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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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