

Titanium Exposure and its Effect on Human Health

Purpose of Scientific Review: to provide guidance for dentists, physicians and other health care providers for the rational scientific clinical application of biocompatible products, procedures, equipment, or information in dentistry for those who request such care or information. As new research is available, the Scientific Review may be changed.

Should the IAOMT position be to: **Provisionally Approve** **Approve** **No Opinion** **No Approval**

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Re evaluation	No Approval

Explanation of IAOMT position: This work comprises a valuable addition of science on the use of Titanium on the human body. The most toxic interactions appear to be the nanoparticulate use followed by its electrochemical interactions and lastly by its immunological impact. The IAOMT position is to be cautious in its use as much as is reasonable and encourage sensitivity testing before using it internally in the human body. Avoidance where other reasonable options exist would be a wise use of the precautionary principle.

Name of SR: Titanium Exposure and its Effect on Human Health	
Alternative name(s) of SR: None	
What is this SR related to?	Dentistry and Medicine
Is this SR of a Product/Procedure?	Product
Do you have a vested financial interest in any part of this SR? NO	
Purpose of the SR: The purpose of the paper is to analyze the potential human health risks of titanium exposure as a result of its use in dental and medical products.	
SR History: Titanium (Ti) has been used in dental and medical products due to its strength, light	

weight, and cost-effectiveness, as well as its touted corrosion resistant and antimicrobial properties. The IAOMT does not currently have a review on the subject. This literature review outlines recently published papers on the risks of titanium, including those from titanium-containing dental implants, which can be regarded as a relatively new field of study. *Note that titanium implants contain a different form of titanium than nanoparticles (TiO₂) but that consumers can potentially be exposed to both of these forms of titanium.*

Briefly describe the SR: This paper serves as a review of titanium (Ti) and its potentially adverse impacts on the human body from its use in dentistry and medicine. The following health effects of Ti are categorized in this SR based on the information described in recent literature:

1. Ti is linked to hypersensitivity, allergy, and corrosion of patients' dental implants.

- a) Ti can trigger clinically significant hypersensitivity and other immune problems in certain individuals (Vijayaraghavan et al., 2012).
- b) Researchers have warned clinicians about allergic reactions to Ti implants (Chaturvedi, 2013; Goutam et al., 2014) and documented such reactions in patients (Pigatto et al., 2011; Pigatto et al., 2014).
- c) Electrochemical activities in the oral cavity can be related to Ti (Goutam et al., 2014; Wachi et al., 2015), and corrosion is known to occur with dental implants (Chaturvedi, 2013; Vijayaraghavan et al., 2012; Pigatto et al., 2014).

2. Radiation Scattering of Ti: Significant radiation scattering can occur when Ti dental implants are irradiated, and such scattering has been associated with osteoradionecrosis (Friedrich et al., 2010; Friedrich et al., 2012).

3. Other considerations related to Ti include the following:

- a) Ti is present in the endodontic material MTA Fillapex (Angelus-MTA Fillapex Scientific Profile; Borges, 2014), and a number of root canal sealers have been shown to be cytotoxic to human cultures and cells (Huang et al., 2002).
- b) An interaction between fluoride and Ti has been reported (Noguti et al., 2012).
- c) Because smoking has been linked to bacteria at implants (Eick et al., 2015), an interaction of smoking and Ti should be considered.
- d) Ti is a known cause of yellow nail syndrome (Berglund and Carlmark, 2011).

4. Nanoparticles (NPs): Titanium dioxide (TiO₂) is a form of NPs used in consumer products.

- a) There is confusion over the definition of nanoparticles (USFDA, 2015) and questions from the U.S. Food and Drug Administration about the safety of NPs (USFDA, 2014).
- b) NPs in general appear to aggravate pathologies in disease models (Fröhlich, 2015).
- c) Titanium dioxide (TiO₂) NPs are considered a possible source of oral toxicity (Bettini and Houdeau, 2014).
- d) Fetuses and children may experience high cumulative doses of TiO₂ NPs that are potentially toxic to the developing nervous system (Rollerova et al. 2015).
- e) Inhalation of TiO₂ may increase the risks from respiratory illnesses such as asthma, according to a recent animal study (Jonasson et al., 2013).
- f) Animal studies also suggest that TiO₂ NPs can impact liver and heart tissues (Husain et al., 2015; Liu et al., 2009).
- g) NPs of TiO₂ can cause risk to the brain and other areas of the body due to oxidative stress (Long et al., 2006).

Specifically, by outline if appropriate, describe the SR:

1. Ti is linked to hypersensitivity, allergy, and corrosion of patients' dental implants.

- a) Ti can trigger clinically significant hypersensitivity and other immune problems in certain individuals (Vijayaraghavan et al., 2012).

Skin rashes, immune system difficulties, and implant failure have been examined in allergic patients with type IV or I reactions triggered by metal dental implants (Sicilia et al., 2008). Scientists summarized this issue as it relates to titanium in their 2012 article published in the *Journal of the Indian Prosthodontic Society*: “Literature suggests that Ti can induce clinically relevant hypersensitivity and other immune dysfunctions in certain patients chronically exposed to this reactive metal” (Vijayaraghavan et al., 2012).

- b) Researchers have warned clinicians about allergic reactions to Ti implants (Chaturvedi, 2013; Goutam et al., 2014) and documented such reactions in patients (Pigatto et al., 2011; Pigatto et al., 2014).

Titanium has been linked to allergic reactions. In 2013, researchers cautioned: “Although titanium is the preferred choice for dental implants as it is an inert material, if used in oral implants, it may encourage toxic or allergic type I or IV reactions” (Chaturvedi, 2013).

Citing evidence that titanium ions can collect in tissues around implants and other areas such as the lymph nodes and lungs, Goutam et al. wrote in a 2014 review: “An allergic reaction can be reasonably suspected after dental implant placement, on the basis of signs or symptoms associated with allergy, such as rash, urticaria, pruritus, swelling in the orofacial region, oral or facial erythema, eczematous lesions of the cheeks or hyperplastic lesions of soft tissue (the peri-implant mucosa)” (Goutam et al., 2014).

Indeed, allergic reactions have been documented in patients with titanium implants. In 2011, Pigatto et al. discussed allergies to intra-oral metals as a potential factor in exfoliative cheilitis, a rare but chronic inflammation of the lips. They reported that a patient possibly suffered from exfoliative cheilitis as a reaction caused by a mercury amalgam filling placed near a titanium dental implant (Pigatto et al., 2011). The researchers even cautioned clinicians not to place titanium dental implants near amalgam fillings, including amalgam used as a root-end filling (Pigatto et al., 2011).

In another case, Pigatto et al. noted that the removal of a mercury amalgam filling and a gold/palladium crown from the top of a dental titanium implant resulted in the resolution of a patient's contact dermatitis and the reduction of an “intra-oral electrochemical process” likely linked to the release of metal ions (Pigatto et al., 2014).

- c) Electrochemical activities in the oral cavity can be related to Ti (Goutam et al., 2014; Wachi et al., 2015), and corrosion is known to occur with dental implants (Chaturvedi, 2013; Vijayaraghavan et al., 2012; Pigatto et al., 2014).

Titanium ions are known to collect in tissues within proximity to implants. Goutam et al. specifically explained that “it has been proven that titanium ions concentrate in tissues surrounding dental and orthopedic implants, as well as in regional lymph nodes and

pulmonary tissue” (Goutam et al., 2014).

Research has related Ti ions to other implant issues as well. In 2015, Wachi et al. found: “Ti ions may be involved in the deteriorating effects of peri-implant mucositis, which can develop into peri-implantitis accompanied by alveolar bone resorption” (Wachi et al., 2015).

Corrosion of dental implants has been examined in numerous scientific articles, such as several of those mentioned in this specific scientific review (Chaturvedi, 2013; Vijayaraghavan et al., 2012; Pigatto et al., 2014). Furthermore, allergy to Ti has been mentioned as a possible reason for implant failure (Chaturvedi, 2013).

2. Radiation Scattering of Ti: Significant radiation scattering can occur when Ti dental implants are irradiated, and such scattering has been associated with osteoradionecrosis (Friedrich et al., 2010; Friedrich et al., 2012).

A study about radiation therapy and dental implants resulted in the researchers reporting: “Studies from both animal subjects and human patients indicate that irradiated bone has a greater risk of implant failure than nonirradiated bone” (Idhe et al., 2009). While these same researchers found the risk from irradiated bone up to 12 times more than nonirradiated bone, they also mentioned that quality improvement is required for studies making such a comparison (Idhe et al., 2009).

This issue was directly related to titanium dental implants by Friedrich et al. in 2010. The researchers of this study stated: “Titanium dental implants in the field of irradiation were capable of causing significant radiation scattering” (Friedrich et al., 2010). Furthermore, they cautioned, “Radiotherapy planning has to consider metallic implants in the irradiation field as a source of significant radiation scattering affecting adjacent soft tissues and bones. This effect may contribute to pathological processes in the bone and adjacent tissues, resulting in osteoradionecrosis” (Friedrich et al., 2010).

3. Other considerations related to Ti include the following:

- a) Ti has been detected in the endodontic material MTA Fillapex (Angelus-MTA Fillapex Scientific Profile; Borges, 2014), and a number of root canal sealers have been shown to be cytotoxic to human cultures and cells (Huang et al., 2002).

The hazards of root canal sealers and other endodontic materials must be taken into regard when evaluating the risks and benefits of using a dental material such as Ti. Other than implants, data demonstrates that Ti is present in MTA Fillapex (Angelus-MTA Fillapex Scientific Profile; Borges, 2014). Because a number of root canal sealers have been shown to be cytotoxic to human cultures and cells (Huang et al., 2002), the potentially hazardous interaction of all of these materials should be taken into account, and forthcoming literature about this possible danger should be open to review.

- b) An interaction between fluoride and Ti has been reported (Noguti et al., 2012).

Fluoride can interact with Ti, as Noguti et al. established in a 2012 study: “These data demonstrate noxious effects induced by high fluoride concentration as well as low pH in the oral cavity. Therefore, such conditions should be considered when prophylactic actions are administrated in patients containing titanium implants or other dental devices” (Noguti et al., 2012).

- c) Because smoking has been linked to bacteria at implants (Eick et al., 2015), an interaction of smoking and Ti must be considered.

More specifically, Eick et al. wrote in their 10-year retrospective study published in 2015: “Smoking and periodontal disease are risk factors for colonization of periodontopathic bacteria at implants” (Eick et al., 2015). This clearly relates to Ti implants and must be valued as an essential factor in evaluating the risks of Ti.

- d) Ti is a known cause of yellow nail syndrome (Berglund and Carlmark, 2011).

In 2011, Berglund and Carlmark clearly stated that yellow nail syndrome is caused by titanium, and the researchers linked the syndrome to “galvanic release of titanium ions by other metals or by the oxidative release of titanium ions by fluorides or by the uptake of titanium dioxide from the digestive tract. Presence of titanium in the nails confirms the diagnosis, even in the absence of characteristic nail changes” (Berglund and Carlmark, 2011).

4. Nanoparticles (NPs): Titanium dioxide (TiO₂) is a form of NPs used in consumer products.

- a) There is confusion over the definition of nanoparticles (USFDA, 2015) and questions from the U.S. Food and Drug Administration about the safety of NPs (USFDA, 2014).

Nanotechnology is used to manipulate materials to very small sizes, but the FDA does not have a legal definition of this technology as of yet (USFDA, 2015). The FDA states that “use of nanomaterials in cosmetic products may raise questions about the safety of the product for its intended use” (USFDA, 2014).

The cytotoxicity of Ti particles has been related to their size in at least one study. Kumazawa et al. stated in their 2002 study: “These results showed that the cytotoxic effect of Ti particles is size dependent, and that they must be smaller than that of cells” (Kumazawa et al., 2002).

- b) NPs in general appear to aggravate pathologies in disease models (Fröhlich, 2015).

The author of a 2015 review of a number of carbon, metal, and metal oxide NPs explained: “Nanoparticles (NPs) present in the environment and in consumer products can cause immunotoxic effects” (Fröhlich, 2015). The researcher also observed: “NPs appear to induce a specific immunotoxic pattern consisting of the induction of inflammation in normal animals and aggravation of pathologies in disease models” (Fröhlich, 2015).

- c) Titanium dioxide (TiO₂) NPs are considered a possible source of oral toxicity (Bettini and Houdeau, 2014).

In 2014, using the example of TiO₂, researchers established the dangers of oral toxicity from NPs in consumer products. They wrote, “As we are faced with the exponential use of nanomaterials in consumer products, including food, the consequences of daily exposure to nanoparticles at low doses set public health issues for humans... The oral and gastrointestinal mucosa are the first regions in contact with the ingested nanoparticles. The latter cross these biological barriers, and distribute to the systemic compartment” (Bettini and Houdeau, 2014).

- d) Fetuses and children may experience high cumulative doses of TiO₂ NPs that are potentially toxic to the developing nervous system (Rollerova et al. 2015).

In their 2015 review, Rollerova et al. studied the possible risks from TiO₂, especially to the nervous system. They warned, “Therefore, from the developmental point of view, there is a raising concern in the exposure to TiO₂ NPs during critical windows, in the pregnancy or the lactation period, and the fact that human mothers, women and men in fertile age and last but not least children may be exposed to high cumulative doses” (Rollerova et al., 2015).

- e) Inhalation of TiO₂ may increase the risks from respiratory illnesses such as asthma, according to a recent animal study (Jonasson et al., 2013).

In an animal study published in 2013, Jonasson et al. concluded that “inhalation of TiO₂ may aggravate respiratory diseases and that the adverse health effects are highly dependent on dose and timing of exposure” (Jonasson et al., 2013). They further noted, “Our data imply that inhalation of NPs may increase the risk for individuals with allergic airway disease to develop symptoms of severe asthma” (Jonasson et al., 2013).

- f) Animal studies also suggest that TiO₂ NPs can impact liver and heart tissues (Husain et al., 2015; Liu et al., 2009).

A study on mice published in 2015 found dangers to several organs after TiO₂ NPs entered the lungs. Husain et al. explained, “This study characterizes the subtle systemic effects that occur in liver and heart tissues following pulmonary exposure and low levels of translocation of nano-TiO₂ from lungs” (Husain et al., 2015). Additional description from these same researchers provided details of this potentially hazardous effect:

We further show that acute translocation of particles to blood and other organs coincides with induction of an innate immune type response, which includes activation of acute stress response in liver, C3 activation in blood and the activation of complement cascade and inflammation response in the heart tissue, all of which are involved in particle recognition and clearance. (Husain et al., 2015)

Researchers had found relevant results of this same effect in a 2009 study. When Liu et al. injected mice with high doses of TiO₂, their data produced the following outcome:

The results showed that, with increasing doses of nano-anatase TiO₂, the coefficients of liver, kidney, and spleen increased gradually, while the coefficients of lung and brain decreased gradually, and the coefficient of heart had little change. The order of the titanium accumulation in the organs was liver > kidneys > spleen > lung > brain > heart.
(Liu et al., 2009)

- e) NPs of TiO₂ can cause risk to the brain and other areas of the body due to oxidative stress (Long et al., 2006).

Obviously, Ti is likely associated with a number of other conditions that research will continue to reveal. One other area that merits mention is the potential for NPs of TiO₂ to impact the brain and other regions of the body. For example, Long et al. wrote in 2006:

Nanosize titanium dioxide (TiO₂) is used in air and water remediation and in numerous products designed for direct human use and consumption. Its effectiveness in deactivating pollutants and killing microorganisms relates to photoactivation and the resulting free radical activity. This property, coupled with its multiple potential exposure routes, indicates that nanosize TiO₂ could pose a risk to biological targets that are sensitive to oxidative stress damage (e.g., brain).
(Long et al., 2006)

3. Conclusion

This review reports the evidence of some of the potential negative impacts on human health when patients are exposed to various forms of titanium, including the titanium used in dental and medical devices and the TiO₂ used in NPs.

Recommendations

1. Identify Ti exposures in humans, with special regard for dental exposures serving as only part of the total Ti exposures to patients/consumers.
2. Evaluate the emerging potential health risks of Ti as reported in scientific literature. Areas to be notably considered should include the use of Ti in implants and TiO₂ in NPs, as well as Ti's interaction with other substances, particularly those used in dental and medical practices.
3. Consider the benefits of avoiding the use of titanium-containing products in medicine and dentistry due to the potential danger to patients' health.
4. Use allergy testing to assist in pre-determining patients' allergic susceptibility to Ti.

Legal Aspects of this SR: "N/A"

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