universal	Cells were incubated 24h with the three adhesive systems; cytotoxicity was measured using the XTT colorimetric	Both XTT colorimetric assay and comet assay showed that only OptiBond Universal significantly decreased the cell viability and increased the DNA damage. For Prime&Bond Universal and Adhese Universal, no significant changes of cell	Prime&Bond Universal and Adhese Universal presented minimal toxic effect on human SC cells, while OptiBond Universal showed significant cytotoxic and genotoxic effect on SC cell line. Only OptiBond Universal showed significant

			n=12-well plates for Comet assay		assay and genotoxicity using a comet assay.	viability or DNA damage were observed. (p<0.001)	ability to induce apoptosis in SC cell line.
The Toxicity of Universal Dental Adhesives: An In-Vitro Study  Wawrzynkiewicz A et al., 2021)	Comparative in-vitro study	To evaluate the biocompatibility of 4 Universal Dental Adhesives in an in-vitro model.	monocyte/macrophage cell line SC (ATCC CRL-9855)  n=96-well plates for XTT assay  n=12-well plates for Comet assay	- All-Bond Universal - CLEARFIL Universal Bond Quick - G-Premio BOND - Single Bond Universal	Cells were incubated 24h with the three adhesive systems; cytotoxicity was measured using the XTT colorimetric assay and genotoxicity using a comet assay.	Only G-PREMIO Bond significantly decreased cell viability during the XTT assay.  A significant increase in DNA damage was observed after the 24 h incubation in the cells treated with G-PREMIO Bond.	All-Bond Universal, Clearfil Universal Bond Quick and Single Bond Universal presented minimal toxic effect on human SC cells, while G-Premio Bond showed significant cytotoxic and genotoxic effect on SC cell line. Only G-Premio Bond showed significant ability to induce apoptosis in SC cell line.
Bonding performance and ultramorphology of the resin-dentine interface of contemporary universal adhesives  (Maciel Pires P et al., 2022)	Comparative in-vitro study	To evaluate the microtensile bond strength ( $\mu$ TBS) and the resin-dentine ultramorphology of 4 universal adhesives	n= 64 human molars divided in 4 groups (n=16) according to the adhesive system used.	-Zip Bond -Prime&Bond -CLEARFIL Universal Bond Quick -Scotchbond Universal	The specimens were cut into sticks and subjected to $\mu$ TBS testing at 24 h or after 10 months of ageing in artificial saliva.  Resin-dentin interface was also analysed	Zip Bond, Prime&Bond and Scotchbond exhibited greater $\mu$ TBS values than Clearfil Universal Bond Quick at 24 h (p < 0.05). Clearfil Universal Bond Quick showed a significant decrease in $\mu$ TBS values after ageing (p < 0.05). Zip Bond exhibited no significant differences in the $\mu$ TBS test after ageing (p > 0.05), while a significant drop in $\mu$ TBS was seen in Scotchbond and Prime&Bond after 10-month ageing (p < 0.05). Clear signs of degradation were evident in the resin-dentine interface created	Clearfil Universal Bond Quick applied in "quick" mode had the lowest bonding performance ( $\mu$ TBS), along with the greatest degradation of the Hybrid layer.

						with Clearfil Universal Bond Quick	
Improving Properties of an Experimental Universal Adhesive by Adding a Multifunctional Dendrimer (G-IEMA): Bond Strength and Nanoleakage Evaluation  (Vasconcelos E Cruz J et al., 2022)	in-vitro comparative study	To investigate the use of dendrimer G-IEMA, creating a BPA-free formulation, on the immediate dentin bond strength.	n=60 human molars Divided in 2 groups (n=36 and n=24) First group for $\mu$ TBS test, second group for Nanoleakage analyse.	-Futurabond -Scotchbond Universal -EM1 (Experimental adhesive with Bis-GMA) -EM2 (Experimental adhesive with G-IEMA)	After 24h, Micro tensile Bond Strength ( $\mu$ TBS) was tested, and the bonded interface was analysed. After 3 months, nanoleakage was observed.	No statistically significant differences in immediate $\mu$ TBS results were observed between adhesives.  EM1 and EM2 showed significantly lower nanoleakage than the commercials Futurabond and Scotchbond Universal. They seem to have a richer and more cohesive hybrid layer using SEM	This study supports the use of dendrimers like the BPA-free G-IEMA instead of classical linear monomer Bis-GMA.  The performances were similar between the two experimental formulations, and they outperformed the two commercials in terms of nanoleakage.
Comparison of Different Universal Adhesive Systems on Dentin Bond Strength  (Brkanović S et al., 2023)	in-vitro comparative study	to compare the dentin bond durability of diverse universal adhesives	n=80 (40 molars, each divided into 2 samples)  Divided in 8 groups depending on the adhesive used and if thermal cycling was processed:	-Scotchbond Universal Plus -Clearfil SE Bond -G2-Bond Universal	After 2 months and potentially thermal cycling (from 5 to 55°C) Shear Bond Strength was analysed using the Ultra Tester machine	Thermal cycling significantly impacted all samples tested in comparison of the samples that didn't.  G2-Bond universal showed significantly better SBS than Scotch Bond Universal Plus.	This study implies that the HEMA-free universal adhesive G2-Bond Universal showed higher or equal dentin bond strength than representative adhesive and the most stable dentin bond
Multi-Parameter Characterization of HEMA/BPA-free 1- and 2-step Universal Adhesives Bonded to Dentin  (Tang C et al., 2024)	in-vitro study	To investigate the bonding effectiveness of two HEMA/BPA-free universal adhesives, to characterize their adhesive-dentin interfacial	n=40 Third molars Divided in 5 groups depending on the adhesive used	HEMA/BPA-free: -Healbond Max -Healbond MP  -Optibond FL -Clearfil SE Bond 2 -Scotchbond Universal	The immediate and aged (after thermal cycling) microtensile bond strength ( $\mu$ TBS) were measured, as well as hydrophobicity.	After aging Scotchbond Universal showed significantly lower $\mu$ TBS. Whereas Healbond Max and Healbond MP showed good results in both cases. Hydrophobicity of the 2 HEMA/BPA-free adhesives was not significantly different from the others.	Healbond Max and Healbond MP revealed bonding performances similar to that of the other adhesive systems



**Figure 2:** Distribution of articles by date of publication.



**Figure 3:** Distribution of articles by their focus.



## 5. Discussion

### 5.1 Universal adhesive systems

#### 5.1.1 A brief overview of universal adhesive systems

The advent of adhesive systems has revolutionized restorative dentistry. Over the past two decades, research efforts have concentrated on two primary fronts: simplifying materials to reduce operator variability and identifying strategies and materials capable of stabilizing the hybrid layer (HL) and inhibiting factors compromising long-term interfacial integrity (1).

Adhesive systems are classified into generations, each marking significant advancements in composition and application. Early first- and second-generation adhesives exhibited weak bond strength and poor durability due to limited knowledge of dentin and inadequate infiltration. The third and fourth generations introduced acid etching, enhancing enamel and dentin adhesion through micromechanical interlocking. Fifth- and sixth-generation adhesives simplified procedures by combining etching, priming, and bonding. Seventh-generation, or universal adhesives, reduced technique sensitivity and improved dentin adhesion (1).

#### 5.1.2 The main monomers

Dental adhesives are solutions of resin monomers that enable interaction between the resin and dental substrate (4). These monomers possess both hydrophilic and hydrophobic functionalities. Hydrophilic groups enhance the wetting of dental hard tissues, while hydrophobic groups promote bonding and co-polymerization with

restorative materials. Additionally, the formulation of adhesives typically includes curing initiators, stabilizers or inhibitors, solvents, and sometimes inorganic fillers (5).

The main monomers used are: Bisphenol A Glycidyl Methacrylate (Bis-GMA), a highly viscous and hydrophobic monomer, is primarily responsible for providing mechanical strength and reducing polymerization shrinkage (3). Due to its high viscosity, Bis-GMA is often combined with lower viscosity monomers like Triethylene Glycol Dimethacrylate (TEGDMA), which acts as a diluent to improve handling properties. However, TEGDMA's hydrophilic nature can increase water sorption and elution of unreacted monomers, potentially affecting the durability of the adhesive interface (1). Next, we have 2-Hydroxyethyl Methacrylate (HEMA) is widely used for its hydrophilic properties, enhancing resin infiltration into moist dentin. However, its hydrophilicity also predisposes adhesives to water sorption and hydrolytic degradation over time (1). Another important monomer, Urethane Dimethacrylate (UDMA), offers a balance between flexibility and mechanical strength. UDMA exhibits a lower viscosity than Bis-GMA and is less hydrophilic than HEMA, contributing to improved mechanical resilience and reduced water uptake in adhesive formulations (1).

The careful selection and combination of these monomers is critical for optimizing the performance of adhesive systems, balancing properties such as viscosity, mechanical strength, water resistance, and polymerization efficiency.

### 5.1.3 The Bisphenol A

Bisphenol A (BPA) is an industrial chemical primarily used in the production of polycarbonate plastics and epoxy resins. BPA derivatives, such as Bis-GMA or Bis-EMA, are components of resin-based dental sealants, composites, and adhesive systems that are increasingly utilised in both preventive and restorative oral health care (6).

BPA has been reported to be still detectable in quantifiable amounts even after long-term storage of polymerized dental composite in ethanol for up to 52 weeks, indicating that dental composites containing bis-GMA are a potential source of BPA exposure (3).

## 5.2 BPA and health, a growing concern

The potential health risks associated with bisphenol A exposure have become a major focus of scientific investigation, prompting regulatory authorities and the dental community to reassess its use in biomaterials. Indeed, in animal studies, several adverse health effects have been linked to BPA, including effects on hormonal activity (2). In response to these concerns, the European Food Safety Authority (EFSA) has established maximum daily exposures for this molecule, known as TDI (Tolerable Daily Intake), and over the years, these limits have evolved. In 2006, the TDI was set at 0,05mg/kg body weight/day; in 2015, a new TDI was established at 0,004 mg/kg body weight/day. In 2023, EFSA established an ultra-low tolerable daily intake for BPA at 0.0000002 mg/kg body weight/day, citing immunotoxic effects observed at extremely low exposure levels, which is 20,000 times less than in 2015 (7) (8). The drastic reduction of EFSA's tolerable daily intake for BPA highlights the growing importance of developing BPA-derivative-free solutions in dental materials.

## 5.3 Analysis and comparison of different universal adhesive systems

### 5.3.1 Cytotoxicity and genotoxicity

One key compound to evaluate if the BPA-derivatives present in the adhesive systems mentioned here is dangerous or toxic for the patient was to analyse their cytotoxicity and/or genotoxicity. Indeed, biocompatibility is one of the most important properties of dental materials. In the study published by *Elias ST et al.* (9), all the universal adhesives tested (Scotchbond Universal and Clearfil SE bond) reduced the cell metabolism of the L929 fibroblasts. For the 24 hours test, they observed a 40 to 50% reduction of cell viability; for the 7-day test, a decrease from 33 to 50% was noted. The adhesives tested also impacted cell morphology; they observed cells with a round shape and small size, characteristics of cells in the apoptosis process, and cells without clear limits, suggesting membrane disruption.

All the adhesives tested contained BPA derivatives such as Bis-GMA, and no significant differences were found among them. However, in the study published by *Wawrzynkiewicz A et al.* (10), some differences were noted. Indeed, among the 3 universal adhesives tested (Optibond U, Prime&Bond U, and Adhese U), Prime&Bond Universal and Adhese Universal exhibited minimal toxic effects on human monocyte/macrophage peripheral blood SC cells, while OptiBond Universal demonstrated significant cytotoxic and genotoxic effects on the SC cell line. OptiBond Universal was the only adhesive to significantly induce apoptosis in the SC cell line, resulting in DNA damage. Although the cause of this result is not explicitly stated, it can be inferred that the differences in their composition are responsible, despite all adhesives containing BPA derivatives

This raises the question of what would occur if the sample contained a universal adhesive formulated without BPA-derivative monomers, a scenario explored in another study published one year later by *Wawrzynkiewicz A et al.* (11). The sample included the following universal adhesive systems: All-Bond Universal, Clearfil Universal Bond Quick, G-Premio Bond, and Single Bond Universal, with G-Premio Bond notably formulated without bis-GMA. The results showed that only the G-PREMIO Bond significantly decreased cell viability compared to the others. A significant increase in DNA damage was observed after 24 h of incubation in the cells treated with G-PREMIO Bond. The other systems used did not induce significant DNA damage in the SC cell line investigated. Moreover, after 24 hours incubation, G-Premio Bond was the only one that significantly induced apoptosis (approximately 39% of cells were at the early and late stages of apoptosis). The authors said that these differences in toxicity could result from differences in the composition of the specific UDA, namely, different monomers and the ratio of the compounds.

Although G-Premio Bond is formulated without bis-GMA, this research has shown that it can exhibit higher cytotoxicity than some adhesives containing bis-GMA. This increased toxicity is likely attributed to the presence of other monomers, which have their own intrinsic cytotoxic potential. The absence of bis-GMA in a formulation does not necessarily imply improved biocompatibility.

### 5.3.2 Bond strength and performance

Adhesion is widely recognized as one of the most critical factors, if not the most crucial one, in restorative dentistry. The long-term success of restorations depends heavily on the quality and durability of the adhesive bond between the material and the dental tissues. This section will compare various universal adhesive systems to evaluate their adhesive performances, highlighting differences that may influence clinical outcomes.

In the study published by *Maciel Pires P et al.* (12), 4 universal adhesive systems were tested: Zip bond, Prime & Bond, Clearfil universal bond quick and Scotchbond Universal.

Their adhesion performance was analyzed by measuring their microtensile bond strength ( $\mu$ TBS) after 24 hours and 10 months in artificial saliva. This study showed that Clearfil UBQ's  $\mu$ TBS at 24 hours was significantly lower than the other adhesives, and at 10 months only Zip Bond didn't suffer a significant drop of its  $\mu$ TBS. Every adhesive in this study contained BPA-derivatives, so we can deduce that other factors in their composition caused the differences observed.

It could now be relevant to compare the different performances with BPA-derivatives-free adhesives. In 4 studies published by *Yamauchi S et al.* (13), *Vasconcelos E Cruz J et al.* (14), *Brkanović S et al.* (15) and *Tang C et al.* (16), Scotchbond Universal and other universal adhesive systems were compared to adhesives that didn't contain Bis-GMA or other BPA-derivative in their formulations. Some of these adhesives are commercial, but other are only experimental. For instance, in the study of *Yamauchi S et al.* (13), two dental adhesives were formulated and prepared by combining a hydrolytically stable ether-based monomer, TEG DVBE (triethylene glycol divinylbenzyl ether), with either UDMA (urethane dimethacrylate) or PMGDMA (pyromellitic glycerol dimethacrylate). Their performance, in terms of shear bond strength (SBS) and microtensile bond strength ( $\mu$ TBS) to human dentin, as well as their bond durability after extended thermocycling, was compared to that of commercial (Scotchbond Universal) and experimental Bis-GMA/HEMA-based adhesives. As a result, the two TEG DVBE based experimental adhesives performed similarly to Scotchbond Universal and better than the experimental

Bis-GMA/HEMA adhesive regarding shear bond strength. Moreover, their  $\mu$ TBS didn't suffer a drop after thermocycling, when the two others did.

The study conducted by *Vasconcelos E Cruz J et al.* (14) aimed to replace the Bis-GMA monomer with the G-IEMA dendrimer. They prepared two experimental adhesives: one with Bis-GMA (EM1) and the other with G-IEMA (EM2); the rest of the composition is strictly identical and were compared to Scotchbond Universal and Futurabond. They analyzed the  $\mu$ TBS after 24 hours and examined the bonded interface. After 3 months, nanoleakage was observed using SEM. The results of their study showed that, after 24 hours, no differences were found between the  $\mu$ TBS of all the adhesives, while the resin-dentin interface characterized by the hybrid layer appeared richer and more cohesive according to SEM. After 3 months, both EM1 and EM2 demonstrated significantly lower nanoleakage than Futurabond and Scotchbond Universal. The authors highlighted that further studies must be conducted to confirm the favourable results obtained.

*Brkanović S et al.* (15) didn't use an experimental adhesive for their study, instead they used G2-bond Universal, a BPA-derivative-free adhesive system, and compared it to Scotchbond Universal and Clearfil SE Bond. After 2 months and, for a part of the sample, thermocycling from 5 to 55°C, they analyzed the shear bond strength (SBS). It resulted that even if all the adhesives suffered a diminution of their SBS after thermocycling in comparison of the samples that didn't, G2-bond Universal performed significantly better than the others.

Another interesting study was published by *Tang C et al.* (16), they also didn't use an experimental composition, but Healbond Max and Healbond MP, two French HEMA/BPA-free adhesives. They compared them to the traditional Scotchbond Universal, Optibond, and Clearfil SE bond 2. They measured the  $\mu$ TBS before and after thermocycling (50,000 thermocycles), analyzed the adhesive-dentin interface, and assessed hydrophobicity. Healbond Max and MP performed similarly to Optibond and Clearfil SE 2, with all of them outperforming Scotchbond Universal. Thermocycling only significantly reduced the  $\mu$ TBS of Scotchbond Universal, and Optibond was the most hydrophobic. This study showed that the BPA-derivative-free adhesives have similar bonding performances compared to the most commonly used adhesive systems.

Overall, these articles suggests that adhesive systems formulated without BPA derivatives demonstrate comparable, and occasionally superior, bonding performance when compared to traditional adhesives containing Bis-GMA-based monomers, supporting the viability of these alternatives in restorative dentistry.

#### 5.4 Limitations of current studies and perspectives

Several limitations can be highlighted in this study. First, cytotoxicity was evaluated exclusively through in-vitro studies on isolated cell lines, rather than in clinical conditions involving human patients. Similarly, the bonding performances of the adhesives were measured in-vitro, using previously extracted teeth, which do not fully replicate the complexity of the oral environment and living tissues. Long-term stability was also estimated only through artificial aging techniques, such as thermocycling or storage protocols lasting several months (a maximum of ten months in the study by *Maciel Pires P et al.* (12) with notable differences in protocols between studies. Furthermore, some of the adhesives tested were purely experimental formulations, not commercially available products, as seen in the studies by *Yamauchi S et al.* (13) and *Vasconcelos E Cruz J et al.* (14).

Finally, it is important to highlight that the studies investigated either cytotoxicity or bonding performance, but not both aspects simultaneously, thereby limiting a comprehensive understanding of the overall clinical potential of these materials.

Further studies need to be conducted to better assess both the biocompatibility and clinical performance of BPA-derivative-free adhesive systems over the long term, as well as their potential use in clinical practice.



## 6. Conclusion

After analyzing the available data, the following conclusion can be drawn:

The null hypothesis is partially rejected, as the use of BPA-derivative-free monomers in the formulation of some adhesive systems had an impact on their performance and biocompatibility. The positive hypothesis is rejected because the adhesives using BPA did not appear to be less biocompatible. Moreover, no significant differences in bond strength could be found.

Regarding cytotoxicity and biocompatibility:

- The absence of BPA derivatives in the composition of dental adhesives does not necessarily correlate with reduced cytotoxicity. In fact, some BPA-free adhesives exhibited higher cytotoxicity than their counterparts containing BPA derivatives.

Regarding adhesive performances:

- BPA-derivative-free universal adhesives demonstrated bonding performance comparable to, and in some cases superior to, traditional adhesives containing Bis-GMA or other monomers that derive from BPA.

Thus, while BPA-derivatives-free adhesives show promising bonding performances, their biocompatibility advantages remain unclear. Moreover, further long-term in-vivo studies are necessary to better assess their clinical potential, biological safety, and overall performance under real oral conditions.



## 7. Bibliography

1. Breschi L, Maravic T, Mazzitelli C, Josic U, Mancuso E, Cadenaro M, et al. The evolution of adhesive dentistry: From etch-and-rinse to universal bonding systems. *Dental Materials*. 2025;41(2):141-58.
2. Richter CA, Birnbaum LS, Farabollini F, Newbold RR, Rubin BS, Talsness CE, et al. In vivo effects of bisphenol A in laboratory rodent studies. *Reprod Toxicol*. 2007;24(2):199-224.
3. De Nys S, Putzeys E, Duca RC, Vervliet P, Covaci A, Boonen I, et al. Long-term elution of bisphenol A from dental composites. *Dent Mater*. 2021;37(10):1561-8.
4. Perdigão J. New developments in dental adhesion. *Dent Clin North Am*. 2007;51(2):333-57, viii.
5. Van Landuyt KL, Snauwaert J, De Munck J, Peumans M, Yoshida Y, Poitevin A, et al. Systematic review of the chemical composition of contemporary dental adhesives. *Biomaterials*. 2007;28(26):3757-85.
6. Fleisch AF, Sheffield PE, Chinn C, Edelstein BL, Landrigan PJ. Bisphenol A and related compounds in dental materials. *Pediatrics*. 2010;126(4):760-8.
7. Vom Saal FS, Antoniou M, Belcher SM, Bergman A, Bhandari RK, Birnbaum LS, et al. The Conflict between Regulatory Agencies over the 20,000-Fold Lowering of the Tolerable Daily Intake (TDI) for Bisphenol A (BPA) by the European Food Safety Authority (EFSA). *Environ Health Perspect*. 2024;132(4):45001.
8. EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP), Lambré C, Barat Baviera JM, Bolognesi C, Chesson A, Cocconcelli PS, et al. Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. *EFSA J*. 2023;21(4):e06857.
9. Elias ST, Santos AFD, Garcia FCP, Pereira PNR, Hilgert LA, Fonseca-Bazzo YM, et al. Cytotoxicity of universal, self-etching and etch-and-rinse adhesive systems according to the polymerization time. *Braz Dent J*. 2015;26(2):160-8.
10. Wawrzynkiewicz A, Rozpedek-Kaminska W, Galita G, Lukomska-Szymanska M, Lapinska B, Sokolowski J, et al. The Cytotoxicity and Genotoxicity of Three Dental Universal Adhesives-An In Vitro Study. *Int J Mol Sci*. 2020;21(11):3950.
11. Wawrzynkiewicz A, Rozpedek-Kaminska W, Galita G, Lukomska-Szymanska M, Lapinska B, Sokolowski J, et al. The Toxicity of Universal Dental Adhesives: An In Vitro Study. *Polymers (Basel)*. 2021;13(16):2653.
12. Maciel Pires P, Dávila-Sánchez A, Faus-Matoses V, Nuñez Martí JM, Lo Muzio L, Sauro S. Bonding performance and ultramorphology of the resin-dentine interface of contemporary universal adhesives. *Clin Oral Investig*. 2022;26(6):4391-405.

13. Yamauchi S, Wang X, Egusa H, Sun J. High-Performance Dental Adhesives Containing an Ether-Based Monomer. *J Dent Res.* 2020;99(2):189-95.
14. Vasconcelos E Cruz J, Delgado AHS, Félix S, Brito J, Gonçalves L, Polido M. Improving Properties of an Experimental Universal Adhesive by Adding a Multifunctional Dendrimer (G-IEMA): Bond Strength and Nanoleakage Evaluation. *Polymers (Basel).* 2022;14(7):1462.
15. Brkanović S, Sever EK, Vukelja J, Ivica A, Miletić I, Krmek SJ. Comparison of Different Universal Adhesive Systems on Dentin Bond Strength. *Materials (Basel).* 2023;16(4):1530.
16. Tang C, Ahmed MH, Yoshihara K, Peumans M, Van Meerbeek B. Multi-Parameter Characterization of HEMA/BPA-free 1- and 2-step Universal Adhesives Bonded to Dentin. *J Adhes Dent.* 2024;26:41-52.

