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Oral Health & Dental Science

Will the US Food and Drug Administration (FDA) Follow the EU's Mercury Dental Amalgam Ban? A Mini-Review

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ABSTRACT

The European Union's comprehensive ban on mercury dental amalgam, effective January 1, 2025, marks a pivotal step toward eliminating a known neurotoxin from dentistry, aligning with the Minamata Convention on Mercury's goal to "Make Mercury History". In contrast, the United States, despite ratifying the treaty in 2013, permits the continued use of mercury dental amalgam, a material deceptively called "silver fillings" despite its approximately 50% mercury content. The U.S. Food and Drug Administration (FDA), a global leader in health policy, maintains a contradictory stance: acknowledging mercury's risks for vulnerable populations while resisting mandatory patient disclosures and a phase-out. This regulatory failure, challenged by legal actions, peer-reviewed studies, and advocacy groups, undermines informed consent, exacerbates health inequities, and hinders global mercury reduction efforts. This mini-review examines the FDA's policies, emphasizing its refusal to mandate disclosures, the health risks of mercury dental amalgam, and the necessity of safe removal protocols. Drawing on recent scientific evidence and international benchmarks, we argue for urgent reform to protect public health, the environment and align with global standards.

Keywords

Mercury dental amalgam, Minamata Convention on Mercury, Food and Drug Administration, Informed consent.

Abbreviations

FDA: Food and Drug Administration; GRAS: Generally Recognized as Safe; POTWs: Publicly Owned Treatment Works; EPA: Environmental Protection Agency; ApoE4: Apolipoprotein E4; CPOX4: Coproporphyrinogen Oxidase; NHANES: National Health and Nutrition Examination Survey; ART: Atraumatic Restorative Treatment; IAOMT: International Academy of Oral Medicine and Toxicology; IABDM: International Academy of Biological Dentistry and Medicine.

Introduction

Mercury dental amalgam, comprising approximately 50% elemental mercury, has been used in restorative dentistry for over 150 years. Often called "silver fillings" due to its metallic appearance, this nomenclature obscures their neurotoxic mercury content, misleading patients and undermining informed consent [1]. The U.S. Food and Drug Administration (FDA), a global benchmark for regulatory oversight, has failed to adequately address these risks, despite mounting incontrovertible scientific evidence and legal challenges. In 1976, the FDA classified mercury dental amalgam as "Generally Recognized as Safe (GRAS)" without the current standard of rigorous safety testing, a decision that continues to shape its permissive stance [2].

The Minamata Convention on Mercury Treaty, effective since 2017, mandates a global phase-down of mercury-containing products, including mercury dental amalgam [3]. In 2021, the US Department of State submitted the first national report from the United States to the Minamata Convention on Mercury Treaty. This report consisted of party measures for mercury-added products in Part II of Annex A, specifically related to mercury dental amalgam, which included:

i. Setting national objectives aiming at dental caries prevention and health promotion, thereby minimizing the need for dental

restoration;

ii. Promoting research and development of quality mercury-free materials for dental restoration;

iii. Encouraging representative professional organizations and dental schools to educate and train dental professionals and students on the use of mercury-free dental restoration alternatives and on promoting best management practices; and

iv. Promoting the use of best environmental practices in dental facilities to reduce releases of mercury and mercury compounds to water and land [4]."

Additionally, the US Environmental Protection Agency (EPA) has identified that dental clinics are "the main source of mercury discharge to publicly owned treatment works (POTWs) [5]. The EPA had implemented mandatory mercury amalgam separators to be installed with the final rule going into effect in 2017. It became compulsory on July 14, 2020, to comply with this rule [6,7]. Over 30 countries, including those with populations exceeding 100 million, have implemented bans, with the European Union enforcing a comprehensive ban on mercury dental amalgam as of January 1, 2025, except in specific medical cases [7]. The United States, the first nation to ratify the treaty, has made no progress toward elimination, perpetuating exposure to a known neurotoxin implanted in tens of millions of patients [4]. Despite these environmental measures, the FDA's endorsement of mercury dental amalgam and refusal to mandate patient disclosures represent a profound regulatory failure, compromising public health and global mercury reduction efforts.

This mini-review evaluates the FDA's policies, focusing on its refusal to mandate patient disclosures, the health risks of mercury dental amalgam, and the critical need for safe removal protocols. By integrating recent peer-reviewed studies, legal critiques, and international benchmarks, it is necessary for immediate reform to align with the Minamata Convention and protect vulnerable populations.

Food and Drug Administration (FDA)

The FDA's mission is to ensure the safety, efficacy, and security of medical devices, including mercury dental amalgam [8]. Until 2009, it classified mercury dental amalgam as a Class I device (low risk), requiring minimal oversight [9]. In response to a citizen's petition submitted by attorney James Love, on behalf of various petitioners, the FDA reclassified amalgam as Class II in 2009, acknowledging risks for vulnerable populations, including pregnant women, children, and individuals with genetic predispositions such as apolipoprotein E4 (ApoE4) or coproporphyrinogen oxidase (CPOX4) variants [7,10-12]. These genetic factors, present in approximately 25% and 28% of the global population, respectively, increase susceptibility to mercury toxicity, with ApoE4 linked to Alzheimer's disease and CPOX4 associated with neurobehavioral deficits. A 2010 Scientific Advisory Panel recommended warnings for these groups, but the FDA took no action, a decision later exposed by a 2015 McClatchy investigation as influenced by a Department of Health and Human Services cost-benefit analysis prioritizing economic factors over health [13].

The US national report to the Minamata Convention cited the updated FDA "Recommendations for Certain High-Risk Groups Regarding Mercury-Containing Dental Amalgam." They remarked that some people may be at higher risk for adverse health effects from mercury exposure. While also stated, "Although the majority of evidence suggests exposure to mercury from dental amalgam does not lead to negative health effects in the general population, little to no information is known about the effect this exposure may have on members of the specific groups who may be at greater risk to potential negative health effects of mercury exposure [4]." This statement is false due to the enormous amount of seminal studies of evidence-based scientific research that have been published on the risks of exposure to mercury dental amalgams going back over a century. For example, a simple keyword search of "risks of mercury dental amalgam" on Google Scholar yielded over 15,000 results in 0.14 seconds [14]. A plethora of peer-reviewed scientific papers on mercury dental amalgam continue to be published and cited worldwide. These papers are irrefutable, demonstrating not only the extensive research on mercury dental amalgam risks but also the negative health effects they cause [15-22].

In 2020, the FDA issued non-binding recommendations acknowledging risks for high-risk groups, including pregnant women, children under six, and those with neurological or renal impairments, but continued to emphasize mercury dental amalgam durability and cost-effectiveness [23,24]. These recommendations fall short of a ban or mandatory disclosures, ignoring safer alternatives like Atraumatic Restorative Treatment (ART) and composite resins [7]. Dr. Anne Summers' 2019 critique (Docket ID: FDA-2019-N-3767) to the FDA's Immunology Devices Panel highlighted critical data gaps in its safety assessment: (1) ignoring epidemiological evidence of elevated mercury levels, (2) overlooking cumulative toxicity in adults and the elderly, (3) underestimating mercury's transformation into toxic forms, and (4) neglecting its role in promoting antibiotic-resistant bacteria [25]. Wiggins et al. linked mercury exposure to multi-antibiotic resistance, a global health crisis costing billions annually [26]. Recent studies, such as Geier et al., further associate mercury dental amalgam with arthritis, with higher incidences in individuals with 4–7 amalgam surfaces, reinforcing the FDA's underestimation of systemic risks [27]. These omissions, coupled with reliance on outdated methodologies, highlight the FDA's regulatory inaction.

FDA's Failure to Mandate Patient Disclosures

The FDA's refusal to mandate patient disclosures about mercury risks in mercury dental amalgam, often misleadingly called "silver fillings," is a critical regulatory failure that undermines informed consent. In its 2009 ruling, the FDA stated:

"FDA believes that the recommended labeling statements in the special controls guidance document will provide dentists with important information that will improve their understanding of the devices and help them make appropriate treatment decisions with their patients. In addition, FDA notes that dental amalgam

is a prescription device and, therefore, patients cannot receive the device without the involvement of a learned intermediary, the dental professional. Based on the reasons described above, FDA has concluded that it is not necessary to require that dentists provide this information to patients in order to provide reasonable assurance of the safety and effectiveness of the device". The FDA further asserts that "after consideration, and based on all available scientific evidence, including evidence submitted in your Petitions, FDA does not believe it is necessary or appropriate to require that dental health care providers provide this information to patients" [28].

This position is scientifically and ethically indefensible. First, the FDA's reliance on dentists as "learned intermediaries" assumes uniform competence, contradicted by studies showing many dental professionals underestimate mercury dental amalgam's risks or prioritize cost-effectiveness due to insurance structures [28-30]. The term "silver fillings" obscures the material's ~50% mercury content, misleading patients about a neurotoxin in their restorations [1]. This violates informed consent, a cornerstone of medical ethics [31].

Second, the FDA's claim that existing evidence does not justify disclosures is untenable. Mercury dental amalgam releases vapor, leading to neurological, immunological, and renal impairments, particularly in vulnerable populations [1,15-22]. Autopsy studies show 2–12 times higher mercury levels in brain and kidney tissues of amalgam bearers, with some exceeding toxic thresholds [32]. Park et al. found elevated urinary mercury levels in women with amalgam fillings, correlating with health risks. Geier et al. linked amalgam surfaces to asthma [33]. The Casa Pia study reported neurobehavioral deficits in children with CPOX4 variants, affecting 28% of the population [7,22]. Over 15,000 published studies on Google Scholar document these risks, contradicting the FDA's dismissal [14].

Third, the FDA's stance diverges from international standards. The EU's 2025 ban, building on 2018 restrictions for children and pregnant women, aligns with the Minamata Convention's precautionary principle, as do bans in Norway, Sweden, and Japan [7,34]. The FDA's inaction, influenced by the American Dental Association (ADA), which defends mercury dental amalgam's economic benefits, raises concerns about industry bias, as seen in the 2015 rejection of warning recommendations [7,13].

Fourth, the failure to mandate disclosures exacerbates health inequities. Underserved communities, with limited access to mercury-free alternatives like Atraumatic Restorative Treatment (ART), face disproportionate risks [7]. The deceptive "silver fillings" label and lack of notifications perpetuate uninformed treatment decisions, particularly for vulnerable groups [1].

Counterarguments from the FDA and ADA claim low mercury release poses minimal risk and dentists are equipped to inform patients [7,16]. These are flawed. Individual variability (e.g., ApoE4, CPOX4) increases risks at low exposures, and disparities in dental care access undermine consistent risk communication [7,11,12,16]. Safer alternatives like ART and composite resins, widely adopted globally, render mercury dental amalgam's use unjustifiable [7]. The FDA's refusal to mandate disclosures violates ethical standards and hinders the Minamata Convention's goals [7,31].

Safe Removal of Mercury Dental Amalgam

As global awareness of mercury dental amalgam's health risks grows, particularly with the European Union's 2025 ban, demand for safe removal is surging [7,34]. This process poses significant health risks due to mercury vapor release, which can result in acute exposure levels far exceeding safe limits, particularly for vulnerable populations such as pregnant women, children, and those with genetic predispositions [7,11,12,17,18,20,25]. Warwick et al. found that mercury vapor concentrations during amalgam removal can reach levels associated with neurological and respiratory harm, necessitating rigorous protocols to protect patients and dental professionals [29]. Zwicker et al. reported reduced urinary mercury levels post-removal, underscoring the need for safe practices to mitigate exposure [37].

Dr. Hal Huggins, a pioneer in mercury-free dentistry, ceased using mercury dental amalgam in the 1970s after learning of its toxicity from Dr. Olympio Faissol Pinto. Huggins developed the "Bubble Operatory," a groundbreaking system incorporating advanced air filtration and protective barriers to minimize exposure [38]. His innovations, driven by early recognition of mercury's neurotoxic effects, set a precedent for safe removal practices and influenced organizations like the International Academy of Oral Medicine and Toxicology (IAOMT) and the International Academy of Biological Dentistry and Medicine (IABDM) [35,36].

The IAOMT and IABDM have established evidence-based guidelines, such as the Safe Mercury Amalgam Removal Technique (SMART) and PROTECT Protocol, to ensure safe mercury dental amalgam removal. These protocols mandate measures like high-volume suction, rubber dams, supplemental oxygen via nasal cannula, and full-body protective coverings to reduce mercury exposure. Additional safeguards include cold water irrigation to minimize vapor release, sectioning amalgams to reduce particle dispersion, and rigorous room ventilation to protect dental staff and patients [35,36]. Adherence to these standards is critical, as improper removal can exacerbate health risks, including neurological and immunological damage, particularly in vulnerable populations [18,20]. The FDA's failure to mandate patient disclosures about mercury dental amalgam's risks, compounded by the deceptive "silver fillings" label, leaves many patients unaware of the need for these specialized protocols, increasing the likelihood of unsafe removal practices [1,35,36].

The global shift toward mercury-free dentistry, exemplified by the EU's ban, underscores the urgency of universal adoption of these safe mercury removal protocols [7]. Non-compliance not only

endangers patients and dental professionals but also undermines the Minamata Convention's goal to "Make Mercury History" [7,39]. The FDA's inaction on promoting safe removal guidelines further highlights its regulatory shortcomings, necessitating immediate reform to align with international standards and protect public health.

Conclusion

The FDA's obstinate defense of mercury dental amalgam, falsely branded as "silver fillings," and its brazen refusal to require patient disclosures expose a shameful betrayal of public health trust. The World Health Organization confirms mercury dental amalgam as the dominant source of human mercury exposure, with NHANES data revealing that over half of Americans aged 15 and older bear these toxic fillings, and 30–40% surpass EPA safety limits, driving such health maladies as neurological, immunological, renal, arthritic, and respiratory harm. These figures likely understate the crisis, as NHANES excludes children with amalgam fillings. Mercury dental amalgam's role in fueling antibiotic-resistant bacteria escalates a global health emergency, threatening the efficacy of critical medical interventions. Dental professionals endure relentless mercury exposure, with evidence of these professionals' heightened health risks, while dental clinics account for roughly 50% of U.S. wastewater mercury, poisoning ecosystems. The FDA's feeble Class II classification dismisses thousands of peer-reviewed studies, including autopsy data revealing toxic mercury in tissues and heightened risks for those with genetic vulnerabilities like ApoE4 or CPOX4. By endorsing the deceptive "silver fillings" label and discouraging mercury disclosure, the FDA obfuscates informed consent, defying ethical mandates like the American Medical Association has recommended. Proven alternatives such as Atraumatic Restorative Treatment (ART) and composite resins, embraced worldwide, render mercury dental amalgam archaic and unjustifiable. The EU's 2025 ban proves mercury-free dentistry is not only feasible but essential, aligning with the Minamata Convention's urgent call to eradicate mercury use. Legal challenges, advocacy critiques, and recent studies highlight the FDA's transparency deficits and potential industry bias. The FDA's obstinacy sabotages global mercury reduction efforts and endangers millions. It must enact mandatory disclosures, enforce stringent safe removal protocols, and ban mercury dental amalgam outright to honor the Minamata Convention, rebuild public trust, and safeguard humanity from this preventable scourge. The FDA must act to "Make Mercury History."

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Review Article

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Dental Amalgam and the Minamata Convention on Mercury Treaty: Make Mercury History for All

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Abstract

Mercury, known as the most toxic non-radioactive element to man, poses a significant threat to all living beings and the environment in all its forms. As a global pollutant, it demands urgent attention and effective measures to mitigate its toxic effects. The Minamata Convention on Mercury Treaty, adopted in 2013 and enforced in 2017, stands as a vital instrument in combating this pervasive toxin. Presently, 144 countries have ratified the treaty, embodying the collective commitment to the mantra "Make Mercury History." As countries work diligently to eliminate mercury from various products and processes, such as thermometers, batteries, lighting, and cosmetics, dental amalgam remains a notable concern. Being one of the top mercury-containing products globally, dental amalgam has drawn attention for its phase-down approach within the treaty. The dental sector alone accounts for an estimated 340 tonnes of mercury usage each year. Alarmingly, mercury derived from dental amalgam infiltrates the black market, ultimately entering the artisanal small-scale gold mining (ASGM) sector, the primary source of global mercury pollution. Furthermore, dental amalgam plays a significant role in municipal wastewater mercury contamination, as it has been identified as the largest source of this toxic element in such environments. Considering its pervasive nature, diverse pathways of contamination, and its ability to bioaccumulate in both humans and the environment, it is evident that the toxic legacy of dental amalgam will persist long after the placement of the last amalgam filling. The pressing issue of mercury toxicity makes it imperative for action to be taken through the Minamata Convention on Mercury Treaty. As we strive to "Make Mercury History" for the well-being of all living organisms, mercury dental amalgam must be proactively addressed to prevent its continued contribution to global mercury pollution.

Keywords: Dental amalgam, Minamata Convention on Mercury Treaty, Mercury, Toxicity

Abbreviations

ASGM -	Artisanal Small-Scale Gold Mining
WHO -	World Health Organization
GRAS -	Generally Recognized as Safe
FDA -	Food and Drug Administration
EU -	European Union
SCENIHR -	Scientific Committee on Emerging and Newly Identified Health Risks
ADA -	American Dental Association
UNEP -	United Nations Environmental Programme
EPA -	Environmental Protection Agency
POTWS -	Publicly Owned Treatment Works
COP -	Conference of the Parties
US -	United States
NHANES -	National Health and Nutrition Examination Survey
ART -	Atraumatic Restorative Treatment
MID -	Minimum Intervention Dentistry, AKA Minimal Invasive Dentistry
PAHO -	Pan American Health Organization
CDC -	Center for Disease Control and Preventions
AD -	Alzheimer's Disease
ApoE -	Apolipoprotein E
OR -	Odds Ratio
NIDCR -	National Institute of Dental and Craniofacial Research
CTONI -	Comprehensive Test of Nonverbal Intelligence
WAIS -	Wechsler Adult Intelligence Scale
MSDS -	Manufacturers Safety Data Sheet
CPOX -	Coproporphyrinogen Oxidase
BDNF -	Brain-Derived Neurotropic Factor
MT-	Metallothionein
COMT -	Catechol-O-Methyltransferase
EMFs -	Electromagnetic Fields/Frequencies
MRI -	Magnetic Resonance Imaging
RF -	Radiofrequency

1. Introduction

The complex nature of mercury speciation and genetic components makes it impossible to set a minimum level of mercury exposure at which its immunotoxic effects won't occur [1]. Mercury, the main component of dental amalgams has been in use for almost 200 years. Since the inception of using mercury dental amalgams, the question of its safety has been controversial and vigorously disputed, this continues even today. Dental amalgam was never tested for its safety in the United States. Instead, in 1976, it was grandfathered in under Generally Recognized as Safe (GRAS) due to long-term usage by the Food and Drug Administration (FDA). It is well established in the scientific literature, that humans who have dental amalgam restorations are chronically exposed to mercury, due to the constant release of mercury vapor from these restorations [2]. Dental amalgams are often referred to as "silver fillings", due to the color, not the content, which is actually about 50% mercury with the remaining 50% a mixture of silver, tin, zinc, and copper. Currently, dental amalgam represents about 1/5th of the worldwide use of mercury. In 1991, the World Health Organization (WHO) reported that the first route of human exposure to mercury is from dental amalgam. Additionally, the WHO has also listed mercury in their top 10 chemicals of principal health concern [2,3].

In 2002, the United Nations Environmental Programme (UNEP) formed its first Global Mercury Assessment. This was the precursor to what would become the Minamata Convention on Mercury Treaty. During the early years, countries around the world were investigating and developing reports on sources, emissions, and transport of mercury, which also included anthropogenic emissions [4].

The European Union-Commission (EU-Commission) appointed the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) to specifically assess the safety and efficacy of dental amalgam [5]. A 2008 report presented by the SCENIHR to the EU Commission claimed that "…no risks of adverse systemic effects exist and the current use of dental amalgam does not pose a risk of systemic disease…" A peer-reviewed scientific paper a, by Mutter (2011), provided a rebuttal to each statement made by the SCENIHR by presenting a plethora of scientific research that refuted each statement. Mutter noted that the SCENIHR report did not address the toxicology of mercury and the studies used had "severe methodical flaws". Mutter included the toxicological impact of mercury dental amalgam and autopsy studies which reported that 60-95% of mercury found in human tissues was from dental amalgam, and persons with 12 or more fillings had 10 times higher mercury levels in several tissues, including the brain. Mutter also stated that the form of methylmercury resulting from dental amalgam may be significantly more toxic than exposure from fish consumption [2,6]. In 2015, SCENIHR updated its opinion, and the word "safe" was deleted in section 4.1. [7]. SCENIHR confirmed that the WHO had determined that the higher number of dental amalgams a person had, may account for 87% of the absorbed inorganic mercury [8].

The Minamata Convention on Mercury Treaty prepared guidelines that the WHO and the parties of the Minamata Convention on Mercury Treaty supported and were adopted by the treaty under, Annex A, Part II to phase down the use of dental amalgam. During the Conference of the Parties (COP) 4 an amendment to Annex A was added that included the exclusion or not allowing the use of bulk mercury, and the excluding or not allowing the use of dental amalgam for the dental treatment of deciduous teeth, of patients under 15 years and of pregnant and breastfeeding women unless deemed necessary by the practitioner" [9].

Positions on Mercury Dental Amalgam

Various organizations have taken different stances on mercury dental amalgam. The WHO submission to COP 4, consulted with public health policymakers in the dental sector and stated a phase-down- and even a phase-out of the use of mercury dental amalgam is feasible [10].

The World Dental Federation (FDI), took a leadership role throughout the treaty process. They lobbied for a phase-down and not a phase-on the use of mercury dental amalgam. Stating "safe, effective, and affordable alternatives" are needed [11]. The EU made a groundbreaking decision in 2023, adopting a proposal for a total phase-out of dental amalgam use from January 1, 2025, citing viable mercury-free alternatives as a reason" [12].

The American Dental Association (ADA) in 2021, stated: "Dental amalgam is a safe, affordable, and durable restorative material" [13].

During the treaty process, many countries deferred to US policies, including the FDA for guidance on various mercury-containing products, including mercury dental amalgam. The FDA guidelines maintained the following: "Benefits: Dental amalgam fillings are strong and long-lasting, so they are less likely to break than some other types of fillings. Dental amalgam is the least expensive type of filling material. Potential Risks: Dental amalgams contain elemental mercury. It releases low levels of mercury in the form of a vapor that can be inhaled and absorbed by the lungs. High levels of mercury vapor exposure are associated with adverse effects on the brain and the kidneys. The FDA has reviewed the best available scientific evidence to determine whether the low levels of mercury vapor associated with dental amalgam fillings are a cause for concern. Some individuals have an allergy or sensitivity to mercury or the other components of dental amalgam (such as silver, copper, or tin). Dental amalgam might cause these individuals to develop oral lesions or other contact reactions. If you are allergic to any of the metals in dental amalgam, you should not get amalgam fillings. You can discuss other treatment options with your dentist" [14].

Mercury Dental Amalgam Environmental Impact

It has been reported that about one gram of mercury, is enough to contaminate a 20-acre lake over time [15]. Of the approximately 340 tons of dental mercury used annually, it is estimated that between 70-100 tons wind up in the solid waste stream [3].

The EU uses about 75 tons of dental amalgam each year, with approximately 50 tons becoming dental waste, through various pathways such as placing or removing mercury amalgam fillings, human waste, cremation, or burial [3,16].

The UNEP Global Mercury Assessment (2013), estimated that dental mercury emissions from cremation are between 0.9-11.9 tons annually, around the world [4]. Emissions from cremation is expected to rise due to land space availability, especially in highly populated urban areas, and also due to burial costs being significantly more expensive [3]. The 2013 UNEP report, however, did not address the contamination of mercury from dental amalgams in sewage sludge, which is sold to farmers to be used as fertilizer and thus entering the food chain. Nor was incineration, preparation, removal, or disposal of mercury dental amalgam reported [3,4]. The saliva from 20% of individuals who had mercury dental amalgams exceeded the mercury limits for sewage [6]. Gworek et al. (2017) affirmed that mercury-contaminated sewage sludge from treatment plants can be a substantial source of mercury and the mercury emissions from incineration are relatively high [17]. Waste management is of particular concern, especially in developing countries since mercury waste during cremation, can be incinerated causing it to enter the atmosphere, soil, water, and ultimately the food chain [18].

A study by the EPA was re-examined by Scarmoutzos, et al. who found the assessed emissions from dental amalgam may have been considerably underestimated when adding releases from dental sources that included dental offices, household sewage sludge, and crematoriums. While the EPA had reported 0.6 tons annually, based on the findings of Scarmoutzos, et al., estimates were between 6 and 35 tons of mercury released each year [19]. Another grossly understudied source of mercury released from dental amalgam is from exhaled air, which according to Cain et al., was projected to be about 150 kg, annually in the United States [20]. Additionally, roughly 37% of total global mercury emissions are released through ASGM and are estimated to be about 410-1400 tons yearly. This includes mercury that is imported into countries for dental use but instead enters the ASGM sector illegally through the black market for this purpose [3]. In accordance with the ratification of the treaty, the United States EPA has passed a national policy to reduce dental mercury waste into publicly owned treatment works (POTWS) by mandating mercury amalgam separators. The EPA estimates about 5.1 tons reduction of mercury from the dental office into the POTWS [21].

Health Effects from Mercury Dental Amalgam

Mercury dental amalgams have been a topic of controversy due to their potential health effects. Sanchez-Alarcon et al. (2021) highlighted that mercury dental amalgams can lead to significant iatrogenic exposure to xenobiotic compounds, causing DNA damage, especially in vulnerable subpopulations [22]. All mercury dental amalgams corrode and release mercury vapor. In the 1970s high copper amalgams were introduced with the intention of being mechanically stronger and corrosion-resistant. These high copper-mercury dental amalgam fillings are actually more volatile and release substantially higher mercury vapor emissions. Bengtsson and Hylander (2017) stated that high copper mercury dental amalgams are the most used filling material in the EU, the US, and other markets worldwide releasing about ten times more mercury than the previous formulas. They noted that it is vitally important that dental workers, politicians, and decision-makers are informed about the instability of modern non-ɣ2-amalgams and the significant risk from mercury vapor that can occur from these fillings [2,23].

There are considerable long-term consequences that are unreported in terms of the actual damage to the tooth structure when placing mercury dental amalgams, versus non-mercury dental restorations. This is due to the techniques needed to prepare and place a mercury dental amalgam filling, which requires the removal of some of the good tooth structure. This weakens the tooth and along with the expansion and contraction of the mercury amalgam filling, can lead to the tooth breaking. This can cause major damage to the remaining tooth, additional dental treatments, and potentially the loss of the tooth. Using non-mercury alternatives preserves good tooth structure. The choice of material needs to be considered in the total cost of mercury dental amalgam versus non-mercury alternatives because of its long-term use [24,25].

Studies have long confirmed that mercury inhaled from dental amalgams crosses the blood-brain barrier, enters the bloodstream, and can translocate throughout the body. Mercury has been found in various organs such as the kidneys, myocardium, skeletal muscles, adrenals, liver, testes, and pancreas [2,6,16,26]. Mercury is released from dental amalgams by brushing teeth, eating, drinking, and simply breathing. Panov and Markova (2020) found that it is definitive that individuals that have mercury dental amalgams display a significant buildup of plaque. Plaque buildup is a precondition for developing carious lesions and periodontal disease which is detrimental to periodontal health [27].

A 2022 published paper by Mark and David Geier investigated mercury vapor exposure from mercury dental amalgam fillings using the National Health and Nutrition Examination Survey (NHANES) database. They noted that the FDA recognizes these dental fillings emit mercury vapor and its exposure may be dangerous to certain individuals. Between 2015-2018, 158,274,824 weighted-adult Americans were examined for mercury dental amalgam vapor exposure. Approximately 91 million adults had >1 mercury amalgam surface and roughly 67 million had no mercury amalgam fillings. Most significantly, approximately 86 million adults' daily mercury vapor doses were in excess of the stringent California Environmental Protection Agency (EPA) safety limit, and when using the least stringent US EPA limit, about 16 million adults were over the limit. They concluded that the US adult population is exposed to significant amounts of mercury vapor from mercury dental amalgam fillings and the use of these fillings needs serious evaluation [28].

Siblerud and Mutter (2021) reviewed the literature providing a snapshot of the toxic health effects of exposure to mercury dental

amalgams. Their findings included mental health disorders, cardiovascular problems, diseases such as Alzheimer's disease, multiple sclerosis, and amyotrophic lateral sclerosis. Other health problems that are related to exposure to mercury amalgam are significant and numerous such as maternal mercury that has been found in the brains of infants inhibiting the enzyme methionine synthetase, and in cord blood, genotoxicity, oxidative stress, cancer, skin problems, autoimmune disorders, mercury hypersensitivity, kidney damage, chronic fatigue, and other maladies [6,29]. Mercury exposure can elicit epigenetic changes that can cause many disorders such as reduced newborn cerebellum size, adverse behavioral outcomes, atherosclerosis, and myocardial infarction [30].

Although mercury dental amalgams were banned in Norway, a 2022 study by the Norwegian Ministry of Health and Care Services did an investigation to discover if removing mercury dental amalgam from patients with medically unexplained physical symptoms would have cost-effective benefits. There was a cost-saving over time by removing mercury dental amalgam over both 5 and 10 years. They noted that there were limitations due to the small sample size and possible biases from the non-randomized design. However, they were based on real program experience and offered reasonable evidence of the beneficial effects of removing dental amalgam in both short- and long-term perspectives in patients who attribute health complaints to dental amalgam restorations, which were consistent with other studies [31].

The Geier's, investigated the relationship between the number of dental amalgams and the incidence of arthritis in US adults ages 20-80 years old, also using the NHANES database between 2015-2016. This cross-sectional study is the first epidemiological evidence that links the increasing dental amalgam filling surfaces with reported arthritis in the US adult population. They observed the association of dental amalgam surfaces and reported arthritis remained significant when considering multiple variables and various statistical models. They estimated about 281 million dollars between lost wages and medical costs were due to individuals diagnosed with arthritis [32].

The Geier's looked at the connection between mercury dental amalgam exposure and reported asthma diagnoses using the same age group of adults from 20 to 80 years old. There was a total of 97,861,577 persons with one or more dental amalgam surfaces and 31,716,558 persons with one or more non-mercury dental restorations. The Geier's noted the location of the respiratory system, its immediate contact with mercury vapor, and its critical importance in whole-body health necessitated their investigation of the consequences of this exposure by analyzing the NHANES data. According to the Centers for Disease Control and Prevention (CDC) (2009), the rate of asthma in the US is growing each year, accounting for about 25 million who have been diagnosed with this disease. The cost of asthma is also rising for example from 2002 to 2007, there was a 6% increase from $53 billion to $56 billion. Geier's calculation using their current data of asthma-related health costs to individuals with mercury dental amalgam would be about $47,838,861, and the cost over 25 years for these individuals would be $1,195,971,525. They concluded that the increase in exposure to mercury dental amalgam was related to an increased risk of reported asthma diagnoses, in the US adult population, and more studies are needed in this area [33,34]. Although there are various methods used for assessing mercury concentrations in hair, breast milk, urine, blood, and feces, there is no available technology that can accurately determine the total mercury body burden in humans or human tissue [15].

Women

Since the Minamata treaty has come into force, many countries have been taking measures to prohibit the use of mercury in pregnant, breastfeeding, and women of childbearing age, unfortunately, in the dental sector, millions of dental workers globally have already been exposed to mercury and even after it is banned globally they will continue to be exposed [35]. Duplinsky and Cichetti (2012) examined the health status of 600 dentists using pharmacy utilization data by matching the controls' age, gender, geographical location, and insurance plan structure to see how exposure to mercury dental amalgam would affect them. The disease categories investigated were neuropsychological, neurological, respiratory, and cardiovascular. Reviewing multiple studies, they found that obvious "high" levels of mercury exposure can create not only neuropsychological and other health complications but more significantly, problems can and do occur at relatively low dose exposures. Based on their statistical analysis, dentists are far more likely to be prescribed medications used to treat neurological, neuropsychological, respiratory, and cardiac diseases [36].

Other studies have shown dental workers have higher mercury concentrations in biological fluids and tissue, and more health problems, including the central nervous system, memory loss, depression, and fertility problems amongst female dental workers [2,37]. Women working in the dental industry show higher risks of exposure to mercury dental amalgams which can be serious. Studies of older dental professionals have been reported to have markedly higher levels of mercury in their blood samples compared to controls [38]. El-Badry, et al. (2018) investigated the potential of mercury-induced oxidative stress having an adverse effect on the pregnancy outcome of female dental workers. They found that exposed dental workers had a higher mean urinary mercury level and a lower blood antioxidant activity during the three trimesters ($p<0.001$), more frequent spontaneous abortion, and pre-eclampsia ($p<0.05$). Their babies tended to be smaller for gestational age compared to the controls [39]. A systematic review by Manyani, et al. (2021) assessed the risks of exposure to mercury dental amalgam in dental staff due to their occupational chronic low level of exposure to mercury. Included were all biomonitoring studies published between 2002 and 2019 that measured hair, blood, urine, and nail mercury levels. The mercury biomarkers in dentists were higher, they also had a higher incidence of neurological symptoms and memory deficiency, than the controls. Since mercury dental amalgam is used globally, they concluded that biomonitoring and preventative measures must be taken to reduce mercury exposure [40]. According to Mutter et al. (2006), the rate of infertility has grown over the past several decades in women

who had more mercury dental amalgams, or after a DMPS challenge had excreted more mercury in the urine than controls. They noted women dental assistants exposed to mercury dental amalgam also had a higher rate of infertility [41].

The New Hampshire birth cohort study was conducted with 1321 participants to examine prenatal mercury exposure and maternal mercury dental amalgams, and their relationship to infant infections, allergies, and respiratory symptoms during the first year of life. Higher maternal toenail mercury concentrations were found in those who ate fish while pregnant. The infants had an increased risk of lower respiratory infections and respiratory symptoms requiring doctor visits among them between 9-12 months (relative risk (RR) 1.4 (95% CI: 1.1, 1.9) and 1.2 (95% CI: 1.0, 1.4) respectively), whereas a reduced risk of lower respiratory infections was observed among infants 0–4 months of age (RR = 0.7 (95% CI: 0.5, 1.0). Modest to no evidence linking toenail Hg with upper respiratory infections, allergy, or eczema at any age to one year, was found. The infants of non-fish-eating mothers who had mercury dental amalgam fillings while pregnant, had an elevated risk of upper respiratory infections requiring doctor's visits (RR = 1.5 (95% CI:1.1, 2.1)). They concluded that both exposures could increase the risk of respiratory infections and respiratory symptoms in the first year of life [42].

Bjorkman et al. (2018) conducted a large population cohort study to investigate perinatal death and exposure from dental amalgam fillings during pregnancy from 1999 to 2008 in Norway. There were 72,038 pregnant women and the number of their mercury dental amalgam fillings were recorded. They found the total risk of perinatal death ranged from 0.20% for women who had no mercury amalgam fillings to 0.67% for women with 13 or more mercury amalgam fillings. Even after adjusting for confounding variables, they found that women with 13 or more mercury amalgam fillings had an adjusted OR (odds ratio) of 2.34, noting these findings suggest the risk of perinatal death could increase in a dose-dependent fashion [43].

Bjorkman et al. (2017) specifically investigated the toxicology of mercury exposure through various pathways such as seafood, vaccines, and dental amalgams. They noted that lead, cadmium, aluminum, and mercury which are naturally occurring, are bound to other substances, and when extracted by humans, they can accumulate in the liver, bones, brain, and kidneys. Exposure of the fetus to these toxic metals is a major concern, particularly during specific periods of development. They found that rats exposed to low doses of mercury and cadmium displayed mitochondria damage and that various studies have shown that mercury exposure could be a factor in the development of autoimmune diseases [44].

A 2016, 5-year study was conducted to evaluate prenatal mercury exposure from fish and mercury dental amalgam, level of lead in cord blood (as a confounder), child neurodevelopment, and the apolipoprotein E (ApoE) genetic polymorphism amongst mother-child pairs from Slovenia and Croatia. The authors found that low-to-moderate mercury exposure can lower both cognitive and fine motor scores at 18 months of age. Stating while there was a small sample of subjects with the ApoE 4 allele, there was substantial evidence that mercury was linked to a decrease in cognitive performance with those carriers who have had at least one ApoE 4 allele, however, the decrease in fine motor scores was independent of the genotype [45].

Men

During the past several decades, research has been conducted on the impact of mercury exposure on women and fertility, however, research on men's exposure to mercury and its influence on male fertility is woefully lacking. Reports have found even low-level mercury exposure has adverse effects such as a decrease in semen quality and alterations in sex hormone levels. Mercury vapor has been shown to cause mercury to build up in the testicles [38]. A systematic review of mercury exposure and reproductive health in humans found that higher levels of mercury were linked to infertility or subfertility status in both sexes. Mercury was reported to have a negative impact on semen quality parameters and can cause sperm DNA damage [46].

Khoramdel, et al. investigated the relationship between cadmium and mercury and their impact on the deficiency of the human sperm nucleus by analyzing blood and semen. The cohort consisted of 62 men, of which 31 were deemed infertile in the age range of 23-38. The sperm count was significantly less in infertile men. Elevated blood levels of mercury reduced 50% of sperm motility along with an elevated percentage of abnormal morphology of sperm. Cadmium was also found to harm sperm motility and sperm count [47].

Animal studies have found that mercury was detected in the Leydig and Sertoli cells by crossing the blood-testis barrier. Mercury toxicity may cause a decrease in sperm motility and affect the process of spermatogenesis [48]. In rats exposed to mercury, there was a decline in spermatozoa, disorganization, and degeneration of some spermatogenic cells and vacuolated areas within the seminiferous tubules. Necrosis, the disintegration of spermatocytes from the basement membrane, undulation of the basal membrane, and severe edema in the interstitial tissue of the testis was also observed [49].

Children

Two concurrent clinical trial prospective studies were referred to as the "Casa Pia Study" and the "CAT Study". These sister studies were designed to determine if low-level exposure from mercury dental amalgam would impact target organs/systems (specifically renal and neurological) in children. Both studies started in the mid-1990s with the CAT study concluding in March 2005 and the Casa Pia study concluding in February 2011 [50,51]. Both studies used the mercury dental amalgam brand, Dispersalloy by Dentsply Caulk (York, PA, USA) stating that it contains about 50% mercury [52]. The (2018) Manufacturers Safety Data Sheet (MSDS) for Dispersalloy-Dentsply mercury dental amalgam includes such warnings as follows may be corrosive to metals, fatal if inhaled, causes severe skin burns and eye damage, and may damage fertility or the unborn child [53]. Dentsply Sirona Inc, announced the following, "In

September 2020, the FDA issued an updated recommendation that certain people are at higher risk for health problems from mercury-containing amalgam dental fillings... Further, we have discontinued sales for all amalgam products as of December 2020" [14,54].

Although the Casa Pia study indicated that an IQ measured by the comprehensive test of nonverbal intelligence (CTONI) of >67 was part of the criteria for inclusion, the CAT study did not have any IQ requirement [50,51]. It is noteworthy that a report by Human Rights Watch stated, "If a person scores below 70 on a properly administered and scored IQ test, he or she is in the bottom 2 percent of the American population and meets the first condition necessary to be defined as developmentally disabled" [55,56]. The Casa Pia researchers looked at subtle neurological signs and cognitive development. Many papers were published by these same researchers who had previously concluded the use of mercury dental amalgams was safe regarding, cognitive, neurologic, and renal effects. Consequently, they assembled both the composite and mercury dental amalgam i.e. all cases, into a single body of data for further analysis, therefore, if there were any differences between the mercury amalgam group and the composite group, that question remained unresolved [57].

Duplinsky, et al. reviewed the Casa Pia and CAT studies and found several critical problems with the conclusions, the most significant was to use IQ as the major outcome variable. They stated, "About 25% of the children that were lost to follow-up analysis differed from the retained sample, which included lower baseline IQs, mostly Hispanic, children of a lower socio-economic class, and inferior education. Duplinksy et al. concluded that "Serious design flaws in each of these three trials cast doubt on the authors' conclusions in both clinical trials that the results confirm that dental amalgams are a safe option for children's dental restorations. The data, as we have demonstrated simply do not support what we view as an incorrect conclusion" [36].

Pigatto and Meroni investigated the Casa Pia and CAT studies in 2006. They disputed the author's conclusions that there was no evidence of harm from mercury dental amalgam, citing that oral lichen planus can occur from mercury vapor exposure and while obvious signs of mercury toxicity may not be apparent, the immune system may still be harmed [58].

Guzzi and Pigatto reviewed another Casa Pia study by Woods, et al. (2007) and addressed their limitations in investigating mercury in the urine because of it being a weak indicator for long-term exposure to mercury vapor from dental mercury amalgams. Autopsy studies have shown that mercury levels from dental amalgam have been retained in tissues and are higher in the brain and thyroid than found in the renal cortex. In the Casa Pia study, bruxism was not mentioned. Previous studies have shown that this may be a confounding factor of increased urinary levels of mercury. The Casa Pia study also found that girls excreted considerably more mercury in urine than boys, which may allude to girls being potentially at a lower risk from mercury exposure, however, their ongoing study found that females were more likely to be affected by long-term exposure from mercury dental amalgams. The Casa Pia study did not address the potential harm to the children's immune system, stating that "mercury-induced immunotoxicity arises far earlier than overt toxicity in the renal and central nervous systems" [59].

A further investigation of the Casa Pia study's relationship between mercury dental amalgam exposure and urinary porphyrins was done by reexamining the original datasets from the parent study. A dose-dependent relationship between the accumulation of mercury from dental amalgam and the specific urinary porphyrins associated with mercury body burden was found. The findings are in complete opposition to the findings of Woods, et al. (2009) that stated, "there were no significant differences between mercury dental amalgam and composite subjects" [60].

A 2014 study by Homme, et al. also reviewed the earlier CAT and Casa Pia studies, stating that even though those earlier studies didn't show changes in neurobehavioral outcomes in either group, those in the amalgam cohort showed a statistically significant increase in urinary mercury levels. The Casa Pia and CAT studies are "widely cited in the literature" as proof that mercury dental amalgams are safe. More recent reviews using refined exposure metrics, now show evidence of harm. The common genetic variant called coproporphyrinogen oxidase 4 (CPOX4), which is found in 28% of the population as reported in the Casa Pia study found that boys with this genetic variant showed mercury-related deficits in 11 of the 23 neurobehavioral tests. Boys with common variants for two metallothionein proteins also showed significant neurobehavioral deficits using the same exposure metric used in the 2012 reanalysis. Looking at the entirety of the studies does not support the theory that mercury dental amalgams are safe, on the contrary, they submit that mercury dental amalgam may be "a significant chronic contributor to mercury body burden and that this may play a causal role in neurobehavioral deficits and other harm to genetically susceptible subpopulations that are only beginning to be identified" [61].

Woods, et al. (2014) published a summary of the Casa Pia study and reported on 330 subjects who were genotyped for 27 variants of 13 genes that have been shown to affect neurologic functions and/or mercury disposition in adults. They stated that the original studies didn't look at "special sensitivities", however, identifying genetic polymorphisms that affect mercury neurotoxicity is critical, for risk assessments in children who are exposed. Their findings included significant adverse effects of low-level mercury exposure due to common genetic variants that cross all populations, children are more susceptible than adults to environmental toxins, especially mercury. They concluded: "Genotype determines the effects of mercury on neurobehavioral functions in children. Boys are more susceptible to genetic modification of mercury neurotoxicity than girls. Multiple common variants underlie the wide prevalence of mercury neurotoxicity and genes identified expose relevant biology underlying susceptibility to mercury toxicity" [62].

Using the NHANES database, Yin, et al. (2022) evaluated mercury levels from seafood and mercury from mercury dental amalgams to determine the effects of these exposures in children. Exposure from these two sources has been fiercely contested as to which exposure causes greater harm. There were 14,181 subjects that were evaluated as to their seafood consumption versus mercury dental amalgam contributions to blood total mercury, inorganic mercury, methyl mercury, and urine creatinine corrected mercury. Their findings clearly established that mercury dental amalgam significantly increased blood and urine mercury levels, but noted these average blood levels are below the safety threshold established by the WHO and the EPA. However, even more significantly, they found that children under 6 years old with more than 5 mercury dental amalgam fillings had the highest blood inorganic mercury and urine creatinine-corrected mercury among all age groups. Their findings were alarming and they concluded that it is urgent that dentists and patients learn about these risks and avoid mercury exposure, especially in vulnerable populations [63].

Genetic Susceptibility Risks to Mercury

Andreoli and Sprovieri (2017) conducted a comprehensive study on mercury exposure in humans, highlighting over 250 symptoms affecting various systems in the body. The complexity of mercury's impact, whether through acute or long-term low-dose exposure, makes diagnosing mercury toxicity challenging. However, recent studies have identified specific genes that may help identify an individual's risk of mercury toxicity [64].

The ApoE4 and CPOX4 genetic traits have been studied and how those carriers that are exposed to mercury are negatively impacted. The only gene that has been specifically linked to mercury intoxication is the ApoE gene, which has been found in epidemiological studies. Neurobehavioral functions such as learning, memory, attention, and motor skills were negatively affected by exposure to mercury dental amalgam in the Casa Pia children who were carriers of the ApoE4 gene. ApoE4 carriers who also have mercury dental amalgams have shown symptoms of chronic mercury toxicity, AD, bipolar disorder, and depression. ApoE2 carriers may show the lowest risk of mercury exposure [62,65].

According to Alzheimer's Disease International the number of people diagnosed with dementia as of 2020, is over 55 million people globally, with a new diagnosis every 3 seconds. This number is expected to grow to 78 million by 2030. The economic impact is over $1.3 trillion US dollars and will more than double by 2050 [66]. The WHO has identified AD as a global health priority. The ApoE4 gene is thought to be the single biggest risk factor for AD [2,67]. A study by Siblerud et al. (2019) was done to determine if mercury exposure could be the causative factor AD, noting mercury is ten times more toxic to neurons than lead. The investigators crossed referenced the effects of mercury with 70 factors linked to AD and found all factors could be attributed to mercury. These changes in the AD brain include plaques, beta-amyloid protein, neurofibrillary tangles, phosphorylated tau protein, and memory loss can be caused by mercury from dental amalgam which is a significant source of exposure. Carriers of the ApoE4 gene have a diminished capability to bind mercury, consequently, mercury damage can occur [68].

Down Syndrome has been identified by the CDC to be the most common chromosomal disorder affecting approximately 1 in every 700 babies born in the US. There has been an increase in Down syndrome births of about 30% between 1979 – 2003. Studies have found that older adults with Down syndrome have an increased risk of developing AD [69]. A study was conducted in prenatal screening for Down syndrome using the ApoE as a potential noninvasive biomarker for this genetic disorder. They reported that the Down syndrome pregnancy had significantly higher plasma ApoE concentrations compared to the healthy controls and that testing for the ApoE can be used as a predictive marker for the disease. They concluded more studies are necessary [70].

Echeverria, et al. (2006) investigated the association between the genetic polymorphism of the CPOX gene, mercury dental amalgam, and neurobehavioral symptoms from this exposure in dental workers. There were mercury-related declines in performance in both genders and were statistically significant with the CPOX4 polymorphism. Their findings support current evidence of genetic susceptibility to mercury exposure in humans and that further studies with low-level mercury exposure are needed in both adults and children [71]. The Casa Pia carriers of the CPOX4 variant also showed greater susceptibility to mercury exposure as was found in neurobehavioral testing [62].

The impact mercury exposure has on other genes has also been investigated. Those carriers of genetic variants such as brain-derived neurotrophic factor (BDNF), metallothionein (MT) polymorphisms, and catechol-O-methyltransferase (COMT), are common in both genders of the global population and mercury has been shown to cause significant adverse effects even in low-level exposure [62].

Electromagnetic Fields/Frequencies - (EMFs) Risk Factors to Mercury Dental Amalgam

Electromagnetic fields (EMFs) have been described as a combination of invisible electric and magnetic fields, caused either naturally by the earth's magnetic field or by anthropogenic sources. Artificial EMFs reverse their direction at regular intervals of time, ranging from high radio frequencies (cell phones, magnetic resonance imaging (MRI)), and intermediate frequencies (computer screens) to extremely low frequencies (power lines) [72].

Mortazavi, et al. investigated the amount of mercury that would be released from dental amalgams when healthy students are exposed to high-field MRIs. Both groups were matched equally. They were divided randomly into either the control or MRI-exposed arms. Both groups showed no significant difference in baseline urinary mercury levels, however, from 48 hours after MRI the mercury level in those who had an MRI increased to levels significantly higher than those in the control group. Vulnerable populations such as the elderly, women, and children or those who are sensitive to mercury may be at greater risk if

they are exposed to high-field MRI within the first 24 hours of receiving mercury amalgam fillings. They also stated that in the few published papers that didn't show any increase in released mercury after an MRI may have methodological errors [73,74].

Mortazavi, et al. also looked at the link between maternal mercury dental amalgams and an increase of mercury released from EMF exposure as a hypothesis for higher rates of autism in children. They remarked that data is showing extremely minimal exposure to mercury can cause toxicity, and perinatal exposure to mercury is a significant risk factor for developmental disorders such as autism spectrum disorders and attention deficit hyperactivity disorder, and neurological problems. They reported that studies have shown a robust link between maternal and cord blood mercury from mercury dental amalgams. Their own studies have also found a strong correlation between EMFs and mercury levels leading them to conclude that pregnant women with mercury dental amalgams can possibly be a causative factor in the increase of autism [74].

Exposure to electromagnetic fields from everyday electronic devices such as Wi-Fi routers, LTE mobile networks, and 3T MRI was investigated to assess the microleakage of amalgam restorations. Forty non-carious extracted teeth were cleaned and debrided then stored in a saline solution for up to 2 months. Those teeth were randomly divided into 4 groups of ten teeth each, three were exposure groups and one was the control group. The results showed the score of microleakage was significantly higher in all mercury amalgam groups compared to the control, with the group exposed to 3T MRI having the highest microleakage [75].

Mortazavi, et al. addressed the flaws of the publication by Colvin et al. titled "Methylmercury Exposure in Women of Childbearing Age and Children". The release of mercury dental amalgams, have been shown to release methylmercury in the saliva of carriers three times higher than those who do not have mercury dental amalgams. Their evidence showed how EMF exposure can release significantly higher amounts of mercury in individuals who have mercury dental amalgams through their various studies, and concluded the study by Colvin et al… "is not considering the well-documented release of methylmercury from dental amalgam restorations [6,76]".

According to Shoukat (2019), about 2.87 billion people worldwide own smartphones as of 2020, about 95 percent of Americans own cell phones, and 77 percent own smartphones. Cell phone addiction, has been linked to anxiety, stress, depression, sleep deprivation, and among teens, suicide risks [77]. A 2017 article published by King University investigated cell phone addiction. They reported that people touch their phones an average of 2,617 times a day, and for the top 10 percent of users, 5,427 touches daily. Screen time was estimated between 2.42 – 3.75 hours daily including various interactions, with the average American spending about 5 hours a day on their devices [78].

Laboratory studies of EMFs on cell cultures and tissues, laboratory animals, and human volunteers have been conducted by Zigar, et al. (2020). They researched EMF exposure and the effects of objects on individuals whether in the body or near the body such as glasses, pacemakers, dental implants, fillings, and especially amalgam fillings because of the significant content of mercury. Their results of the simulation showed the increased values of the electric field in the model with mercury dental amalgam fillings compared to the model without, at all frequencies. These values present that the mercury dental amalgam filling leads to the increase of electric field intensity in the space above the fillings for teeth in the upper jaw. They concluded that radiation from cell phones is transformed into heat energy and may cause an increase in temperature inside the tooth, which can increase mercury vaporization causing toxic effects that can threaten human health [79].

Countries that Have Banned or are Banning Mercury Dental Amalgam

According to documents submitted to the Secretariat of the Convention in preparation for the COP 4th session, the following countries have completely banned mercury dental amalgam for all populations, have banned it for specific vulnerable populations, or have announced a date certain to end the use of mercury dental amalgam.

Country	Population	Banned Dental Amalgam	Phase Out Dental Amalgam	Vulnerable Populations
Mauritius Island	1,271,768	Import ban Specific Population		Children (2017)
Tunisia	11,818,619	Banned Specific Population		Children -Young Girls -Women
Bangladesh	164,689,383	Banned Specific Population		Children -Pregnant Mothers (2018)
Indonesia	273,523,615		2020	
Japan	126,476,461		1990s	
Nepal	29,136,808	Banned Specific Population	2019	Children <15 -Pregnant -Breastfeeding women
Philippines	109,581,078	Banned Specific Population	Total ban in 3 years from May 19, 2020	Children <14 -Pregnant -Breastfeeding women
Vietnam	97,338,579	Banned Specific Population	April 1, 2019 ban by January 1, 2021	Children <15 -Pregnant -Breastfeeding women
Former Soviet Union - Armenia Azerbaijan Belarus Estonia Georgia Kazakhstan Kyrgyzstan Latvia Lithuania Moldova Russia Tajikistan Turkmenistan Ukraine Uzbekistan	---------- --2,963,243 10,139,177 9,449,323 1,326,535 3,989,167 18,776,707 6,524,195 1,886,198 2,722,289 4,033,963 145,934,462 9,537,645 6,031,200 43,733,762 33,469,203	Banned Specific Population		Children <18
Georgia	3,989,167	Banned		
Moldova	4,033,963	Banned 2020		
Syria	17,500,658	Banned Specific Population		Children -Pregnant -Breastfeeding women
Bolivia	11,673,021	Banned 2019		
Guyana	786,552	Banned 2021		
Suriname	586,632	Banned 2018		
St. Kitts and Nevis	53,199		Phased out 2018	
Uruguay	3,473,730		Phased out 2007	
European Union & Monaco	447,700,000	Banned 2018 Specific Population Total ban - 2025		Children <15 -Pregnant -Breastfeeding women
Romania	19,237,691	Banned Specific Population		Children <18
New Caledonia (France)	292,559	Banned 2019		
Sweden	10,099,265	Banned 2009		
Denmark	5,792,202	Banned		
Iceland	341,243	Banned 2017 Specific Population		Children <15 -Pregnant -Breastfeeding women
Norway	5,421,241	Banned 2011		
Switzerland	8,654,622	Banned		
Tanzania	64,339,150	Banned 2023 Specific Population		Children <15 -Pregnant -Breastfeeding- child bearing age women

Nigeria	219,830,879	Banned Specific Population	Phase out 2024	Children (2022)
Children (2022)	28,317,105	Banned Specific Population	Total Ban 2025	Children-Pregnant women -vulnerable patients

Table 1: Countries that Have Banned or are Banning Mercury Dental Amalgam [9,80,81]

The United States' submission to COP 4, noted the EPA's policy on amalgam separators is now mandatory and in force. The US deferred to the FDA's 2020 update "that called for non-mercury restorations (fillings), such as composite resins and glass ionomer cement, to be used, when possible and appropriate, in people who may be at higher risk for adverse health effects from mercury exposure" [82]. However, based on current information, there is no indication of the US banning the use of mercury dental amalgam. The US population is over 331,000,000, ranking it the third-highest population in the world. The premise of a study by Estrich, et al. using the NHANES database was to discover how many individuals over 15 years old have teeth restored with dental amalgam Its data collection provided exactly what materials were used by identifying either non-mercury or mercury dental amalgam. They found that about half (51.5) of the dental restorations were mercury dental amalgams. With an estimated five mercury dental amalgams per bearer, the persistent, prolonged exposure, use, and ultimate environmental impact will continue to be significant [81,83].

Canada's submission to COP 4 reported that they have implemented the following measures listed in Part II of Annex A, measure (i), measure (ix), and (viii). Like the US, there is no indication that Canada is planning to ban mercury dental amalgam. Their population is 38,580,643 [9,81].

Atraumatic Restorative Treatment (ART) Technique - Minimal Invasive Dentistry -Biomimetic Dentistry a Paradigm Shift in Dentistry

In the 1980s the University of Dar el Salaam with the support of the WHO developed the Atraumatic Restorative Treatment (ART) technique in a pilot project in Tanzania. ART was designed and developed due to the need of providing dentistry in areas that had no electricity, water, or ability to use anesthesia. The technique was simply for the dentist to use a small spoon-shaped hand instrument for the removal of decay, as well as possible. The tooth was then restored with glass ionomer cement for populations in remote areas. ART was a completely different approach from what GV Black had taught, and what had been the standard of care for over a century. Black stated his vision for the future of dentistry as follows: "The day is surely coming and perhaps within the lifetime of you young men before me when we will be engaged in practicing preventive rather than reparative dentistry". Sajjanshetty, et al. reported that the survival rates of ART restorations were similar or superior to mercury dental amalgam after 6 years [84,85].

Zanata, et al. investigated the survival rate of ART over a ten-year period and found that even with an excessive subject dropout rate the survival rate was successful after 10 years of clinical service and that it was particularly successful in single-surface restorations noting ART is a viable technique to restore teeth, and it saves posterior permanent teeth [86]. Other positive aspects of using ART include, its low cost, availability, reduction of damaging the healthy tooth structure and tissue, less pain and sensitivity, and reduced anxiety for the dental patient [87]. A South African study using ART showed not only a 50% reduction in cost using this technique versus mercury dental amalgam or composite resin, but - reduced the number of primary posterior teeth extractions by 36% annually [88].

The Pan American Health Organization (PAHO) made a comprehensive evaluation of the costs of utilizing the ART technique versus the use of mercury dental amalgam in various locations in Ecuador, Panama, and Uruguay. They determined ART is the less invasive, lower-cost solution to dental caries, even when failures occur, and concluded that the cost is about half the amount of using mercury dental amalgam. They recommended training and using more auxiliary personnel, especially in remote areas, which can be successfully achieved to serve even more patients [89]. The elderly are excellent candidates for the use of the ART technique. Advantages for older patients such as significantly lower cost, stress, and panic that are associated with dental treatments are avoided, making ART not only more accessible but also more affordable. Using ART will help in promoting not only good oral health, but also improve the general health of these patients [90].

Like ART, biomimetic, and minimal invasive dentistry (MID) has only recently become more recognized as a viable technique in the dental profession. MID can best be described as the management of caries with a conservative biological approach, versus the more invasive approach of traditional surgical operative dentistry. Similar to the ART technique, this new approach to oral health is designed to preserve the natural tooth structure, as much as possible. This paradigm shift in dentistry is critically important in oral health care worldwide, as studies have proven that more invasive dental procedures can often cause harm to the patient, either from the procedure itself or the materials used. Utilizing the biomimetic or the MID method in dental restorations is slowly being introduced into mainstream dentistry. Biomimetic or MID in the long-term, is significantly better for the patient and the life of the tooth. The following criteria are essential for MID, early detection, remineralization of early enamel lesions, reduction in cariogenic bacteria in order to eliminate the risk of further demineralization and cavitation, minimal surgical intervention, repair rather than the replacement of defective restorations, and disease control [91].

The key factor in successful MID is to repair old restorations rather than replace them. Achieving this will mitigate such problems as weakening the tooth structure by increasing the

surface area of the cavity, increasing surface area that tends to make a more complex form of restoration, and creating larger restorations which usually have a shorter life span than their predecessor's possible damage to adjacent teeth [91,92].

Technology is a major driver of how MID can be accomplished successfully using tools such as digital radiology with low radiation emissions, diagnostic lasers, dental operative microscopes, ozone therapy, air abrasion, and rotary instruments for micro preparation. According to Jingarwar, et al. (2014), MID allows for "dental caries to be treated as an infectious condition rather than an end product of it…and instead of extension for prevention is now changed to constriction with conviction" [93].

Several papers have investigated how knowledgeable general dentists are in utilizing MID in their practices. Kumar, et al. (2021) used a cross-section observational survey that included 285 currently practicing dentists. The survey included questions on general knowledge of the MID approach. The data collected were tabulated and statistically analyzed. Males represented 53.33% of the study respondents and 46.66% were female. They reported that 75.08% of responders use this approach. They concluded that MID meets the standard of care and this study was indicative of a "paradigm shift" away from conventional dentistry [94].

Another survey was conducted in the UK on the understanding and perceptions of MID of general dental practitioners. Questions included: demographic details, postgraduate training in MID, number of years in clinical practice, working environment, perceptions of the methods and rationale for the choice of restorative materials in clinical practice, and knowledge of MID. Their results showed that just 28 percent of the participants had a basic knowledge of MID, which demonstrated a clear absence of knowledge among participants. They concluded that knowledge of MID amongst dental practitioners in the UK is "generally poor", GV Black techniques are archaic, but still in use today, and it is absolutely necessary to provide more training in MID [95].

Biomimetic dentistry has been described as "the science, principles, and techniques of adhesive dentistry respecting the philosophy that to restore sufficiently teeth is necessary to mimicking life and understanding the natural tooth in its entirety". The aim of biomimetic dentistry is to restore the tooth to its function, esthetics, and strength, by using materials that will regenerate dental structures and replace lost dental tissues with processes that simulate natural ones. The same philosophies of MID and ART are also found in biomimetic dentistry by concentrating on the preservation of dental pulp, repair or elimination of tooth defects, removal of pathology, saving and strengthening the intact tooth structure, and delaying the re-treatment cycle [96]. Various techniques and materials have been developed using biomimetic principles such as bioceramics, due to their biocompatibility and stability in the oral cavity, regenerative technologies i.e. stem cell therapy, pulp implantation, gene therapy, and biomimetic remineralization of dentin, together these approaches lead the way to an innovative era of biological dentistry in the 21st century [97].

Conclusion

A vast array of evidence-based, peer-reviewed scientific studies unequivocally establish that mercury dental amalgam fillings pose significant life-long health risks without providing any discernible benefits. The undeniable truth is that mercury dental amalgams are not safe. The far-reaching negative consequences of their continued use on human health and the environment are incalculable. This demands urgent attention and immediate action to safeguard public health and preserve our planet. The detrimental impact of mercury dental amalgam on human health arises from the necessity to destroy actual healthy tooth structures during the placement process. Additionally, this outdated practice perpetuates constant environmental contamination. These alarming facts have garnered international recognition, prompting widespread support for a global ban on this known neurotoxin. Many developing countries, with populations exceeding one hundred million, have already taken the progressive step of banning mercury dental amalgam, demonstrating that a complete phase-out is both feasible and necessary worldwide.

The recent commitment by the European Union to ban mercury in the dental sector by 2025 holds significant weight due to the diverse economic realities of EU member states. Even the WHO has acknowledged the feasibility of such a ban. Scientific research has consistently highlighted the adverse effects of mercury exposure on all populations, leaving us to question why developed countries like the United States, Canada, Australia, and the UK have not yet enacted similar bans. After all, viable mercury-free alternatives like ART (Atraumatic Restorative Treatment) have been in successful use for over three decades. The WHO's lack of promotion of ART, despite being instrumental in its development and implementation, raises concerns about its stance on the continued use of mercury dental amalgam. Given the established health risks and environmental impact, the precautionary principle should dictate immediate action. Modern dentistry in the 21st century calls for a transformation utilizing innovative approaches like Minimal Intervention Dentistry (MID), Atraumatic Restorative Techniques (ART), and biomimetic methods, collectively setting the new "standard of care." This biological approach has proven to be viable and well-documented, benefitting both patient health and the longevity of their teeth. It is evident that decisive action is imperative to protect human health, promote sustainable dentistry, and secure a healthier future for generations to come. By embracing mercury-free alternatives and advocating for a global ban, we can pave the way for safer dental practices and contribute to a cleaner, healthier world. The time for action is now. As mercury dental amalgam is the only product in the treaty that is directly implanted in the human body, a global ban on this toxic material is an essential step in achieving the goal to "Make Mercury History."

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Review Article

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Alarming Findings on Mercury Dental Amalgam – Latest Research Using the National Health and Nutrition Examination Survey (NHANES) Database: A Mini-Review

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ABSTRACT

Mercury dental amalgam has been used as a dental restorative material for almost 200 years. Even though mercury is the most toxic non-radioactive material known to man, there has been an ongoing controversy about its safety since it was first introduced for use in dentistry. In 2013, a global treaty was adopted to address the dangers of mercury-containing products and processes called the Minamata Convention on Mercury Treaty, which went into force in 2017. This global mercury treaty listed mercury dental amalgam as a "phase-down" product. It is the only product in the treaty that is implanted in the human body and the only product listed simply as "phase-down". While many evidence-based scientific papers have reported that mercury dental amalgam negatively affects human health, it is still the most commonly used dental restorative material in the world. Since the treaty has gone into force, many developed countries, countries with emerging economies, and developing countries have banned the use of mercury dental amalgam in the spirit of the treaty whose mantra is "Make Mercury History". However, a date certain to ban mercury dental amalgam's use globally has not yet been achieved. The latest significant findings on human exposure to mercury dental amalgam using the "Gold Standard" National Health and Nutrition Examination Survey (NHANES) database, may finally be the catalyst that will achieve the goal and "Make Mercury History" in the dental sector.

Keywords

Arthritis, Asthma, Infertility, Mercury Dental Amalgam, Minamata Convention on Mercury Treaty, National Health and Nutrition Examination Survey (NHANES).

Abbreviations

NHANES: National Health and Nutrition Examination Survey; WHO: World Health Organization; UNEP: United Nations Environmental Programme; ASGM: Artisanal and small-scale gold mining; FDI: World Dental Federation; ADA: American Dental Association; EPA: Environmental Protection Agency; FDA: Food and Drug Administration; GRAS: Generally Recognized as Safe; ART: Atraumatic Restorative Treatment; THg: Blood total mercury; MeHg: Methylmercury; IHg: Inorganic mercury; UTHg: Urine creatinine corrected mercury; CDC: Center for Disease Control and Preventions.

Introduction

The World Health Organization (WHO) deemed the first route of mercury exposure to humans is from dental amalgam [1]. Mercury dental amalgam is approximately 50% mercury, and various amounts of silver, tin, copper, and zinc. According to the United Nations Environmental Programme (UNEP), as much as 20% of the annual total global mercury consumption is used for dental restorations. Mercury which has been allocated for dental use worldwide also finds its way into the black market for artisanal-

small-scale gold mining (ASGM). This is of particular concern because ASGM is the greatest user/polluter of mercury globally, and is a priority of the Minamata Convention on Mercury Treaty [2]. The two key non-governmental organizations (NGOs) who were also major industry stakeholders of the treaty, the World Dental Federation (FDI), and the American Dental Association (ADA) are still in favor of the continued use of mercury dental amalgam. These NGOs maintain that mercury "dental amalgam is a durable, safe, and effective cavity-filling option" [3,4].

The Environmental Protection Agency (EPA) defers to the Food and Drug Administration (FDA), on the safety of mercury dental amalgam, while acknowledging that placing, removing, and chewing can cause mercury dental amalgam fillings to off-gas mercury and those vapors can be absorbed by inhaling or ingesting them [5]. The FDA continues to mislead consumers about the safety of mercury dental amalgam stating, "Mercury is used to bind the alloy particles together into a strong, durable, and solid filling." While also stating under Potential Risks of Dental Amalgam Releases that "Low levels of mercury in the form of vapor can be inhaled and absorbed by the lungs. Exposure to high levels of mercury vapor, which may occur in some occupational settings, has been associated with adverse effects on the brain and the kidney. Developing neurological systems in fetuses and young children may be more sensitive to the neurotoxic effects of mercury vapor [6]."

The FDA contends that there is very limited to no clinical data on long-term health outcomes of the use of mercury dental amalgam on women, developing fetuses, children under six, and breastfed infants, but then lists vulnerable populations that may be more susceptible to potential adverse effects from this exposure, i.e., pregnant women, women of childbearing age, nursing women, children, especially under six years old, individuals with pre-existing neurological disease, impaired kidney function, and sensitivity (allergy) to mercury or other components of mercury dental amalgam.

The FDA says mercury from dental amalgam can bioaccumulate in bodily fluids, tissues, kidneys, and the brain, but then states that "studies have not shown that increased mercury levels and bioaccumulation due to dental amalgam result in detectable damage to target organs". This contradicts their previous statements, which can confuse the consumer who is trying to decipher if there are serious health risks, or not. For example, the FDA does not recommend removing mercury dental amalgam because of the destruction of the healthy tooth structure and a temporary increase in mercury vapor exposure. But doesn't discuss the potential toxicity of this acute mercury exposure if extremely significant and rigorous engineering controls are not followed during the drilling process and the dangerous risks of this exposure not only to the patient but also to dental workers [6].

Dental workers including dental assistants, dental hygienists, and dentists are exposed to higher levels of mercury due to occupational exposure. As previously mentioned, mercury is absorbed by inhalation or through the skin. Various common dental procedures involve mercury dental amalgam removal, which is often performed using a high-speed dental drill. Warwick et al. (2019) designed a study to answer numerous questions such as:

- "What concentration of mercury vapor can be reached from particulate generated from the removal of dental amalgam restorations using a high-speed drill?
- How long can the particulate volatilize mercury vapor?
- Is the peak vapor generated associated with the mass of the mercury in the particulate?
- Does the amount of amalgam removed in each sample affect the peak Hg vapor?
- Does the amount of amalgam removed in each sample affect the mass of mercury in particulate collected?"

They noted that while there are diverse occupational safety levels depending on territories and governments, it is mutually agreed that mercury vapor can be absorbed by the lungs and skin.

There are engineering controls that have been established which are recommended to minimize mercury exposure that include:

- "Copious amounts of water
- Reduced drilling of the amalgam by cross-hatching the material and removing bulk pieces
- High volume suction with custom isolation tip (Clean Up brand)
- Secondary air evacuation
- Non-latex dental dam on the patient
- Full facial and body barrier for patient
- Patient saliva suction behind the rubber dam
- Alternative air supply to the patient face shield, mercury-rated gown and head protection, nitrile gloves, mercury-rated breathing protection for dentist and assistant"

Warwick et al. found that mercury vapor volatilization from particulate generated from mercury dental amalgam removal with a high-speed dental drill was a significant source of mercury exposure, even when a variety of engineering controls were used. They concluded that it is imperative to use all engineering controls when removing mercury dental amalgam, to minimize the risk of mercury exposure [7].

It is significant to note that mercury dental amalgam was grandfathered in under Generally Recognized as Safe (GRAS) due to long-term usage in 1976. Therefore, it has never been clinically tested for safety and efficacy even though it is implanted in the human body [8].

In 2017, the WHO stated that "Exposure to mercury – even small amounts – may cause serious health problems, and is a threat to the development of the child in utero and early in life. Mercury may have toxic effects on the nervous, digestive and immune systems, and on lungs, kidneys, skin, and eyes." However, during the treaty process, the WHO (2009) only recommended a "phase down" for mercury dental amalgam as the proper approach, stating it would be problematic for public health and the dental sector to

ban its use [9]. The same stakeholders mentioned above, continue to discuss mercury dental amalgam's inexpensive cost, durability, ease of use, and the need for the development of mercury-free dental materials. However, a pilot project developed in Tanzania that was supported by the WHO over 30 years ago created what is called "Atraumatic Restorative Treatment" (ART), which uses glass ionomer cement, a non-mercury filling material. ART doesn't require the use of electricity or water and is used without anesthesia which is especially important for dental care in remote regions. Using the ART technique has the lowest cost, reduces destruction to the healthy tooth structure and tissue, is less painful, causes less sensitivity, and reduces dental patient anxiety. It is well documented that the success of ART and its survival rate shows it as being equal to or better than mercury dental amalgam [10,11].

Mercury Dental Amalgam

According to Sanchez-Alarcon et al. (2021) mercury dental amalgams "provide significant iatrogenic exposure to xenobiotic compounds". They noted that the number of mercury dental amalgams and exposure time can cause DNA damage, which can be dangerous for vulnerable subpopulations [12].

Andreoli and Sprovieri (2017) reported on over 250 symptoms related to mercury exposure in humans, involving the neurological, renal, respiratory, gastrointestinal, cardiovascular, hepatic, reproductive, and immune systems, with fetotoxicity and genotoxicity, noting methylmercury may possibly be carcinogenic. Because of the complexity and multitude of pathways that mercury affects humans, with either acute exposure or long-term low dose exposure, it is very difficult to diagnose mercury toxicity. Studies have now determined, however, that specific genes can assist in identifying an individual's risk of toxicity to mercury [13].

Siblerud and Mutter (2021) reviewed the literature to provide a snapshot of the toxic health effects produced by exposure to mercury dental amalgams. Some of their findings included:

Mental Health Disorders

- depression, anger, irritability
- schizophrenia and bipolar disorders

Cardiovascular Problems

- high blood pressure
- heart rate
- hemoglobin
- hematocrit
- red blood cells

Diseases Linked to Mercury Dental Amalgam

- Alzheimer's disease (AD)
- Multiple sclerosis
- Amyotrophic lateral sclerosis

They remarked that there is a preponderance of evidence that exposure to mercury from dental amalgam is a causative factor in many health maladies. The negative effects of exposure to individuals are diverse. Health problems that are related to mercury dental amalgam are significant and numerous [14].

Latest Findings National Health and Nutrition Examination Survey (NHANES) Database and Mercury Dental Amalgam

The NHANES database is considered the "Gold Standard" for the health and nutritional status of the United States population [15]. The NHANES database is the only existing national survey that captures both environmental and clinical data and provides an invaluable database unmatched by any size or content. Starting in the 1960s it was designed to assess the health status of children and adults of all demographics, races, and ethnicities using personal interviews, physical exams, and lab testing [16].

Using the NHANES data from 1999-2000, Dye et al. investigated the link between urinary mercury concentrations and dental restorations in US women of reproductive age. They noted that this was the first study to assess the relationship between mercury dental amalgam restorations and mercury concentrations in a nationally represented US population sample. They found that the women who had higher levels of mercury in their urine also had a greater number of mercury dental amalgam surfaces. They also stated that they did not investigate the adverse health effects of low thresholds of mercury exposure, but their reference data would be a significant contribution to the ongoing scientific and public health policy debate on the use of mercury dental amalgam [17].

Richardson et al. (2011) examined mercury exposure and risks from dental amalgam in the US population, post – 2000, using the NHANES database. It was reported that between 2001 – 2004, 181.1 million Americans had a total of 1.46 billion dental restorations. This included children as young as 26 months and the majority of these dental restorations were mercury dental amalgam. By utilizing various scenarios, they calculated that about 67 million Americans would exceed the mercury reference dose determined by the EPA, and almost double that number of people would exceed the reference dose by California EPA standards. It is widely accepted that mercury dental amalgam constantly releases mercury. Regardless of how small the dose is, it can present a health risk if "the substance is sufficiently toxic and received in sufficient dose to exceed a reference level considered 'safe' [18]."

A study using the NHANES database from 2001-2010 was designed to investigate the relationship between socioeconomic status and environmental toxicant concentrations in adults. Exposure to environmental pollutants has been linked to various widespread chronic diseases. They found that mercury dental amalgams may explain increased levels of mercury levels in individuals of higher socioeconomic status because they visit their health care providers more often. This may include more mercury dental amalgams, which would allow for higher levels of mercury exposure [19].

For the first time ever, Estrich et al. (2021) was able to calculate the number of mercury dental amalgam fillings in the US population using the NHANES dataset from 2015-2016. They only included individuals 15 years and older. They found that non-Hispanic

Whites had the highest number of teeth that included a mercury dental amalgam restoration, while non-Hispanic Blacks had the lowest number of mercury dental amalgam restorations. They also stated that over half of the US population does have mercury dental amalgam restorations, however, that percentage may be significantly higher when counting the mercury dental amalgam restorations of individuals under the age of 15 years old [20].

Chewing, brushing teeth, drinking hot liquids, and simply breathing will release mercury vapor from mercury dental amalgams. Exposure to mercury vapor has been identified as a significant health risk. The objective of a recent study by David and Mark Geier was to investigate the mercury vapor safety limits from mercury dental amalgams using the NHANES database. Their results found that roughly 91 million adults had one or more mercury amalgam fillings, and approximately 67 million had no mercury amalgam fillings. There were differences noted for gender and racial groups. The daily mercury vapor dose from the exposure to mercury dental amalgams was in excess of approximately 86 million people when using the exposure safety limits of the California EPA, which are the most stringent in the US. When using the US EPA safety limits mercury vapor exposure was in excess for about 16 million adults. Like previous studies, the Geier's observed that higher amounts of urinary mercury correlated with a higher number of mercury dental amalgam fillings. This study showed that a significant portion of the US population is exposed to mercury vapor over the current safety limits which should be cause for alarm in the general population [21].

Infertility is a global problem affecting over 185 million people. While it has been found that there are causative factors such as endometriosis, autoimmune disease, fallopian damage, etc. it is still complicated and ambiguous. Zhu et al. (2020) examined elevated blood mercury levels and their association with infertility in American women using the NHANES data from 2013-2016. There have been multiple studies on animals that show that mercury exposure could cause reproductive harm but studies on infertility in women have yet to be conducted. What has been shown is there are elevated mercury levels found in infertile women. Using 1796 NHANES participants, they intended to establish the linear and non-linear relationship between mercury and infertility. Their study found a positive and non-linear relationship between mercury and infertility and noted that infertile women must consider mercury exposure sources as potentially harmful [22].

It is universally recognized that the two most common exposures to mercury in a non-occupational setting are mercury dental amalgams and seafood. Using the NHANES database Yin et al. investigated this hotly contested subject as to which exposure is a greater risk to humans. They noted that previous NHANES data from 2003-2004 and 2010-2012 recorded the number of dental surface restorations, but they did not state the type of restorative materials that were used. However, by counting the number of dental restorations they were able to significantly predict blood mercury in all demographics using the NHANES data.

Regarding fish/seafood consumption, both the FDA and EPA have been publishing advisories on the dangers of eating certain species that are of particular concern due to high levels of mercury contamination for vulnerable populations such as women and children. However, it is only recently that there are advisories to these same vulnerable populations about mercury dental amalgams. Studies have shown that the number of mercury dental amalgams has been linked to brain, blood, and urinary concentrations of mercury. By using the NHANES data from 2015-2018 they found that the higher number of mercury dental amalgam restorations significantly raised blood concentrations of blood total mercury (THg), methylmercury (MeHg), inorganic mercury (IHg), urine creatinine corrected mercury (UTHg). Their results indicated that individuals with more than five mercury dental amalgam fillings could be a significant source of mercury exposure. They found that children with mercury dental amalgam fillings had significantly elevated blood and urine mercury levels. Most significantly they reported that children under six years old with more than five mercury dental amalgam fillings had the highest blood IHg and urine UTHg amongst all age groups [6,23].

Again, using the NHANES database the Geier's looked at the connection between mercury dental amalgam exposure and reported asthma diagnoses using the age group of adults from 20 to 80 years old. There were a total of 97,861,577 persons with one or more dental amalgam surfaces (exposed group) and 31,716,558 persons with one or more non-mercury dental restorations (non-mercury control group). It had been previously suggested that most researchers are looking at the negative systemic effects of exposure to mercury in humans. The Geier's noted that the location of the respiratory system, its immediate contact with mercury vapor, and its critical importance in whole-body health necessitated their investigation and the consequences of this exposure. According to the Centers for Disease Control and Prevention (CDC) (2009), the rate of asthma in the US is growing each year, accounting for about one in twelve people or about 25 million who have been diagnosed with this disease. The cost of asthma is also rising for example from 2002 to 2007, there was a 6% increase from $53 billion to $56 billion. The Geier's calculations using their current data of asthma-related health costs to individuals with mercury dental amalgam would be about $47,838,861, and the cost over 25 years for these individuals would be $1,195,971,525. They concluded that the increase in exposure to mercury dental amalgam was related to an increased risk of reported asthma diagnoses, in the US adult population, and more studies are needed in this area [24].

The CDC has stated that arthritis is a leading cause of disability and causes pain, aching, stiffness, and swelling of the joints with accompanying physical and mental adverse effects.

Another investigation by the Geier's (2021) studied the relationship between mercury dental amalgam and arthritis diagnoses amongst adults ages 20 to 80 using the NHANES database. They theorized that while arthritis may have a genetic, or epigenetic vulnerability as a causative factor, they also submitted that environmental toxins like mercury could be a risk factor. Included in their

investigation were a total of 86,305,425 weighted -persons with 1mercury dental amalgam and 32,201,088 weighted -persons with ≥1 non-mercury dental restoration (controls). They observed a significant increase in the arthritis exposed group compared to the controls noting that they also found a significant link between mercury dental amalgam and arthritis risk and a dose-dependent mercury dental amalgam associated immune-stimulation/immune-suppression with arthritis. Their cost analysis based on new-onset arthritis diagnosis between medical and lost wages was a total of $281,633,494 annually. They advocated for dentists to inform their patients of the risk factors associated with mercury dental amalgam and arthritis [25].

Conclusions

The monumental yet meticulous data collection that creates the NHANES database is the "Gold Standard" in the world. Now that the NHANES database shows the actual number of mercury dental amalgam fillings in the US population, for the first time ever researchers are able to analyze that data and investigate the health risks associated with that exposure. Even though we have included some of the most recently published papers, we believe that this is just the tip of the iceberg as to what diseases will be investigated using the NHANES database and the link between mercury dental amalgam. There is no doubt that the continued use of mercury dental amalgams may not only cause harm to those individuals that have them but also the legacy pollution that results from its continued use, clearly shows mercury can never be captured or contained once it enters the environment. Therefore, the long-term environmental impact is incalculable.

In several of the papers in this mini-review, health care costs were calculated based on the NHANES data and showed the staggering financial implications of just two diseases. As more studies are conducted it is likely that they too will reveal astronomical costs for health care that are related to individuals who have mercury dental amalgams. Meanwhile, the ADA and FDI industry stakeholders, continue to lobby against an outright ban, even as recently as the 4th Conference of the Parties (COP 4), where the African Group's proposal to ban mercury dental amalgam was rejected. This is the second time the collective African Group which represents 54 countries and is the largest regional group at the UN level, has tried unsuccessfully to get a ban on mercury dental amalgam.

The intentional continued push-back from banning the use of mercury dental amalgam in the dental industry continues. What their feeble arguments fail to address, is the continued use of mercury dental amalgam will prolong human exposure which has been linked to many health problems, and also the mercury waste problem that will continue indefinitely. The industry stakeholders do, however, continue to promote biased and deceptive messaging to the public at large regarding the safety of mercury dental amalgam when evidence-based science confirms that plainly, it is not safe. Additionally, the FDA provides consumers with mixed messages that are extremely confusing to the reader. The toxicity of mercury dental amalgam has been widely established around the world with evidence-based scientific research, while industry stakeholders continue to say it is "safe". Even though there have been many mercury-containing products such as blood pressure cuffs, lighting, switches, and thermometers that have been banned globally, the refusal to ban mercury dental amalgam continues.

Another question that needs to be asked is with all that is known about mercury dental amalgam being sold illegally for use in ASGM, which is the greatest polluter of mercury worldwide, why are the countries where ASGM is a monumental problem, are they not pushing for a ban on mercury dental amalgam? Many of the researchers who have been cited in this paper are sounding the alarm as to the devastating effects that can occur from exposure to mercury dental amalgam. Their findings are irrefutable and not only health care policymakers, but governments who have ratified the treaty must take action to finally "Make Mercury History".

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Biological Dentistry-Whole Body Health-Shifting the Paradigm in the 21st Century

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Short Communication

For almost two hundred years dentistry has gone through many changes. Some of the changes have been good, and some of the good changes, have been dismissed as bad. The dismissal of "The Focal Infection Theory" for example, is now proving to have been very bad. In the early 1900's, Dr. William Hunter brought forward the idea of dental infections as being the cause of diseases [1]. Others came after Hunter, such as Dr. Frank Billings, where the term, "Focal Infection Theory" was first introduced.

Billings noted that the focus of infection usually occurred in the head, and in teeth that had excessive dental work. He stated that tonsils were especially at risk. Dr. Edwin Rosenow, followed Billings, and continued researching the Focal Infection Theory, saying that root canal procedures should cease [2]. The dentists and doctors who were devotees of the Focal Infection Theory were called the "one hundred percenters", because they took what would have appeared to be drastic measures in oral health care, by removing all teeth to prevent diseases from allergies to schizophrenia.

They also would perform tonsillectomies as part of their protocol [3]. While all the of the doctors mentioned above, made tremendous advancements in dentistry, the research of Dr. Weston Price, was the most prolific and meticulous. Price worked with the highly regarded luminaries of the day, such as Charles Mayo, Victor Vaughn, Milton Rosenau and others. In fact, he had a research team of sixty scientists from various branches of medicine and dentistry that included experts in bacteriology, pathology, rheumatology, immunology, chemistry, cardiology, and surgery.

He spent 25 years investigating endodontically treated teeth and pulp less teeth as a continuation of the Focal Infection Theory. Dr. Price's impeccable research on root canal teeth and its causation of many diseases was done by removing the tooth and placing it into a rabbit. Whatever the disease of the patient, the rabbit would develop the same disease symptoms. Price would replicate this thousands of times. Many times, the original donor sample would be placed in multiple rabbits and again, the rabbits would develop the same disease [4].

Some years later, the Focal Infection Theory was deemed to be "flawed" citing poor controls and massive doses of bacterial inoculum that were used in the scientific studies. The endodontic practioners completely rejected this theory, even though it had been shown to have a basis of fact in the scientific literature [3]. The Focal Infection Theory is now being revaluated, and current research is proving that many of today's diseases do in fact start in the mouth. The World Health Organization (WHO) has stated that oral infections affect half of the world's population, with severe periodontal disease as the eleventh most prevalent disease globally. Dental disease is now a global pandemic [5]. Many of the most common dental procedures such as; root canal treatments, dental implants, nickel braces, and ordinary tooth extractions are being investigated as the causation of diseases.

There are still missing pieces in dentistry, however, one very important piece that dentists are not looking at, is the toxicity of the dental materials they are using, and how these materials interact with each other over a period of time. This is a serious problem, particularly when multiple metals are used that were

once thought to be inert, such as; mercury dental amalgam, a restorative material that has been used for almost as long as modern dentistry has been in existence. Dental mercury amalgam contains about 50% mercury, a known neurotoxin.

Titanium is not only used in dental implants, but also in many dental materials and has shown to be toxic. Nickel braces, are often called "stainless steel", as are nickel crowns. Nickel has been deemed to be carcinogenic, according to the National Toxicology Program, Department of Health and Human Services. When oral galvanism occurs, particles are released from the oral cavity and can translocate to other areas in the body, causing potential toxicity and biological hazards. These common dental metals and materials are not only a risk of exposure for the patients, but also for the dentist and the dental workers, when placing and removing these materials [6].

What has also happened is that dentists have taken the role of "tooth mechanics" without the understanding that the oral cavity is the foundation, for whole body health. This is because the majority of dental professionals are only looking at the functionality of the procedures that are all too common in dentistry. Naturally the ears, eyes, nose, and throat, are closest to the oral cavity, which is why they too, would be affected by the mouth.

Harper et al. [7] noted that about 70% medical teaching institutions commonly have only 4 hours or less on oral health, with 10% having no oral health in their curriculum, at all. Health care providers have performed physical assessment of the head, ears, eyes, nose, and throat (HEENT) in the same fashion since its inception centuries ago. For the majority of primary care providers, the traditional HEENT examination excludes examination of the oral cavity, as well as omitting oral health and its linkages to overall health in the health history. By adding an O (oral) to HEENOT, the NYU College of Nursing and the College of Dentistry are working to bridge the gap and make it an essential element in primary care [7].

Since the majority of medical students are not being introduced to ear, nose, throat, otolaryngology and dentistry, this area of the body continues to be a mystery. Their only encounter with this area is because of trigeminal pain due to trigeminal neuralgia, which are explored in the cases of neurosurgical procedures. While there are many possible reasons for severe orofacial pain, its origin is usually from a dental source. Orofacial pain conditions include sinuses, salivary gland, ears, eyes, throat, mandibular, and maxillary bone pathology. Therefore, it is critical to have an understanding of how common dental problems can be successfully treated and eliminate the source of pain safely and effectively [8].

There has long existed a colossal chasm between medical doctors and the dental profession that is only now starting to close, particularly in the world of integrative medicine. Current research has shown that 30-40% of chronic maxillary sinusitis cases are caused by oral conditions. The infections of the maxillary posterior teeth, pathologic lesions of the jaws and teeth, dental trauma, or by iatrogenic causes, such as dental and implant surgery, are linked to sinusitis [9]. Using the data base of the Korean National Health Survey, Kim et al. looked at the relationship between temporomandibular joint disorder (TMD) and tinnitus.

After adjusting for all covariates of the 11,745 participants, they found that those who had TMD had more tinnitus than those without TMD. Furthermore, individuals that had dental pain in addition to TMD had a higher occurrence of tinnitus than TMD alone [10]. According to Zope et al. [11] ear pain is often very easy to establish and resolve, however, while the pain presents itself in the ear, the source may actually be dental related. Common ear pain can be caused by impacted teeth, dental infections, neuralgia, sinus infections, TMD, and myalgia of masticatory muscles along with other conditions. They concluded that it is important to work in conjunction with a dental professional for positive outcomes [11].

A pilot study was conducted to investigate the relationship between the oral microbiome and dental health in primary open angle glaucoma. Open angle glaucoma is the most prevalent of all glaucoma cases worldwide, affecting about 70% of those who are diagnosed with this condition. While the study sample size was small, along with limited resources and other limitations, from the research gathered, they felt from a public health perspective that it would be "worthwhile exploring the possibility of glaucoma prevention in high risk populations by improving dental care" [12]. Akhtar et al. [13] reported that dental infections and dental extractions are a predisposing risk factor for conceivable life-threatening infections of the head and neck. This is a particular risk, due to unsanitary conditions and for patients with compromised immune systems, in developing countries [13].

The link between oral manifestations of autoimmune rheumatic diseases was investigated by Abrao et al. [14] noting that it is commonly ignored in clinical practice. Many autoimmune rheumatic diseases are possibly originating in the mouth, such as rheumatoid arthritis, inflammatory myopathies, systemic sclerosis, systemic lupus erythematosus, relapsing polychondritis, and Sjögren's syndrome. These oral indications such as hypo salivation, xerostomia, temporomandibular joint disorders, and lesions of the oral mucosa, periodontal disease, dysphagia, and dysphonia may be precursors of rheumatic diseases [14].

A study by Gera and Kumar investigated the awareness and practice amongst a group of 29 otolaryngologists, to see their knowledge base on otolaryngologic indicators of rheumatic diseases. The above-mentioned rheumatic diseases are frequently seen by otolaryngologists, because patients that have ENT problems, go to them first. This paper reports that awareness of these symptoms are slight, and that early and precise diagnosis, along with pre-emptive treatment or referral to specialists, may prevent illness or death. They found that while there was an awareness of otolaryngologic manifestations of rheumatic diseases, their index of suspicion, as well as practical knowledge

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and confidence for evaluation of such diseases were not sufficient [15].

What can we do to really achieve remarkable healing results for the patient, instead of simply treating disease symptoms? A simple visual examination of a patient's mouth can often provide insight as to what may be causing health issues, or can possibly prevent a potential disease risk. All medical professionals can easily implement this straightforward procedure with each patient. We believe that it is necessary to create a real partnership between both the medical and dental profession, and most importantly the patient. We also believe that this is a feasible solution, because one profession cannot do this alone, and of course, this cannot be achieved without the patient's participation.

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Mercury Contamination from Dental Amalgam

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Background. Mercury in dental amalgam is a hidden source of global mercury pollution, resulting from the illegal diversion of dental mercury into the artisanal and small-scale gold mining sector, to crematoria emissions from the deceased and sewage sludge that is sold to farmers. These significant mercury sources result in air, water, and food contamination that consequently have a negative impact on human health.
Objectives. The aim of the present study was to investigate and report on all of the various pathways mercury in dental amalgam can enter the environment.
Methods. The present study searched the electronic data bases of PubMed and Google Scholar. Peer reviewed journals and references of studies included for full-text review were examined for potentially relevant studies. Articles published between 2000 to 2018 were searched and specifically screened for articles that referenced "Dental Amalgam," and the following key words in various combinations: "Minamata Convention on Mercury Treaty," "Sewage Sludge," "Cremation," and "Artisanal and Small-Scale Gold Mining." Data were included on the most populous countries of China, India, the United States, Brazil, and the European Union collectively. We also included data on cremation statistics and current global trends, looking at populations where cremation is a common practice, such as Japan and India.
Discussion. Dental amalgam represents a significant, but understudied area of global mercury pollution that includes cremation, sewage sludge, burial, and small-scale gold mining.
Conclusions. Mercury used in products and processes, including dental amalgams, is a global pollutant. Even after the last mercury dental amalgam is placed, its toxic legacy will continue for decades, because of its pervasive bioaccumulation in the environment. Government regulatory agencies should make it mandatory to utilize available technologies, not only in developing countries, but also in developed countries, to reduce mercury contamination.
Competing Interests. The authors declare no competing financial interests.
Keywords. mercury dental amalgam, Minamata Convention on Mercury Treaty, sewage sludge, cremation, artisanal and small-scale gold mining
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Introduction

Mercury is a pervasive environmental pollutant that has a variety of adverse health effects in humans. Mercury has three forms: elemental, inorganic and organic, which each have their own profile of toxicity. Human exposure to mercury generally occurs by inhalation or ingestion.[1] According to the World Health Organization (WHO), the principal human exposure to mercury is from dental amalgams.[2] The WHO also lists mercury as one of their top ten chemicals of major health concern.[3] Anthropogenic activities have nearly tripled the amount of atmospheric mercury and it is increasing at 1.5 percent annually. Once mercury enters the food chain it can bioaccumulate in humans and cause adverse health problems. Dental amalgam is a source of human exposure to elemental mercury.[4]

Dental amalgam has been used as a restorative treatment in dentistry for well over 170 years. It is a mixture of several metals, consisting of silver, tin, zinc, and copper; however, about 43-54% of the main component is mercury.[5] Dental amalgams are not inert, either chemically or environmentally. Dental amalgam enters discharge systems that contain sanitants, cleaners, and other compounds that can generate soluble and colloidal mercury, which will be mobilized into the environment. Environmental action includes erosion or oxidation (air and sunlight) and microbial transformations, which can also mobilize mercury into the environment. A review of a study done by the Environmental Protection Agency (EPA) that estimated emissions from dental amalgam may have been significantly underestimated. The EPA's previous study estimated that 0.6 tons/year of dental amalgam is being released, however, the present account indicates that between 6 and 35 tons of mercury is discharged into the environment from dental amalgam, which is considerably higher than the EPA's estimate.[6]

The United Nations Environmental Programme (UNEP) reported that the dental sector uses about 340 tons of mercury in dental amalgams each year. It is estimated that 100 tons of dental mercury enters the waste stream annually.[7] There are several serious problems that are created from dental amalgam pollution. First, mercury pollution is caused by the historical use of dental amalgam. Additionally, the current use adds up to mercury releases from historical practices. Some emissions associated with dental amalgam are from dental waste incineration, burial, cremation, and off-gassing of mercury from dental amalgam corrosion in the mouth.[8]

Cain *et al*. attempted to quantify mercury releases of the most significant categories of mercury-containing products, using a life cycle approach from production to disposal of these products in the US. They used substance flow models and estimated mercury releases for 1990, 2000, and 2005. Regarding the use and disposal of dental amalgam, human waste, tooth loss, cremation and infectious waste were considered. While these routes may result in significant releases of mercury, it was determined that cremation is the most critical. Additionally, their model calculated that approximately 150 kg of mercury is released annually in exhaled breath as a result of dental amalgam fillings.[8,9]

Throughout the last several decades, mercury used in products and processes have had a tremendous impact on environmental mercury pollution. Dental amalgam amounts to about 1/5th of the global consumption of mercury. Mercury is a persistent toxic pollutant, traveling between the atmosphere, land, and water. The atmosphere is the principal transport route. Atmospheric mercury can globally transport for up to a year; therefore, mercury pollution created in one region can contaminate another through the air, at great distances from the original source.[10]

The aim of the present study was to investigate and report on the many different ways that mercury in dental amalgam enters the environment.

Abbreviations			
ASGM	Artisanal and small-scale gold mining	*EPA*	Environmental Protection Agency
DSRs	Dental surface restorations	*UNEP*	United Nations Environmental Programme

Methods

To our knowledge, this is the first paper to investigate and report on all of the various pathways mercury in dental amalgam enters the environment. The present study used the electronic data bases of PubMed and Google Scholar and searched for articles from peer reviewed journals. Additionally, references of studies included for full-text review were examined for potentially relevant studies. Articles published between 2000 to 2018 were searched and specifically screened for articles that referenced "Dental Amalgam," and the following key words in various combinations: "Minamata Convention on Mercury Treaty," "Sewage Sludge," "Cremation," and "Artisanal and Small-Scale Gold Mining."

Due to a research gap, there were very few peer reviewed published articles in the areas of cremation, sewage sludge, and artisanal and small-scale gold mining (ASGM). Therefore, we also conducted a grey literature electronic search using targeted websites and Google search engines to access additional relevant sources. We used the same key words and the different combinations as mentioned above. The full text of publications were screened that provided the following supplementary references from various governmental and non-governmental organizations including the Cremation Association of North America, the World Health Organization, the Food and Drug Administration, the United Nations Environmental Programme, the Arctic Monitoring and Assessment Programme, the European Commission, and the Environmental Protection Agency.

Data were included on the most populous countries of China, India, the United States (US), Brazil, and the European Union (EU) collectively, and their number of dental schools, as mercury use in dental amalgam is still being taught around the world. We also included data on cremation statistics and current global trends, looking at populations where cremation is a common practice, such as Japan and India. While some statistical data was found on cremation in terms of populations worldwide, information on mercury pollution from this source was woefully lacking and this lack of studies was consistently mentioned by the authors in the few articles that we found. Therefore, we included data on large-population studies on tooth surfaces restored with dental amalgam, because the legacy of dental amalgam will impact the environment over the life of the individual, and even after death.

There were no exclusions of the literature based on the country of origin, however, the majority of the included studies for this paper were from the US and the EU. Only English language articles were included. There exists a tremendous amount of research on mercury in general—we presented an overview on articles that were related to dental amalgam and how it enters the environment. Our search strategy is illustrated in Figure 1.

Results

A total of 433 articles were screened from PubMed and Google Scholar, as well as grey literature that included WHO, EPA, UNEP, Cremation Association of North America (CANA), government and non-government sources. After screening for duplicates, abstracts, and articles that did not meet the inclusion criteria, 59 articles were included (*Table 1*). The results of our research demonstrate that dental amalgam is an understudied source of mercury pollution in the environment. There is limited knowledge in its contribution to global air pollution through cremation, ground water and soil pollution from burial, sewage sludge that is sold to farmers, and the true amount being used in ASGM. Based on information from the various existing research that we found, cremation is a much larger source of global mercury pollution that continues to grow and needs further study. Our results lead to similar conclusions from the previous studies. The main limitation is the lack of research that is linked to the global pollution from this source in areas outside of the obvious, which is the dental office.

Discussion

The following sections discuss the various pathways that dental amalgam has become a significant contributor of mercury pollution, and the lack of existing research.

Dental amalgam use globally

The current world population is more than 7.5 billion. In 2004, it was estimated that there were 1.8 million dentists around the globe.[11] China is the most populated country in the world; however, according to Huang *et al*., in 2007 there were only 40 dental schools in the country.[12] The second most populated country, India, has over 1.3 billion people. India's dental industry has 289 dental schools, the most worldwide. According to Sandhu *et al*., in the early 2000's there were approximately 26,000 graduating dentists annually.[13] Toxics Link stated that in 2012, about 70% of the Indian population had cavities, and about 58% of that population went to a dentist for treatment. There were 121,000 listed dentists and the use of dental amalgam was estimated at 72 tons annually.[14]

In 2009, Saliba *et al*. reported that Brazil had more dental schools and graduated more dentists each year than the US and the EU combined, second only to India. Brazil's dental professionals represent 12% of all dental professionals in the world, having one of the largest numbers of dentists per capita globally.[15] According to the American Student Dental Association, there are 66 dental schools in the US and Puerto Rico.[16] The EU had more than 160 dental schools in 2009 as reported by Murtomaa.[17] As of 2007, dental amalgam was the second largest use of mercury, after chlor-alkali production in the EU. This study estimated the range to be between 55 and 95 tons a year of mercury for dental use, with an average of 75 tons.[8]

The World Health Organization confirmed that decreasing the use of dental amalgam is not only important in reducing human exposure, but also to lessen the considerable amount of mercury that is estimated to be released into the environment from this source. The use of dental amalgam and its applications, such as illegal sales and use in ASGM, improper waste management, or even through cremation, is contributing to the problem of global mercury pollution.[18]

Dental amalgams off-gas mercury vapor. The newer high copper amalgams are less stable and create a much greater release of mercury vapor. These amalgams emit about ten times more mercury than the mercury fillings prior to the 1970's.[19] Estimates from the EU study suggest that dental amalgam is a major contributor to the overall EU environmental emissions of mercury from anthropogenic activities. Mercury released into the air can be partly deposited into other environmental locations such as soil, vegetation, or surface water.[8]

Dental amalgam and sewage sludge

The European Federation of National Associations of Water Services represents national drinking and waste water services for the public and private sector in 29 countries. In a 2016 document titled, "Dental Amalgam and Mercury Regulation", the European Federation of National Associations of Water Services advocated for a ban on dental amalgam in order to decrease mercury in the sludge from the wastewater treatment plants. They noted that the major source of the mercury in wastewater in most treatment plants in the EU is from dental amalgam.[20]

According to the US EPA, dental offices contribute the largest source of mercury into sewage treatment plants. Nationally, dentists discharge

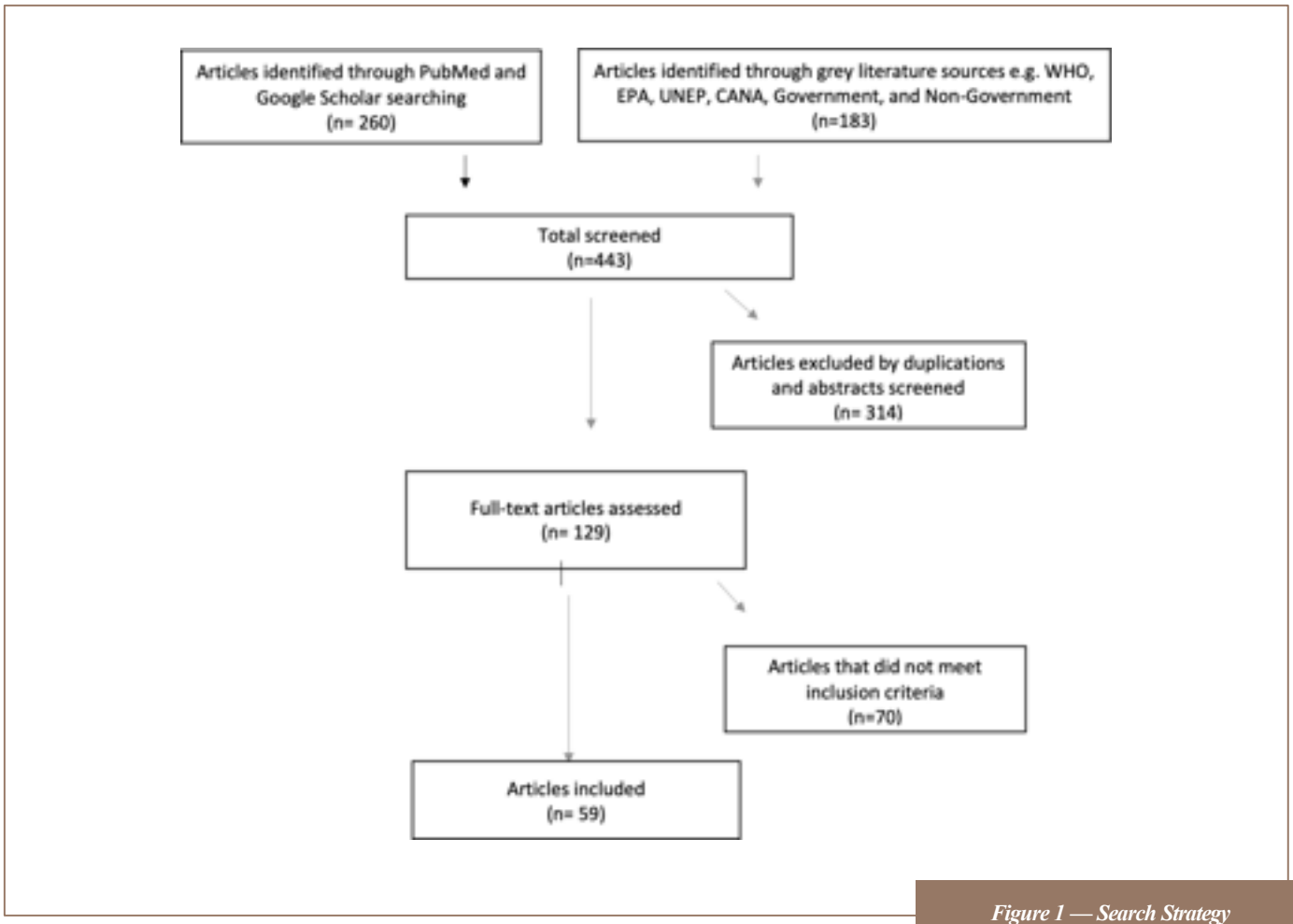

Figure 1 — Search Strategy

about 5.1 tons of mercury into publicly owned treatment works, and most of this mercury will end up in the environment.[21] Once the amalgam waste has gone through the sewage treatment plant, the remaining amalgam waste becomes sewage sludge. This sewage sludge is then disposed of in landfills, incinerated, or sold as fertilizer for agriculture purposes. These pathways of disposal of sewage sludge release mercury into groundwater or air.[22] Dentists typically dispose of excess amalgam into specific medical waste containers, however, if this waste is incorrectly disposed of, the amalgam may be incinerated, causing the mercury to enter the air where it will eventually end up in the water or

Study Source	Studies (n)	Countries (n)
PubMed/Google Scholar	25	15
Grey literature: World Health Organization (WHO), United States Environmental Protection Agency (USEPA), Cremation Association of North America, United Nations Environment Programme (UNEP), Government and non-Government	34	11
Total	**59**	**21 (counting duplicate countries)**

Table 1 — Included Studies

on land.[23]

Dental amalgam and cremation

A substantial source of mercury pollution comes from cremation. Estimations of the amount of mercury released via this pathway vary considerably, due to the large number of dental restorations.[24] Cremation emissions add to both environmental pollution in areas close to the source and also countrywide emissions due to atmospheric transport. These emissions are deposited primarily through rain. Mercury is persistent and can change in the environment into methylmercury, which is extremely toxic.[25] During cremation, mercury will enter the process, since it is not only from dental amalgam in teeth, but also due to bioaccumulation of mercury in the body.[14]

Global cremation rates are increasing for various reasons, such as cost, consumer preferences for an easier, less formal funeral service, fewer religious restrictions, and environmental impact. India, where cremation is an ancient custom, and Japan, where it is the most common practice for disposing of human remains, have extremely high cremation rates. Meanwhile, Taiwan, Hong Kong and Switzerland have cremation rates of over 80%. Internationally, in concentrated urban areas, cremation rates are often greater than 70%. This is due to population density and lack of burial space. As of 2015, the national cremation rate in the US was expected to exceed burial rates and is projected to grow to 78% by 2035.[26]

According to the European Environment Agency inventory guidebook in 2016, mercury in dental amalgams may contain 5 to 10 grams of mercury depending on the number of fillings and type of material used. The emissions factors from cremation have a very high uncertainty due to the methods used, such as the operating temperature, residence time in the secondary combustion chamber, and fuel (such as fuel oils in Sweden or natural gas in North America). The extremely high variation is also due to limited testing performed to derive emission factors or design characteristics.[27]

In 2005, the top three emission countries for all products and processes using mercury were China, India, and the US. At that time, cremation emissions were reported to be an average of 26 tons, ranging from 20 tons to 30 tons. This does not include additional releases from the production of mercury in dental amalgam, but indicates that this release amount is ambiguous.[28] A 2009 study projected that by 2012, 42% of the Indian population would have access to a dentist and estimated 574 tons of mercury in dental amalgam would be captured in the population, leading to a 2.8- fold increase of mercury in fillings since 2000. Using a conservative estimate of 50% mercury present in original fillings, it is estimated that India emits around 1.4 tons of mercury during cremations annually.[14]

A study in Switzerland estimated that each cremation released between 2 and 4 grams of mercury, with a maximum of 8.6 grams in an individual cremation.[24] In 2012, Richardson updated a risk assessment on mercury exposure and risk from dental mercury amalgam in the Canadian population that was originally published in 1996. New data became available from the Canadian Health Measures Survey (2007 to 2009) that specifically recorded the number of tooth surfaces restored with dental mercury amalgam. Based on the Canadian Health Measures Survey (CHMS) data, 17.7 million Canadians aged ≥ 6 years collectively carry 191.1 million mercury amalgam surfaces, representing 76.4 million mercury amalgam-restored teeth. Like the EU report, Richardson stated that dental amalgam is a major source of mercury exposure in Canada.[8] The values were lower than those reported in other studies, thereby reducing the potential for an overestimated calculation of mercury exposure to the Canadian population.[29] The Cremation Association of North America reported that in 2016 the percentage of cremation in Canada was 70.2% and was expected to increase to 79.8% by 2020.[30]

Yin *et al*. used data collected by the National Health and Nutrition Examination Survey, which is similar to Canada's CHMS, to analyze associations of blood mercury, inorganic mercury, methylmercury, and bisphenol A with dental surface restorations (DSRs) in the US population. They looked at populations from 2003-2004, which showed that there were DSRs in 32%, 51%, 78% and 60% of those from 3-12, 13-21, 22-65, and over 66 years of age, respectively. In total, about 31% of subjects had 1-8 DSRs, and 28% had ≥ 8 DSRs. From 2011-2012, the percentages increased by approximately 10% as follows: 45%, 58%, 81%, and 64% DSRs for those from 3-12, 13-21, 22-65, and over 66 years of age, respectively. The increase in DSRs correlated with significantly elevated blood total mercury, inorganic mercury, and methyl mercury.[31] As reported by the CANA, in 2016, the cremation rate in the US was 50.1%, and projected to be 56.3% by 2020.[30] This would also be indicative of an increase of atmospheric mercury pollution due an increase in cremations in the US and Canada over this period.

In 2015, the Ministry of Civil Affairs in China announced that of the 9.77 million Chinese who died in 2014, 4.46 million (45.6%) were cremated.[32] Gworek *et al*. looked at various

pathways of air contamination by mercury and its transformations from both natural and anthropogenic sources, noting that it is difficult to distinguish between them. It was estimated that just one dentist using dental amalgam contributes about 3.4 g/day into the environment. Emissions from cremation go directly into the air, burial releases mercury into the soil and groundwater, and the dental office releases mercury into the soil, groundwater and air.[33] According to the Scientific Committee on Health and Environmental Risks, the demand for dental mercury amalgam in Japan has decreased from 5.2 tons in 1970 to 700 kg in 1999 and 314 in 2004. This reduction of dental amalgam will decrease atmospheric mercury pollution in the long-term future, since almost 100% of the Japanese population is cremated after death.[34]

In 2010, data was compiled and reported by the Arctic Monitoring and Assessment Programme for the 2013 UNEP Global Mercury Assessment of various sources of anthropogenic mercury emissions by country, region, and industry sector. The top ten countries with mercury emissions from cremation were China (794.0 kg), India (607.7 kg), the US (437.8 kg), Mexico (113.6 kg), Vietnam (95.7 kg), the Philippines (94.3 kg), Canada (91.0 kg), the United Kingdom (85.8 kg), Australia (82.2 kg), and Russia (75.8 kg). The Arctic Monitoring and Assessment Programme's global total estimate of emissions for cremation was 3,582 kg.[35]

A more recent look at dental amalgam was published in 2016 by the UNEP, titled "Lessons from countries phasing down dental amalgam use," which listed dental mercury amalgam emissions at between 50-70 metric tons a year into the atmosphere. They noted that the removal and replacement of old dental amalgam is not a closed system, and that the waste and release of mercury generated in the dental sector is challenging to monitor and manage. The majority of mercury in dental amalgams (about ⅔rds) ultimately enters the environment.[36] This is also due to the increasing number of consumers seeking dental care, resulting in more teeth containing dental amalgam, which will continue to release mercury into the environment.[9] The American Dental Association reports that many variables affect the longevity of dental mercury amalgam restorations, as they can last up to 40 years.[37]

Health risks from mercury in cremation

Crematoriums have many risk factors, not just to the funeral workers, but also to the population in surrounding neighborhoods. Living near these environmental toxic exposures can having negative health effects, particularly in vulnerable subpopulations.[38] Corns *et al*. reported that while atmospheric mercury emissions in the United Kingdom (UK) fell from 40.7 tons to 6.9 tons between 1982 and 2001, mercury emissions from cremation have increased significantly. One estimate reported that annual emissions from 1982-2002 more than doubled from 0.36 tons to 0.82 tons, with little change in the number of cremations preformed. They used the PS Analytical Sir Galahad amalgamation-atomic fluorescence spectrometer to study mercury emissions on a single crematory stack in the UK. It was determined that mercury was emitted in a short period of approximately 40 minutes into the cremation process. The concentrations emitted varied significantly, but could be as high as several mg/m^3. Both elemental and ionic mercury were emitted during the cremation process. The ratio of the two forms depended on the total level of mercury being emitted.[39]

Mari *et al*. reported that as of 2010, there were over 1000 crematories in Europe, while in 2006, China had 1549 and Japan had 1500. Toxic emissions from cremation include persistent organic pollutants such as combustion gases, polychlorinated dibenzo-p-dioxins and dibenzofurans, and heavy metals. These toxins stand out because of their ability to bioaccumulate in humans; however, mercury is the most significant of these pollutants.[40] In 2010, the CANA estimated that there were 2204 crematories in the US, an increase from 1971 in 2005.[41]

Exposure to mercury has been associated with over 250 symptoms in humans, resulting in complications for proper diagnoses. Mercury can be quickly removed from the blood and transported and sequestered into various tissues; in other words, there may not be a direct correlation between blood mercury concentration and the gravity of mercury poisoning.[3] There are serious health risks associated with populations who are exposed to mercury emissions from crematoriums. Low-level exposure to vaporized metallic mercury can be inhaled, causing mercury poisoning. The principal toxic effects of this exposure include excitability, tremors, and gingivitis. Exposure to vaporized metallic mercury can also be toxic to the immune system, nervous system, kidneys, cardiovascular system, gastrointestinal system, lungs, muscle, liver, blood cell count, skin, and eyes. Human fetuses and small children who are exposed are more likely to have mercury concentrated in the brain and kidney.[42]

Heavy exposure to mercury vapor (approximately 5-10 mg/m^3 or higher) inhaled directly from heating metallic mercury may cause erosive bronchitis, and bronchiolitis will occur

in a few hours, followed by interstitial pneumonitis and, ultimately, respiratory distress. If a large enough quantity of mercury is inhaled, renal failure can develop.[43]

Kato *et al*. conducted a study to assess workers' exposure to nanoparticles released in crematoriums. They measured nanoparticle exposure in crematoriums and estimated the respiratory deposition of nanoparticles by number and size distribution. Field surveys revealed the inhalation exposure during each working process. They found that alveolar exposure during the cremation process was significantly higher than that in other respiratory regions.[44] Crematorium workers, especially administrators, have significantly higher mercury levels in their hair, particularly those who worked in a closed environment with limited air ventilation.[45] Vaporization or the burning of mercury-containing materials can form toxic vapors. These vapors can enter the respiratory system and pass effortlessly into the circulatory system. Studies have shown that even chronic inhalation of low concentrations of mercury can produce tremors, sleep disturbances, and impaired cognitive skills in workers.[4,42] Inhalation of mercury vapor can cause necrotizing bronchitis and pneumonitis, which can result in respiratory failure. Mercury is neurotoxic, and can be highly devastating, especially in the central and peripheral nervous systems of children.[43,46]

A retrospective cohort study by Dummer *et al*. investigated the risk of stillbirth, neonatal death, and lethal congenital anomaly among babies of mothers who lived close to incinerators and crematoriums in Cumbria, northwest England, from 1956-1993. They found that during that time frame there was a substantial increased risk of stillbirth for those closer to crematoriums, consistently increasing from 1961 forward. The risk of anencephalus also increased significantly from 1961-1971. From 1972 on, there was an increased risk of all other congenital anomalies, excluding neural tube and heart defects, with increasing proximity to crematoriums, which was considerable for the period of 1983-1993.[47]

In 2012, the Crematorium Working Group reported that crematoria are significant sources of mercury, dioxin, and particulate matter. Incineration of bodies, body parts, and infectious and chemotherapeutic wastes collectively represent the second largest known source of dioxin and mercury pollution in the US. The World Health Organization, the US EPA and other public health experts consider any level, no matter how low, of emissions of mercury, dioxins, furans, and particulate matter from incineration to be a threat to human health. Vulnerable populations such as babies, children, women of childbearing age, and the elderly are particularly at risk from exposure to these toxins. Employees who work in these environments, as well as those populations who live near the source are exposed to higher levels of these pollutants.[40,42,48] The effects of mercury vapor exposure can last long after the exposure has ended. While typical symptoms and signs, such as tremors, gingivitis and salivation may quickly disappear after exposure has stopped, mechanisms of long-lasting or remote effects have not been investigated. This is possibly due to the damage caused by mercury vapor exposure remaining for a long period of time, or by mercury remaining in the body and continuing to cause adverse effects, or to the prior exposure somehow stimulating aging, resulting in poorer neurobehavioral performance.[42,43]

The final report of the Senate Crematoria Study Committee was prepared in 2012. This report noted that while there are emissions of other chemicals during the cremation process, mercury is of the most concern to communities near crematoriums. When mercury is burned, it becomes a colorless and odorless gas that can travel long distances. While mercury exposure has the potential to cause a variety of health problems, the brain and kidneys are especially vulnerable. According to Dr. Anne Summers of the University of Georgia, there is no known lower level for toxicity of mercury, and scientists clearly agree that mercury toxicity can have serious consequences on human health.[4,42,49]

Dental amalgam diverted to artisanal small-scale gold mining

Artisanal small-scale gold mining is the largest source of mercury emissions worldwide. Artisanal small-scale gold mining is active in approximately 70 countries throughout Asia, Latin America, and Africa. Around 15 million people are estimated to be working in this sector and about 5 million are women and children. Artisanal small-scale gold mining has devasting effects not only to the local inhabitants, but also to the environment, especially rivers, due to mining locations. It is estimated that 400 metric tons of gold is produced worldwide through ASGM.[50] In 2006, the UNEP reported on the global impact of mercury supply and demand in ASGM. The official amount of mercury imported in Brazil (2005) was 43.3 tons of mercury, with the majority of the mercury coming from Spain and the UK. While this mercury was identified for dental usage, most ends up in ASGM, even though it is illegal to mine with mercury in Brazil.[51]

Research shows that populations in these areas, as well as those downstream, eat fish that are highly

mercury toxic. These communities are also subjected to tremendously harmful levels of mercury vapor, causing neurological, kidney, and possibly immunotoxic/autoimmune effects from mercury exposure.[52] According to Esdaile *et al*., the approximate amount of mercury released through ASGM is between 410-1400 tons annually, which is about 37% of total global mercury emissions. Easy access to mercury, along with its low cost and the soaring price of gold make this a sustainable livelihood for miners. For the above reasons, the Minamata Convention has made reforming this sector a priority.[53]

Steckling *et al*. looked at chronic mercury intoxication in Zimbabwe, one of the top 10 countries that use mercury for gold extraction. It was estimated that Zimbabwe used 25 tons of mercury annually in ASGM. The study found that miners had 72% chronic mercury intoxication, while the controls showed none. They stated that in 2004, chronic mercury intoxication was likely one of the top 20 leading causes of disability for the population in Zimbabwe.[54]

Mercury-free alternatives in artisanal small-scale gold mining

A 2018 report by the UNEP titled "Going for gold: can small-scale mines be mercury free?" investigated the plight of ASGM workers and their unregulated worksites. As demonstrated in this report, mercury pollution due to AGSM activities is an enormous worldwide problem, and cyanide pollution is a concern as well. It is estimated that the global workforce in ASGM indirectly supports over 100 million people in rural economies. Under the Minamata Convention, these methods of gold mining are considered "worst practices". Thirty-two countries have begun working on national action plans to counter mercury pollution. The UN and the Global Environment Facility are financing projects to teach best practices and helping to facilitate mercury-free mining.[55]

The EPA published a report offering mercury-free techniques for miners, suggesting that using alternatives to mercury may allow for higher gold prices. Some recommendations are the use of concentration methods, increasing the amount of gold in ore or sediment by selectively removing lighter particles. Panning uses water to separate heavy gold particles from lighter ones. Sluicing uses water to wash ore down a series of platforms, where gold will sink and be captured, normally by a carpet. Shaking tables, spiral concentrators, vortex concentrators, centrifuges, magnets, and flotation are other methods that have been developed that do not use mercury.[56]

An alternative to mercury in ASGM is the borax method. Gold is gravitationally separated by sluicing and panning, with iron shavings possibly removed by a magnet, then gold concentrates are mixed with an equal mass of borax. This mixture is heated and the gold solidifies in a relatively pure form when cooled. The borax complexes to silicate and oxide impurities. The authors recommend that this chemistry problem be addressed in the Chemistry and related fields to devise solutions that are "low-cost, easy to use, and provide immediate and obvious benefits to the miners."[53]

A study by Drace *et al*. investigated four ASGM sites in Mozambique. Clean Tech Mining used new technology that eliminated the use of mercury in all of their mining practices. This was done by utilizing magnets to manually separate the magnetic gangue materials from the gold. The owner, a former miner, used his own resources to fund this project and has developed a viable and sustainable mining operation that is not only safe for employees, but also safe for the environment.[57]

Mercury-free dental materials

Mercury free dental materials have been widely used and available for many decades. Atraumatic restorative treatment, a non-mercury dental filling technique, was developed in the 1980's in Tanzania as a minimally invasive way to fill teeth. Using atraumatic restorative treatment saves teeth that would have otherwise been extracted due to decay. It is a viable solution for dental treatment, particularly in developing countries or in countries with emerging economies. Atraumatic restorative treatment requires no electricity, water, or conventional dental equipment. Only hand instruments are needed to clean the decay and a high-viscosity glass-ionomer is then placed in the tooth. Atraumatic restorative treatment is a proven restorative dental technique that has been successfully used in developing countries around the world, and is also being used in developed countries.[58] There are other mercury-free dental restorative materials, such as resin composites made from plastic resin and powdered glass. These materials are strong and are tooth-colored. Another common material is glass ionomer cement, which is a mixture of acid and powdered glass, that is durable and also tooth-colored. Additionally, dental materials such as zinc oxide-eugenol cements, polyacid-modified resin composite, also known as compomer, and resin modified glass-ionomer cement are commonly used worldwide.[18,59]

Conclusions

Mercury use in products and processes, including dental amalgams, is a cradle-to-grave deadly poison and a global pollutant. Even after the last mercury dental amalgam is placed, its toxic legacy will continue

for decades, because of its pervasive bioaccumulation in the environment. Due to the ratification of the Minamata Convention, many mercury-containing products and processes will be banned in 2020, including medical devices such as thermometers and manometers, as well as mercury in soaps and cosmetics. However, dental amalgam is only listed as a phase down product. On July 1, 2018, the EU banned the use of dental amalgam for children under 15 years of age, and pregnant and breast-feeding women. Other countries are banning bulk mercury for dental use, which will make it more difficult to use in ASGM. Affordable mercury-free dental restorative materials are widely available, even for developing countries and countries with emerging economies. By ending the use of dental amalgam, the current illegal flow from that source into ASGM will be eliminated, which will help promote existing non-mercury mining methods. As reported, the practice of cremation is growing around the world. Estimations of the total amount of mercury released during cremation vary greatly due to a lack of monitoring, as well as uncertainty over the total body burden of mercury in the deceased. Technology, however, is available to mitigate the discharge of mercury into the atmosphere from crematoriums. Mercury amalgam separators for dental offices are recommended in accordance with the Minamata Convention, as part of the mercury reduction into the environment from this source. While mercury amalgam separators will decrease mercury from dental offices, dental amalgam can still enter wastewater from human waste and sewage sludge, which will either end up in the land via fertilizer, or landfills or air through incineration. At the Conference of the Parties second meeting of the Minamata Treaty, a recommendation was brought to the plenary that harmonized customs codes for dental amalgam to include not only bulk mercury for dental use, but also encapsulated dental amalgam. This would assist in the tracking of mercury for dental use around the globe. Government regulatory agencies should make the use of available technologies mandatory, not only in developing countries, but also in developed countries to reduce mercury contamination. All countries can stop the use of dental amalgam, as proven by Norway, Denmark, and Sweden. This can be achieved by using mercury-free alternatives such as atraumatic restorative treatment, thereby eliminating a major source of mercury pollution.

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From COVID to Cancer, is Vitamin C the Answer?

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Short Communication

The controversy between pharmaceutical drugs and supplements is ever present in global society, especially now, in the media during the current Covid-19 virus. One of the most important, yet, provocative supplements is vitamin C. While historically, its positive benefits have long been known, during the last decades the push for pharmaceutical drugs, instead of supplements like vitamin C, has created a heated debate against this, and other very affordable supplements. The majority of primates, including humans, guinea pigs, some birds and fish do not make vitamin C, however, most mammals are able to synthesize it in their liver or kidneys. The result of this genetic mutation in humans, therefore, requires vitamin C to be consumed through dietary sources. Clinical studies indicate that vitamin C neither increases nor reduces the occurrence of kidney stones, it also has no mutagenic effect with up to 5000mg per day [1].

During the era that was known as the Age of Sail, vitamin C deficiency was recognized and referred to as "scurvy", a disease that was an extremely common affliction amongst sailors. The major signs of scurvy included swollen and bleeding gums, tooth loss, and delays in wound healing. Scurvy was the leading cause of death to sailors during the 16th to 18th centuries [2]. Even though scurvy was referenced in the late 1400's, it has taken hundreds of years to fully understand the importance of vitamin C, and its necessary and positive impact on human health. In more recent times there have been notable figures who advanced the scientific knowledge of vitamin C. One such person was Albert Szent-Gyorgyi, a Nobel Prize winner for his work in Physiology and Medicine, who isolated vitamin C in 1928, which subsequently led to the treatment and prevention of scurvy [3].

Like Nobel Prize winner Szent-Gyorgyi, decades later, two-time Nobel Prize winner, Dr. Linus Pauling, an American theoretical physical chemist, was the only person to have ever won two unshared Nobel Prizes. His first prize (1954) was awarded for research into the nature of the chemical bond and its use in elucidating molecular structure; the second (1962) recognized his efforts to ban the testing of nuclear weapons. His contributions to science and humanity earned him the title of one of the 20 greatest scientists of all time, by New Scientist, and the 16th most important scientist in history. Later in his career, Pauling became interested in "Orthomolecular" medicine, a term he coined, and defined as medicine that treats and prevents diseases, by utilizing optimal amounts of substances natural to the body. He developed a keen interest in vitamin C, researched and published the best seller, "Vitamin C and the Common Cold (1970)", which introduced taking mega doses of vitamin C to help fight the common cold and other diseases [4].

A scientific paper titled, "Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer* (vitamin C)" by Cameron and Pauling (1976), found that cancer patients were considerably deficient in ascorbic acid. Their clinical study presented 100 terminally ill cancer patients who were given ascorbate as part of their treatment protocol. The controls consisted of 1000 similarly treated patients, who did not receive ascorbate in their protocol. The patients who were on ascorbate survived more than 4.2 times longer, than the controls. They noted that this simple and safe treatment, was of great value to terminally ill cancer patients [5].

Intravenous (IV) vitamin C has been used in various therapeutic protocols to treat cancer since the 1970's. Like Pauling had discovered, those whose cancers were most destructive, were also most deficient in vitamin C. Current clinical trials are showing that vitamin C reduces the negative effects of chemotherapy. When mega doses of vitamin C, in addition to anticancer therapies are used, tumor growth is inhibited in models of pancreatic, liver, prostate, ovarian cancer, sarcoma and malignant mesothelioma. It was observed that vitamin C provides valuable positive effects through more than one mechanism, some are linked to the metabolism of transformed cells, and others may involve direct interactions with specific drugs [6].

Harris et al. investigated the survival among women with breast cancer, the most commonly diagnosed cancer of women globally. They found that various supplementation is widespread amongst breast cancer survivors, with vitamin C being the most frequently consumed. In their meta-analysis, they observed that the consumption of vitamin C had a statistically significant correlation with a decreased risk of total death, and breast cancer-specific death [7]. A study by Lv et al. [8] examined the effects of vitamin C on hepatocellular carcinoma (HCC) and liver cancer cells in 613HCC patients, who had liver resection as their first treatment. *In vitro* and *in vivo* experiments revealed that clinically achievable concentrations of vitamin C provoked cell death in liver cancer cells and preferentially destroyed liver cancer stem cells.

Therefore, this evidenced based study supports vitamin C as a novel therapy for HCC treatment [8]. The side effects caused by conventional treatments for cancers such as surgery, chemotherapy, and radiation can in themselves be devastating to the patient. More recently, research is focusing on cancer stem cells and how they impact the beginning of tumors, progression, metastasis, drug resistance, and recurring disease. Traditional cancer treatments are shown to fail when cancer stem cells are not targeted, but also show the toxic effects to normal cells caused by those treatments. Ascorbic acid/vitamin C is a powerful antioxidant, and is a cofactor for several biosynthetic and gene regulatory enzymes and is critical for a healthy immune system. Studies are showing that using a combination therapy that includes vitamin C, should be utilized in cancer treatment plans [9].

Using vitamin C to treat viruses is also not a novel idea, in fact a scientific paper published in 1935, found that extremely small amounts of vitamin C had the ability to inactivate diphtheria toxins *in vitro* and *in vivo*. Because of these revolutionary findings, a study was conducted to see what the results would be on the poliomyelitis virus. The study used 30 rhesus monkeys and 5 controls by injecting them with the Aycock passage virus strain, 0.1cc. Of the supernatant of a centrifuged 10% poliomyelitis cord suspension and vitamin C. The controls received the same amount of virus mixed with saline or distilled water.

The doses of vitamin C varied from as much as 100mg. to as little as 0.05mg. The quantities were obtained by progressive dilutions with distilled water of a freshly prepared 5% solution of vitamin C, the respective doses always contained in a volume of 1cc. The same method was utilized in preparing the control mixtures for both the test subjects and controls. The injected monkeys were vigilantly monitored for 1 month and the symptoms were noted. This experiment concluded that multiple paralytic doses of poliomyelitis virus, in combination with very small amounts of vitamin C, were rendered non-infectious, as established by intracerebral injection of such mixtures into rhesus monkeys [10].

Several mosquito transmitted viruses have been successfully treated using high doses of IV vitamin C. For example, Gonzalez et al. [11] presented a case report on a 54-year-old Hispanic female who had Zika like symptoms. Some of the symptoms may include mild headaches, fever, joint pain, malaise, and conjunctivitis. These symptoms are also similar to dengue and chikungunya. While oral doses of vitamin C do not have the same ability to reach high blood levels, IV vitamin C is shown to produce clear clinical and pharmacological benefits, from 30 to 70 times higher than orally, which appears necessary in treating viruses. Due to the antiviral and antioxidant properties of vitamin C, after their patient was tested for Glucose-6-Phosphate Dehydrogenase (G6PD), IV vitamin C was administered by increasing the doses from 25g and upping the dose by 25g a day for three consecutive days, reaching 75g on the third day.

Within 24 hours the symptoms had substantially improved and by the third day were gone. From this case it was established that IV vitamin C should be investigated further, as a possible treatment for acute viral infections [11]. Marcial-Vega et al. [12] used IV vitamin C from 25-50 grams with a 3cc of a 3% hydrogen peroxide solution on 56 patients with the chikungunya viral infection. Using a Verbal Numerical Rating Scale-11, immediately before and after treatment. The mean Pain Score before treatment was at 8 and dropped to 2 after treatment for 60% of the patients, with 5 patients reporting 0 pain after the treatment, with no observed adverse reactions in any patient [12].

Hemila [13] reported on a new coronavirus in 2003, as the causative factor of severe acute respiratory syndrome (SARS). At that time there was no known treatment for SARS. Based on the available research it was known that vitamin C was beneficial to the immune system, by reducing viral respiratory infections, and may support pneumonia patients. Noting that under certain circumstances that it may assist in reducing lower respiratory tract infections, and deserved further investigation [13]. According to Fowler et al. [14], their case presented the first report of virus-induced acute respiratory distress syndrome (ARDS) caused by an enterovirus/rhinovirus respiratory infection that used high dose IV vitamin C as a treatment.

From their clinical experience using IV vitamin C to treat acute sepsis, they used the same intervention for a 20-year-old, previously healthy female who had gotten enterovirus/rhinovirus that quickly became ARDS. They reported in treating sepsis that high doses of IV vitamin C not only reduced multiple organ

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injury, but also inflammatory biomarker levels. After a 12-day hospital stay and a follow-up visit one month later, the patient was completely recovered without lung damage, suggesting larger trials utilizing IV vitamin C should be conducted to treat ARDS [14].

COVID-19, was first reported in Wuhan, China. ARDS is a main component of COVID that can be deadly due to cellular injury and organ failure. Studies have shown that high-dose oral vitamin C guards against viral infections. IV vitamin C, as well as high oral doses of vitamin C have presented without serious side effects. Fifty moderate to severe COVID -19 patients received high-dose IV vitamin C in China. Doses fluctuated from 10g and 20g per day, administered over an 8-10 hour-period, with high-doses of vitamin C being given to critical patients. All of the patient's oxygenation index improved and all were eventually cured and released. An expert panel from NIH, stated that high-dose of vitamin C is a safe and effective treatment, without serious side effects. Due to its known safety record, and since it is readily available, vitamin C, as well as other antioxidants may mitigate COVID-19 associated ARDS [15].

Boretti et al. [16] reported on the efficacy of IV vitamin C to treat the COVID-19 virus, because of the current controversy of using antiviral treatments that were developed for other diseases, to treat this new virus. Shanghai, as well as other medical doctors in China are now treating COVID patients with IV vitamin C, and are having positive results. COVID viruses increase oxidative stress and tax the immune system, which can lead to ARDS and death. They reported that over 300 clinical and scientific studies found vitamin C to be beneficial to treat sepsis and septic shock.

Other studies have shown positive outcomes using vitamin C to treat viruses, such as poliovirus, Venezuelan equine encephalitis, human lymph tropic virus type 1 (HTLV-1), human immunodeficiency virus (HIV) and rabies virus, in addition to demonstrating activity against influenza and herpes virus. Due to acute lung infections that may develop with COVID-19, clinical studies are showing that a timely intervention with mega dose vitamin C improves the outcome of COVID-19. They recommend continued studies on this therapy [16].

Thediagnosisof any disease, especially cancer, isoverwhelming to not only the person who receives this distressing information, but also to their family and friends. With exorbitant health care costs, both old and new research is proving that vitamin C, does in fact have a place as an important, inexpensive therapy that can potentially be a lifesaving treatment. When the work of Cameron and Pauling was dismissed, what was barely mentioned in the scientific literature was that the form of vitamin C administered by them, was IV vitamin C in conjunction with oral vitamin C, when the Mayo Clinic trial supposedly replicated the same study, they only used oral doses, that were administered for only 2.5 months, while Pauling and Cameron's trials treated the patients for the entire study period or up to 12 years [17].

Padayatty et al. [18] analyzed both the Mayo Clinic study and Pauling's study, and found that the Mayo Clinic's oral doses would have produced peak plasma concentrations of less than 200 μM, while Pauling's intravenous dose would have peak plasma concentrations of nearly 6mM, more than 25 times higher [18]. While vitamin C is generally considered safe, there are certain ethnicities, such as those from African, Asian, and Mediterranean descent who may have G6PD deficiency that can be harmed with high doses of vitamin C. This hereditary X-linked disorder affects at least 329 million people globally. Even though most G6PD patients may be asymptomatic during their lifetime, it is important when treating the above-mentioned ethnicities that screening is done as to avoid any potential contraindication to the patient [19].

The research on the safety and efficacy on various forms of vitamin C over the last 80 plus years, is widely established. Currently, there are clinical trials and case studies taking place on vitamin C mega dose's, as a single therapy or in conjunction with other therapies around the globe. Essentially, all of these studies are proving that mega dose vitamin C is highly beneficial by enhancing the quality of life for the patient and mitigating the toxic effects of chemotherapy, shortening cold symptoms, and treating viruses with promising results. What the research is showing, even with COVID-19, is that vitamin C is a safe and effective treatment and is readily available to treat patients from COVID to cancer.

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REVIEW ARTICLE

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Titanium exposure and human health

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Abstract

Historically, titanium (Ti) has maintained the reputation of being an inert and relatively biocompatible metal, suitable for use in both medical and dental prosthesis. There are many published articles supporting these views, but there is recent scientific evidence that Ti, or its corrosive by-products, may cause harmful reactions in humans. It is important for all medical and dental professionals to understand the implications, complexities, and all potential pathways of exposure to this metal. These exposures are not only from the environment but also through various commonly used products in medicine that are often completely overlooked. These external (intermittent) and internal (constant) exposures have an impact on whole-body health. This review examines possible harmful effects, risks, and often ignored potential complications of Ti exposure to human health.

KEYWORDS

electromagnetic frequency, nanoparticles, titanium dental implants

1 | INTRODUCTION

Titanium is widely distributed and constitutes 0.44% of the earth's crust. The metal is found combined in practically all rocks, sand, clay, and other soils. It is also present in plants, animals, natural waters, deep-sea dredgings, meteorites, and stars. Ti's atomic number is 22.[1] Ultrafine Ti dioxide (TiO_2) is commonly used in a number of applications, including food additives, food packaging material, sunscreens, cosmetic creams, and as a component of surgical implants. There are rising concerns over exposure to TiO_2 nanoparticles (NPs) during critical windows, such as pregnancy and lactation, for women and men of reproductive age, and last but not least, childhood exposure to high cumulative doses.[2] We have included in our discussion various source points of Ti and how its use with other metals may lead to increased health risks due to galvanic corrosion.

2 | TITANIUM DIOXIDE NANOPARTICLES (TIO_2 NPS)

The cytotoxic effect of Ti particles is size dependent, since they must be smaller than that of cells.[3] TiO_2 exists naturally, mainly in the form of three crystalline structures: rutile, anatasa, and brookite. In Ti implants, the passivant oxide layer is made up of anatasa and rutile or anatasa alone.[4] Ti in dentistry is widely used as an implant in the form of membranes, grids, reduction plates, screws, and distractors, among other applications. In 2009, about 300 000 patients in the United States received dental implants. Since no metal or alloy is entirely inert, in vivo corrosion can occur.[4] Khan et al[5] compared the cytotoxic and genotoxic potential of zinc oxide NPs (ZnO) and TiO_2 NPs using various concentrations. Both NPs were found to create reactive oxygen species (ROS) concomitant with the depletion of glutathione (GSH) and glutathione S-transferase (GST) levels and increased superoxide dismutase (SOD), chloramphenicol acetyl transferase (CAT), and lipid peroxidation in a dose-dependent manner. Both NPs exerted roughly equal oxidative stress in terms of the above stress markers. This study affirmed that ROS generation is the main mechanism to cause various types of toxicities by ZnO and TiO_2 NPs. These results clearly suggest that both ZnO and TiO_2 NPs are significantly cytotoxic, and also genotoxic at all concentrations with respect to untreated samples or controls. While comparing with ionic forms, no significant difference was found.[5] Ghosh et al[6] evaluated the toxic effects of commercial TiO_2 NPs by using a series of

cytotoxic, genotoxic, hemolytic, and morphological parameters. Their results suggest that the TiO_2 NPs could induce significant reduction in mitochondrial dehydrogenase activity in human lymphocyte cells. This study showed that TiO_2 NPs provoked DNA damage and cell death in a dose-dependent manner. Dobrzyńska et al[7] aimed to investigate the cytotoxicity and genotoxicity of TiO_2 and silver (Ag) NPs at different doses and particle sizes to bone marrow cells. Negative responses were shown in reticulocytes (micronuclei) and in leukocytes (Comet assay) of bone marrow. Results indicated that different bone marrow cells display different susceptibilities toward genotoxicity mediated by both investigated NPs. The use of materials containing NPs and the potential health implications of exposure to them should be monitored.[7] The presence of metallic particles in peri-implant tissues may not only be due to a process of electrochemical corrosion but also to frictional wear, or a synergistic combination of the two.[8] Additionally, mechanical disruption during insertion, abutment connection, or removal of failing implants has been suggested as a possible cause of the release of particles from metal structures. The release of particles/ions from the implant into the surrounding biological compartment, their biodistribution in the body, and their final destination are issues that lie at the center of studies on biocompatibility and biokinetics.[8] Clinical studies have already demonstrated that TiO_2 NPs together with metallic ions released from implants accumulate in peri-implant tissues. Particles size range from nanometer to micrometer scale.[9] Therefore, if the removal of an existing Ti implant is being considered, extreme care should be taken so that the patient (in particular pregnant women) and dental personnel are protected from the potential inhalation of Ti particles. In recent years, nanomaterials have been widely used in the production of dental materials. However, the dental applications of nanomaterials yield growing concerns regarding their safety. Disdier et al[10] recently reported their findings on time-related responses from single-dose intravenous (IV) administration of 1 mg/kg TiO_2 NPs to rats, with particular emphasis on Ti quantification in the brain. Ti content in tissues was analyzed using inductively coupled plasma mass spectrometry. Integrity and functionality of the blood-brain barrier (BBB), as well as brain inflammation were characterized using a panel of methods including RT-PCR, immunohisto chemistry, and transporter activity evaluation. Their results showed Ti biopersistence in the liver, lungs, and spleen up to 1 year after TiO_2 NPs administration. A significant increase of Ti in the brain was observed at early end points followed by a subsequent decrease. Exposure of an in vitro BBB model to sera from TiO_2 NPs-treated animals confirmed the tightness of the BBB and inflammatory responses. While some studies have shown that NPs can cross the placenta barrier in pregnant mice and cause neurotoxicity in their offspring, Yamashita et al[11] showed that silica and TiO_2 NPs with diameters of 70 and 35 nm, respectively, can cause pregnancy complications when injected intravenously into pregnant mice. The silica and TiO_2 NPs were found in the placenta, fetal liver, and fetal brain. Mice treated with these NPs had smaller uteri and smaller fetuses than untreated controls. Mohammadipour et al[12] found that exposure to TiO_2 NPs during pregnancy on Wistar rats significantly reduced cell proliferation in the hippocampal and significantly impaired the learning and memory in the offspring. Observations made with a transmission electron microscope demonstrated the incorporation of TiO_2 NPs into vacuoles of the cells. TiO_2 NPs significantly enhanced the Interleukin-1 beta (IL-1β)-induced prostaglandin Estradiol (E2) production, which, induces uterus contractions and cyclooxygenase (COX-1 and 2) protein expression. IL-1β reduced the intracellular concentrations of overall primary metabolites, especially those of amino acid, urea cycle, polyamine, S-adenosylmethione, and GHS synthetic pathways.[13] The addition of TiO_2 NPs further augmented these IL-1β-induced metabolic changes, recommending careful use of dental materials containing TiO_2 NPs with regard to patients with gingivitis or periodontitis.[13] Tissue distribution and blood kinetics of various TiO_2 NPs were investigated in rats up to 90 days postexposure after oral and IV administration of a single or five repeated doses. Single and repeated IV exposure of Ti resulted in rapid distribution from the systemic circulation to all tissues evaluated. The main target tissue was the liver, followed by the spleen, and lung. The present oral and IV study concluded that very low oral bioavailability, along with slow elimination might result in potential tissue accumulation.[14] Xu et al[15] found that exposure to TiO_2 NPs increased *Staphylococcus aureus* infection of HeLa cells. In their experiment when HeLa cells were pretreated with TiO_2 followed by exposure to *S. aureus* bacteria, their data showed that the number of bacteria associated with the HeLa cell membrane increased. Also, a substantial increase in the number of bacteria per cell indicated that the cell membrane became more permeable to the bacteria. Their results indicate that exposure of tissue to TiO_2 NPs may significantly increase the risk of bacterial infection.[15] Subacute and chronic changes from TiO_2 NPs exposure were reported to induce pulmonary response in rabbits. There were limitations in that the sequential acute changes following TiO_2 exposure were not investigated.[16] Choi et al[16] used image analysis in their study to evaluate acute lung inflammation following TiO_2 NPs intratracheal instillation. They observed ground glass opacities of acute pneumonitis at 1 hour after single P25 TiO_2 NPs exposure. Also observed was persistent pneumonitis in the P25 TiO_2-exposed lung, as well as newly developed pneumonitis in the P25 TiO_2-unexposed opposite lung at 24 hours. These results indicate that a single instillation of P25 TiO_2 can induce severe acute pulmonary inflammation. Additionally, previous studies reported that high-dose TiO_2 NPs cause more severe lung inflammation compared with that of low-dose TiO_2, as well as inducing persistent pulmonary inflammation. This information may have clinical implications regarding safety in handling of TiO_2 NPs.[16] Husain et al[17] showed that a small fraction of TiO_2 NPs translocate from the lungs to blood and extrapulmonary organs, using a nano-hyperspectral microscope. Adult female mice C57BL/6 exposed via intratracheal instillation to 18 or 162 μg of industrially relevant TiO_2 NPs alongside vehicle controls showed translocation to the heart and liver at both doses, and the blood at the highest dose, in mice analyzed 24 hours postexposure. Acute translocation of particles to blood and other organs coincides with the induction of an innate immune type response, which includes the activation of acute stress in liver. Adding to this, C3

activation in blood was found, and the activation of complement cascade and inflammation response in the heart tissue, all of these processes are involved in particle recognition and clearance.[17] IV injection of TiO_2 NPs at high doses in mice caused acute toxic effects in major target organs.[18] Ti accumulates in many organs mainly liver, kidneys, spleen, lungs, brain, and heart. Nano-anatase TiO_2 at a higher dose caused serious damage to the liver, kidney, and myocardium of mice and disturbed the balance and metabolism of blood sugar and lipid in mice.[19] Mice subacutely exposed to 2-5 nm TiO_2 NPs showed a significant, but moderate inflammatory response among animals exposure after 1 or 2 weeks, which resolved by week 3 postexposure.[20] Using naïve mice and mice with ovalbumin (OVA)-induced airway inflammation showed that the inhalation of TiO_2 might aggravate respiratory diseases, and the adverse health effects are highly dependent on dose and timing of exposure. Data imply that inhalation of NPs may increase the risk for individuals with allergic airway disease of developing symptoms of severe asthma.[21]

3 | EFFECTS OF ELECTROMAGNETIC RADIATION ON TI IMPLANTS

Crouzier et al[22] investigated magnetic resonance imaging (MRI), electromagnetic frequency/field (EMF), radiofrequency radiation (RFR), and its relationship with implantable devices. It has been discovered that a significant part of the population bears metallic devices including orthopedic plates, rods, screws, prosthesis but also dental implants, stents, electrodes wires, or electronic devices. Metallic devices are well known to strongly interact with EMF by diffraction or focusing thus, leading to a significant local enhancement of field intensity.[22] With the use of electronic devices, such as cellphones or personal computers (PCs), becoming increasingly prevalent in recent years, many articles only emphasize the convenience of these electronic devices without addressing the potentially negative influences of the emitted electromagnetic waves on the body.[23] Metals present within the body can act as an antenna to collect harmful radio waves, thus inducing many general and severe symptoms, such as headaches, fatigue, tinnitus, dizziness, memory loss, irregular heartbeats, and whole-body skin symptoms, which are considered to be caused by electromagnetic hypersensitivity. In dentistry, Ti dental implants may be the material most commonly associated with antenna activity and may promote harmful effects of electromagnetic waves. Dental treatments should be performed in a manner that avoids the harmful influences of radio waves on patients.[23] We believe this can be accomplished by using biocompatible nonmetal dental materials. Metallic implants amplify high frequency (HF)-EMF 100-700 folds nearby and exceed the safety levels. If dental metals (crowns, fillings, bridges, Ti implants) are implanted in the upper jaw, HF-EMF is enhanced in the cranial nerves and brain. The presence of dental metals may increase the risk for HF-EMF-induced brain cancers several fold and should be acknowledged as confounding variable in future studies, exploring brain cancer risk in dependence of HF-EMF exposure.[24] Patients with severe or fatal illnesses (like amyotrophic lateral sclerosis (ALS), Alzheimer's, Parkinson's, cancer, multisystemic atrophy, multiple sclerosis (MS), severe elektrohypersensitivity, Multiple chemical sensitivity (MCS), chronic fatigue syndrome (CFS), and severe chronic pain (neuralgia, migraine) often have pieces of dental metals, mostly mercury (Hg) amalgam, in the jaw bone.[24] Yakymenko et al[25] looked at 100 available peer-reviewed studies dealing with low-intensity RFR; 93 of these studies confirmed that RFR induces oxidative effects in biological systems. The oxidative efficiency of RFR can be mediated via changes in activities of key ROS. ROS and their involvement in cell signaling pathways explains a range of biological/health effects of low-intensity RFR, which include both cancer and noncancer pathologies. In turn, a broad biological potential of ROS and other free radicals, including both their mutagenic effects and their signaling regulation, makes RFR a potentially hazardous factor for human health. The modern data on the biological effects of low-intensity RFR leads to a firm conclusion that this physical agent is a powerful oxidative stressor for living cells.[25] The database used by Yakymenko[25] was about 18 months old, when that paper was published. As of July 8, 2015, there had been 153 papers published on the oxidative stress effect of RFR, of which 90% (137 papers) showed effect vs 10% (16 papers) reporting no effect. Thus, there is overwhelming peer-reviewed research confirming the potential harmful effect of radiofrequency radiation.[26] Sometimes head and neck cancer patients treated with high-energy X-rays and gamma rays have Ti dental implants. Ti dental implants in the field of irradiation were capable of causing significant radiation scatter. Therapists involved in radiation planning should consider dental implants on the radiation beam as a presumed cause of osteoradionecrosis.[27] The calculations showed that the presence of a dimension-reduced implant results in remarkable differences in the dose distribution all around the implant. Similar to standard implants, the risk for dose enhancement was notably important for the bone in direct contact with the implant.[28] For the different radiation beams studied, the irradiation angle between scattering Ti dental implants and the central axis does not significantly affect the total dose that may lead to osteoradionecrosis of the mandible.[29] Animal and human studies indicate that irradiated bone has a greater risk of implant failure than nonirradiated bone. This increase in risk may be up to 12 times greater.[30] Implant therapy is no longer considered impossible for patients who have received radiation treatment for head and neck cancer. However, the risk of osteoradionecrosis and failed osseointegration are barriers to implant therapy for this population.[31] There is a significant increase in the risk of implant failure in irradiated patients (risk ratio: 2.74; 95% confidence interval: 1.86, 4.05; $P < 0.00001$) and in maxillary sites (risk ratio: 5.96; 95% confidence interval: 2.71, 13.12; $P < 0.00001$). Conversely, hyperbaric oxygen (HBO) therapy did not reduce the risk of implant failure (risk ratio: 1.28; 95% confidence interval: 0.19, 8.82; $P = 0.80$). Radiotherapy was linked to higher implant failure in the maxilla, and HBO therapy did not improve implant survival.[32] There is a risk of radio frequency (RF) heat generation within Ti. 3.0 T-MRI scanners are becoming increasingly common. The specific absorption rate (SAR) of 3.0 T-MRI is quadruple that of SAR compared

with 1.5 T-MRI, due to its being proportional to the square of the strength of a static magnetic field. The effect of heat generation on 3.0 T-MRI can thus be greater than on 1.5 T-MRI. The rise in temperature of Ti implants was measured to be a maximum of 0.4°C.[33] The impact of magnetic force from an MRI on dental materials will attract iron-containing (or ferromagnetic) objects and may cause them to move suddenly and with a great force like a "missile". This can cause possible risks to patients or anyone in an objects "flight path". It can pull any ferromagnetic object in the body too. Tissue injury can be caused due to heating the prosthesis. RF heating was confirmed to take place at both ends of the implants in spite of their different shapes. It is recommended to treat all material as MR unsafe, if the dentist is not sure about the type of prosthesis/appliance. It is advisable to remove the prosthesis/appliances prior to MRI.[34]

4 | ROOT CANAL SEALERS USING TI

There are many contraindications for dental materials that are commonly used, however, in-depth health histories are often not examined prior to dental treatments, nor are there follow-up visits with patients for any potential negative reactions from these materials. For example, even after a complete root canal therapy, reinfection may occur as a result of incomplete seal and activation of residual bacteria. Thus, antimicrobial activity is an important characteristic of root canal sealers. These two filling materials, MTA Fillapex and AH 26, were exposed to the bacterial suspension of Enterococcus faecalis, Escherichia coli, Streptococcus mutans, and Candida albicans after setting. Regarding all four bacterial groups, the bacterial count was significantly lower in the MTA Fillapex group when compared to the AH 26 group.[35] AH 26 showed in vitro estrogenic effect, but not AH Plus. AH 26-powder induced MCF-7 cell proliferation in a dose-dependent manner. The endodontist must consider the possible estrogenic effect of AH 26, as well as the cytotoxic effects of root filling materials, and avoid the leakage of sealer through the apex during root canal treatment.[36] DENSTPLY AH 26 Root Canal Sealing and Filling Materials are composed of the following: (AH 26, powder): Bismuth oxide, Methenamine, Silver, TiO_2; (AH 26 silver free, powder): Bismuth oxide, Methenamine, and AH 26 resin: Epoxy resin.[37] The contraindications, warnings, and precautions are as follows: hypersensitivity against epoxy resins or "other components" of the root canal filling material. AH 26 and AH 26 silver free contain epoxy resins, which may cause sensitization in susceptible persons. During the setting reaction of both materials, traces of formaldehyde are produced.[37] Do not use AH 26 and AH 26 silver free in persons allergic to epoxy resins. We recommend that these contraindications be discussed with patients prior to treatment, and as mentioned earlier, biocompatibility testing be preformed on all potential materials that may be used. Avoid contact of powder or resin and unset paste with skin or oral mucosa. After incidental contact, wash and rinse with plenty of water. Wear protective gloves and glasses. Interaction with other dental materials: AH 26 and AH 26 silver free may react with hydrogen peroxide accidentally left in the root canal after irrigation. Adverse Reactions: With sealers containing epoxy resins, the following adverse reactions were reported, including reversible acute inflammation of the oral mucosa after contact with the unset paste. In individual cases, local and systemic allergic reactions have been reported.[37] MTA Fillapex composition is as follows, salicylate resin, bismuth trioxide, fumed silica, TiO_2, mineral trioxide, aggregate (40%), and base resin. MTA Fillapex is a root canal sealer intended for the permanent sealing of root canals and may be used in combination with root canal obturation materials. Contraindications and warnings are as follows: In patients with hypersensitivity against the resins or other components of the product.[38] MTA Fillapex contains resins, which may sensitize susceptible individuals. Do not use it in patients allergic to the resins or "other components" of the product; avoid contact with eyes or skin. In case of contact, rinse immediately with water; avoid contact with oral mucosa. In case of contact, rinse with water and prevent swallowing of product. In case any sensitivity persists, seek medical attention promptly; if the syringe becomes contaminated with saliva or blood during application, dispose of the syringe and do not use on an additional patient. Ensure that the lids of the base paste and catalyst are not switched, because switching them can cause hardening of the product inside the tube.[38] The cytotoxicity of three different types of root canal sealers on human periodontal ligament (PDL) cells and a permanent hamster cell line (V79 cells) were examined. The results showed that elutes from resin-based, zinc oxide-eugenol-based, and calcium hydroxide-based sealers were cytotoxic to primary human PDL cultures and V79 cells.[39] Calcium hydroxide-based sealer was the least toxic sealer among the chemicals tested in both cultures. The results confirmed that root canal sealers constantly dissolve when exposed to an aqueous environment for extended periods, possibly causing moderate or severe cytotoxic reactions.[39] GuttaFlow (Roeko) silicone-based sealer, AH plus (De Tray-DENTSPLY) epoxy resin-based, Apexit (Vivadent) calcium hydroxide-based, and Endorez (Ultradent) methacrylate-based sealers were tested on primary cell lines of human gingival fibroblasts. All four sealers showed different cytotoxicity effects on primary cell lines of human gingival fibroblasts, but all of them are slightly cytotoxic.[40] Reszka et al[41] evaluated the chemical elements in two new calcium silicate-containing root canal sealers, BioRoot RCS and Well-Root ST and compared them to MTA Fillapex and AHPlus sealer. Studies have assessed the chemical elements and heavy metals in MTA Fillapex and AHPlus, but the authors noted that the two novel calcium silicate-containing root canal sealers, to the best of their knowledge had not been analyzed. Using energy-dispersive spectroscopy (EDS) X-ray microanalysis and scanning electron microscopy (SEM), EDS showed that BioRoot RCS did not have heavy metals or other toxic elements, while microanalysis revealed that Well-Root ST contained aluminum and Ti in addition to calcium, zirconium, oxygen, carbon, and silicon. This study concluded that BioRoot RSC had the highest degree of purity. Further investigation of the heavy metals contained in Well-Root, MTA Fillapex, and AHPlus is warranted due to the clinical implications for the patients.[41]

5 | CORROSION OF TI

5.1 | Galvanic corrosion

Titanium implants used outside of the mouth have exhibited failure through a foreign body reaction. Phenomena occurring in the body, such as passive dissolution, osteolysis, and metallosis have not been discussed relative to dental implants. The dental community must consider the full spectrum of implant interactions within the body to understand the differences and similarities within the mouth.[42] Also, what is alleged to be commercially pure Ti has been shown to contain impurities of other metals, such as nickel (Ni), which may have clinical significance.[43] Studies have shown that Ti is released in the presence of biological fluids and tissues. There are some signs of Ti penetration through the oral mucosa. While the structure of skin and the oral mucosa are similar, the permeability of the floor of the mouth is up to 4000 times higher than the skin. Although there are some methods for testing reactivity to Ti, Ti allergy is mainly diagnosed through clinical evaluation.[43] The oral cavity is one of the most inhospitable environments in the human body and is subject to larger temperature and pH variations than most other parts of the body. Corrosion caused by the graded degradation of materials by electrochemical attack, is of concern, particularly when dental implants are placed in the hostile electrolytic environment provided by the human mouth. Allergic reactions may occur from the presence of ions produced from the corrosion of implants.[44] The issue of corrosion may not be limited to a local problem because particles produced as a result of corrosion may migrate to sites far from the implant. This subject is of particular interest in studies of biocompatibility.[4] The abnormal electrical currents produced during corrosion can convert any metallic implant into an electrode, and the negative impact on the surrounding tissue due to these extreme signals is an additional cause of potential poor performance and rejection of implants. Metal traces originating from dental implants have been found in blood, liver, lungs, and lymph nodes.[4,19,45] These metal ions and wear debris may also contribute to aseptic loosening by promoting inflammatory complications that may result in macrophage activation, bone reabsorption, and, rarely, in the potential development of neoplasia. Recently, TiO_2 was classified as possibly carcinogenic to human beings by the International Agency for Research on Cancer (IARC).[4,45] Corrosion can occur in any dental prosthesis, and it may be accelerated by the use of a high proportion of base metal.[46] Chaturvedi[44] found that Ti implants and their presence in the human body may also cause internal exposure, which ultimately leads to Ti ions to concentrate in tissues, regional lymph nodes, and pulmonary tissue. The potential toxicity and biological risks associated with ions and/or particles released, due to corrosion of metallic implants is a health concern for patients with prostheses (orthopedic and/or dental) due to the long duration that these implants stay inside the body.[44] Six basic factors are involved in galvanic corrosion: (a) potentials, (b) polarization, (c) electrode areas, (d) resistance and galvanic current, (e) the electrolyte medium, (f) aeration, diffusion and agitation of the electrolyte. Galvanic coupling is a galvanic cell in which the more negative metal (anode) is the less corrosion-resistant metal than the more positive metal (cathode).[47] The galvanic corrosion of dental devices is important in two respects: (a) the biological effects which may result from the dissolution of alloys and (b) the current flow resulting from galvanic cell that could cause bone destruction.[47] Ti was anodic to noble alloys and cathodic to iron (Fe)- and Ni-based passivizing alloys. It was shown that the galvanic corrosion resistance of mentioned alloys coupled with Ti from the highest to lowest are as follows: High Copper (Cu) dental amalgam > Low Cu dental amalgam > Gallium-based direct filling.[47]

5.2 | Common oral treatments

Toothpastes, mouthwashes, and prophylactic gels contain from 200 to 20 000 ppm fluoride and can impair the corrosion resistance of dental alloys in the oral cavity. Adding fluoride to the solution made the Ti's potential more active and enhanced the corrosion of Ti in combination with high-Cu amalgams. The combination of low pH and the presence of fluoride ions in solution severely affects the breakdown of the protective passivation layer that normally exists on nitinol and Ti alloys, leading to pitting corrosion.[47] Galvanic corrosion occurs more actively and many metal ions are released with a higher potential difference or poorer corrosion resistance. The release of metal ions into the oral cavity can be harmful to the cells of the adjacent tissues, and they may cause side effects including cytotoxicity, allergies, and mutagenesis. Cytotoxicity was significantly increased in all groups where Ni-Chromium (Cr) alloys were in contact with Ti.[46] Corrosion release of the several substitutional alloying elements from various Ti alloys used in dentistry have been widely known. It has been reported that these metal ion releases are associated with the carcinogenic and mutagenic activity of the oral cavity. Several studies have further shown that the cellular uptake of hexavalent Cr is many folds greater than the trivalent Cr ion and its increased uptake causes a reduction in the alkaline phosphatase activity of the osteoblastic cells.[48] Increasing evidence is found that Ti and various substitutional alloying elements leach into the crevicular space around the implant. The potential adverse effects of metal ion release into living tissues can be proposed based on information from literature and various clinical, preclinical, and animal trial studies in vivo and in vitro. It is clear that corrosion is bound to occur and its consequences can be quite severe.[48] The potential toxicity and biological risks associated with ions and/or particles released due to corrosion of metallic implants is a public health concern for any patient who has a prosthesis (orthopedic and/or dental), since these prostheses remain inside the body over long periods of time, sometimes a lifetime. Likewise, the subject of corrosion is of interest to researchers; corrosion studies aim at avoiding the possible corrosion-related health problems that may arise when metallic implants are placed in humans.[7]

6 | TI's HEALTH RISKS AND RELATED DISEASES

6.1 | Hypersensitivity

A systematic review by Javed et al[49] examined whether Ti sensitivity is associated with allergic reactions in patients with dental implants. Their investigation showed that impurities, while small were consistent in the Ti alloys such as sponge Ti, TiAl6V4, and iodide Ti. Also found were other elements such as beryllium (Be), cobalt (Co), Cr, Cu, (Fe), Ni, and palladium (Pd) and these elements may contribute to triggering an allergic response in patients with dental implants. Patch testing (PT) and lymphocyte transformation testing (LTT) was preformed on 16 patients with revised metal-on-metal arthroplasty and peri-implant lymphocytic inflammation. In 13/16 (81%) of the patients, systemic metal sensitivity was found based on the PT and/or LTT testing. Thomas et al[50] concluded that the lymphocyte dominated peri-implant inflammation might well reflect an allergic hyperreactivity in these patients, due to the high rate of concurrent metal allergy found among them. There is supporting literature that Ti can induce clinically relevant hypersensitivity and other immune dysfunctions in certain patients chronically exposed to this reactive metal. There are reports about the corrosion of dental implants and their significance when hypersensitivity is present.[51] Müller and Valentine-Thon[52] reported on 56 patients who had developed clinical symptoms after receiving Ti-based implants. The patients were tested in the optimized lymphocyte transformation test MELISA against 10 metals including Ti. Fifty-four patch-tested patients were negative to Ti. Following removal of the implants, all 54 patients showed remarkable clinical improvement. In the 15 retested patients, this clinical improvement correlated with normalization in MELISA reactivity. These data clearly demonstrate that Ti can induce clinically relevant hypersensitivity in a subgroup of patients chronically exposed via dental or endoprosthetic implants.[52] One of the most fundamental criteria is the interaction between the surrounding physiological environment and the surface of the implant itself. This interaction can lead to either the failure of the implant to function, as it was intended, or have an adverse effect on the patient. Metal sensitivity may arise after exposure to Ti for some patients in certain circumstances.[51] Sodor et al[53] examined a variety of orthodontic biomaterials to evaluate the biocompatibility like stainless steel arch wires, brackets, and Ni-Ti alloy coil springs. These studies were performed in vitro using human fibroblasts cells on which the orthodontic materials were applied. The positive control was the Cu amalgam. Readings of the cell reactions were performed at 3 and 6 days. They concluded that *all* biomaterials analyzed caused cellular changes of varying intensity without necessarily showing a cytotoxic effect.[53]

Hypersensitivity to biomaterials is often defined in terms of ambiguous pain, skin rashes, lethargy, and malaise and in some cases implant loss.[54] At present, little is known about Ti hypersensitivity, but it cannot be excluded as a reason for implant failure. Ti can induce hypersensitivity in susceptible patients and could play a critical role in implant failure.[54]

6.2 | Allergic reaction

Syed et al[55] showed that more reports were published in which dekeratinized hyperplastic reactions of the peri-implant tissues and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome suggestive of Ti allergy were observed in association with Ti implants. A patient demonstrating a DRESS syndrome, which reflects a serious hypersensitivity reaction to drugs, in association with Ti bioprosthetic implants was recently reported. Ti implants can corrode and release ions or micro-particles, which can induce inflammation in affected tissues.[51] Sicilia et al[56] evaluated 1500 patients with dental implants. Thirty-five subjects out of 1500 implant patients treated and/or examined (2002-2004) were selected for Ti allergy analysis. Sixteen presented allergic symptoms after implant placement or unexplained implant failures in the allergy compatible response group (ACRG), while 19 had a history of other allergies, or were heavily Ti exposed during implant surgeries or had explained implant failures (predisposing factors group [PFG]). Thirty-five controls were randomly selected (CG) in the Allergy Centre. Cutaneous and epicutaneous tests were carried out. Nine of the 1500 patients displayed positive reactions to Ti allergy tests (0.6%): eight in the ACRG (50%), one in the PFG (5.3%) (P 1 ⁄4 0.009), and zero in the control group. Five positives were unexplained implant failures (five of eight). Harloff et al[57] used spectral analysis as a diagnostic tool for different Ti implant alloys to determine the percentage of components and additions that are known to cause allergies. Different materials, such as sponge Ti, TiAl6Nb7, Ti21SRx, TiAl6V4 (forged alloy), TiAl6V4 (cast alloy), TMZF, pure Ti (c. p. 1), and iodide Ti were analyzed for the presence of the elements associated with allergic reactions using spectral analysis. All of the implant material samples contained traceable amounts of Be, cadmium (Cd), Co, up to a maximum of 0.001% by weight (wt.%), Cr up to 0.033 wt.%, Cu up to 0.007 wt.%, hafnium (Hf) up to 0.035 wt.%, manganese (Mn) up to 0.007 wt.%, Ni up to 0.031 wt.%, and Pd up to 0.001 wt.%. This paper demonstrates that all the investigated implant material samples contained a low but consistent percentage of components that have been associated with allergies. Therefore, they can be virtually classified as "impurities".[57] A rat model revealed degenerative changes in osseous integration and/or in the bone around implants upon excessive occlusal loading. These results emphasize the risks associated with immediate loading and overloading. This is the first study to reveal the possibility of bone loss around overloaded implants in the absence of infection based on a small animal model.[58] Oral allergies are often underdiagnosed by dental health professionals. Patients with an oral allergy complain of various symptoms, such as burning or tingling sensations, with or without oral dryness or loss of taste, or of more general symptoms, such as headache, dyspepsia, asthenia, arthralgia, and myalgia.[59] The signs of oral allergy include erythema, labial edema (or purpuric patches on the palate), oral ulcers, gingivitis, geographical tongue, angular cheilitis, and perioral eczematous eruption (or lichenoid reactions localized on the oral mucosa). There is an increase in the prevalence of oral allergies to metals used in dental materials.[59] In order to provoke

an allergic reaction, Ti must have antigenic properties and must be in contact with the organism. The insertion of Ti implants and their permanence in the human body enhances the amount of internal exposure, and it has been proven that Ti ions concentrate in tissues surrounding dental and orthopedic implants, as well as in regional lymph nodes and pulmonary tissue.[60] Concentrations of between 100 and 300 ppm have been measured in peri-implant tissues, and are often accompanied by discolorations. 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).[60]

6.3 | Disease symptoms

Recent reports have questioned whether metal sensitivity may occur after exposure to Ti. The emergence of facial eczema occurred in association with a Ti dental implant placed for a mandibular overdenture supported by two implants. Complete remission was achieved by the removal of the Ti material. This clinical report raises the possibility that in rare circumstances, for some patients, the use of Ti dental implants may induce an allergic reaction.[61] The incidence of Ti hypersensitivity or allergy is still unknown and the discussion on its existence is ongoing. Unexplained implant failures have also forced dental clinicians to investigate the possibility of Ti hypersensitivity or allergy.[62] Placing permanent metal dental implants in allergic patients can provoke type IV or I reactions. Several symptoms have been described, from skin rashes and implant failure, to nonspecific immune suppression. A significantly higher risk of positive allergic reaction was found in patients showing postoperative allergy compatible response group (ACRG), in which cases allergy tests could be recommended.[56] This review supports the need for long-term clinical and radiographic follow-up of all implant patients who are sensitive to metals.[54] Covani et al[63] showed that histologic analysis at the level of abutment/implant interface in two-stage implants identified heavy bacterial colonization. These findings appear to support those studies showing bacteria penetration at the level of the micro-gap, which can legitimate the hypothesis that the micro-gap at the bone level could present a risk for bone loss caused by bacterial colonization. Pigatto et al[64] reported on a case of severe systemic allergic contact dermatitis was caused by allergy to metals released by galvanic corrosion between an Hg amalgam tooth filling and an endosseous Ti dental implant. Removing the Hg-containing amalgam filling and the metal-ceramic crown on the dental Ti implant reduced considerably intraoral electrochemical corrosion process, which likely released metal ions (Hg, Cu, Ni, and Ag) into the saliva and the oral mucosa. Systemic contact dermatitis resolved completely within 8 months after the removal of both Hg amalgam tooth filling and a single metal-ceramic crown restoration (gold/Pd-based crown), which were in close proximity to each other.[64] Peri-implant diseases are a cluster of "contemporary" oral infections in humans that have emerged as a result of the routine application of osseointegrated dental implants in clinical practice. They are characterized by the inflammatory destruction of the implant-supporting tissues, as a result of biofilm formation on the implant surface.[65] The microbial composition of peri-implantitis-associated biofilms is mixed, nonspecific, and very similar to that of periodontitis. A considerable exception is the frequent presence of high numbers of staphylococci and enteric bacteria in peri-implantitis. Peri-implantitis is marked by a more extensive inflammatory infiltrate and innate immune response, a greater severity of tissue destruction, and a faster progression rate.[65] Dental peri-implantitis is characterized by a multifactorial etiology. In a prospective pilot study, Fretwurst et al[66] biopsied 12 patients (seven bone samples, five mucosal samples) who were included and analyzed. In 9 of the 12 samples (75%), the synchrotron radiation X-ray fluorescence spectroscopy (SRXRF) examination revealed the existence of Ti and an associated occurrence with Fe. Metal particles were detected in peri-implant soft confirmed with polarized light microscopy (PLM). In samples with increased Ti concentration, lymphocytes were detected, whereas M1 macrophages were predominantly seen in samples with metal particles. Ti and Fe elements were found in soft and hard tissue biopsies retrieved from peri-implantitis.[66] Studies also show the progression of periodontal disease in subjects who initially showed no traditional signs or symptoms of periodontal disease; these often have bacteria, especially those of the spirochete morphogroup, in the gingival sulci. Patients with these types of spirochetes were three times more likely to develop periodontitis within a year in the implant sites tested than those that remained healthy.[67] The pathogentic-related spirochetes are the most likely to cause infection. Based on many years of microscopic examination of bacteria-populating infections associated with failing implants, many morphologic types of spirochetes have been observed. Spirochetes seem to be a "marker bacteria" in periodontal infections that cause bone loss and implant failure.[67]

Exfoliative cheilitis is possibly caused by Hg-containing dental amalgam in close proximity to dental Ti implant. There was a strong temporal relation between last Ti dental implant and the onset of exfoliative cheilitis. "Dental implants should not be implanted in the vicinity of the Hg-containing dental amalgam filling, even in the presence of Hg amalgam as root-end filling material".[68]

Pigatto et al[68] also found in their cohort between 2001 and 2010, that the incidence of cheilitis associated with alloy-based dental restorations was 6.7% (33 of 492 patients, median age 51 years, and 75,76% were women). Patient-related risk factors for cheilitis associated with metals include mainly orthodontic appliances, dental Ti implants, and/or Hg amalgam. Acidic environments coupled with rubbing are able to introduce noticeable morphological changes and corrosion on the surface of pure Ti (cpTi) and the alloy Ti6Al4V Ti grades.[69] Ti ions may be partly responsible for the infiltration of monocytes and osteoclast differentiation by increasing the sensitivity of gingival epithelial cells to microorganisms in the oral cavity. Therefore, Ti ions may be involved in the deteriorating effects of peri-implant mucositis, which can develop into peri-implantitis accompanied by alveolar bone resorption.[70] Environmental conditions adversely affect implants' fatigue performance. This fact should

be taken into account when evaluating the mechanical properties of dental implants.[71] Data demonstrate that noxious effects are 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 Ti implants or other dental devices.[72]

Yellow nail syndrome is characterized by nail changes, respiratory disorders, and lymphedema. Yellow nail syndrome is caused by Ti.[73] Yellow nail syndrome and Lichen planus or lichenoid reactions can originate from close or identical etiologies. They may result from dental restorative materials or metal allergy. Interestingly, the nail sometimes returns to its normal condition, months after the withdrawal of the offending agents.[74] Numerous systemic emergency situations, such as hypotension or allergic reactions, may be encountered during dental treatment. In addition, rare but life-threatening complications such as foreign body aspiration in the air passages may also be seen. Aspirated foreign bodies include teeth, implants, mechanical supports, or materials used during procedures.[75] Within limitations, a history of periodontitis is estimated to be a statistical risk factor for the long-term survival of dental implants. This negative effect would be most evident in patients with aggressive periodontitis, severe periodontitis, or after a longer follow-up.[76] Several systemic diseases (and relative medications) have been reported to impair or in some cases complicate dental implant surgery. When dealing with patients suffering from systemic diseases, the monitoring of the medical condition and of the related postoperative complications is of great importance in order to avoid risks, which could jeopardize the health of the patient.[77]

7 | CONCLUSION

This review is based on current Ti research demonstrating the many factors that can pose a negative impact on human health when exposed to the various forms of Ti, including its relationship and interactions with other metals. We looked at environmental, medical, and dental devices to show how these exposures can impact human health. Most of the literature available indicates an increased risk to allergies due to Ti exposure. These allergies are also associated with particular genetic individual factors, which validate the need for the use of precision medicine in these particular patients. We need to continue to expand our knowledge on the genetic factors associated with Ti and metal exposure in order to provide better management and care to this group of susceptible populations, which are at a higher risk. There are many available tests that can be administered prior to any medical or dental procedure that can determine allergic reactions and biocompatibility for individual patients. Most of the medical and dental practitioners commonly overlook these allergy tests increasing a health risk to the patients. These types of tests should always be utilized to allow for the most suitable materials to be used on an individual patient. Based on this review, it would be prudent to reduce the risk to all patients when considering exposure to Ti, and to avoid its improper use as much as possible. Moreover, when a patient has Ti implants it is critically important to take the utmost care to protect the patient from any and all risks of potential harm.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Mini Review

Biocompatibility in Dentistry: A Mini Review

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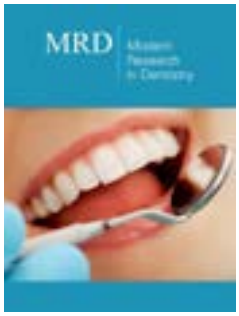

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Abstract

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®, 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®, 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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Will the US Food and Drug Administration (FDA) Follow the EU's Mercury Dental Amalgam Ban? A Mini-Review

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ABSTRACT

The European Union's comprehensive ban on mercury dental amalgam, effective January 1, 2025, marks a pivotal step toward eliminating a known neurotoxin from dentistry, aligning with the Minamata Convention on Mercury's goal to "Make Mercury History". In contrast, the United States, despite ratifying the treaty in 2013, permits the continued use of mercury dental amalgam, a material deceptively called "silver fillings" despite its approximately 50% mercury content. The U.S. Food and Drug Administration (FDA), a global leader in health policy, maintains a contradictory stance: acknowledging mercury's risks for vulnerable populations while resisting mandatory patient disclosures and a phase-out. This regulatory failure, challenged by legal actions, peer-reviewed studies, and advocacy groups, undermines informed consent, exacerbates health inequities, and hinders global mercury reduction efforts. This mini-review examines the FDA's policies, emphasizing its refusal to mandate disclosures, the health risks of mercury dental amalgam, and the necessity of safe removal protocols. Drawing on recent scientific evidence and international benchmarks, we argue for urgent reform to protect public health, the environment and align with global standards.

Keywords

Mercury dental amalgam, Minamata Convention on Mercury, Food and Drug Administration, Informed consent.

Abbreviations

FDA: Food and Drug Administration; GRAS: Generally Recognized as Safe; POTWs: Publicly Owned Treatment Works; EPA: Environmental Protection Agency; ApoE4: Apolipoprotein E4; CPOX4: Coproporphyrinogen Oxidase; NHANES: National Health and Nutrition Examination Survey; ART: Atraumatic Restorative Treatment; IAOMT: International Academy of Oral Medicine and Toxicology; IABDM: International Academy of Biological Dentistry and Medicine.

Introduction

Mercury dental amalgam, comprising approximately 50% elemental mercury, has been used in restorative dentistry for over 150 years. Often called "silver fillings" due to its metallic appearance, this nomenclature obscures their neurotoxic mercury content, misleading patients and undermining informed consent [1]. The U.S. Food and Drug Administration (FDA), a global benchmark for regulatory oversight, has failed to adequately address these risks, despite mounting incontrovertible scientific evidence and legal challenges. In 1976, the FDA classified mercury dental amalgam as "Generally Recognized as Safe (GRAS)" without the current standard of rigorous safety testing, a decision that continues to shape its permissive stance [2].

The Minamata Convention on Mercury Treaty, effective since 2017, mandates a global phase-down of mercury-containing products, including mercury dental amalgam [3]. In 2021, the US Department of State submitted the first national report from the United States to the Minamata Convention on Mercury Treaty. This report consisted of party measures for mercury-added products in Part II of Annex A, specifically related to mercury dental amalgam, which included:

i. Setting national objectives aiming at dental caries prevention and health promotion, thereby minimizing the need for dental

restoration;

ii. Promoting research and development of quality mercury-free materials for dental restoration;

iii. Encouraging representative professional organizations and dental schools to educate and train dental professionals and students on the use of mercury-free dental restoration alternatives and on promoting best management practices; and

iv. Promoting the use of best environmental practices in dental facilities to reduce releases of mercury and mercury compounds to water and land [4]."

Additionally, the US Environmental Protection Agency (EPA) has identified that dental clinics are "the main source of mercury discharge to publicly owned treatment works (POTWs) [5]. The EPA had implemented mandatory mercury amalgam separators to be installed with the final rule going into effect in 2017. It became compulsory on July 14, 2020, to comply with this rule [6,7]. Over 30 countries, including those with populations exceeding 100 million, have implemented bans, with the European Union enforcing a comprehensive ban on mercury dental amalgam as of January 1, 2025, except in specific medical cases [7]. The United States, the first nation to ratify the treaty, has made no progress toward elimination, perpetuating exposure to a known neurotoxin implanted in tens of millions of patients [4]. Despite these environmental measures, the FDA's endorsement of mercury dental amalgam and refusal to mandate patient disclosures represent a profound regulatory failure, compromising public health and global mercury reduction efforts.

This mini-review evaluates the FDA's policies, focusing on its refusal to mandate patient disclosures, the health risks of mercury dental amalgam, and the critical need for safe removal protocols. By integrating recent peer-reviewed studies, legal critiques, and international benchmarks, it is necessary for immediate reform to align with the Minamata Convention and protect vulnerable populations.

Food and Drug Administration (FDA)

The FDA's mission is to ensure the safety, efficacy, and security of medical devices, including mercury dental amalgam [8]. Until 2009, it classified mercury dental amalgam as a Class I device (low risk), requiring minimal oversight [9]. In response to a citizen's petition submitted by attorney James Love, on behalf of various petitioners, the FDA reclassified amalgam as Class II in 2009, acknowledging risks for vulnerable populations, including pregnant women, children, and individuals with genetic predispositions such as apolipoprotein E4 (ApoE4) or coproporphyrinogen oxidase (CPOX4) variants [7,10-12]. These genetic factors, present in approximately 25% and 28% of the global population, respectively, increase susceptibility to mercury toxicity, with ApoE4 linked to Alzheimer's disease and CPOX4 associated with neurobehavioral deficits. A 2010 Scientific Advisory Panel recommended warnings for these groups, but the FDA took no action, a decision later exposed by a 2015 McClatchy investigation as influenced by a Department of Health and Human Services cost-benefit analysis prioritizing economic factors over health [13].

The US national report to the Minamata Convention cited the updated FDA "Recommendations for Certain High-Risk Groups Regarding Mercury-Containing Dental Amalgam." They remarked that some people may be at higher risk for adverse health effects from mercury exposure. While also stated, "Although the majority of evidence suggests exposure to mercury from dental amalgam does not lead to negative health effects in the general population, little to no information is known about the effect this exposure may have on members of the specific groups who may be at greater risk to potential negative health effects of mercury exposure [4]." This statement is false due to the enormous amount of seminal studies of evidence-based scientific research that have been published on the risks of exposure to mercury dental amalgams going back over a century. For example, a simple keyword search of "risks of mercury dental amalgam" on Google Scholar yielded over 15,000 results in 0.14 seconds [14]. A plethora of peer-reviewed scientific papers on mercury dental amalgam continue to be published and cited worldwide. These papers are irrefutable, demonstrating not only the extensive research on mercury dental amalgam risks but also the negative health effects they cause [15-22].

In 2020, the FDA issued non-binding recommendations acknowledging risks for high-risk groups, including pregnant women, children under six, and those with neurological or renal impairments, but continued to emphasize mercury dental amalgam durability and cost-effectiveness [23,24]. These recommendations fall short of a ban or mandatory disclosures, ignoring safer alternatives like Atraumatic Restorative Treatment (ART) and composite resins [7]. Dr. Anne Summers' 2019 critique (Docket ID: FDA-2019-N-3767) to the FDA's Immunology Devices Panel highlighted critical data gaps in its safety assessment: (1) ignoring epidemiological evidence of elevated mercury levels, (2) overlooking cumulative toxicity in adults and the elderly, (3) underestimating mercury's transformation into toxic forms, and (4) neglecting its role in promoting antibiotic-resistant bacteria [25]. Wiggins et al. linked mercury exposure to multi-antibiotic resistance, a global health crisis costing billions annually [26]. Recent studies, such as Geier et al., further associate mercury dental amalgam with arthritis, with higher incidences in individuals with 4–7 amalgam surfaces, reinforcing the FDA's underestimation of systemic risks [27]. These omissions, coupled with reliance on outdated methodologies, highlight the FDA's regulatory inaction.

FDA's Failure to Mandate Patient Disclosures

The FDA's refusal to mandate patient disclosures about mercury risks in mercury dental amalgam, often misleadingly called "silver fillings," is a critical regulatory failure that undermines informed consent. In its 2009 ruling, the FDA stated:

"FDA believes that the recommended labeling statements in the special controls guidance document will provide dentists with important information that will improve their understanding of the devices and help them make appropriate treatment decisions with their patients. In addition, FDA notes that dental amalgam

is a prescription device and, therefore, patients cannot receive the device without the involvement of a learned intermediary, the dental professional. Based on the reasons described above, FDA has concluded that it is not necessary to require that dentists provide this information to patients in order to provide reasonable assurance of the safety and effectiveness of the device". The FDA further asserts that "after consideration, and based on all available scientific evidence, including evidence submitted in your Petitions, FDA does not believe it is necessary or appropriate to require that dental health care providers provide this information to patients" [28].

This position is scientifically and ethically indefensible. First, the FDA's reliance on dentists as "learned intermediaries" assumes uniform competence, contradicted by studies showing many dental professionals underestimate mercury dental amalgam's risks or prioritize cost-effectiveness due to insurance structures [28-30]. The term "silver fillings" obscures the material's ~50% mercury content, misleading patients about a neurotoxin in their restorations [1]. This violates informed consent, a cornerstone of medical ethics [31].

Second, the FDA's claim that existing evidence does not justify disclosures is untenable. Mercury dental amalgam releases vapor, leading to neurological, immunological, and renal impairments, particularly in vulnerable populations [1,15-22]. Autopsy studies show 2–12 times higher mercury levels in brain and kidney tissues of amalgam bearers, with some exceeding toxic thresholds [32]. Park et al. found elevated urinary mercury levels in women with amalgam fillings, correlating with health risks. Geier et al. linked amalgam surfaces to asthma [33]. The Casa Pia study reported neurobehavioral deficits in children with CPOX4 variants, affecting 28% of the population [7,22]. Over 15,000 published studies on Google Scholar document these risks, contradicting the FDA's dismissal [14].

Third, the FDA's stance diverges from international standards. The EU's 2025 ban, building on 2018 restrictions for children and pregnant women, aligns with the Minamata Convention's precautionary principle, as do bans in Norway, Sweden, and Japan [7,34]. The FDA's inaction, influenced by the American Dental Association (ADA), which defends mercury dental amalgam's economic benefits, raises concerns about industry bias, as seen in the 2015 rejection of warning recommendations [7,13].

Fourth, the failure to mandate disclosures exacerbates health inequities. Underserved communities, with limited access to mercury-free alternatives like Atraumatic Restorative Treatment (ART), face disproportionate risks [7]. The deceptive "silver fillings" label and lack of notifications perpetuate uninformed treatment decisions, particularly for vulnerable groups [1].

Counterarguments from the FDA and ADA claim low mercury release poses minimal risk and dentists are equipped to inform patients [7,16]. These are flawed. Individual variability (e.g., ApoE4, CPOX4) increases risks at low exposures, and disparities in dental care access undermine consistent risk communication [7,11,12,16]. Safer alternatives like ART and composite resins, widely adopted globally, render mercury dental amalgam's use unjustifiable [7]. The FDA's refusal to mandate disclosures violates ethical standards and hinders the Minamata Convention's goals [7,31].

Safe Removal of Mercury Dental Amalgam

As global awareness of mercury dental amalgam's health risks grows, particularly with the European Union's 2025 ban, demand for safe removal is surging [7,34]. This process poses significant health risks due to mercury vapor release, which can result in acute exposure levels far exceeding safe limits, particularly for vulnerable populations such as pregnant women, children, and those with genetic predispositions [7,11,12,17,18,20,25]. Warwick et al. found that mercury vapor concentrations during amalgam removal can reach levels associated with neurological and respiratory harm, necessitating rigorous protocols to protect patients and dental professionals [29]. Zwicker et al. reported reduced urinary mercury levels post-removal, underscoring the need for safe practices to mitigate exposure [37].

Dr. Hal Huggins, a pioneer in mercury-free dentistry, ceased using mercury dental amalgam in the 1970s after learning of its toxicity from Dr. Olympio Faissol Pinto. Huggins developed the "Bubble Operatory," a groundbreaking system incorporating advanced air filtration and protective barriers to minimize exposure [38]. His innovations, driven by early recognition of mercury's neurotoxic effects, set a precedent for safe removal practices and influenced organizations like the International Academy of Oral Medicine and Toxicology (IAOMT) and the International Academy of Biological Dentistry and Medicine (IABDM) [35,36].

The IAOMT and IABDM have established evidence-based guidelines, such as the Safe Mercury Amalgam Removal Technique (SMART) and PROTECT Protocol, to ensure safe mercury dental amalgam removal. These protocols mandate measures like high-volume suction, rubber dams, supplemental oxygen via nasal cannula, and full-body protective coverings to reduce mercury exposure. Additional safeguards include cold water irrigation to minimize vapor release, sectioning amalgams to reduce particle dispersion, and rigorous room ventilation to protect dental staff and patients [35,36]. Adherence to these standards is critical, as improper removal can exacerbate health risks, including neurological and immunological damage, particularly in vulnerable populations [18,20]. The FDA's failure to mandate patient disclosures about mercury dental amalgam's risks, compounded by the deceptive "silver fillings" label, leaves many patients unaware of the need for these specialized protocols, increasing the likelihood of unsafe removal practices [1,35,36].

The global shift toward mercury-free dentistry, exemplified by the EU's ban, underscores the urgency of universal adoption of these safe mercury removal protocols [7]. Non-compliance not only

endangers patients and dental professionals but also undermines the Minamata Convention's goal to "Make Mercury History" [7,39]. The FDA's inaction on promoting safe removal guidelines further highlights its regulatory shortcomings, necessitating immediate reform to align with international standards and protect public health.

Conclusion

The FDA's obstinate defense of mercury dental amalgam, falsely branded as "silver fillings," and its brazen refusal to require patient disclosures expose a shameful betrayal of public health trust. The World Health Organization confirms mercury dental amalgam as the dominant source of human mercury exposure, with NHANES data revealing that over half of Americans aged 15 and older bear these toxic fillings, and 30–40% surpass EPA safety limits, driving such health maladies as neurological, immunological, renal, arthritic, and respiratory harm. These figures likely understate the crisis, as NHANES excludes children with amalgam fillings. Mercury dental amalgam's role in fueling antibiotic-resistant bacteria escalates a global health emergency, threatening the efficacy of critical medical interventions. Dental professionals endure relentless mercury exposure, with evidence of these professionals' heightened health risks, while dental clinics account for roughly 50% of U.S. wastewater mercury, poisoning ecosystems. The FDA's feeble Class II classification dismisses thousands of peer-reviewed studies, including autopsy data revealing toxic mercury in tissues and heightened risks for those with genetic vulnerabilities like ApoE4 or CPOX4. By endorsing the deceptive "silver fillings" label and discouraging mercury disclosure, the FDA obfuscates informed consent, defying ethical mandates like the American Medical Association has recommended. Proven alternatives such as Atraumatic Restorative Treatment (ART) and composite resins, embraced worldwide, render mercury dental amalgam archaic and unjustifiable. The EU's 2025 ban proves mercury-free dentistry is not only feasible but essential, aligning with the Minamata Convention's urgent call to eradicate mercury use. Legal challenges, advocacy critiques, and recent studies highlight the FDA's transparency deficits and potential industry bias. The FDA's obstinacy sabotages global mercury reduction efforts and endangers millions. It must enact mandatory disclosures, enforce stringent safe removal protocols, and ban mercury dental amalgam outright to honor the Minamata Convention, rebuild public trust, and safeguard humanity from this preventable scourge. The FDA must act to "Make Mercury History."

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