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Objective: To explore the controversial issue of the safety and use of mercury in amalgam dental fillings. **Methods:** Using a variety of scientifically oriented studies, overall trends and conclusions were analyzed. Relevant articles include Children's exposure to Amalgam, fetal exposure, environmental mercury, occupational exposure, and mercury and Multiple Sclerosis. Additional literatures available to the public were also analyzed to provide background on the general public's access to information regarding amalgam. **Results:** Many studies used analyzed mercury content of the urine, a key factor when deciding the toxicity of mercury in amalgam fillings. Most studies found little or no correlation between amalgam fillings and toxicity to the human body. **Conclusion:** The bulk of the evidence to date supports the use of mercury amalgam as probably safe.

Key Words: Amalgam, Dental Fillings, Mercury, Dentistry

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Dental Amalgam Fillings: The Scientific Evidence for Safety

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Dental Amalgam Fillings: The Scientific Evidence for Safety

Introduction

The debate about whether the mercury contained in amalgam dental fillings causes adverse health consequences is an important and ongoing discussion. Internet search tools as well as a variety of opinions from dentists, the American Dental Association (ADA) and research scientists' information on amalgam disease are readily accessible for patients. Upon reviewing primary literature, it is clear that the science of toxicology in general, and of dental amalgam in particular, is highly complex. It is also apparent that while there is substantial scientific evidence to suggest that the mercury in dental amalgam is safe, there remains good reason to be concerned, support ongoing research and continue to explore the safety of amalgam and its alternatives.

After reviewing articles discussing the safety of amalgam, it is clear that many complex factors are involved when addressing the scientific evidence for its safety (Clarkson and Magos, 2006, Aminzadeh and Mahyar, Bellinger et al. 2007. The ultimate study on mercury and its effects would control for numerous variables, which is extremely difficult to accomplish. Thus, despite analyzing hundreds of studies published in peer-reviewed journals, no definitive conclusions have been reached. As pointed out by Clarkson and Magos (2006), few things in health care are absolutely certain but rather, choices are typically made after carefully weighing risks and benefits.

The issues involved as to the safe usage of dental amalgam are so complex that patients may find it difficult to understand their treatment options. In order to fully understand the concerns surrounding amalgam fillings**,** toxicology of mercury in its different forms must be explored. Additionally, the primary literature on the toxicology of mercury is often so filled with scientific terminology that it is difficult for the lay

person to understand. For example, in Clarkson and Magos (2006), the authors focused entirely on refuting another's work (Mutter et al.) regarding the confounding importance of which form of mercury was measured as well as the matter of using appropriate control groups. This serves as an example illustrating the technical literature patients must wade through when evaluating treatment options. Despite the complicated scientific nature of this topic, I intend to help patients sort through this difficult information and help them to make an individual choice that is best for them.

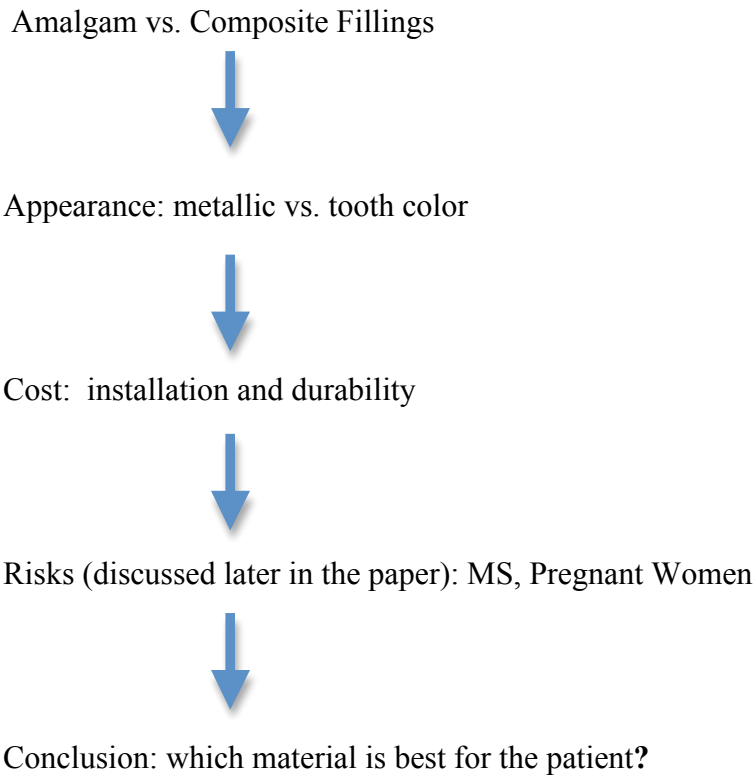
Following a brief review of the chemical properties of mercury, I will explore several toxicological studies focused on amalgam fillings and their safety. My goal is to provide a factually based exploration of amalgam fillings and to present the findings of several scientific studies that researched the use of mercury in amalgam fillings in relation to human health in a readily accessible form to the lay person. I plan to enhance my ability to educate my future patients by expanding my knowledge of this controversial subject, and will likely learn more about this next year at Oregon Health Sciences University School of Dentistry.

Background on the use of mercury in dental amalgam

Mercury has been used in dental fillings for over 150 years (Clarkson and Magos 621). Mercury is combined with silver and copper or zinc to make a compound that is inexpensive, durable, and technically reasonable to work with. Mercury binds the various metals of the amalgam together strongly, yet has the unique ability to allow molding of the material in the mouth prior to setting in place (Khosla).

Composite fillings were implemented much more recently (1960s), using a more advanced matrix of plastic and glass materials compared to earlier alternative (Hall). This material combination allows dentists to match the filling material with the tooth color using a variety of colored filling materials, ranging from dark yellow to nearly white. While ascetically pleasing and functionally sound, some composite fillings can contain BPA (bisphenol-A), a hazardous material found in plastic water bottles. According to the Oregonian, "evidence is mounting that chemicals found in food packaging, including baby bottles, could harm the brain and contribute to early puberty, heart and liver disease and diabetes" (Parker D7). Issues have been raised regarding the safety of this material, but the details specific to this material will not be discussed here. Moreover, this material does not tend to be as durable as amalgam and is more expensive making it a less likely choice for many patients. The flowchart below summarizes some of the considerations when choosing a filling material.

Figure 1: Amalgam vs. Composite filings



Please note that these are only two of the filling options, as the scope of this paper does not include gold.

Mercury: its chemical compounds and presence in the environment

A basic understanding of the role of mercury in the environment, human physiology, its metabolism, its biological measurements and its toxic effects, both acute and chronic are vital to interpreting any claims of safety for either mercury in dental amalgam, methyl mercury in fish or thiomerosol (ethyl mercury) in certain vaccines. The goal of this review is to discuss what is known about mercury's useful properties as well as to balance this information with data about toxicity issues. The following short review based on Clarkson and Magos's (2006) paper will address these aspects of mercury's use in the dental setting.

The inorganic forms of mercury (Hg^{o}) include the liquid metallic mercury, its vapor, and the oxidized form mercuric mercury (Hg^{2+}). While dental amalgam releases some mercury vapor to humans, the vast majority of mercury vapor released into the atmosphere comes from natural and man-made sources (Clarkson and Magos 613). Inorganic mercury vapor is released from volcanoes, and erosion of soil. Mercury may also be released from soil processed by mining operations or exposed to erosion from mining locations. Coal burning power plants, incinerators, and recycling processes also release mercury into the atmosphere. This mercury circulates in the atmosphere for about a year, becomes distributed throughout the planet's atmosphere, oxidizes to mercuric mercury and then finds its way into the soil and water. Some of this mercuric mercury re-vaporizes and re-enters the atmosphere, creating an endless cycling of mercury.

When inorganic mercury undergoes oxidation (loses one or two electrons) via a process of biomethylation, primarily by sulfate-reducing bacteria in both marine and fresh water sediment, and becomes linked covalently to at least one carbon atom, it is then called "organic" mercury (Clarkson and Magos 618-620). This form of mercury is referred to as methylmercury and is the major form of mercury found in fish protein.

Another version of organic mercury is the vaccine preservative thimerosal. Recent concerns about the potential toxicity of this form of mercury led to a decision to remove this preservative from all vaccines given to children in the United States (Clarkson and Magos 612).

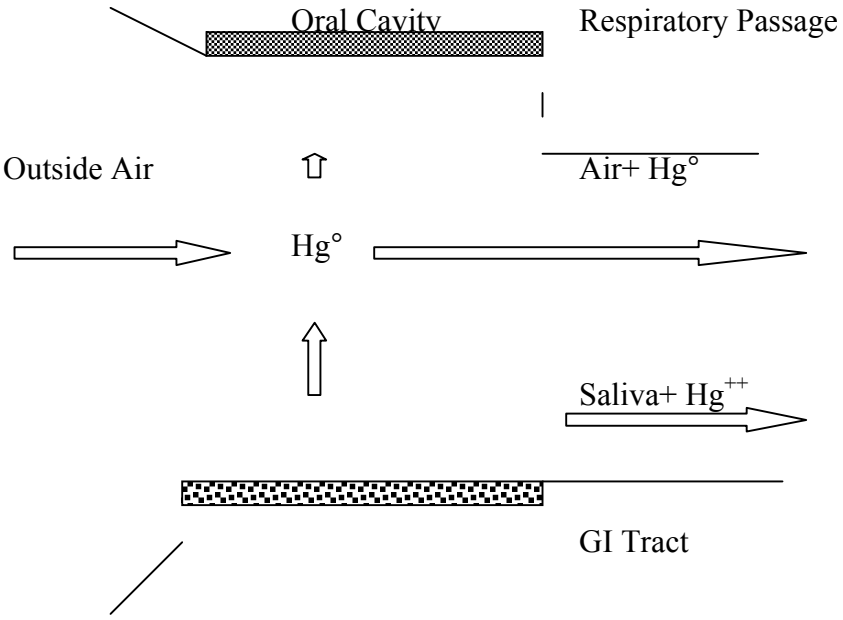
Human exposure to mercury

The process of bioaccumulation in aquatic food chains of organic methylmercury results in potentially significant quantities of mercury entering the human diet not just from fish, but also from other food sources. These foods may also be a source of inorganic mercury as some organic mercury may be converted in the animal body to inorganic mercury. Methylmercury forms complexes with proteins and is distributed through the body. Some of this mercury seems to be converted to inorganic mercury by processes that are poorly understood, and some of this inorganic mercury may end up in the brain causing a variety of outcomes from hand tremors to increased salivation in the mouth. Furthermore kidney damage is also common (Clarkson and Magos 619).

The atmospheric cycling of inorganic, mercury vapor is discussed above. However, the concentration of mercury is so low as to be considered a negligible source of human exposure and the World Health Organization (WHO) in 1991 concluded that most human exposure to inorganic mercury vapor (outside industrial settings) is from dental fillings (Clarkson and Magos 621).

Importantly, except for those occupationally required to handle mercury, most individuals receive the most mercury exposure in the form of mercury vapor from their dental fillings. Additionally, there are several factors that influence the rate of release of mercury vapor from dental fillings.

Figure 2: Release of Mercury From Amalgam Fillings (Clarkson and Magos 622)



The number of filled surfaces, especially ones on chewing areas directly determines the rate of mercury vapor release. Excessive chewing such as seen in nighttime tooth grinding (bruxism) or use of nicotine gum can cause the intra-oral mercury level to approach the occupational unsafe limits (Clarkson and Magos 622-623). Removing fillings can also cause a temporary rise in the blood mercury levels (three to four times higher) pretreatment levels due to increased mercury vapor exposure when high-powered dental drills remove the filling (Clarkson and Magos 622), although this exposure may still be significantly less than that associated with occupational exposure (Clarkson and Magos 623).

Mercury vapor, Hg^{o}, is rapidly absorbed as an uncharged monatomic gas, is very lipid soluble, and diffuses easily to all bodily tissues (Clarkson and Magos 618-619). Mercury rapidly crosses blood-brain and placental barriers causing a range of neurological effects discussed later in the paper. Once the vapor is distributed, oxidation occurs resulting in mercuric mercury (loses two electrons) Hg^{2+}. On average, 74% of

inhaled mercury vapor is stored in the body. This vapor is retained in the lungs as well as diffusing into the bloodstream (Clarkson and Magos 617). Some is exhaled in the lungs. The remaining mercury is excreted in urine and feces (Clarkson and Magos 618).

Interestingly, it may be that the mercuric ion Hg^{2+} is the toxic element rather than mercury vapor, Hg^{o} itself. Little is known about the specifics of how mercury vapor becomes oxidized to the mercuric state but some studies have shown that alcohol intake inhibits this conversion process and may be protective. In a 1988 study, beer drinking Danish factory workers were able to exhale more mercury vapor before it was oxidized (Clarkson and Magos 618) and there is also recent evidence of oxidative processes in mitochondria showing genetic variation in how mercury is metabolized from vaccine intake (Clarkson and Magos 618). This may prove to be a factor for mercury vapor metabolism from dental amalgam as well (Clarkson and Magos 619).

Once in the body, the most crucial mechanism for excreting mercury is in the urine, where it can be measured as a concentration in μg Hg/L (urine). The urine in many studies is the best indicator for mercury vapor exposure and risk. Unlike methyl mercury from fish sources, inorganic mercury does not accumulate in hair and those studies which measure hair mercury levels mistakenly attribute the source to be from fillings.

Liquid metallic mercury has a high vapor pressure. The safe occupational limit is 25 μg Hg/m^3 (air) with a saturated room of mercury being 14 mg Hg/m^3 (Clarkson and Magos 619). While these levels of mercury vapor exposure are unusual, such exposures could occur in a spill of liquid mercury in a small space or heating the liquid over an open flame. Indications of acute toxicity include shortness of breath, cough, chills, nausea and vomiting (Clarkson and Magos 620-621). Death may occur.

Long term exposure is the more relevant issue to humans with dental amalgam use. A prolonged occupational exposure typically leads to hand and arm tremors, personality changes, as well as cognitive disturbances (Clarkson and Magos 619).

Sometimes severe kidney damage occurs with large volumes of poorly concentrated urine and death may also occur. Severe cases of chronic exposure have been associated with urine levels of 500 μg Hg/L urine (Clarkson and Magos 619). However, adverse effects on kidney and nervous system have also been reported in association with urine mercury levels in ranges of 50-100 μg Hg/L urine (Clarkson and Magos 621). Symptoms associated with urine levels less than 50 μg Hg/L are not well accepted. However, in a recent analysis of 12 studies with over 700 study subjects**,** urine levels range from 6-115 μg Hg/L and still there is no consistent pattern between urinary levels and symptoms (Clarkson and Magos 2006). The authors note that more recent studies contain urine levels that are lower compared to studies before 1950**,** where urinary levels for most occupational exposures were an order of magnitude higher than they are currently due to increased safety measures. This may explain why levels of 50 μg Hg/L were not associated with evidence of harm. Additionally, population variation in Hg metabolism and sensitivity may explain these variables' symptoms and a lack of a clear dose-response relationship.

Many other studies have shown that occupational exposure to mercury vapor does not increase incidence of Alzheimer's or Parkinson's disease (Clarkson and Magos 623). For example, many research articles focus on the findings of brain mercury levels at autopsy. But to date**,** the most recent and case matched studies find no difference in mercury amounts in demented versus unaffected functioning patients (Aminzadeh and Mahyar 64). And Clarkson and Magos, reviewing a total of five studies in various countries with about 2000 patients, found no association between urinary mercury or fillings and any cognitive defects (2006, 624).

Children

A study by Bellinger et al. published in 2007 explored the concern with childrens' exposure to mercury in the vaporized form from dental amalgam fillings. This research team studied children, ranging from six to ten years of age, who have had amalgam fillings in the past compared to a similar matched group of children whose dental cavities were filled with composite materials. Over a five-year period, the children were tested for a variety of parameters including intelligence, language, memory, spatial skills and motor function. Children were matched for health, birth weight, and many other factors.

The authors did find higher mercury concentrations in the urine of the amalgam group compared to the composite group, a difference of 0.3μg/g creatinine with an average urinary concentration was 0.9 μg Hg/g mercury for which group (Bellinger et al. 443). These values are far below the 50 μg Hg/L believed to cause symptoms in the Clarkson and Magos review. The measurements of μg Hg/g creatinine and μg Hg/L used for urinary concentration are used interchangeably, relating the Bellinger et al. study to Clarkson and Magos' review (Clarkson and Magos 618). Thus, Bellinger et al. concluded that "exposure to elemental mercury in amalgam at the levels experienced by the children who participate in the trial did not result in significant effects on neuropsychological function within the 5-year follow-up period" (Bellinger et al. 440). These results seem to suggest the safety of amalgam fillings.

However, this study took place over a fairly short five year period, offering no long-term correlation with mercury-based fillings. In the discussion of the study, the researchers conceded, "this might not be the period of greatest susceptibility to elemental mercury" (Bellinger et al. 473). Due to their young age, mercury could take much longer to manifest unhealthy consequences. Additionally, only healthy children were included in the study with more dental cavities than the average US child, whereas unhealthy

children with diseases such as cancer and thus weakened immune systems and potentially compromised metabolism, may be more susceptible to mercury in amalgam. The researchers also mentioned that there may be specific subsets of genotypes among children who have greater susceptibility than other more common genotypes due to differences in metabolizing mercury (Bellinger et al. 473).

Fetal exposure and toxicity

Another research team studied the effects of amalgam fillings on the mercury concentration in human amniotic fluid (Luglie et al., 2005). This paper addresses the potential effect of mercury amalgam on fetal development. Amniotic fluid is inside the uterus and surrounds the developing fetus. For this study, seventy-two pregnant women with multiple amalgam fillings were identified. On average, each pregnant woman in the study had 4 amalgam fillings. Because fetal skin tissue cells are found in the amniotic fluid, if mercury is detectible in these cells then it must have been passed across the placental barrier from the mother to fetus. If there were high levels of mercury in the amniotic fluid, then its negative effects could influence sensitive brain development. The authors found that while there was detectable mercury in the amniotic fluid, there were no adverse outcomes in terms of obstetric history or perinatal complications.

This study also measured the surface area of the amalgam fillings in relation to mercury levels in the amniotic fluid and found no statistically increased amniotic mercury associated with larger maternal amalgam surface area. Similarly, there was no clear relationship between fish consumption or smoking and mercury levels in the amniotic fluid (Luglie et al. 138).

This study suggests no significant relationship between amalgam surface area and fetal development. Furthermore, previous researchers have studied the relationship between other bodily fluids such as blood, saliva, and urine, and have also found no significant correlation between the number of amalgam fillings and mercury levels present (Luglie et al. 141). However, it was suggested that mercury in the amniotic fluid had no measurable impact on the developing fetus because it was not present in the baby's body for a long-enough period of time to cause harm. However, a small number of pregnant women were used and with a small sample of only seventy-two women, rare

events become more difficult to detect because the study was limited to only the pregnancy period

Severe methylmercury exposure in Iraq

As an example of the long term effects of severe mercury exposure, Clarkson and Magos summarize the results of high methylmercury exposure in a group of citizens of Iraq during the 1970s. These people's health statuses were similar to those of US citizens', so the study is comparable to possible outcomes of exposure in US populations. These individuals consumed grain seed that had been treated with a fungicide containing methylmercury. They found that children born after mothers consumed large quantities of this bread had severe physical and developmental deformities and decreased brain function. And children analyzed at developmental milestones, such as first walking, evidenced an impact on their ability to achieve these normal functions (Clarkson and Magos 635). Notably, this was a very high dose of mercury and evidences the possible outcomes of extreme exposure.

Mercury and multiple sclerosis

A meta-analysis by Aminzadeh et al. (2007) compiled four previously researched amalgam studies and looked for correlations between dental amalgam exposure and multiple sclerosis. Their conclusions were that "the risk of [Multiple Sclerosis] among amalgam users was consistent, with a slight, nonstatistically significant increase between amalgam use and risk of [multiple sclerosis]" (Aminzadeh and Mahyar 64). Furthermore, they state that "future studies that take into consideration the amalgam restoration size and surface area along with the duration of exposure are needed in order to definitively rule out any link between amalgam and [multiple sclerosis]" (Aminzadeh and Mahyar 64). This compilation of results does support amalgam fillings as safe dental materials but with some reservations. Unfortunately however, a small number of studies were used. While as many as 16 studies have been done on this topic, the researchers state, "this investigation was limited to four studies with significant heterogeneity" (Aminzadeh and Mahyar 65). This heterogeneity lies with the fact that some studies lack control for confounding variables. The authors conclude that future studies are needed that take into account amalgam surface area and duration of exposure to ultimately rule out a link between multiple sclerosis and dental mercury.

Occupational exposure to amalgam

Jones et al. examine the effects of mercury exposure on the health of dental nurses (2007). Thirty years after a group of nurses began being exposed to mercury amalgam, their general health was measured. The authors concluded that while some significant differences were present compared to controls, such as poorer subjective health and early hysterectomy, cognitive functioning and other psychiatric symptoms were no different. This study is interesting in that it represents the encounters of a number of individuals who were estimated to experience very significant mercury exposure over a period of years. However, the authors did not mention whether the dental nurses were using safe practices while exposed to the filling material (they heated the filling material over open flames with no ventilation) (Jones et al. 368). In more recent decades, safer practices for handling amalgam, such as providing adequate ventilation have been established and this study raises some concerns about the potential for mercury exposure causing health risks in an obsolete occupational setting. Furthermore, this study also analyzed people around the age of 51, on average too young to develop Alzheimer's or other diseases of concern.

Scope of work

In comments on the Clarkson and Magos (2006) article by Mutter et al. (2007), major issues are revealed. For very rare conditions such as autoimmune disorders, many studies have been conducted to try to determine whether there is a relationship between mercury exposure and illness. However, these studies may not include a large enough sample size to detect a significant relationship between mercury and these uncommon illnesses. There is also extensive literature that multiple sclerosis occurred after acute exposure to mercury vapor or other heavy metals (Mutter et al. 541). Several good studies show improvements in health in multiple sclerosis patients with amalgam removal. Mutter et al. also make the point that while there is some value in measuring urine levels of excreted mercury and attempting to correlate that with the presence or absence of disease, there may be a limited relationship between the two, especially if a disorder is rare. They also point out that some illnesses could develop only after many years of mercury exposure, which can be very expensive and difficult to track in a research project. Mutter et al. note that while urine levels of mercury may be measured to be low in some patients with significant diseases, the low urine level may not correlate with the amount of mercury in the brain.

Finally, there are issues with amalgam and the environment. In the US, there are an estimated 1000 tons of mercury in filled teeth (Mutter et al. 543). This is the 3rd greatest source of mercury in the environment. In Europe, there are wastewater separators but not in the US (mercury from wastewater in dental clinics, in urine from patients with fillings and from cremated persons with fillings). This potential and as yet unknown "cost" to public health was not mentioned in any other article.

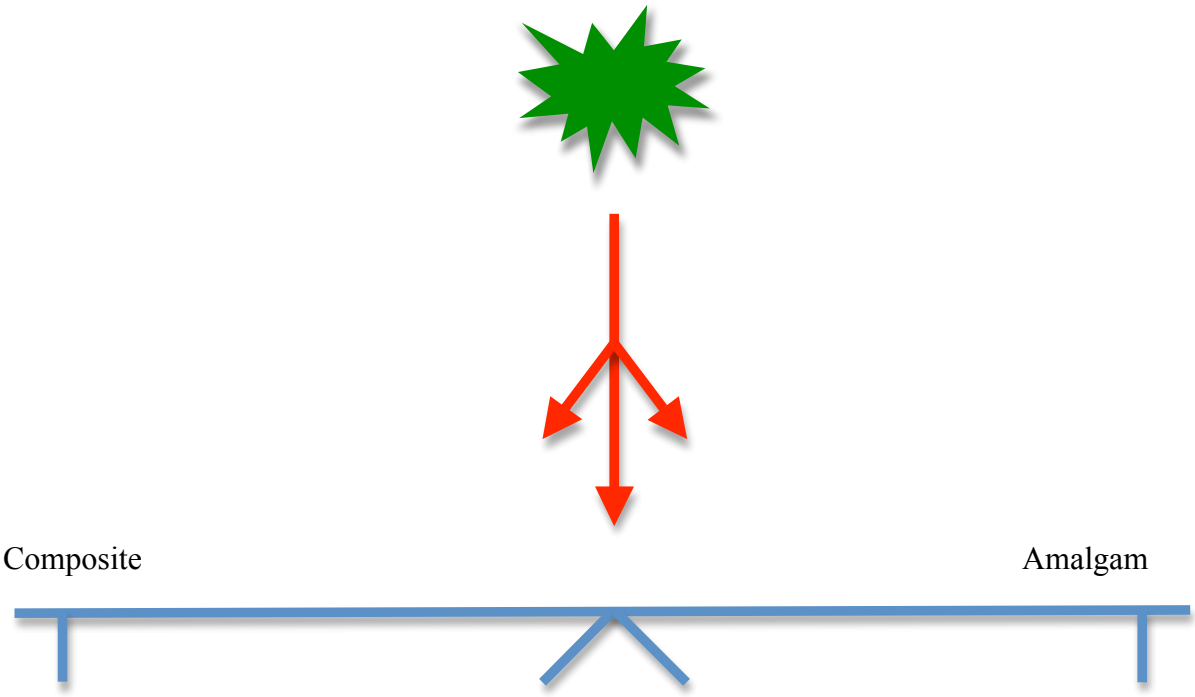
Summary

The bulk of the evidence to date supports the use of mercury amalgam as probably safe. The strongest evidence were the many studies reviewed by Clarkson and Magos (2006) concerning very low urinary trends with mercury amalgam compared to the levels found in people who have experienced occupational exposure and have experienced known mercury related illness. There is also substantial literature, although not in universal agreement**,** that there is a lack of correlation between mercury levels in the urine and with many disease states. The paper discussing mercury amalgam use in children compared to composite fillings was very strong in suggesting the safety of amalgam (Bellinger et al.).

Below is a chart, which presents the factors that could influence the choice of filling material. If the diagram tips toward a filling option, then that option would be more favorable. The factors below 'amalgam' and 'composite' represent factors favoring that choice.

Figure 3: Addressing Patients' Concern Between Composite and Amalgam Fillings Choice

Factors Influencing Material Choice
1.Costs
2. Appearance
3. Durability
4.Unknowns with composite
5. Amalgam used in larger filling areas
6. Risks (MS, pregnant women, young children, mentally disabled)



As a future dentist, I am most impressed with questions relating to patients with multiple sclerosis, but this link is still not certain. I would possibly recommend different filling materials. I would also be careful with restorative work on pregnant women, as that is a very sensitive time for fetal development. It is likely that future studies will more definitively address this important topic, and will probably influence the care I provide to my patients, and the options I discuss with them. There may be future genetic testing that would allow determination of genetically susceptible patients, and thus a re-

evaluation of risks and benefits. New materials may be discovered, but they would certainly undergo similar studies comparing toxicity with mercury.

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