

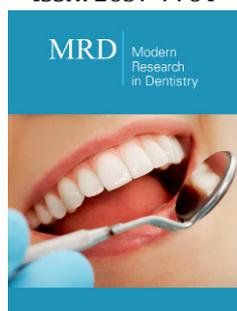
## Biocompatibility in Dentistry: A Mini Review

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### Abstract

The term “biocompatibility” has been gaining recognition, not only in medicine, but particularly in dentistry. It basically means, biocompatible materials should not have a negative impact on the recipient. Currently, there are literally thousands of different components that makeup the materials that are used in common dental procedures, with more being developed each year. Scientific literature is now reporting on the importance of using the most biocompatible material for the patient. Research is finding that not only using the least reactive material is important, but also how that material may interact with other materials that may have already been implanted into the oral cavity. Unfortunately, even today, dental procedures are often designed simply for the functionality of the treatment, or for cosmetic purposes, even though it is well established that all foreign materials introduced into the human body will elicit an immune response. Therefore, materials that are being used, which are not investigated for reactivity prior to treatment, pose a potential risk of toxicity, or allergic reaction to the individual patient. Since the mouth is considered the most hostile environment in the human body, it is critical to understand and evaluate the long-term effects of dental materials, since these materials are often used due their lasting durability.

**Keywords:** Biocompatibility; Dental materials; Mercury; Root canal; Titanium; Toxicity; Allergy

### Introduction

Dental amalgam, one of the oldest, most commonly used restorative treatments globally, is often referred to as “silver” fillings. They have been in existence for over 150 years and continue to be used throughout the world. Yet, the main component is approximately 50% mercury, in addition to silver, tin, zinc, and copper [1]. The World Health Organization has deemed mercury as one of the top ten chemicals of major concern. They have also identified the first route of human exposure to mercury, is actually coming from dental amalgam [2]. It has only been since the conclusion of the Minamata Convention on Mercury Treaty in 2013, that countries that are a party to the treaty, are now trying to end the use of dental amalgam [3]. Originally, aesthetics had been the main driver to non-mercury fillings, however, biological/holistic dentistry is now educating patients about the dangers of mercury exposure from dental amalgams, as well as the risks of other commonly used dental materials and procedures. Until recently, dental amalgam was considered inert, however, it is now known to off gas mercury vapor, as well as release particulate matter [4]. In some of the earlier published research on dental amalgam, it had been discovered that papers that found no correlation of risks from the exposure to mercury from dental amalgams, were deemed to be fraught with flaws [5]. Unfortunately, the American Dental Association’s (ADA) official Statement on Dental Amalgam, continues to deceptively refer to dental amalgam as, silver-colored fillings, even though the main ingredient is in fact, mercury. The ADA states: “Dental amalgam is considered a safe, affordable, and durable material that has been used to restore the teeth of more than 100 million Americans. It contains a mixture of metals such as silver, copper and tin, in addition to mercury, which binds these components into a hard, stable

and safe substance. Dental amalgam has been studied and reviewed extensively and has established a record of safety and effectiveness [6]. Mutter [7] responded to the European Commission Scientific Committee, whose branch identified as the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), stated "...no risks of adverse systemic effects exist, and the current use of dental amalgam does not pose a risk of systemic disease..." Mutter published a point-by-point analysis of the SCENIHR paper, and like his previous work cited [5], identified "severe methodical flaws". In the 295 referenced articles used in preparation of the research, autopsy studies were cited, noting that they are the most trustworthy for evaluating mercury levels in tissues. Mutter also provided research on the toxicity of mercury *in vitro* and *in vivo*. Additionally, he investigated mercury in dental amalgam and its relationship to Alzheimer's disease, maternal amalgam, mercury in infant tissue, and how that affects infant brain development. He also addressed the toxicity and synergistic effects of mercury with other heavy metals, such as lead. In closing, he stated that those in organized dentistry, are the only group of health care professionals who support the use of a product which is about 50% mercury [7].

### Root canal-endodontic treatment

According to the American Association of Endodontists (AAE), there are about 25 million root canal procedures performed annually, which is more than 41,000 a day. Root canal treatments are done by both, general dentists and endodontists [8]. In 2011, the AAE stated that bacteria are the main cause of pulpal and periapical disease, due to the intricacy of the root canal system. They observed that bacteria can be reduced using saline irrigation, but antibacterial irrigant are superior. However, none of the irrigant that they reported on, have all of the qualities of an ideal irrigant, with issues such as toxicity being a concern. They concluded that the quest for the perfect material and or technique, has yet to be found [9]. A meta-analysis was conducted on the biotoxicity of commonly used root canal sealers such as zinc oxide eugenol, calcium hydroxide, and resin-based sealers. The meta-analysis was performed by searching various online databases of peer-reviewed journals, between 2000 and 2012, and by comparing toxicity at 24 hours and between 3 and 7 days. Calcium hydroxide sealer and zinc oxide eugenol were found to be significantly biotoxic, as compared to resin-based sealers after 3 days. They stated that all of the current endodontic sealers are known to have some toxic properties [10]. Jung et al. [11] investigated the cytotoxic effects of four root canal sealers on human osteoblasts using the precise preparation protocols of the manufacturers. One epoxy resin-based (AH-Plus), one zinc oxide eugenol (Pulp-Canal-Sealer), and two calcium silicate containing sealers (MTA-Fillapex and BioRoot-RCS) were studied. They found BioRoot may be recommended for root canal obturation, showing the lowest toxicity in both a freshly mixed state and when the sealer was set. AH-Plus was cytotoxic in a freshly mixed state, but not when set. MTA-Fillapex and Pulp-Canal-Sealer were cytotoxic,

in both states. They recommended that contact of MTA-Fillapex and Pulp-Canal-Sealer or freshly mixed AH-Plus to osteoblasts should be averted [11]. In addition to the four sealers investigated by Jung et al. [11] & Poggio et al. [12] included the investigation of the cytotoxicity of four more root canal sealers, TotalFill BC Sealer, Sealapex, EasySeal, and N2, by incubating immortalized human gingival fibroblasts, over a period of 24, 48 and 72 hours. They stated that the biocompatibility of an endodontic sealer is the foundation for a positive treatment outcome, and healing of the periodontium. Again, the eight root canal sealers were prepared following the specific protocols of the manufacturers. Only BioRoot RCS, TotalFill BC Sealer and AH Plus showed no cytotoxic effects at least in the first 24h. The other sealers that were tested, revealed moderately or severely cytotoxic activity during all the extraction times [12]. A study by Bojar et al. [13] investigated Endodontic Cement N2<sup>®</sup>, which contains 50mg of paraformaldehyde in 1g of material. They stated that well established research has definitively confirmed that paraformaldehyde-containing filling materials and sealers, can not only cause permanent damage to tissues near the root canal system, but also other serious problems, such as chronic infections of the maxillary sinus. Specifically, they noted that the active ingredients of Endodontic Cement N2<sup>®</sup>, have been found in various parts of the body that infiltrated the blood, lymph nodes, adrenal glands, kidney, spleen, liver, and brain [13].

### Titanium implants

In 2014, the ADA had reported that there are over 5 million dental implants placed each year [14]. Like dental amalgam fillings, titanium implants are not inert and also contain other components, such as the heavy metals, aluminum and vanadium. Originally titanium was thought to be a biocompatible material, however, new research is finding that exposure to titanium nanoparticles can cause DNA damage and cell death in a dose dependent manner [15]. Due to harsh oral conditions, corrosion of metals does occur, especially when there are various metals present. Not only can this corrosion affect the integrity of the implant, but it can also cause a cytotoxic or neoplastic effect on the tissue encompassing the implant. Exposure to these various metals have been shown to cause serious health consequences [16]. Other environmental factors can cause considerable corrosion, such as low pH or high concentrations of fluoride. Using SEM imaging, Penarrieto-Juanito et al. studied ion releases from dental implants when exposed to fluoride and hydrogen peroxide. They found excessive oxidation in the implant-abutment joint surfaces and the discharge of titanium, aluminum and vanadium after being submerged in 1.23% sodium fluoride gel, while minimal corrosion was detected in the hydrogen peroxide environment [17]. Another risk factor is the formation of biofilm on the surface of implants and prostheses, which may increase the risk of biological complications. Both peri-implant mucositis and peri-implantitis are biofilm-related diseases that can result primarily because of an individual's vulnerability, as well as

other factors such as smoking, oral hygiene or systemic conditions. Monitoring oral biofilm is critical because it can determine the success or failure of implant treatments. The two most significant standards that should be met in dental implantology are, superior biocompatibility and superior resistance to microbial colonization [18]. Regrettably, while material studies are done prior to availability in the marketplace, long term effects are unavailable. Since dental amalgam and titanium implants have now been used for a very long time, the current research which includes case studies, are now showing negative health consequences from that exposure. Internal and external exposure to metals can also cause allergic reactions, which is why biocompatibility testing is essential to achieve the best outcome for the patient [19].

### Biocompatibility of dental materials

In 1984, the International Organization for Standardization (ISO) Technical Report 7405, implemented the following series of tests to assess dental materials, the first tests were for cytotoxicity and mutagenicity, followed by sensitization, implantation tests, mucosal irritation, and usage. The relevancy of biocompatibility for dentists includes first and foremost, the patient's safety, the dental workers safety, regulatory compliance issues, and legal liability [20]. A systematic review was conducted between 1996-2006 by Schedle et al. [21] to discover the adverse effects of dental materials. Patients and dental personnel were analyzed separately. The principal materials linked to adverse and occupational effects were polymer-based materials, natural rubber latex, alloys used in prosthodontics, orthodontics, and amalgam. Colophony, eugenol, and other materials also had the ability to generate an adverse reaction. Due to dental workers constant contact with these materials, their risks from exposure are believed to be higher [21]. According to Wataha [22] due to the complexity of measuring the biocompatibility of materials *in vivo* and *in vitro*, greater understanding of biologic responses is possible, but not 100% certain. Additionally, problems with biocompatibility of materials can lead to legal liabilities for the dentist [20,22].

Shahi et al. [23] also identified a plethora of dental materials that have the potential to be toxic to humans such as filling materials, restorative materials, intracanal medicines, prosthetic materials, various implants, liners, and irrigant. They stated that while clinical advantages of using composite resin is possible, due to the risk of toxicity, they may not always be suitable. For example, Bisphenol A (BPA) has been identified as being toxic and should be avoided [23]. According to Scoipan et al. [24] dental implants may cause inflammation, which in turn can affect the immune system. They noted that a study of 56 patients with titanium implants developed nonspecific symptoms, such as joint or muscle pain, neuralgia, chronic fatigue syndrome, neurological disorders, or psychiatric disorders. They concluded that more *in vitro* studies and clinical trials are needed, and it is imperative to test materials

prior to treatment [24]. Exposure from mercury in dental amalgam and the role of apolipoprotein E (ApoE) gene, has been identified as a genetic risk factor in the development of late onset Alzheimer's disease. Dental amalgam exposure in genotypes: (epsilon 3/epsilon 4 and epsilon 4/epsilon 4) would have decreased ability to bind or chelate the metal compared to individuals presenting the ApoE2 or ApoE3 isoforms. In children, several studies have found that exposure to dental amalgam caused neurobehavioral function such as learning, memory, attention and motor coordination of those that are carriers of ApoE4 [25]. In 2002, Noda et al. [26] stated that it widely reported that dental materials degrade in the oral cavity. The chronic low dose exposure releases components, and cell damage may occur if there is a secondary exposure. This chronic exposure must be considered, even if initially, no obvious negative effect is observed [26]. A systematic review by Caldas et al. investigated the *in vitro* cytotoxicity of dental adhesives to discover if self-etch adhesives or etch- and-rinse systems are the most cytotoxic. They found that only four studies confirmed the use of standardized methods recognized by ISO. The lack of ISO standards hampered the establishment of the link between the type of dental adhesives and their toxicity. However, the studies using dentin barriers showed greater cytotoxicity for etch-and-rinse adhesives. They stated that it is necessary for both dental adhesives and dental materials in general to have a standardized exposure protocol to assess toxicity and safety [27]. Williams [28] opined that "biocompatibility is an acceptable term, but that it subsumes a variety of mechanisms of interaction between biomaterials and tissues or tissue components and can only be considered in the context of the characteristics of both the material and the biological host within which it placed. De facto it is a property of a system and not of a material. It follows that there can be no such thing as a biocompatible material." He also stated that, "the phrase 'intrinsically biocompatible system' would be the most appropriate [28]."

### Conclusion

New dental materials are constantly being created, it is understood that the negative impact that may develop over time is not known, until the material can be studied years or even decades later. This is why it is prudent to follow the precautionary principal and not guess which is the "best" restorative materials to use on the patient. The importance of knowing what materials to use prior to treatment, and how to protect the patient when removing any dental material, especially any type of metal restoration due to the exposure of particulate matter, is extremely important. Using strict protocols in all of these procedures and or processes and most importantly to perform biocompatibility testing to ensure that the restoration is the least reactive specifically for the individual patient, is essential. Sadly, much of the current research does not look at long term exposure of dental materials, which due to the continuous wear and tear, breaks down and can translocate to various organs far from the oral cavity. Several of the studies

mentioned above were investigated for only one day to several days, while this may be an indicator of the potential biocompatibility of a particular material, it doesn't tell the whole story. Regrettably, the dentist is not looking at the etiological harm from the toxicity of dental materials, therefore, it is not reported as a possible cause of disease manifestation. Since dental amalgam has not been banned globally, an ApoE genetic test should be done, prior to its use. Dental amalgam absolutely should not be used on those who are ApoE4 carriers, thus, by proper testing they would avoid a lifetime of mercury exposure and the negative health problems that it can cause. With the aging global population, testing for this genetic predisposition can potentially alter an otherwise poor outcome, to a positive one, and at the very least, removing the mercury amalgam fillings will stop the exposure. Ultimately bringing awareness of the potential harm that can be caused by dental materials is imperative, not only from the exposure to the dental workers, but also to the consumers. Fortunately, there are tests available so that the doctor can choose the proper restorative materials, because there is no one size fits all dental material.

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