
Mercury in dental amalgam: a risk analysis

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Abstract

Mercury is a highly potent cell toxin with effects on human and animal nervous systems. Mercury vapour released from dental amalgam is the predominant source of mercury in the human adult and foetal central nervous system in populations of developed countries. Only in small populations with high consumption of methyl mercury containing fish can the contribution from fish consumption reach or surpass that of amalgam fillings. The most severe health risk is that of interference with foetal and child brain development. This effect of mercury vapour exposure has been demonstrated in animal experiments on monkeys and rats and in nerve cell cultures at nanomolar concentrations. The effect is also supported by epidemiological studies on women occupationally exposed to mercury vapour during pregnancy. However, there is no data permitting an assessment of dose-response relations for this effect in humans. In epidemiological studies on populations with occupational exposure to mercury vapour, subclinical effects on kidneys, the immune system, thyroid function, and CNS function have been observed at an exposure level equal to the upper range of the exposure range seen in amalgam bearers and measured as urine excretion rate of inorganic mercury. The cell toxic effect of mercury is likely to be based on the ability of mercury to modify protein tertiary and quaternary structure. As protein structure is genetically determined, there is ample scope for genetic polymorphism to manifest itself in varying sensitivity and reaction to mercury exposure. It is also likely that mercury exposure from dental amalgam exerts side effects like most potent pharmaceuticals. The clinical support for this assumption is reviewed. An incidence of side effects exceeding 10% is unlikely considering available epidemiological evidence. However, an incidence of 1% or below is highly probable. It is recommended that use of amalgam for dental restorations is abandoned and substituted with available less toxic material and that amalgam restorations in children and women of childbearing age should be avoided due to the potential risk of interference by mercury with brain development.

Key words mercury, amalgam, side effects, risk analysis, foetal brain development

Introduction

From the time amalgam was first introduced for dental fillings, there were concerns raised that mercury toxicity could give rise to unacceptable health risks. With an increased use of amalgam up until the present situation, when the majority of the population in industrialised countries are amalgam bearers, it has clearly emerged that the predominant proportion of amalgam bearers do not display

any signs of toxic effects from amalgam. Despite many attempts, it has not been demonstrated in a scientifically indisputable way that amalgam gives rise to any side effects apart from individual cases of local reaction. Despite this, the use of amalgam within the dental service has continued to generate anxiety in the population. Drugs administered to humans may induce side effects in a fraction of the population due to genetic or acquired polymorphism in metabolism and mode of reaction. The incidence of common side effects is typically around 1%. This amounts to 10 000 patients in a population of 1 million amalgam bearers, a sizeable health problem. In WHO's criteria document on inorganic mercury (1), an attempt at a quantitative risk assessment for inorganic mercury is reported. It was established, however, that the scientific knowledge base was not sufficient for a risk assessment for the low exposure levels arising from dental fillings with amalgam. It was also established that the body's uptake of mercury from amalgam constitutes the dominant source for mercury retention which contributes at least as much as all other sources of inorganic mercury intake together.

Owing to political pressure from groups critical of the use of amalgam for dental restoration, in 1997 and 2003 Swedish authorities assigned the author to summarise, assess, and evaluate published research findings on health effects of mercury exposure from dental amalgam. This article summarises the reports (2-3) published from this exercise and recent publications relevant to risk evaluation of mercury exposure from dental amalgam.

Exposure to mercury from amalgam in dental fillings

Mercury from amalgam fillings primarily contributes to the daily absorption of mercury in two ways. Mercury is released in vapour form, inhaled, and up to 80% is reabsorbed in the airways. Abraded amalgam particles are swallowed and to a smaller extent oxidised in the intestinal tract. Less than 10% of such ingested mercury is reabsorbed as Hg^{+2} . Mercury can also be taken up in the nerve ends and transported in a retrograde direction to ganglia and central nerve cells (2). In WHO's criteria document (1), the average daily retention in the population from amalgam is estimated at 3-17 μ g with the addendum that substantial individual variations exist. The validity for this dose interval has since been confirmed in several studies (4-6). Mercury uptake from amalgam is the dominant source for uptake of inorganic mercury in the

central nervous system and represents the overwhelming share of total mercury uptake in the population. Mercury concentration in plasma and urine in amalgam free subjects amounts to 0.2 µg/l and 2 µg/l respectively (6).

Factors that are of great importance for risk calculation are the size of the variation and the worst probable scenarios for mercury uptake. Bruxism (teeth grinding) and chewing increase the release of mercury from amalgam fillings. Barregård et al (7) described three patients experiencing symptoms of mercury toxicity who all had the common feature that they eliminated large quantities of mercury in their urine (54, 53 and 25 µg/g creatinine¹ respectively) and had no source of exposure other than their amalgam fillings which they worked on with nicotine chewing gum. When the amalgam fillings were removed in the first two cases with the highest elimination, the mercury elimination fell to expected values and the symptoms disappeared. In the third case the patient refused to have the amalgam removed, but the elimination seemed to decrease with reduced chewing gum consumption. A further similar case has been published since then (8). These cases demonstrate a mercury uptake, which amounts to 100 µg/day, which is around 10 times higher than the average uptake from amalgam according to WHO. On the basis of their material, Barregård et al (7) estimated the prevalence of amalgam bearers with an elimination of around 50 µg/g creatinine at one in every 2,000-10,000 amalgam bearers or between 500 and 2,500 persons in Sweden.

Mercury uptake from amalgam increases tissue concentrations in the brain, plasma and kidneys in proportion to the number of amalgam fillings. Mercury content in the brains (occipital cortex) of non-amalgam bearers was found in a study of autopsies to be around 7 ng/g (6.7, range 1.9-22.1). The brains of amalgam bearers contained around 15 ng/g (15.2, range 3.8 - 121.4) (1). In the foetus, an increase also occurs in the brain and kidneys, with an average mercury concentration in those with amalgam bearing mothers around twice that of those with amalgam free mothers (9-10).

Toxic effects of divalent mercury

It has long been known that mercury is cytotoxic. The cytotoxic effect is exercised by Hg²⁺. Mercury vapour, which is transported by the blood, can diffuse into the cell. Being relatively fat soluble, mercury vapour easily passes through cell membranes. Intracellularly, Hg⁰ is oxidised enzymatically to Hg²⁺. The mercury ion does not pass as easily through cell membranes but is bound in the first instance to the outside of the membrane. In some cases it can then be transported intracellularly actively, via receptors or bound to another transferable molecule. Exposure to mercury vapour and mercury salt is therefore not equivalent from a toxicological viewpoint.

The mercury ion binds to sulphhydryl (SH-) and selenohydryl (SeH-) groups. SH-groups constitute an important component in proteins. Mercury binding to these can entail a change in the proteins' tertiary and quaternary structure and other binding conditions in prosthetic groups in enzymes (11-14) and block or modify receptor binding (15-17) and potassium or calcium ion flows in the cell membrane's pores and ionic channels (18-25). This can affect cell membrane potentials and intra- and inter-cellular signals. The release of transmitter substances in nerve cells is inhibited or accelerated, as is cytokine production in the cells of the

¹ µg/g creatinine is on a group basis approximately the same as µg/l urine

immune system and hormone production in endocrine glands. It has been possible to observe these effects in *in vitro* experiments with cell cultures of different types of cells, or with the help of intracellular electrodes in single cells, with a 0.1-1 µM mercury concentration in the medium (2).

On the other hand, mercury has occurred in the environment throughout evolution and organisms have acquired the ability to manage limited quantities. Special molecules containing SH-groups or SeH-groups and with an ability to bind strongly to Hg²⁺ have been identified (26). Glutathion and metallothionein are such molecules, which can neutralise the mercury ion and prevent it from disturbing the cell's dynamic biochemical systems. Bound to these molecules, mercury can be transported, stored and eliminated from the body. It has also been shown experimentally that the sensitivity of different cell types to the mercury's cytotoxic effects is related to their ability to synthesise glutathion or metallothionein (27-29). Binding to metallothioneins explains, for example, why such high mercury concentrations can be encountered in the kidneys without disturbances arising.

Clinical, animal experimental, and epidemiological observations have shown that during exposure to mercury vapour, which gives rise to plasma concentrations of mercury of between 0.1 and 1 µmol/l (20 - 200 µg/l) or above, clinical signs of disturbances from several organ systems appear. Symptoms appear early on from the nervous system. These include neurological signs such as tremor, poorer performance in psychomotor tests, reduced colour vision, peripheral nerve conduction velocity, and memory function, altered electrophysiological parameters (evoked response), psychological symptoms such as increased irritability and exhaustion, sleep problems, and an increased tendency to anxiety. In the event of long-term exposure to concentrations of mercury producing symptoms, permanent functional impairment and dementia appear (2).

In the immune system, reduced function of leucocytes and macrophages, and in individual cases autoimmune reactions, have been demonstrated. Sometimes the toxic symptoms first appear with immunological syndromes such as acro-dynia (pink disease) or baboon syndrome, a syndrome, which often includes non-specific central nervous system symptoms. In the kidneys, signs of tubular damage appear with leakage of tubular enzymes to the urine (2).

The determination of the risk of effects on health from mercury from amalgam requires that a type of health effect be identified based on scientific information obtained from experimental, clinical or epidemiological observations. A reasonable suspicion of risk can be considered to exist if health effects arise in the dose range closest to the relevant dose or if theoretical preconditions exist in order for the effect to arise. We can thus identify the following health risks:

- Risk of disturbances in central nervous system function
- Risk of disturbances in renal function
- Risk of disturbances in the immune system
- Risk of disturbances in thyroid function
- Risk of disturbances in foetal development, especially the development of the nervous system.

Dose-response relations

The diagram in Figure 1 shows that the range for mercury exposure from amalgam overlaps the dose interval in which subclinical signs from the CNS, kidneys, immune system, and thyroid arise. The first sign from the CNS is a decline in motor performance (30), from the kidney an increase in excretion of NAG (N-acetyl-β-D-glucosaminidase) in urine

(31), from the immune system an appearance of autoantibodies against myeloperoxidase and proteinase 3 (31), and from the thyroid an increase in rT₃ (reverse triiodothyronine) in plasma (32). The LOAEL (lowest adverse effect exposure level) for all these effects corresponds to a mercury excretion in urine of around 10 µg/l and an incidence around 20%. The median excretion of mercury in amalgam bearers can be estimated to half this value or around 5µg/l.

In order to be able to demonstrate effects of mercury exposure in a population of less than a hundred workers, prevalence around 20% is required. If there is a prevalence of 20% at an exposure that gives a urine elimination of 10 µg mercury per litre of urine, what exposure then gives rise to a prevalence 1%? The only thing that can be said with certainty is that this exposure is lower than the exposure corresponding to 10 µg mercury per litre of urine, and we then find ourselves in the dose interval to which most amalgam bearers are exposed. We can thus state that the dose response curve for the effects of mercury vapour runs within the dose interval that corresponds to exposure from amalgam.

The effects for which the LOAEL has been discussed give rise to sub-clinical signs but have little or no influence on the function or work capacity of the exposed subject. However, as with other potent substances or pharmaceuticals, mercury is likely to induce more serious side effects with illness or in those who are especially susceptible genetically. Several reports in the literature describe patients who, during removal of amalgam restorations and for some days thereafter, experience and exhibit neuropsychological symptoms. These symptoms disappear when the exposure to mercury concomitant to the amalgam removal has ceased and returns at renewed exposure (3). Such mercury sensitive patients have been subjected to blind provocation tests with inhalation of low concentrations of mercury vapour in air (33) or percutaneous patch tests with mercury or mercury compounds (34-37). These tests have confirmed the deviant high sensitivity to mercury of these patients.

These mercury sensitive individuals are not common. Several epidemiological studies have been carried out in which the health status among amalgam bearers or dental service personnel with low exposure and non-amalgam bearers and persons with no occupational exposure were compared, including studies on twins discordant with regard to amalgam fillings in the teeth (38-41). In none of these or earlier studies have any health effects which can be related to the mercury exposure been demonstrated. From these studies we can draw the conclusion that the prevalence of health effects from mercury in amalgam probably does not exceed 10%.

Effects on the immune system

In animal experiments, mercury has been shown to modify the functioning of the immune system in various pathological states. Mice treated with injections of subtoxic doses of HgCl₂ are, for example, more susceptible to leishmaniasis infestation than untreated animals (42).

Both mercury sensitive and mercury resistant mice show reduced immunity against malaria protozoa after injection of subtoxic doses of HgCl₂ (43). In mice with a genetically conditioned tendency to develop the autoimmune syndrome systemic lupus erythematosus (SLE), development of the disease is accelerated if mercury is injected in subtoxic doses (44). In mice with a genetic predisposition for diabetes (non-obese diabetic [NOD] mice), the development of diabetes is inhibited if subtoxic doses of HgCl₂ are injected (45).

Mercury vapour exposure as a contributory or causative agent in MS and Alzheimer's disease has been studied and discussed in the literature. So far there is no conclusive evidence (3). However, where patients are suffering from unclear pathological states and autoimmune diseases, every doctor and dentist should consider whether side effects from mercury released from amalgam may be one contributory cause of the symptoms.

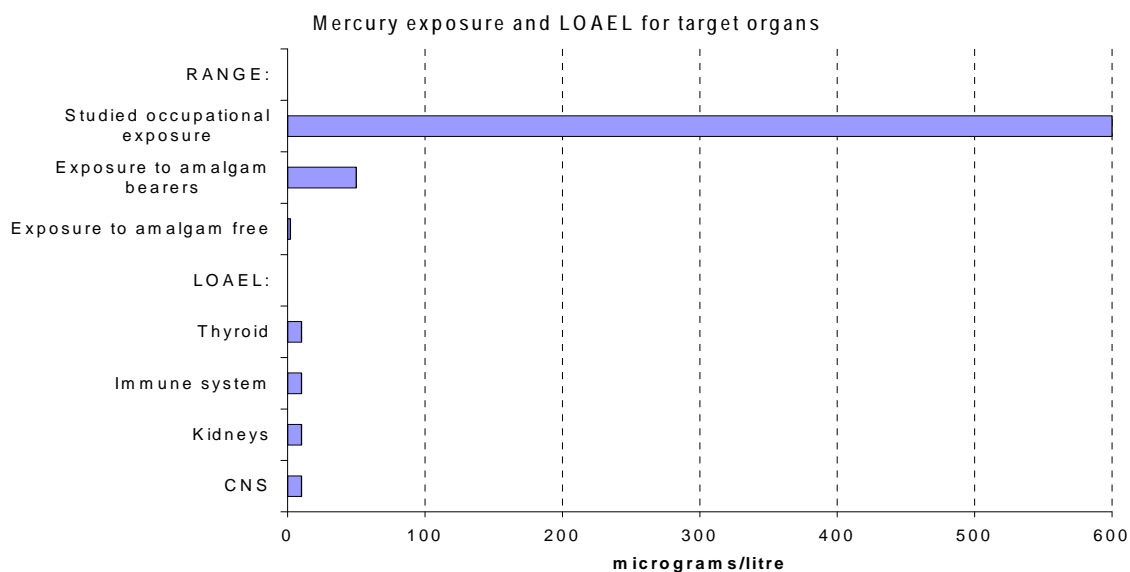


Figure 1 The mercury exposure range, measured as mercury excretion rate in urine, for amalgam bearers, amalgam free subjects, and occupationally exposed workers studied. The LOAEL (lowest adverse effect exposure level) for the central nervous system (CNS), the thyroid, the kidney, and the immune system are also shown

Effect on foetal development

The risk of inhibited brain development in the foetus and child is a special problem. Foetal nerve tissue contains the type of cell which shows most sensitivity to the mercury ion Hg^{2+} . Clear effects arise at the concentration level 5-50 nM or 1-10 ng/g tissue (46-49), which is the concentration level found in neonatal infants of amalgam bearing mothers (9-10). Experimental studies on rats and primates have shown that exposure to mercury vapour gives rise to developmental disorders in the brain resembling those seen after exposure to methylmercury. This means migration disturbances and permanent behavioural changes with reduced abilities / capacity to learn and adapt (50-53). The effects are seen from a mercury concentration in a monkey foetus brain of 10-200 ng/g brain tissue, which is 10 times lower than the concentration required with exposure to methylmercury. In rats, it has been shown that methyl mercury exposure and exposure to mercury vapour has an additive effect on foetal brain development (54). The prevalence of disturbed development in the experiments on monkeys was almost 100% in the studied dose range. There is no reason to assume that the human foetal brain would be less sensitive than other primate brains.

In a Dutch case control study the occupational exposure during the later stages of pregnancy of the mothers of 306 children with mental retardation of unknown origin was compared with the same exposure for mothers of 322 control children, who were mentally retarded for known reasons. A significant odds ratio (OR) of 8.7 for having children with disturbed brain development was found among mothers exposed to mercury as compared to those not exposed (55). A German prospective study of 3946 pregnant women was carried out. The women were interviewed regarding mercury exposure at the workplace. The mothers-to-be exposed to mercury or mercury compounds showed a significantly elevated risk of giving birth to babies who were small for their gestational age (56).

Conclusion

With present knowledge it is impossible to estimate the risk of effects on the foetal brain induced by the mother's exposure to mercury from amalgam. Available facts, however, do not support a dismissal of the risk. Therefore treatment of children and women of childbearing age with amalgam should be avoided. It is also recommended that use of amalgam for dental restorations in the population in general is abandoned and substituted with less toxic material, whenever this is available and affordable.

Competing interests None declared.

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