

Amalgam risk assessment with coverage of References up to 2005

J. Mutter¹, J. Naumann¹, H. Wallach^{1,2}, F. Daschner¹

¹ Institute for Environmental Medicine and Hospital Epidemiology, University Hospital Freiburg, Hugstetter Str. 55, 79106 Freiburg, Germany E-mail: jmutter@iuk3.ukl.uni-freiburg.de

² University Northampton, School of Social Sciences, Northampton, United Kingdom

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Abstract

Amalgam has been used world-wide as a tooth filling material for 150 years. It consists of about 50% elemental mercury and a mixture of silver, tin, copper, and zinc. Finished amalgam fillings continuously release small amounts of mercury vapor. Amalgam thus significantly contributes to the human mercury burden. Mercury can accumulate in organs, particularly in the brain, because proteins have a greater affinity to it than other heavy metals (e.g. lead, cadmium) do. Its half-life in the brain is thought to be 1 – 18 years. Mercury counts as the most poisonous non-radioactive element. There is evidence that mercury vapor is more neuro-toxic than methyl mercury from fish.

Recent publications point to the risk that kidney damage, neuro-psychological impairment, induction of auto-immune diseases or sensitization, heightened oxidative stress, autism, skin and connective tissue diseases and non-specific complaints are caused by amalgam exposure. Both Alzheimer's disease and the development of MS are also thought to be connected to it.

Various individual differences in sensitivities, possibly congenitally determined or acquired, exist for the development of negative effects of an amalgam burden. Measurements in bio-markers for the assessment of mercury burden in critical organs can only be used in a limited way. Because of methodological deficiencies some amalgam studies have only limited significance.

In some studies containing a relevant number of patients, amalgam removal made lasting improvement or healing of several, for the most part chronic, complaints possible.

Taking all available data into account, amalgam can neither in medicinally, nor in the field of occupational medicine, nor ecologically be considered a safe tooth filling material.

Key words: Amalgam, Quicksilver, Toxicity, Side-Effects, Auto-Immunity, Neuro-Degenerative Diseases.

Introduction

Amalgam is produced easily, quickly and inexpensively, and, as a tooth filling material, it displays excellent material properties and durability. It has been used for over 150 years. However, amalgam has been discussed as a subject of controversy since its first use in dental medicine because amalgam is compounded from poisonous metals that are not tightly bound together. There is still no uniform agreement about the health related bothersome effects of this heavy metal at this time. Since even current risk analyses differ diametrically in their conclusions, we have personally performed an analysis of the very extensive literature that already exists about this subject. We are primarily citing newer studies that describe possible adverse effects of amalgams. That is because possible adverse effects, i.e. the exposure to small amounts of mercury, would impact a significant part of the population as a result of its wide application even if it shows only minimal effectiveness.

Also included are studies that investigate the toxicity of mercury in small doses. Because experimental studies on humans are for the most part not allowable for ethical reasons, studies of cell and animal experiments are included, as well. Important and often cited studies that are meant to prove the harmlessness of amalgam are covered in detail.

Methodology

Using the Medline data bank and entering the search words “mercury,” and “amalgam” an attempt was made to cover the subject literature as completely as possible. This literature was chosen by assessing titles and abstracts for risk analysis. As much as possible we used primarily recent literature starting in 1985. Furthermore current advisories by institutions (e.g. the Federal Institute for Medicines and Medicinal Products, U.S House of Representatives, Dental Commission of Sweden), or experts regarding publications that are available only through the internet were taken into account for the analysis when they were important for the subjects in question.

Results

Bases

Significance of Amalgam for the Human Mercury Burden

There are about 200 - 300 million amalgam fillings in the teeth of German citizens [1]. Over 20,000 kg of mercury (Hg) are being used for amalgam fillings in Germany [2]. However the use of amalgam is declining among children in Germany because of the use of alternative materials and the small number of caries cases whereby migrants' children clearly have a higher number of fillings than German children do [3]. Because so little amalgam is used there is a clear decline in mercury burden in children in comparison to earlier investigations [4]. Amalgam fillings consist of 50% metallic (HgO) to which a pulverized alloy of variable parts of silver, tin, copper, and mercury has been added. Amalgam fillings allow mercury vapors to escape continuously (increased by provocations, e.g. laying, polishing, and removing as well as chewing, grinding, the contact with acids and hot drinks, and the presence of different metals etc.). The mercury vapor is being absorbed 100% through the nasal and oral mucous membranes and alveolar surfaces (net absorption 80% because of dead air-space in the breathing passages). After absorption into the blood, 50% of the mercury vapor is dissolved in plasma, and only 50% is bound to erythrocytes (methyl-Hg >90% to erythrocytes). Because of that and because of its lipophilic nature, Hg-vapor can be transported relatively quickly by the blood to the organs and through the blood-brain barrier (BBB) into the brain while methyl mercury is being freed only at the end of the erythrocytes' lifespan. The half-life in blood for mercury vapor is only three days (methyl-Hg 60-90 days). Inside the organs it is being oxidized to the very toxic Hg⁺⁺, which is bound tightly to cell structures (mainly thiol-groups) and at that point cannot pass the BBB any longer [5]. It is very likely that Hg-vapor exposure over time causes an accumulation in the organs. Mercury is also freed by abrasion from amalgam. The gastro-intestinal absorption is being estimated at 5 – 15% [6]. Furthermore mercury vapor penetrates the oral and nasal olfactory membranes. A direct retro-grade axonal transport of Hg vapor into the CNS via sensory, motor and sensitive brain neurons (e.g. olfactory nerve) are being discussed [7–13]. Mercury also diffuses through dental bone and is being taken up by the pulp and the jaw, which is being seen as the reason for chronic local infections [14].

Amalgam is a primary source for mercury burden [15] as animal and human studies show [6, 16-22]. People with amalgams were observed to have a 2 to 5 times higher concentration of mercury in blood and urine as well as a 2 to 12 times higher content of mercury in organs [6, 17, 18, 23 – 40]. From these figures it was concluded that amalgam contributes more to the mercury burden of the greater part of the population in industrial nations than does fish consumption [6, 27-29, 35, 37, 40, 41]. In Germany there are, however, differences in mercury burden. Although persons in Leipzig showed the same mercury values in liver and kidney as those in Munich, they had higher values

in the brain [42]. Mercury from maternal amalgam fillings also leads to a significant rise in mercury concentrations in organs and hair of fetuses and newborns whereby the mercury content of organs of fetuses and nursing infants correlates with those of the mother's number of amalgam fillings [27, 43-50]. The Hg-concentration of breast milk, too, correlates significantly with the number of amalgam fillings of the mother. Here amalgam is the main source of mercury in the mother's milk [51-53]. Micro-organisms in the oral cavity and the gastro-intestinal tract are capable of synthesizing organic mercury varieties from inorganic ones [54-57]. Leistevuo et al. [54-57] found that amalgam bearers have a 3 times higher methyl-mercury concentration compared to persons without amalgam. Here the fish consumption in both groups was the same. In spite of the above-mentioned studies, which were, for the most part, published in internationally recognized trade journals, the dental organization maintains in current publication that amalgam in comparison to other sources contributes little or negligibly to the Hg-burden of the people [58-65].

Toxicity of Mercury

Mercury is considered to be the most non-radioactive element.

Hg⁺⁺ develops intra-cellularly from resorbed mercury vapor. It is more poisonous than other metals like Pb⁺⁺ or Cd⁺⁺ because its ability to bind to thiol-groups of proteins is stronger (Binding constant 10³⁰⁻⁴⁰), which leads to irreversible inhibitions of protein function. That could explain the very long half-life of mercury of several years to decades in non-regenerating tissue (i.e. the brain) [66-69]. Other heavy metals form reversible bonds to proteins and they are less toxic because of that. Hg⁺⁺ also does not form a strong enough bond to carboxyl-groups of organic acids (e.g. citric acid) that weaken the toxicity. Chelators, such as for instance EDTA, that normally prevent the toxic effects of heavy metals do not have an inhibitory effect on the toxicity of mercury or might even increase it [70, 71]. Other chelators (e.g. DMPS and DMSA) prevent the toxicity of Cd⁺⁺ and Pb⁺⁺ but not that of Hg⁺⁺ [72]. Neither DMPS and DMSA nor natural organism-specific chelators, such as Vitamin C, Glutathione or Alpha Lipoic Acid have the ability to remove mercury deposits from nerve tissues of animals [73]. DMPS led to an increase in the Hg concentration of spinal cord tissue [74]. DMPS and DMSA even increase the inhibition of enzymes by Hg and Cd, but not by Pb [75]. Methyl-mercury (Me-Hg) that exists in fish bound to cysteine seems to be far less toxic (only about 1/20) than the experimentally used Me-Hg-Cl or Me-Hg-J [76]. Besides that sea-fish is an important source of selenium and fish-oils that are important in protecting against the toxic effects of mercury. Nevertheless, the experimentally more toxic Me-Hg-J is less neuro-toxic for the growing nervous system than mercury vapor [77]. Exposure to both Hg-forms results in a synergistic effect. Investigations by Drasch et al. [78] reveal similar connections: Gold-miners who, next to methyl-mercury from fish, had been exposed to additional mercury vapors clearly showed more neurological signs than a control group whose

exposure consisted primarily of methyl-mercury from fish, and whose Hg-values in hair and blood were higher than those who had received additional mercury-vapor exposure (Median values: Blood: 9.0 vs. 7.0 $\mu\text{g/l}$, Hair: 2.65 vs. 1.71 $\mu\text{g/l}$) [78, 79]. Another report points to less neuro-toxicity from Me-Hg originating in fish in comparison to iatrogenic Hg-sources (amalgam, Thimerosal) [44]. In contrast to maternal amalgam and thimerosal there was no relationship between maternal fish consumption during pregnancy and the risk of autism of their children (See: results) [44].

In the presence of other metals the toxicity of Hg is synergistically increased. That means that 100% of the rats die when they are given Hg (LD1) and lead (LD1) simultaneously while each toxin given separately under normal circumstances causes only 1% of the animals to die. (LD1(Hg) + LD1(Pb) = LD100 [80].

The derivation of studies of mercury threshold values coming from amalgams for workers exposed to mercury has to be evaluated critically:

1. Mercury exposure of workers in the chlor-alkali industry is often used for comparison. However, the simultaneous chloride exposure significantly impedes the uptake of mercury in animals' bodily organs.
2. Mercury-exposed workers, as a rule, represent a cohort that is exposed to Hg in adulthood (and only for the limited duration of the time worked) while amalgam bearers starting in infancy (possibly also as a fetus through the mother) and into old age may be exposed to mercury for 24 hrs each day.
3. Workers might represent a select cohort of especially healthy persons. That might happen because sensitive individuals (vide infra) or pregnant women, children or sick people as a result of worker protection regulations or early adverse effects exit the work force or, as the case may be, do not even start that kind of work and thus are not being taken into account in these studies.

Limited Applicability of Hg-Values in Bio-Markers

There are studies that prove that mercury concentrations in blood and urine do not mirror adequately the actual amounts of mercury in the body. For example it was proven in studies on animals and people [6, 16, 19, 20, 22, 29, 78, 44, 66, 68] that high mercury values were present in organs in spite of normal or low mercury values in blood, hair, or urine. Furthermore, Drasch et al. [78, 79, 81] showed that 64% of mercury-exposed workers in Philippine gold mines showed clinically neurological signs of mercury intoxication while their urine mercury concentration registered under the HBM1 (Human Bio-Monitoring Value 1) of 5 $\mu\text{g/l}$ that generally is thought not to be dangerous. These most recent data intimate that mercury does not circulate freely. But, instead, is deposited to a great degree in body tissue. Therefore, studies using Hg-values in blood or

urine as gold standard for the evaluation of clinical symptoms or for the estimation of Hg-organ-content carry limited diagnostic relevance. The results presented by Drasch et al. [79] were critically assessed [82] and received comments about their critical assessment [83].

For lead levels in blood it has been accepted by now that negative health effects can occur far below the heretofore known acceptable limits [84-90]. A similar assumption might be made for mercury because of corresponding studies; i.e. certain lowest acceptable levels can be listed neither for mercury nor for lead.

Listed Side-Effects in Amalgam or as the Case May be in Low Level Mercury Exposure.

Kidney Diseases

In animal studies the impairment of kidney function as a result of amalgam filling has been observed [18, 91, 92]. Persons with amalgam fillings show signs of tubular and glomerular damage when compared to persons without amalgam fillings [34].

Gene-Toxicity and Oxidative Stress

In cell cultures amalgam causes chromosomal aberrations [93]. In amalgam bearers a significantly raised oxidative burden can be found in saliva. [94, 95] and in blood [37, 96] that correlates with the number of amalgam fillings. Low mercury concentrations led to raised oxidative stress and reduction in glutathione content in nerve cells [97, 98]. The deposited mercury is preferentially bound to selenium so that the Hg-bound selenium is not available any more for bodily needs. Mercury from amalgam may therefore trigger or worsen a possible selenium deficiency. This may happen in countries with suboptimal selenium supply (as e.g. in Germany) [67, 99].

Auto-immune Diseases and Individual Sensitivities

Low dose mercury exposure as it occurs in amalgam bearers is thought, by some authors, to be the cause of auto-immune diseases such as, e.g., rheumatoid illnesses, multiple sclerosis, auto-immune thyroiditis or systemic lupus erythematosus (SLE) [100-108]. These effects can occur at exposures below the threshold limits [109]. The prevalence of particularly notable persons is being estimated at 1% according to a fairly recent Swedish risk analysis [101]. The Human Bio-Monitoring Commission of the Federal Environmental Administration in Berlin estimates [2] that about 1 - 4% of the population react with particular sensitivity to amalgams. Those findings are in agreement with studies that estimate the frequency of immunological complaints at 1 - 3% of the

population [110] that considering the wide-spread use of amalgams presents a significant medical and economic problem. Other researchers estimate that up to 25% of all amalgam bearers are medically impaired by amalgam (all complaints including auto-immune phenomena) [111].

Alzheimer's Dementia

Some authors believe that mercury is a cause of Alzheimer's Dementia (AD) [71, 112-114]. In a recent review the possible connections were reported in detail [115].

That is why only a brief overview of the study results is given here.

In cell and animal experiments only Hg (not Aluminum, Cadmium, Cobalt, Chromium, Copper, Manganese, Lead, Zinc, Iron) was able to trigger Alzheimer-typical structural and biochemical cell changes [70, 71, 97, 98, 115-121]. Other metals that were also present worked synergistically with Hg [114]. The experimentally used Hg-concentrations were sometimes up to 1,000 times smaller than those mercury concentrations that would be found in e.g. the brains of amalgam bearers [115]. The reason for Hg as a possible cause of AD might thus be explained by the increased AD-risk for carriers of Apo-lipoprotein E-4 allele (ApoE4), and the lowered AD-risk in carriers of ApoE2-allele [71, 114, 115, 122] (vide infra).

In a few autopsy studies increased amounts of mercury were present in AD brains, which, however, did not always reach the required level of significance [117, 123-127]. Two studies even found mercury in the blood of living Alzheimer's patients. However there was one study where no increased mercury concentration in the brain of AD patients could be proven, nor was it possible to establish a correlation to amalgam fillings, which contradicts all other autopsy studies [227].

About 95-97% of all AD cases are not attributable to inherited factors. That is why an as yet unrecognized external factor is thought to be the cause, and it must exist mainly in industrialized nations (AD is practically unknown in populations untouched by modern civilization; after emigration into industrialized countries an increased AD-risk develops (age corrected)). This factor has to be present in persons already at a young age because

1. already a significant part of a population of 20-year-olds shows brain changes that must be classified as being Alzheimer-typical [130-132],
2. their frequency strongly increases with age, and
3. it takes about 50 years for Alzheimer's to develop [131, 132].

Furthermore 30-50% of people over 85 years of age are affected with AD, currently about

900,000 persons in Germany [133], and over 90% in this age group show Alzheimer-typical brain changes [130-132] so that very many people in industrial countries must be exposed to this possible external factor.

The brain changes do not belong to the normal signs of aging in the brain [131]. It was also shown that the risk of AD decreases again in advanced age [134]. Currently the disease is experiencing a strong increase [115, 135]. Because Alzheimer's takes 50 years to develop, this external factor must have spread greatly about 50 years ago. Amalgam use increased greatly after World War II and could, looking at the named studies, be considered to be the original external factor. Consumption of fish on the other hand, which leads to an increase in methyl-mercury burden, lowers the risk of Alzheimer's. Protective factors in fish, e.g. omega-3 fatty acids and selenium, seem to counteract the methyl-Hg burden from fish. In addition the mercury in fish seems to be far less toxic than previously thought (see basic facts).

In 10,263 tested persons AD-risk was found to be clearly dependent on the status of the teeth. The risk of AD was higher the fewer teeth were present [136]. Even Saxe et al. [137] found this dependency. This was interpreted by the authors as proof that amalgam fillings could not be the cause of Alzheimer's disease [136].

It might be surmised that in patients, who currently have fewer teeth, a worse tooth status existed, and that they had been treated with amalgams for a longer time period. That can be interpreted to mean that persons with few or no teeth, had, in the past (during the vulnerable phase), a higher exposure to Hg than persons who in old age still were in possession of their own teeth. In other studies this dependency existed as well [136, 138-141] (vide infra: Methodological Mistakes in Often Cited Amalgam Studies).

With the help of therapeutic administration of brain accessible chelators that can bind sulfhydryl-affin, bi-valent heavy metals such as zinc, copper, and also Hg, a promising therapy option was recently found [142, 143].

Autism and Prenatal Hg-Exposure by Amalgam

Maternal amalgam fillings can be a risk factor in the development in autism in children [44]. In healthy infants there is usually a positive correlation between the number of maternal amalgam fillings and the mercury concentration in their hair (hair samples from the first haircut) [44]. On the other hand autistic children do not show this correlation (instead, they show a slight but insignificant decrease) [44]. Furthermore autistic children, in comparison to healthy children, show clearly lower hair mercury levels although autistic children were exposed to a significantly greater amount of mercury (through a significantly greater amalgam burden of their mothers and more frequent administrations of mercury containing immuno-globulins) [44]. Interestingly fish

consumption did not correlate with an autism risk in their children. It is known that Hg from maternal amalgam fillings reaches the placenta and the fetus [43]. It is known from autopsy-studies that the mercury content in the organs and brains of infants and children correlates with the number of amalgam fillings in the mother [27, 43-50]. The number of amalgam fillings as well as the removal, and laying of amalgam fillings during pregnancy increased the Hg-concentration in the hair of newborns [144]. These findings point to the fact that autistic children in the study done by Holmes et al. [44] supposedly have to show an increase in mercury content in the brain in spite of the lower hair values. Autistic children possibly have a decreased ability to excrete mercury from their body cells into the blood and subsequently into the hair [44]. Another observation strengthens this hypothesis: The mercury values in hair were significantly lower in the worst autism cases than in those with a lesser expression of that illness [44]. It was shown in animal studies that a low-dose maternal mercury vapor exposure leads to a decreased ability to learn, hyper-activity and a decreased ability to react in their off-spring. Methyl-Hg was not able to dissolve these changes but acted synergistically with Hg-vapor [77]. During pregnancy the formation of the nerve growth factor in the fetus is being prevented by minimal Hg-vapor exposure [145].

Furthermore a low mercury burden causes animals to be more susceptible to developing epilepsy [146].

Another significant source of mercury until recently was Thimerosal-containing vaccines. The burden caused by this preservative is currently being added as a possible cause for autism [44, 147-151].

Diminishment of Cognitive Functions Resulting from Professional Amalgam Exposure

Dentists who work with amalgams suffer from increased mercury exposure [36, 152, 153]. Amalgam burdens that are seen as being safe and are acknowledged to be below the acceptable threshold values lead to measurable cognitive changes [155-160]. A low mercury vapor exposure as occurs in the oral cavity of amalgam bearers causes behavior changes in adult mice [156]. Color vision is impaired by low Hg-exposure [161]. Personnel in dental offices were neuro-psychologically affected [146, 162-164] and, related to that, had pathological muscle biopsies [165]. The visual evoked potentials in Hg-exposed persons (including dentists) were significantly changed in comparison to control persons [166]. In a meta-analysis of 686 mercury vapor-exposed persons a neuro-psychological impairment was found with 579 persons serving as controls [167]. The mercury excretion in urine by these persons can certainly be reached by a part of the amalgam bearers [6].

Skin Allergies

Amalgam fillings may lead to lichenoid reactions [110, 168-171]. These were healed to 90% by amalgam removal regardless whether an allergy could be proven via Epicutan test; granulomatoses are healed in the same manner [172].

Infertility

The frequency of infertility has risen from 8 to 15% in the last two decades. Women with a greater number of amalgam fillings or, as the case may be, an increased excretion in urine (after DMPS) were more often infertile than controls [173-175]. Dental assistants who are exposed to amalgams display a greater rate of infertility [176]. Heavy metal detoxification led to spontaneous pregnancies in a relevant part of infertile female patients [175]. Hg-exposure is among other things connected to decreased fertility in males [177] whereby Hg is not necessarily the reason for infertility, but instead may influence it negatively [178].

Diseases of the Heart and Circulatory System

A 22,000 times higher mercury concentration was found in heart muscle biopsies in patients with dilatative cardio-myopathy when compared to controls [179]. It was postulated that this might have been a consequence of the amalgam burden because amalgam is a main source of human Hg-burden [180]. Antimony, which also may occur in amalgam fillings, was increased 12,000 times in the damaged heart [179]. An increased Hg-level in the nails, which as a rule originates from fish, was connected to a heightened risk of heart attack [181, 182]. Each microgram of mercury that is excreted in urine increased the risk of heart attack by 36% [182]. The authors conclude that eliminating Hg from fish would represent an important contribution to the decrease of heart and circulatory disease [182]. In an animal study the impairment of heart muscle cells could be observed after the addition of small amounts of mercury [183, 184]. Hg was also capable of increasing the susceptibility and mortality of the myocardium to viral infections [185]. Work-related exposure is accompanied by a raised mortality from heart and circulatory diseases [186]. Amalgam was reported to be connected to high blood pressure and heart disease [187].

Multiple Sclerosis

The frequency of multiple sclerosis (MS) has been connected to the frequency of caries [188, 189] and amalgam [190, 191]. Some MS epidemics occurred after acute exposure to mercury vapor or lead [192]. Inorganic Hg has led to the loss of Schwann cells in animal models that build up myelin sheaths [193]. An auto-immune pathogenesis that

includes anti-bodies to myelin basis protein (MBP) can be triggered by mercury and other heavy metals [105].

A 7.5 times higher mercury concentration was found in a study of the liquor of MS patients [194]. MS patients who had their amalgam fillings removed after the Outbreak of their illness had fewer episodes of depression, hostile aggression, psychotic behavior, and bothersome compulsions than a comparable group of MS patients with amalgam fillings [157]. MS patients had significantly better blood values, were less depressed, had fewer symptoms of MS and fewer relapses [195]. A normalization of the liquor content was seen in MS patients after amalgam removal with the help of electrophoresis. Here even the oligoclonal bands in the liquor disappeared [196]. Some patients were cured after amalgam removal [197, 198]. There was an insignificant connection of MS-risk between caries incidence and number of amalgam fillings [199, 200]. Bates et al. [201] found only a slightly increased risk with rising numbers of amalgam fillings in military personnel who had been well at the onset of their service. However, no comparison with a control group was conducted that had never been treated with amalgam fillings [201]. In further studies it is important to take into account not only to the current amalgam status but also to the number of amalgams and the duration of how long the amalgams had been in place previously, and that amalgam-free persons are being included as a control group. In some studies healing of MS was observed after amalgam removal (vide infra).

Amyotrophic Lateral Sclerosis

Mercury vapor is taken up by motor neurons [12], and there it leads to increased oxidative stress, and that can favor the development of motor-neuron diseases such as ALS [201, 203]. Case reports show a connection between accidental mercury exposure and ALS [204, 205]. From Sweden came a report about a woman with 34 amalgam fillings with ALS. After removal and treatment with selenium and vitamin E she was healed completely [206]. An auto-immune pathogenesis triggered by mercury and other heavy metals is being suggested [105].

Symptoms, Individual Sensitivities, and Healing Rates Following Amalgam Removal

It is being reported that in some persons (“amalgam-sensitive persons”) a multitude of complaints may be triggered by amalgam fillings. Among the most common symptoms reported are: Chronic fatigue, headaches, migraine, increased susceptibility to infection, muscle aches, disturbances in concentration, digestive disturbances, sleep disturbances, forgetfulness, joint pains, depression, heart sensations, vegetative dysregulation, mood swings and many more [122, 157-159, 195, 197, 207]. Neither mercury measurements in bio-markers nor Epicutan test are able to distinguish “amalgam sensitive” from

“amalgam resistant” persons so far [31, 39]. It was, however, possible to show that persons, independent of the appearance of an allergic skin reaction, may react to the amalgam allergy test (Epicutan) with psychosomatic complaints [208]. Furthermore neutrophile granulocytes in amalgam sensitive persons produce variable reactions when compared to amalgam resistant persons [209] or, as the case may be, varying activities of super-oxide-dismutases were found [210]. It could also be shown that amalgam sensitive persons had significantly more apo-lipoprotein E4-allele and less often the apo-lipoprotein E2-allele than the symptom-free controls [122] Apo-lipoprotein E4 is considered one of the main risk factor for Alzheimer’s dementia, and is being connected to a lowered ability to detoxify heavy metals while Apo-lipoprotein E2 lowers the risk of acquiring AD because it possibly binds heavy metals better [71, 114, 115, 122, 211].

Other researcher found a lowered selenium level or a changed distribution of trace elements in blood in “amalgam-sensitive” persons in comparison to “amalgam resistant” persons [212, 213]. Amalgam sensitive persons often show signs of sensitivity vis-à-vis mercury and nickel in a specific validated lymphocyte transformation test (MELISA) [106, 107, 214, 215]. In this test lymphocytes are exposed to the allergens in question. If there is sensitivity, the lymphocytes change in a characteristic fashion.

In, at times, large numbers of cases clear health improvements or healings (with rates of improvement of 65 – 80%) of the above-mentioned complaints (those also included MS) were reported in studies after amalgam removal (most times with elaborate protective measures to minimize mercury exposure) [106, 107, 195-198, 207, 216-221]. As a rule these studies are, however, observation studies without control groups. Therefore conclusions about causation can only be drawn conditionally. Yet, they are indirectly plausible because of the long pre-observation period, the intractability of the complaints, and the convergent structure of data. However, it must be emphasized that studies with sufficient validity, i.e. randomized comparative studies, are still unavailable. Other authors think that amalgam, as cause for the above-mentioned complaints, is very unlikely and recommend against amalgam removal in persons with suspected amalgam-illness. They instead would treat them psycho-therapeutically or psychiatrically [31, 39, 222, 223]. There are no published success rates for this type of therapy. Additionally, there are numerous reports about complaints and healings after amalgam removal; they are at times published in foreign language scientific literature or other journals and books. A collection of scientific quotes up through 1997, about the subject of amalgam are given by Hamre [217] (1550 citations), Wassermann et al. [224] and Ruprecht [225].

Methodological Mistakes in Often Cited Amalgam Studies

In a Swedish study 587 twins were investigated, in which 57 pairs of twins were analyzed according to their complaints in groups with and without amalgams [141]. The average age was 66 years; 25% did not have teeth any longer and an unmentioned percentage had

crowns and bridges made from other materials. Persons without teeth or with other tooth treatments were classified as “amalgam-free”. The amalgam group was in a significantly better state of health. It was disregarded that “amalgam-free” persons (without teeth or with crowns and bridges) might have had amalgam fillings in the past and might have been exposed to amalgam fillings longer than the amalgam group. Since Hg accumulates in organs, it is possible that this group had a higher Hg-burden. Neither was investigated whether there still were amalgam fillings under the gold fillings or bridges, which was often done in the past. An additional basis for arriving at this conclusion is that persons with poor dental health or, as the case maybe, no teeth (independent of the possible impairment by an earlier amalgam exposure) because of earlier caries-causing nutrition (refined sugar, refined flour) altogether are in a worse state of health [226] than persons who are still in possession of their own teeth in old age.

The same methodological mistakes were made in another Swedish study where again no really amalgam-free group was used as control group [138-140]. In this study the average age of the female subjects was 60 years. The “non-amalgam-group,” women with 0-4 amalgam fillings, was made up of women without teeth (15%) and women with only a few teeth, bridges, crowns and implants. Here, too, the amalgam-group was physically and psychologically healthier. The possibility that the “amalgam-free” group had an increased amalgam exposure in the past and thus a higher Hg-concentration in their organs was not taken into account. A asked the authors to allow us to re-analyze the material, but that was answered negatively.

Even in Saxe et al.’s [137, 227] studies no amalgam-free control groups were used. Furthermore, even here, there was a tendency for persons with fewer teeth to do less well in tests [137]. A “meta-analysis,” which technically is only a survey, suggests that amalgam is a safe material [58]. As “proof” of amalgam’s harmlessness again the above-mentioned methodologically flawed studies were cited.

Because in amalgam bearers, who base their complaints on their amalgams, equal midlevel concentrations in blood and urine were found in comparison to a control group that did not base its complaints on amalgams nor exhibited any complaints (with an equal number of fillings), recent studies evaluated amalgam fillings as unlikely cause for these complaints [31, 39, 223]. Since the complaint group suffered more often from depressions or somatic pain disturbances, it was recommended that patients with amalgam-based symptoms should be treated mainly psychiatrically or psychotherapeutically. [31, 222, 223]. These studies were criticized because of their methodological flaws [228, 229]. It is especially questionable in these studies that both groups showed the same numbers of amalgam fillings and the mercury concentration in blood, urine or saliva were used as a measure of the organ burden (vide supra: Bases; concerning the lacking correlation of Hg in bio-monitors and organs in particular). In the studies by Zimmer et al. [39] and Bailer et al. [223] the complaint group, however, shows no significantly differing Hg-concentrations in blood and urine. That leads to the

conclusion that individuals in this group might have problems in excreting amalgam-derived Hg from their bodies [228], similar to what is happening to autistic children in the Holmes et al. [44] study.

Furthermore it is known from animal experiments and pharmacological studies that persons given equal amounts of a toxin might react differently. An example is that not every smoker develops lung cancer, although smoking is now accepted as the cause of the cancerous tumors.

It would be necessary in future amalgam studies to compare the state of health in amalgam bearers with persons who have never had amalgams in their whole lives. So far this has never been done.

Current Risk Analyses Relating to Amalgam

A risk analysis requested by the Swedish government, taking into consideration the 1997-2002 literature, arrives at the conclusion that amalgam should become illegal as soon as possible because of medical, work-related, and ecological reason [101].

A bill is currently being voted on in the USA. It suggests initially a ban on amalgam by 2005 for children, women of child-bearing age, and high-risk patients, and by 2008 a general ban on amalgam [230-232]. The American Dental Association (ADA), worldwide the leading dental association, tries to influence members of congress because of this bill [232].

The Federal Institute for Medical Products (BfArM) asserts in publications from 2001-2003 that amalgam should, according to an internally produced literature analysis, be viewed as a safe tooth filling material, the use of which should be continued in the future [234, 235]. Here again the above-mentioned methodologically flawed studies are cited as proof of harmlessness. When it comes to the question of Hg-content in amalgam fillings, a new patient handout wrongly gives the impression that only 3% Hg is contained in amalgam filings (instead of >50%) [234]. It was the dental associations that were primarily involved in the production of this handout [234].

The international publications of various dental associations, or, as the case may be, the dental associations' publications see amalgam as a safe tooth filling material, which (except in extremely rare allergic reactions) cannot lead to illness or complaints. For this reason amalgam is being recommended as a safe filling material. Prophylactic or therapeutic removal is being advised against [58, 236, 237]. A publication by the American Dental Association [236] that appeared in 2002 that equated amalgam toxicologically to table salt was criticized in a commentary [32].

Amalgam and the Environment

Mercury cannot be degraded in the environment but instead constantly accumulates [238]. Because of the anthropogenic release of mercury, the mercury content in the environment has risen 270 times in the last 100 years [240] and 3-5 times in the last 25 years [238]. About 8% of all women of child-bearing age in the USA show blood mercury values above the lowest acceptable safe threshold limits established by the American EPA (Environmental Protection Agency) [239]. As described above (*Bases*) the largest part of human organ mercury burden stems from amalgam. In the USA about 100 million new amalgam fillings are being laid per year and with that 30-40 tons of mercury are used [240]. There dental offices are the main source of the mercury burden in the environment [240, 241]. Waste water from dental offices is clearly burdened more with Methyl-Hg [242].

Amalgam also contributes to the environmental mercury burden because of the mercury containing bodily fluids such as saliva [243], urine, and stool of living amalgam bearers. Furthermore the mercury that has accumulated or that is still in amalgams in the teeth reaches the environment after death through burning in crematoria [244-246] or burial.

When adding exogenous sources (e.g. fish) to determine the total mercury uptake in a human it has to be taken into account that the mercury contamination was caused partly by amalgam and its worldwide use for over 150 years [41]. Although the use of amalgam separators has considerably reduced the Hg-content in waste water from dental offices – in Germany this has been regulated since 1991 – they are not yet standard equipment in many countries [e.g. USA]. In addition mercury is channeled into the environment through refuse from dental offices (cotton rolls, extracted teeth etc.)

World-wide the frequency of caries is growing in threshold and third-world countries because of Western food preparation with processed food ingredients. Because of that the global consumption of amalgam is going to increase because amalgam is easy to use and more expensive alternatives are not affordable for the greater part of the population. Because environmental regulations are lacking in those countries, the majority of the mercury is going to reach the environment in those countries, and over the food chain it will finally return to be again consumed by humans.

Discussion

We have tried to give the most comprehensive depiction possible about the most current literature covering the subject “Amalgam and Possible Health Risks.” It was our goal to show the potential magnitude of this problem. For this purpose the broadest grasp and description of the literature were of importance to us. That excluded a so-called

systematic overview in which the literature is extracted from previously defined parameters. Rather our work was to be the basis so that an investigation of partial areas could take place in the future whether the connection we had found between amalgam and health problems was really scientifically tenable.

We consciously omitted a methodological critique of details of individual studies except where this was apparently necessary. This would presuppose detailed knowledge of the material and methods. Instead, we accepted the authors' results and conclusions. This seemed to be not only acceptable but necessary after authoritative agencies and trade organizations that, in our opinion informed inappropriately with expressly incomplete and selective citations of literature. The next step should be that a multi-disciplinary working-group critically analyses studies from individual areas and tries to find out how valid the conclusions found in them are. The basis is our explorative overview that is not meant to be all-encompassing but still an as complete as possible depiction of literature through 2004.

A randomized, controlled study of the safety of amalgam has as yet not been carried out. Similar to the recent clarification about the safety of hormone replacement therapy using a randomized study that triggered a paradigm shift in the knowledge of women's health, a first-rate study on amalgam could bring new insights about its safety.

If, however, the researched and partially incomplete results concerning the individual illnesses are being evaluated in toto, it is possible - already at this time based on the current state of data - that amalgam can neither medically, nor from an occupational medical point of view, nor ecologically be considered to be a safe tooth material.

There are possibly a number of persons who, for genetic reasons, react particularly sensitively to amalgam or, as the case may be, show a greater risk of developing symptoms or illnesses after mercury exposure. Because of spreading amalgam use and the described frequency of symptoms and illnesses that are at times being caused by or worsened with amalgam, the use of amalgam vis-à-vis other dental work materials is presumably also health-economically un-advantageous. Stopping amalgam use could, with other preventative measures, lead to the retreat of the e.g. the prevalence of Alzheimer's disease over a period of time. Independent research in the individual study areas is urgently needed.

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