Side effects caused by biomaterials used in dentistry

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Abstract

Introduction: A dental biomaterial is any material used in dental practice, except drugs, that interact with living tissues and perform a particular function without causing local or systemic damage to the host, so the objective of this bibliographic review is to present the main adverse effects caused by the most used dental biomaterials in dentistry.**Methodology:** The search criteria complied with the Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols (PRISMA) guidelines. The following databases were searched: 1) MEDLINE through PubMed and 2) Elsevier through ScienceDirect. The strategy used was: (Biocompatible Dental Materials) AND (Side Effects).**Results:** Eight studies were included in the bibliographic review, seven in vitro studies and one in vivo study that analyzed the cytotoxicity of nine pulp capping materials, four obturation cements, four restorative base materials for subgingival margin elevation, seven universal adhesive systems, four indirect restorative materials, seven denture adhesives, two sodium fluoride varnishes, three direct restorative materials. All materials showed variable levels of cytotoxicity, from null to severe.**Conclusions:** The most biocompatible materials were ProRoot, BioRoot-RCS, Bulk Flow, Optibond Solo Plus, Adhese Universal, Vita Enamic, Lava Ultimate, Vita AC-12, InSync, Poligrip Flavor Free Fixative Cream Ketac Molar, Ionofil Molar, Twinky Star. While the least biocompatible were Biopulp, Durphat, Fixodent Pro Duo Protection and Fixodent Pro-Plus Duo Protection.

Key words: Dental biomaterials, cytotoxicity.

1.

2. Introduction

A dental biomaterial is any material used in dental practice, except drugs, which interact with living tissues and perform a particular function without causing both local and systemic damage to the host (1). An important part of the production process of dental biomaterials is the research, modification and improvement of these in search of the ideal materials for each clinical application. (2)

All biomaterials are subjected to various requirements due to their intimate relationship with living tissues, so all the factors involved in their use are analyzed, including the risks associated with their clinical use, their possible degradation products and sterilization residues, evaluating them throughout their useful life. Mainly their biological factors or acceptance of the organism, physicochemical or their resistance in good conditions are studied. Through the tests that are applied to them, a clear knowledge of the adverse reactions they produce is obtained, thus providing a regulation for their safe application avoiding any cytotoxic behavior. (1)(2)(3)

Cytotoxicity or cellular toxicity is defined as "adverse effects resulting from interference with cellular structure, processes, or both, that occur in all cells and are essential for cell functioning, survival, and proliferation (4)." Therefore, cytotoxicological and biocompatibility tests are essential in establishing the safety of a biomaterial, since they estimate the possible alterations that they could cause in basic cellular functions. According to European Directive 63/2010/EU, the application of in vitro cytotoxicological studies in cell cultures is recommended for its advantages over in vivo assays. (5)(6)

There is a wide range of dental biomaterials used daily in clinical practice, so the objective of this literature review is to present the main adverse effects caused by the most used dental biomaterials in the dental field.

3. Methodology

Protocol

The protocol was designed in accordance with Cochrane standards for systematic reviews. The search criteria met the Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols (PRISMA) guidelines.(7)

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Inclusion and exclusion criteria

The inclusion criteria were: studies published in the last 5 years, in vitro studies, studies conducted in Spanish, English or Portuguese, studies addressing adverse reactions caused by dental biomaterials.
The exclusion criteria were: studies older than 5 years, conducted on animals, studies in a language other than Spanish, English or Portuguese, theses and non-indexed articles.

Search strategy

We searched the following databases from 2017 to 17 June 2022: 1) MEDLINE via PubMed and 2) Elsevier via ScienceDirect. The search strategy used was: (Biocompatible Dental Materials) AND (Side Effects).

Study eligibility and data extraction

We screened the full texts of potentially relevant studies to support the greatest amount of information to enrich the research. A matrix was generated for data extraction from selected studies. The matrix is detailed in Figure 1.

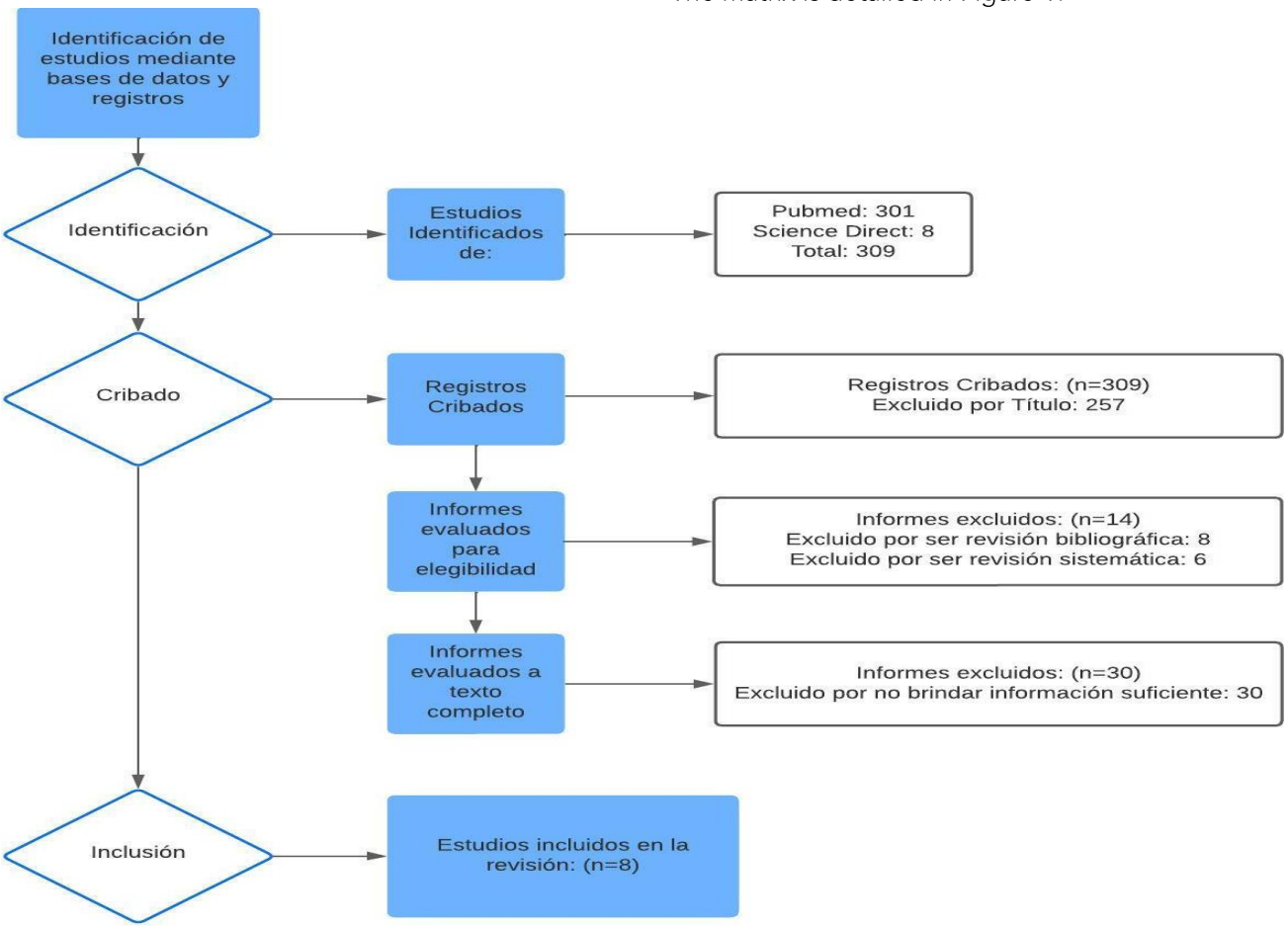

Figure 1. Selection matrix of scientific articles considered in the bibliographic review. Fountain. Own elaboration.

4. Results

The European Society for Biomaterials Consensus Conference defined dental biomaterials as "*a substance or material used alone or in the manufacture of a medical device designed to interact with human tissues in the monitoring of bodily functions or to treat some pathological condition of the body*",(8) these have the ability to induce an activity in biological systems so they must be biocompatible to integrate harmoniously into tissues. with whom you will be in contact. They must maintain their properties in the short and long term, not alter their physicochemical structure and be biostable, which implies that they meet a series of requirements before being launched on the market.(9)
A new biomaterial must undergo a series of tests that simulate the physiological environment, such as cell cultures, in vitro studies, biomechanical simulations, toxicological analysis, biocompatibility and use in animals, prior to approval for clinical use. The requirements that any biomaterial approved for human use must meet are: be biocompatible (biologically tolerated by the body), be insoluble in the oral environment, be aesthetic and anticariogenic but have adhesion and sealing, be non-toxic or carcinogenic, be chemically stable and resistant throughout the time of use, have an adequate design, size and shape. (9)
Dental biomaterials can be classified according to their composition into: organic, ceramic, plastic and metallic(10) . Knowledge of the adverse reactions of these materials allows rules to avoid their toxic behavior in the host. It is for this reason that in this bibliographic review eight studies have been compiled that cover the most used materials in each specialty of dentistry, highlighting their cytotoxic behavior.
Below are the studies that show the cytotoxicity of several biomaterials used in dentistry, and the branch of this science where they have application.

5. Endodontics

Luczaj-Cepowicz et al in their cytotoxicity evaluation study of nine pulp coating materials (MTA Angelus white (Angelus Ind. De Productos Odontologicos LTDA, Londrina-Parana, Brazil), MTA-Angelus (Angelus Ind. De Productos Odontologicos LTDA, Londrina-Parana, Brazil), ProRoot (Dental specialties of Dentsply Tulsa, Johnson City, TN, USA), ProRoot Regular (Densply Tulsa Dental Specialties, Johnson City, USA), Biopulp (Chema-Elektromet, Rzeszów, Poland), Calcipro (lege artis Pharma GmbH+Co., Dettenhausen, Germany), Calcipulpe (Septodont, Saint Maur des Fosses, France), Dycal (Dentsply De Tray GmbH, Constance, Germany) and Life (Kerr Italia Srl, Salerno, Italy)), applied to human gingival fibroblasts using culture plate inserts. It was found that after 3 hours of incubation, Angelus White and ProRoot showed no cytotoxicity. Regular ProRoot, Calcipulpe, Life and Dycal demonstrated mild cytotoxicity, Angelus and Calcipro a moderate cytotoxicity, and Biopulp was severely cytotoxic. After 24 hours of incubation none of the materials studied demonstrated severe cytotoxicity, ProRoot and Dycal were not cytotoxic, Angelus White, Calcipulpe, Life, Calcipro showed mild cytotoxicity and Angelus, ProRoot Regular and Biopulp a moderate cytotoxicity. It was also found that in both experimental periods (3 and 24 h) the gray forms of MTA demonstrated significantly higher cytotoxicity than the white forms (11).

In a study conducted by Jung S. et al. whose objective was to evaluate the cytotoxic effects of four different filling cements in human osteoblasts because they come into direct contact with the periapical tissue through the apical foramen, the cements evaluated were: based on epoxy resin (AH-Plus), one containing zinc oxide and eugenol (Pulp-Canal-Sealer) and two containing calcium silicate (MTA-Fillapex and BioRoot-RCS) in the freshly mixed state and Setting. It was shown that the AH-Plus cement was cytotoxic as soon as it was mixed, but not when setting, MTA-Fillapex and Pulp-Canal-Sealer presented cytotoxicity in both states, so contact with osteoblasts should be avoided when they are recently mixed, while BioRoot-RCS showed the lowest cytotoxicity in both states, being the one that presented bioactivity and biocompatibility (12).

6. Operating

According to Ismail H. et al. in the in vitro study in which they performed biocompatibility tests of different base materials used for the elevation of proximal subgingival margins in human gingival epithelial cells. The materials used were resin-modified glass ionomer (RMGI), glass hybrid (HV-GIC), fluid block filler resin composite (Bulk Flow) and bioactive ionic resin (Activa). They were evaluated for 24 or 72 hours. It was found that the block filler resin composite was the most biocompatible, followed by the bioactive composite, and with the lowest results the glass ionomer-based materials, especially those containing 2-hydroxyethyl methacrylate, however, all materials showed an increase in cell viability after 72 hours compared to 24 hours, indicating that its safety and biocompatibility may increase when placed under gingival tissues(13) .

Other important materials within the operative area are adhesive systems, so Pagano S. et al. in their study evaluates the cytotoxicity of universal dental adhesive systems through an evaluation of in vitro assays carried out in human gingival fibroblasts. Seven universal adhesives for enamel Ibond Universal (IB; Heraeus Kulzer, Hanau, Germany), Optibond Solo Plus (OB; Kerr Corporation, Orange, United States), Universal Bond (UB; Tokuyama Corporation, Tokyo, Japan), G-Bond Award (GPB; GC Corporation, Tokyo, Japan), Universal Adhese (AU; Ivoclar Vivadent, Amherst, NY, USA), Prime& Bond Active (PBA; Dentsply De Trey, Konstanz, Germany) and Futurabond M+ (FB; Voco GmbH, Germany), finding that Optibond Solo Plus (OB) and Universal Adhesive (UA) were the least cytotoxic and the cytotoxic effects of these adhesive systems are considered to be reduced in a dose-dependent manner(14) .

7. Prosthesis

Zaccaro M. et al. tested Vita Enamic (VITA Zahnfabrik, Bad Säckingen, Germany) (PICN nanohybrid fiberglass UDMA + TEGDMA), Lava Ultimate (3M ESPE, St. Paul, MN, USA) (UDMA compound dispersed filler), Vita AC-12 (VITA Zahnfabrik, Bad Säckingen, Germany) (CAD/CAM scale ceramics), and InSync (Chemical, Vaduz, Liechtenstein) (stratification ceramics) by means of a standardized multiparameter test in primary gingival fibroblasts, the elimination of toxic components by means of biological fluids was simulated by daily washing, resulting in the cytotoxicity being null all the materials submitted for evaluation, checking their safety to be used in intimate contact with soft tissues(15) .

Denture adhesives are commonly used, especially in the senile population, so López S. et al. conducted a study with the aim of analyzing the cytotoxicity of six adhesives positioned in the market: Poligrip Flavor Free Fixative Cream, Fixodent Pro Duo Protection, Novafix cream, FittyDent, Polident Total Action and Fixodent Pro-Plus Duo Protection, in human gingival cells. Among the main results obtained are that all adhesives produced a decrease in pH. Fixodent Pro Duo Protection and Fixodent Pro-Plus Duo Protection significantly decreased cell viability, while Polygrip Unflavored Fixing Cream showed the highest cell viability. Zinc-containing adhesives showed great decrease in cell viability, induced cells to apoptosis and their number was very small, with aberrant morphology and pyknotic nucleus. Finally, Fixodent significantly promoted the production of ROS (*"set of free radicals that have the ability to produce oxidative damage"*)(16) in gingival cells.(17)

8. Pediatric Dentistry

Prevention has become a priority for the field of oral health, especially focused on the child population, fluoride varnishes have provided great support in this task, so their biological effects have been studied.

Through an in vitro study, Escobar D. et al evaluated the cytotoxicity of two sodium fluoride varnishes (Duraphat and Clinpro White Varnish) each in two different concentrations, in fibroblasts of human primary pulp. The main findings found were that all varnishes analyzed produced changes in the mitochondria of fibroblasts, while Duraphat was the least biocompatible and induced a change in the number of mitochondria, decreasing them by up to 59(18) %.

On the other hand, despite the preventive measures taken in recent decades, one of the main reasons for consultation in pediatric dentistry is caries, so Gavic L. et al. conducted an in vivo study of the genotoxicity of several restorative materials in oral cells of children. The materials studied were: two glass ionomers (Ketac Molar and Ionofil Molar) and a compomer (Twinky Star), through a prospective longitudinal clinical study, it was determined that DNA damage occurs temporarily, but there is long-term biocompatibility (sample at 90 days) of all materials studied in pediatric use(19) .

When biomaterials generate adverse effects, a tissue reaction occurs and the surrounding tissue is affected due to the alteration of physiological cellular metabolism, for example, biomaterials made from metals can produce corrosion that induces chronic inflammatory reaction, the only way to avoid it is to use materials with high anticorrosive properties. On the other hand, ceramic-based materials do not usually present unwanted effects talking about biocompatibility and are not susceptible to microbial attack and the development of biomaterials based on bioceramics and bioglasses has begun. Biomaterials based on synthetic polymers generally have a good biocompatibility because they are biodegradable, but their behavior will also depend on their composition. Finally, materials of biological origin that are generally constituted by connective tissue may present as an adverse effect an immune response and its consequent rejection by the host.(9)

Table 1. It details the biomaterials mentioned in the previous sections, but focusing on the information on their direct application and the effect they generate.

Table 1. Biomaterials, application and adverse effects.

BIOMATERIAL	APPLICATION	SIDE EFFECTS
Angelus White	Pulp coating.	After 3 hours: showed no cytotoxicity. After 24 hours: showed mild cytotoxicity
ProRoot	Pulp coating.	After 3 hours: showed no cytotoxicity. After 24 hours: showed no cytotoxicity
ProRoot Regular	Pulp coating.	After 3 hours: showed slight cytotoxicity. After 24 hours: showed moderate cytotoxicity.
Calcipulpe	Pulp coating.	After 3 hours: showed slight cytotoxicity. After 24 hours: showed mild cytotoxicity.
Life	Pulp coating.	After 3 hours: showed slight cytotoxicity. After 24 hours: showed mild cytotoxicity
Dycal	Pulp coating.	After 3 hours: showed slight cytotoxicity. After 24 hours: showed no cytotoxicity
Angelus	Pulp coating.	After 3 hours: showed moderate cytotoxicity. After 24 hours: showed moderate cytotoxicity.
Calcipro	Pulp coating.	After 3 hours: showed moderate cytotoxicity. After 24 hours: showed mild cytotoxicity
Biopulp	Pulp coating.	After 3 hours: showed severe cytotoxicity. After 24 hours: showed moderate cytotoxicity.
AH-Plus	Sealing cement.	Barely mixed: it was cytotoxic Setting: non-cytotoxic
Pulp-Canal-Sealer	Sealing cement.	Barely mixed: it was cytotoxic Setting: cytotoxic
MTA-Fillapex	Sealing cement.	Barely mixed: it was cytotoxic Setting: cytotoxic
BioRoot-RCS	Sealing cement.	Barely mixed: low cytotoxicity Setting: low cytotoxicity Bioactivo y biocompatible.
RMGI	Elevation of subgingival margins. Glass ionomer modified with resin.	Lower biocompatibility. Increase in cell viability after 72 hours.
HV-GIC	Elevation of subgingival margins. Glass hybrid.	Lower biocompatibility. Increase in cell viability after 72 hours.
Bulk Flow	Elevation of subgingival margins. Fluid block filler resin compound.	Very biocompatible. Increase in cell viability after 72 hours.
Active	Elevation of subgingival margins. Bioactive ionic resin.	Biocompatible. Increase in cell viability after 72 hours.
Ibond Universal	Universal adhesive system	Cytotoxic effects are reduced in a dose-dependent manner.

Table 1. Biomaterials, application and adverse effects.		
Optibond Solo Plus	Universal adhesive system	Less cytotoxic. Cytotoxic effects are reduced in a dose-dependent manner.
Universal Bond	Universal adhesive system	Cytotoxic effects are reduced in a dose-dependent manner.
G-Bond Award	Universal adhesive system	Cytotoxic effects are reduced in a dose-dependent manner.
Adhese Universal	Universal adhesive system	Less cytotoxic. Cytotoxic effects are reduced in a dose-dependent manner.
Prime& Bond Active	Universal adhesive system	Cytotoxic effects are reduced in a dose-dependent manner.
Futurabond M+	Universal adhesive system	Cytotoxic effects are reduced in a dose-dependent manner.
Life Enamic	PICN nanohybrid fiberglass UDMA + TEGDMA	No cytotoxicity
Lava Ultimate	UDMA compound dispersed filler	No cytotoxicity
Life AC-12	Embedded CAD/CAM ceramics	No cytotoxicity
InSync	Stratification ceramics	No cytotoxicity
Poligrip Flavor Free Fixative Cream	Total prosthesis adhesive.	It produced a decrease in pH. Higher cell viability.
Fixodent Pro Duo Protection	Total prosthesis adhesive.	It produced a decrease in pH. Significantly decreased cell viability. They induced the cells to apoptosis, with aberrant morphology and pyknotic nucleus. It significantly promoted the production of ROS.
Novafix cream	Total prosthesis adhesive.	It produced a decrease in pH.
FittyDent	Total prosthesis adhesive.	It produced a decrease in pH.
Polident Total Action	Total prosthesis adhesive.	It produced a decrease in pH.
Fixodent Pro Plus Duo Protection	Total prosthesis adhesive.	It produced a decrease in pH. It significantly promoted the production of ROS. They induced the cells to apoptosis, with aberrant morphology and pyknotic nucleus Significantly decreased cell viability.
Duraphat	Sodium fluoride varnish.	Less biocompatible. The number of mitochondria in fibroblasts decreased.
Clinpro White Varnish	Sodium fluoride varnish.	Change in mitochondria
Ketac Molar	Restoration material. Glass ionomer.	Temporary DNA damage. Long-term biocompatibility.
Ionofil Molar	Restoration material. Glass ionomer.	Temporary DNA damage. Long-term biocompatibility.
Twinky Star	Restoration material. Composite.	Temporary DNA damage. Long-term biocompatibility.

Table 1. It presents a compendium of adverse effects and the use of the main biomaterials used in dentistry, detailing their cytotoxicity, biocompatibility and cell damage observed in the studies carried out. **Fountain.** Own elaboration.

9. Discussion

The results presented in this research may warn dental professionals of the use of several materials that were shown to have cytotoxic effects. Different dental biomaterials that have the same clinical application were compared in order to determine their toxic effects at the cellular level in tissues that will be in direct contact for long periods of time or that at some point in the clinical procedure could come into contact with them.

The studies were carried out under the European Directive 63/2010/EU regulation and were mostly in vitro tests on incubated cell cultures, as recommended, except for the analysis of restorative materials used in children, which was an in vivo study. According to ISO 10993, the endpoints must measure cell damage, evaluate damage morphologically, measure cell growth and metabolism. (6)(6) The biomaterials studied aimed at an endodontic application proved to have large variations in cytotoxicity according to its components, presenting variations between its behavior as soon as the mixture was made and when they were already in a setting state, confirming that the study of a biomaterial must be carried out throughout the useful life time to affirm its safety and analyze all its risks(11,12)(1). One of the main findings presented was that gray forms of MTA demonstrated significantly higher cytotoxicity than white forms regardless of the time elapsed since their application(11), complementing the evidence already widely reported by Vallés Rodriguez M. about its color instability since the application of gray MTA ends up compromising the

aesthetics of the treated dental organs, staining the dental crown with a grayish coloration. (20)

In the field of dental surgery the most used biomaterials are restorative materials and adhesive systems, in general, the filling materials studied presented a biocompatibility that increases over time, showing themselves safe for use, especially resinous biomaterials; However, the cytotoxicity of adhesive systems remains the subject of study as it has been shown that they could cause important alterations in the dynamics of the cellular cytoskeleton, but also coincide with the data presented in this research on the close dependence it has with the applied dose and time. Another factor that should be emphasized is that cytotoxicity is reduced when the material is photopolymerized. (13)(21)(14)(21)

The materials used for the indirect rehabilitation of dental organs that were analyzed in this study did not present cytotoxicity, being very beneficial to know that its application can occur without concerns in areas with direct contact to living oral tissues(15).

As for the adhesives of total prostheses, it was found that all those studied, caused a decrease in pH, thus altering the functioning of numerous enzymes, developing an unhealthy oral environment and facilitating the proliferation of aciduric microorganisms (17)(22). Those containing zinc proved to be the least biocompatible since they induced cell death, however a contradiction was found with a literature review that states that adhesives with zinc in their composition have no consequence in the body with moderate use, but if there is a high intake of this material for many years, It can cause a deficiency of copper in patients, as well as cases of gastric alterations have been reported due to its intake, so it is recommended to avoid adhesives that include this component. (17)(23)

The fluoride varnishes studied were shown to affect the normal activity and quantity of cellular mitochondria, and because mitochondria are "the (18)*cellular organelles that generate most of the chemical energy necessary to activate the biochemical reactions of the cell"* it (24) is recommended to carry out more studies on the cytotoxic effects of these materials especially focused on the child population, who are the target of this type of biomaterials.

The restorative materials studied, which were ionomers and compomers, proved to be safe and biocompatible in pediatric patients, guaranteeing their use without toxic effects, which results in a great advantage since according to several authors the main reason for consultation in pediatric dentistry is dental caries (19)(25). The issue of side effects caused by biomaterials used in dentistry is complex and multifaceted, and may be viewed differently depending on individual perspectives and beliefs

. Despite the use of biomaterials in dentistry being generally safe and effective, their potential side effects and uncertainty around their long-term effects highlight the relevance of neutrosophy's focus on uncertainty and imprecision(26)(27)(28)

10. Conclusions

Based on the evidence collected, it can be concluded that within the biomaterials studied:

- The pulp coating material that did not present cytotoxicity was ProRoot, while the most cytotoxic was Biopulp.
- Within the sealing cements, the least cytotoxic both freshly applied and in the setting state was BioRoot-RCS, presenting bioactivity and biocompatibility.
- Bulk Flow fluid block filler resin composite was the most biocompatible subgingival margin elevation material. All biomaterials showed an increase in cell viability after 72 hours of application.
- Optibond Solo Plus and Adhese Universal are the least cytotoxic universal adhesive systems. The cytotoxic effects of these materials are reduced in a dose-dependent manner.
- The restoration materials Vita Enamic, Lava Ultimate, Vita AC-12, InSync presented zero cytotoxicity, being totally safe for application near living tissues for prolonged times.
- All total prosthesis adhesives showed a decrease in pH. Poligrip Flavor Free Fixative Cream had a higher cell viability. Fixodent Pro Duo Protection and Fixodent Pro-Plus Duo Protection, which in their composition include zinc, significantly decreased cell viability, being the least recommended.
- Duraphat was the least biocompatible sodium fluoride varnish.
- For pediatric use Ketac Molar, Ionofil Molar, Twinky Star demonstrated their long-term biocompatibility, being safe materials.
- Biomaterials vary their cytotoxicity according to the time and state in which they occur.

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