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Is dental amalgam safe for humans? The opinion of the scientific committee of the European Commission

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Abstract

It was claimed by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)) in a report to the EU-Commission that "....no risks of adverse systemic effects exist and the current use of dental amalgam does not pose a risk of systemic disease..." [1, available from: http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_016.pdf].
SCENIHR disregarded the toxicology of mercury and did not include most important scientific studies in their review. But the real scientific data show that:

(a) Dental amalgam is by far the main source of human total mercury body burden. This is proven by autopsy studies which found 2-12 times more mercury in body tissues of individuals with dental amalgam. Autopsy studies are the most valuable and most important studies for examining the amalgam-caused mercury body burden.
(b) These autopsy studies have shown consistently that many individuals with amalgam have toxic levels of mercury in their brains or kidneys.
(c) There is no correlation between mercury levels in blood or urine, and the levels in body tissues or the severity of clinical symptoms. SCENIHR only relied on levels in urine or blood.
(d) The half-life of mercury in the brain can last from several years to decades, thus mercury accumulates over time of amalgam exposure in body tissues to toxic levels. However, SCENIHR state that the half-life of mercury in the body is only "20-90 days".
(e) Mercury vapor is about ten times more toxic than lead on human neurons and with synergistic toxicity to other metals.
(f) Most studies cited by SCENIHR which conclude that amalgam fillings are safe have severe methodical flaws.

Dental amalgam is the main source of mercury in human tissues

SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks) from the European Commission claim [1]: "Exposure to mercury is difficult to measure. The indications for mercury exposure are therefore normally obtained by measuring mercury levels in urine and blood of individuals."

SCENIHR did not cite any autopsy studies, which are the most reliable studies for assessing mercury levels in tissues.

An approx. 2-5-fold increase of mercury levels in blood and urine in living individuals with dental amalgam as well as a 2-12 fold increase in several body tissues was observed in deceased individuals with dental amalgam [2-21]. Additionally, studies with animals have confirmed the fact that dental amalgam leads to significantly increased levels in the tissues [22-28].

According to these studies, dental amalgam is responsible for at least 60-95% of mercury deposits in human tissues. This was not acknowledged by SCENIHR.

No organic mercury compounds through dental amalgam?

SCENIHR [1] state that "there is no evidence that biotransformation of amalgam derived mercury takes place intra-orally in association with bacterial activity."

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In contrast to this claim studies have shown that mercury (Hg) from dental amalgam is transformed into organic mercury compounds by microorganisms in the human gastrointestinal tract [29-31]. Leistevuo et al. (2001) found a three-fold increase of methylmercury levels in saliva of individuals with dental amalgam compared to individuals without amalgam, although frequency and kind of fish consumption were identical in both groups. Mercury levels in saliva exceed mercury limits for sewage in 20% of individuals with amalgam [30]. The form of methylmercury derived from dental amalgam may be much more toxic (up to 20 times) than the form of methylmercury found in fish (see section "toxicity of mercury").

Toxic mercury levels in vitro and in vivo

Inorganic mercury levels of 0.02 ng Hg/g (2 μl of 0.1 μMolar Hg in 2 ml substrate) led to the total destruction of intracellular mircrotubuli and to the degeneration of axons [32]. In other experiments inorganic mercury levels of 36 ng Hg/g (0.18 μMol Hg) led to increased oxidative stress as a prerequisite for further cell damage [33,34].

Mercury vapor inhalation in doses which also occur in humans with many amalgam fillings and chewing led to pathological changes in the brains of animals after 14 days [35,36].

No toxic mercury levels in humans through dental amalgam?

In a recent autopsy study, it was found that individuals with more than 12 amalgam fillings have more than 10-times higher mercury levels in several tissues including the brain, compared to individuals with only 0-3 amalgam fillings [11].

The average mercury level in the brain of EU citizens with more than 12 amalgam fillings was 300 ng Hg/g brain tissue [11], which is well above mercury levels proven to be toxic in vitro on neurons (0.02 -36 ng Hg/g) (see above).

In another autopsy, individuals with more than 10 amalgams have 504 ng Hg/g in their kidney tissues (0-2 amalgams: 54 ng Hg/g) and 83.3 ng Hg/g in the liver (0-2 amalgams: 17.68 ng Hg/g) [5].

Mercury levels in thyroid- and pituitary glands were 55 ng Hg/g and 200 ng Hg/g respectively and again, these levels correlates significantly with numbers of amalgam fillings [37].

Because the levels found in these studies are only average levels, a significant portion of individuals with dental amalgam have more than twice (standard deviation) these toxic mercury levels in their body tissues. It is important to note that mercury levels found in subcellular fractions like microsomes, mitochondria and other cell compartments even exceed the average levels of the brain samples analysed in these studies [38].

Toxic mercury levels in Alzheimer's disease

The average mercury load in brain tissues of individuals with Alzheimer`s disease was 20 to 178 ng Hg/g; in some cases the load exceeded up to (236- 698 ng Hg/g). In 15% of the human brain samples the mercury load was above 100 ng Hg/g [39-41]. The average mercury load in the pituitary gland was 400 ng Hg/g [42]. These levels are again well far above established toxic levels (see above).

Pathological changes, caused by mercury, in most german human brains?

About 20% of individuals in the age group of 20 years, 50% of individuals in the age group of 50 years, and 90% of people in the age group of 85 years living in Germany show pathological changes in their brains that are typical for Alzheimer's disease [43] and mercury toxicity. This coverage of pathological brain changes caused by very low levels of mercury in experiments and not by low levels of other metals (like lead, iron, aluminum, copper, manganese, chromium, cadmium) [32,36] resembles the frequency of dental amalgam fillings implanted in humans: About 80-90% of people living in Germany have dental amalgam over decades. It must be noted that about 30-50% of german people above the age of 85 years have Alzheimer's disease (AD) and there are many hints that mercury plays the major pathogenetic role in AD [44].

Maternal amalgam as the main source of mercury in infant tissues

Maternal amalgam fillings lead to a significant increase of mercury levels in fetal and infant body tissues including the brain [6]. Furthermore, placental, fetal and infant mercury body burden correlates with the number of amalgam fillings of the mothers [6,45-52].

Mercury levels in amniotic fluid [53] and breast milk [54-56] also significantly correlate with the number of maternal amalgam fillings.

Mercury in infant tissues: Increased risk of neurodevelopmental disorders?

Drasch et al. found mercury levels of up to 20 ng Hg/g in German infant brain tissues which were mainly caused by dental amalgam fillings of their mothers [6]. As described above, mercury levels of 0,02 ng Hg/g led to degeneration of axons [32]. Furthermore, the mercury levels found in the brains of infants whose mothers were dental amalgam bearers are sufficient enough to inhibit the function of the important enzyme methionin synthetase [57,58]. Methionin synthetase is crucial for

methylation, a central step for most important metabolic reactions the the body, including the development of the brain, the maturation of nerve cells and the production of neurotransmitters.

Maternal amalgam fillings also increase significantly mercury levels in cord blood [59,60]. The risk for delayed neurodevelopment of children was 3.58- times increased when mercury levels in cord blood were higher than 0.8 ng Hg/ml [61]. It is important to note that mercury levels of 0.2 - 5 ng Hg/ml cord blood are considered "normal" in Germany [62], thus leaving many infants with mercury levels that may cause neurodevelopmental deficits.

No correlation between mercury in urine or blood and in body tissues

The SCENIHR report is based on studies which have measured mercury levels in biomarkers such as urine for the assessment of clinical symptoms or mercury body burden. However, the WHO states (1991) that

> "Mercury typifies a "retention" toxicity and much of the mercury taken into the body is absorbed by the solid tissues. The amount in urine represents mercury being excreted. However, the main question is how much is being retained in the different body tissues".

It has been shown in experiments with animals and men that in spite of normal or low mercury levels in blood, hair and urine high mercury levels are found in critical tissues such as brain and kidney [7,13,20,22,25,28,46,63,64]. A recent study on deceased individuals confirm that there exists no correlation between inorganic mercury levels in urine or blood and mercury levels in brain tissues [37].

Drasch and coauthors have shown that 64% of individuals occupationally exposed to mercury vapor and having typical clinical signs of mercury intoxication had urine levels of mercury below 5 μg/l, which represent the No Observed Adverse Effect Level (NOAEL). The same results were found for mercury levels in blood and hair [65-67].

Paradoxical association between mercury levels in urine and clinical symptoms

There is even a paradoxical correlation between mercury levels in urine, blood or hair and clinical symptoms: Subjects with highest urine levels of mercury showed best recovery rates from neuropsychological complaints after removing their amalgam fillings [68]. Also children with highest mercury levels in hair showed better performance in developmental tests [69]. Another study indicates that in spite of a significantly higher exposure to mercury in their mothers` womb autistic children had up to 15-times lower mercury levels in their infant hair than healthy children [46]. Furthermore, the lower the mercury levels in infant hair, the higher was the severity of autism [46].

Despite higher mercury body burden, a "amalgam hypersensitivity" group showed slightly lower levels of mercury in their saliva, blood and urine [70]. Even after provocation with the mercury chelator DMPS, the "amalgam hypersensitivity" group excreted in mean only 7,77 μg Hg via urine in 24 h whereas healthy amalgam bearers excreted 12,69 μg Hg/24h [70].

Furthermore, studies confirm that the ratio of fecal to urine excretion is 12 to 1 [13]. This proves that the majority of excreted mercury leaves through the bilary transport system of the liver via the fecal route. Urine mercury therefore represents a minor excretory route of less than 8% of mercury being excreted. Also, urine mercury is a measure of mercury being excreted by the kidney—not a measure of total mercury body burden.

Safety levels for mercury?

In view of the data presented above, it is impossible to determine any safety levels below which adverse effects can be excluded [71]. SCENIHR used safety limits which were deduced from studies with workers occupationally exposed to mercury. However, these limits cannot be applied to individuals with amalgam fillings and must be critically evaluated:

a) Frequently, mercury exposure of workers in the chlorine-alkali industry is used for comparison although the simultaneous exposure to chlorine considerably diminishes the absorption of mercury into the body tissues of animals by 50-100% [72].
b) Workers exposed to mercury usually represent a group whose mercury-exposure starts only with adulthood (for about 8 hours a day, 5 days a week), while amalgam bearers can be exposed to mercury in the womb through maternal amalgam fillings during their childhood and until death at a rate of 24 hours per day, 7 days per week.
c) Workers are a selected healthy group, while pregnant women, infants, children and individuals with illnesses (such as multiple sclerosis, autoimmunity, cancer, psychiatric diseases) do not start working at all either due to industrial safety regulations or to early health problems during working.
d) Despite mercury exposure below "safety limits", significant adverse health effects were found in most studies in workers exposed occupationally to mercury, even several years after the exposure had ceased [73-81].

Body half-time period of mercury

SCENIHR state that the body half-time (of mercury) is "20-90 days".

Particularly in the brain, mercury has a significantly longer half-time of more than 17 years [63,64,82-87].

Toxicity of mercury

SCENIHR did not mention the specific toxicity of mercury vapor coming off dental amalgam fillings. This should be mentioned in a risk analysis:

Mercury has been shown to be 10 times more toxic than lead (Pb) in vitro [88-90]. Mercury is the most toxic non-radioactive element. Mercury vapor is one of the most toxic forms of mercury along with some of the organic mercury compounds. This extraordinary toxicity is also determined by the following properties:

a) Mercury is the only metal representing a volatile gas at room temperature, which is readily absorbed (80%) by the respiratory system.
b) Mercury vapor from amalgam penetrate into tissues with great ease, because of its monopolar atomic configuration.
c) Once inside the cells, mercury vapor is oxidized to Hg^{2+}, the very toxic form of mercury which binds covalently to thiol groups of proteins inhibiting their biological activity.
d) Hg^{2+} is more toxic than Pb^{2+}, Cadmium (Cd^{2+}) and other metals because it has a higher affinity due to "covalent bond" formation with thiol groups (cysteines in proteins) causing irreversible inhibition. Other metals form reversible bonds with proteins and are therefore less toxic.
e) Hg^{2+} does not bind tightly enough to the carboxylate groups of natural organic acids (natural chelators like citrate) for its toxicity to be prevented.
f) Chelating agents, like EDTA, which normally inhibit the toxic effect of heavy metals like lead, have no inhibitory effect on the toxicity of mercury or may even increase it [91,92]. Other chelating agents (DMPS and DMSA) inhibit the toxic effect of Cd^{2+} and $Pb^{2+,}$ but not of Hg^{2+} [93]. DMPS, DMSA or natural chelators like vitamin C, glutathione or alpha-lipoic acid are not able to remove mercury from nervous tissues [94]. DMPS or DMSA may even increase the inhibitory activity of Hg^{2+} and Cd^{2+}on enzymes but not of Pb^{2+} [95]. Furthermore, DMPS in animals led to an increase of mercury concentrations in the spinal cord [96].

The toxicity of methylmercury which is bound to cysteine in fish seems to be far lower (only approx. 1/20) than methylmercury compounds usually used in experiments [97].

Furthermore, marine fish represents a significant source of selenium and essential omega-3-fatty acids, which are known to protect effectively against mercury toxicity. Nevertheless, methylmercurychloride, which proved to be more toxic than methylmercury in fish, showed less neurotoxicity for the growing nervous system in vivo than did mercury vapor [98].

Investigations by Drasch et al. show similar correlations: The population of a goldmining area, which was exposed to mercury vapor, showed significantly more neurological symptoms of mercury intoxication than a control group which mainly was exposed to methylmercury from fish consumption, despite their mercury levels in hair and plasma being higher compared to the individuals exposed to mercury vapor [65,66]. Another study also points to smaller neurotoxicity of methymercury from fish compared to iatrogenic mercury sources (amalgam, thimerosal) [46]. Here, in contrast to the numbers of dental amalgam in the mothers, no correlation between maternal fish consumption during pregnancy and the risk of autism for their children was found.

In summary, mercury vapor coming off dental amalgam or methylmercury derived from amalgam in the gastrointestinal tract has not reacted with anything yet and has the full toxic potential. On the other hand, methylmercury in fish has already reacted with fish proteins and other protective molecules or atoms in fish tissues such as glutathione or selenium, which are enriched in fish. Furthermore, newest studies confirm that most individuals with dental amalgam fillings are exposed to toxic mercury levels [99,100].

Synergistic toxicity of mercury to lead (Pb)

Some scientists try to argue that results gained by animal or cell testing are overestimated and not comparable to the situation of the human body. However, in contrast to test animals in experiments, humans are exposed to many other toxins simultaneously, thus the effects add up or are even synergistic [101,102]. For example, it has been proven that the combination of the Lethal Dose 1% of mercury ($LD1_{Hg}$) together with the LD1 of lead (Pb) results in the death of all animals, so the following toxicological equation can be assumed: LD1 (Hg) + LD1 (Pb) = LD 100 [101].

In this context, it must be considered that modern humans have more mercury and between 10-1,000-times more lead in their body tissues than ancient humans.

In other experiments, the addition of aluminumhydroxide (often in vaccines), antibiotics, thimerosal (sometimes in vaccines) and testosterone increased the toxicity of mercury [108,109]. The synergistic toxicity of testosterone explain the observation, that much more

males than females suffers from autism or amyotrophic lateral sclerosis.

No adverse effects through dental amalgam?

SCENIHR states "It is generally concluded that no increased risk on adverse systemic effects exists and we do not consider that the current use of dental amalgam poses a risk of systemic disease" and "....some local adverse effects are occasionally seen with dental amalgam fillings, but the incidence is low and normally readily managed"

SCENIHR has neglected numerous scientific studies which find significant adverse health effects from dental amalgam:

Cytotoxicity of amalgam in comparison to composites

SCENIHR compare the toxicity of amalgam with composites. However, in most experiments, even inorganic mercury, which is much less toxic than mercury vapor (because inorganic mercury is not able to penetrate easily into the cells), was proven to be much more toxic than any composite compound: Mercury was shown to be 100-800- fold more toxic than composite components for human cells [110-114].

Genotoxicity, oxidative stress, cancer

Dental amalgam fillings have been found to cause DNA damage in human blood cells. [115]. Even low levels of inorganic mercury lead to significant DNA damage in human tissue cells and lymphocytes [116]. This effect, which trigger cancer, has been found with mercury levels below those normally causing cytotoxicity and cell death. Furthermore, aberrations of chromosomes can be provoked by amalgam in cell cultures [117]. Amalgam bearers show significantly increased oxidative stress in saliva [118,119] and blood [120,121]. The increase of oxidative stress correlates with the numbers of amalgam fillings. Mercury levels normally seen in tissues of individuals with amalgam fillings lead to increased oxidative stress and reduction of glutathione levels, thus inducing cellular damage [33,34]. Significantly elevated mercury levels have also been observed in breast cancer tissues [122]. Mercury deposited in the tissue is mostly bound to selenium, which means that the this selenium is no longer available for the body. Therefore, amalgam may aggravate a latent deficiency of selenium, particularly in countries with suboptimal selenium supply (e.g. in Central Europe) [123,124].

Antibiotic resistance

It has been shown that mercury from dental amalgam can induce mercury resistant bacteria [125-127]. This leads to a general antibiotic resistance in oral bacteria and in other body sites [127], which is particularly true when the antibiotic resistance genes are contained within the same mobile element as the mercury resistance operon [128,129]. Mercury resistance is common in human oral bacteria [130,131]. Monkeys with dental amalgam also showed an increase in antibiotic resistant bacteria in their stools [127,132].

Penetration of amalgam in tooth bone and jaw

Experiments on monkeys and sheep have shown that mercury from amalgam penetrates easily into the dentin roots as well as into the jaw bone [25,26]. The fact that this was also shown for humans [133] confirms an alternative route of mercury exposure caused by amalgam.

Skin

There is a correlation between atopic eczema and IgE-levels and the body burden of mercury [134]. Amalgam fillings can induce lichenoid reactions [135-139]. In more than 90% of the cases, these lesions have been found to recover upon removal of amalgam, no matter whether an allergy patch test was positive or not. Granulomatosis improved likewise [140]. Also, other forms of dermatitis seem to be related to dental amalgams [141,142].

Autoimmune disorders and mercury hypersensitivity

Constant low-dose mercury exposure, as is common in amalgam bearers, has been considered a possible cause for certain autoimmune diseases, e.g. multiple sclerosis, rheumatoid arthritis or systemic lupus erythematosus (SLE) [135,143-152]. These effects occur with exposure below mercury safety limits [153]. Recent research has shown that mercury and ethylmercury have the ability to inhibit the first step (phagocytosis) in the innate and acquired immune response of humans at very low levels [154]. This shows that mercury exposures quite below the average exposure through amalgam exposure can cause disruption of the immune system at all ages.

Only "rare cases of proven allergic reactions"?

SCENIHR only accept the "proof" of allergic reactions to amalgam, which is a positive cutaneous patch test. However, it has been shown that in more than 90% of the cases with mucosal reactions these lesions have been found to recover by removal of amalgam, no matter whether a cutaneous patch test was positive or not [137,139,140]. Therefore the relevance of the cutaneous patch test in detecting sensitivity or allergy to mercury implanted in the oral cavity without any epicutaneous contact has been severely questioned [155].

The results with another validated test system reveal that there are more than just "rare cases" with

immunological complaints due to dental amalgam [148,150,152,156-162].

There may also be a correlation between atopic eczema, IgE-levels and the body burden of mercury, which is also not detected by means of cutaneous patch tests [134].

Because mercury from maternal dental amalgam is one of the main sources of mercury body burden in fetal and infant tissues, postnatal atopic eczema disappear after mercury detoxification of the infants [163].

Heart diseases

Mercury may cause hypertension and myocardial infarction [164].

Significant mercury accumulation (22,000 times higher than controls) has been found in heart tissues with a form of heart insufficiency [165].

Urinary system

SCENIHR cited only one review performed by a dentist and published in a dental trade journal [166] as well as 5-7 year studies on initially healthy children, also performed mainly by dentists, to back up their argument that "there is no evidence that dental amalgam fillings affect kidney function in humans". However, there are many other studies suggesting quite the opposite:

In animal experiments, an impairment of renal functions due to amalgam fillings has been observed [23,146,167]. Humans with amalgam fillings show more signs of tubular and glomerular damage when compared to individuals without dental amalgams [15]. The frequently mentioned children amalgam trial study found first signs of kidney damage (microalbuminuria) [168] even after only 5 years of amalgam exposure.

Alzheimer's disease (AD)

SCENIHR questioned that mercury may contribute to the development of AD. As a proof of this statement they cited only one study [41] published in the trade journal of the world-wide leading American Dental Association (ADA) [102]. In contrast, other studies have shown that mercury play a major pathogenetic role in AD [108,109,169,170]. A new systematic analysis of the literature regarding the role of mercury in AD found a significant association [124].

Parkinson's disease (PD)

Heavy metals have long been suspected to be a cause of PD, with several studies showing a relation, including epidemiological studies [171-180]. Elemental mercury has induced PD [175], and in a case report, the condition of PD substantially improved after treatment with a mercury chelator [173] and remained unchanged during a 5-year follow-up period [173]. In another study, significantly elevated blood mercury levels were found in 13 of 14 patients with PD compared to healthy controls [172]. This supports the conclusion of a previous study which found a correlation between blood mercury levels and PD [176]. Another study found significantly higher amalgam exposure in individuals with PD compared to healthy controls [179].

Adverse health effects in dental staff?

SCENIHR state that "the incidence of reported adverse effects [in dental staff and dentists] is very low".

A simple literature research reveals quite the opposite: Dentists working with amalgam have an increased mercury exposure [17,181,182]. In most studies available, mercury exposure in dental clinics resulted in significant adverse health effects in dental workers. In some studies, the clinical outcome was not correlated with mercury levels in urine or blood, and some authors falsely concluded that mercury was therefore not the cause of the adverse effects. However, this is not scientific since urine- or blood mercury levels did not correlate with tissue levels (see above). Lindbohm et al. (2007) found a two-fold increased risk for miscarriage through occupational exposure to mercury (OR 2,0; 95% CI 1,0- 4,1). The effect from mercury exposure was stronger than from exposure to acrylate compounds, disinfectants or organic solvents [199].

Even 30 years after cessation of mercury exposure, dental nurses showed significant adverse health effects [200]. In spite of the fact that 85% of the dentists and dental technicians tested showed mercury related toxicities in both behavior and physiological parameters, and 15% showed increased mercury induced neurological deficits with polymorphism of the CPOX4 gene [186,188,201], SCENIHR still maintain that amalgams do not cause any significant medical problems in dental workers, because urine and blood levels are below "safety limits".

Infertility

SCENIHR stated that "There is no evidence of any association between amalgam restorations and either male or female fertility or obstetric parameters". As a proof of this statement, SCENIHR cited just one study, which examines only semen parameters in men. However, other studies point to the opposite direction, especially when examining women:

Female dental assistants exposed to amalgam showed a higher rate of infertility [198]. Women with more amalgam fillings or increased mercury levels in urine (after mobilization with DMPS) had a higher incidence of infertility [202-204]. Heavy metal detoxification led to spontaneous pregnancies in a considerable part of the infertile patients [203]. Exposure to mercury also lead to

decreased male fertility [205-207]. A Norwegian study which is often cited as a proof that mercury exposure in dental clinics does not cause infertility suffers from methodological flaws insofar as only women were included who had already given birth to at least one child. Women without children were excluded. Such a study certainly cannot answer the question if working with amalgam leads to infertility or not. Moreover, the exposure time to amalgam was not calculated and thus not included as a covariate into the study.

Multiple Sclerosis (MS)

A 7,5-fold increased level of mercury was found in the cerebrospinal fluid (CSF) of MS patients [208]. It would be difficult to speculate that the presence of this increase in the CSF would not at least exacerbate the problems associated with MS or any other neurological disease. The prevalence of MS has been shown to be correlated with the prevalence of caries [209,210] and the prevalence of amalgam [211,212]. Several MS epidemics occurred after acute exposure to mercury vapor or lead [213]. In animal models inorganic mercury caused a loss of Schwann cells which build the myelin sheaths and stabilize the axons of neurons [214]. Autoimmune pathogenesis, including antibodies against myelin basic protein (MBP), can be provoked by mercury and by other heavy metals [148].

MS patients who had their amalgam fillings removed showed fewer depressions, less aggression and less psychotic and compulsory behaviors when compared to a group of MS patients with amalgam fillings [215]. They also had significantly lower levels of mercury in blood [216]. After amalgam removal, pathological oligoclonal bands in the CSF disappeared in MS patients [217]. Removal of dental amalgam also led to a recovery in a significant proportion of MS patients [147]. A retrospective study on 20,000 military individuals revealed a significantly higher risk for MS in individuals with more amalgam fillings [218]. This risk was underestimated, because the study cohort which was selected by means of medical examination consisted exclusively of individuals with good health at the time of joining the military [218]. Another problem occurring in some studies is the absence of documentation of the dental status before or at the time of the onset of multiple sclerosis. In spite of these limitations [219] a reanalysis found a 3.9- fold increased risk for multiple sclerosis in individuals with amalgam compared to individuals with no amalgam. A recent systematic review also found an increased risk for MS caused by dental amalgam in spite of the fact that most studies did not use proper amalgam-free controls [220].

Amyotrophic Lateral Sclerosis (ALS)

SCENIHR state that "there is no evidence for a relationship between Amyotrophic Lateral Sclerosis (ALS) and mercury"

In contrast to the statement of SCENIHR, there are many studies which suggest that mercury may play a pathogenetic role in ALS:

Mercury vapor is absorbed by motor neurons [221] where it leads to increased oxidative stress. In experiments, mercury vapor was found to promote motor neuron diseases such as ALS [222-226]. It was proofed that mercury enhances glutamate toxicity in neurons, which is one factor in ALS. Case reports show a correlation between accidental mercury exposure and ALS [227,228]. There is a reported case of a Swedish woman with more than 34 amalgam fillings who suffered from ALS. After removal of these fillings she recovered [229]. A retrospective study reported a statistically significant association between an increased number of amalgam fillings and the risk of motor neuron diseases [218].

"Amalgam disease" and markers of sensitivity

Among the most frequently reported symptoms due to amalgam fillings are: Chronic fatigue, headache, migraine, increased susceptibility to infections, muscle pain, lack of concentration, digestion disorders, sleeping disorders, low memory capacity, joint pain, depression, heart sensations, vegetative disregulation, mood disorders and many more [161,215,216,230-234].

Until recently it was not possible to differentiate between „amalgam-sensitive" and „amalgam-resistant" persons by their mercury levels in blood or urine or an epicutaneous test (patch test) [9,21]. However, it could be shown that subjects could react to a mercury patch test with psychosomatic complaints, although there was no allergic reaction of the skin [235]. In addition, neutrophil granulocytes in amalgam-sensitive subjects react differently compared to those in amalgam-resistant subjects [236] and different activities of the superoxide dismutase could be found [237].

Increased susceptibility to mercury and amalgam

SCENIHR did not mentioned any susceptibility parameters which make a significant proportion of the population more susceptible to mercury from dental amalgam:

a) Abnormal porphyrine profiles due to mercury exposure

It is known that mercury exposure leads to aberrant urine porphyrine profiles in dentists [238] and autistic children and that this aberrancy was reversed by treating these children with a mercury chelator [239-241].

A genetic polymorphism of coproporphyrinoxidase (CPOX4) [188,201] leads to increased susceptibility to

mercury and thus to a higher risk for neurobehavioral complaints [242].

The critical question here is the effect of mercury vapor exposure on brain porphyrine profiles since an aberrancy in brain heme has been associated with the inability to remove beta-amyloid protein from brain cells, which in turn may lead to Alzheimer's disease [243].

It should be noted that porphyrins lead to heme, and heme is critical for several biochemical mechanisms: (i) heme is the oxygen carrying cofactor for haemoglobin, (ii) heme is a critical cofactor for the P450 class of enzymes that are responsible for detoxifying xenobiotics from the body, (iii) heme is a necessary cofactor for one of the complexes in the electron transport system of mitochondria and therefore ATP-synthesis.

Therefore, mercury inhibition of heme production could have a multitude of secondary effects causing human complaints and illnesses.

In spite of the fact that 85% of the dentists and dental technicians tested showed mercury related toxicities in both behavior and physiological parameters, and 15% showed an increase of mercury induced neurological deficits with polymorphism of the CPOX4 gene, organized dentistry and SCENIHR still maintain that amalgams do not cause any significant medical problems because the urine and blood levels are below safety limits.

b) Brain derived neurotrophic factor

Another genetic polymorphism of the brain derived neurotrophic factor (BNDF) increases also the susceptibility to very low level mercury exposure [186,187].

c) Apolipoprotein E diversity

It could be shown that amalgam sensitive persons are significantly more likely to be carriers of the apolipoprotein E4-allel (APO-E4) than symptom free controls and that they are less likely to carry the APO-E2 [231,234]. APO-E4 is known to be the major genetic risk factor for Alzheimer's disease, whereas APO-E2 decreases the risk. It has been postulated that this is due to the difference in capacity to remove heavy metals from the cerebrospinal fluid [44,92,102,124,231,234,244]. APO-E2 possesses two cysteines with metal binding sulfhydryl-groups whereas APO-E4 does not have any cysteine residues.

d) Glutathione metabolism

Reduced glutathione (GSH) is the main natural chelator for heavy metals in the body due to its sulfhydryl-containing cysteine. Only mercury, which is bound to glutathione (or selenium), is capable of leaving the body via urine or biliary excretion. Thus, a high level of glutathione is crucial for mercury metabolism. It has been described that polymorphisms in genes leading to impaired GSH production cause higher retention of inorganic and organic mercury in the body. Other factors which may increase susceptibility to low dose mercury exposure, e.g. low levels of selenium, abnormal reaction of neutrophil granulocytes, activity of super oxide dismutase, D4-receptor positive methionine synthetase and impaired methionine transulfuration- and methylation pathways (about 15% of the population), led to decreased mercury protecting agents, like S-adenyl-methionine, cysteine, GSH and metallothionine [44,245-247].

Improvement after removal of amalgam

Significant improvement of health and above mentioned diseases (including Multiple Sclerosis and other autoimmune diseases) have been reported after amalgam removal (in most studies with elaborate protective measures to minimize mercury exposure) [68,147,149, 150,159,161,217,230,233,234,248-251].

No neurodevelopmental disorders through mercury?

SCENIHR stated that "There is no evidence of a causal relationship between dental amalgam and autism" and "... that no link has been yet established between vaccines, thimerosal and autism".

Nonetheless other authors come to opposite conclusions:

> "...mercury exposure altered cell number and cell division; these impacts have been postulated as modes of action for the observed adverse effects in neuronal development. The potential implications of such observations are evident when evaluated in context with research showing that altered cell proliferation and focal neuropathologic effects have been linked with specific neurobehavioral deficits (e. g., autism)." [252]
>
> Cheuk and Wong (2006) in patients diagnosed with attention-deficit hyperactivity disorder and Desoto and Hitlan (2007) in patients diagnosed with autistic disorders found significant elevations in blood mercury levels in comparison with controls [253,254]. Adams et al. (2007) observed significant increases in the mercury levels of baby teeth in infants with autistic disorders in comparison with controls [255]. Mercury in baby teeth mirrors mercury exposure in the womb.

Recent brain pathology studies have revealed elevations in mercury levels and mercury-associated oxidative stress markers in patients diagnosed with autistic disorders. The level of mercury in the urine of autistic

children shows an increase of 3-5 times after appropriate treatment with the mercury chelator DMSA compared to healthy children [259]. Autistic children also excrete higher concentrations of coproporphyrine which is specific for mercury intoxication [239,240,260,261]. Detoxification of mercury with DMSA normalizes the abnormal coproporphyrin levels in autistic children [239,240] and led to improvement of symptoms [262]. Additionally, experimental as well as epidemiological studies indicate that mercury exposure is responsible for autism or a deterioration of the disease. Prenatal exposure to maternal amalgam [46,263], maternal thimerosal [46,264] and postnatal sources (mercury from vaccines for the child) together with a genetic sensitivity may trigger autism. In animal experiments vaccination with thimerosal led to symptoms similar to autism [265]. Epidemiological studies confirm a significant association between low-dose mercury exposure and neurodevelopmental disorders [266][267][268][269][270][271]. Autistic children show decreased levels of the natural mercury chelator glutathione [272]; it is known that mercury is capable of causing this phenomen [273]. In some preliminary therapy studies with chelation therapy led to improvement of symptoms [263]. The Autism Research Institute therefore lists chelation as the most effective therapeutic approach among 88 therapies including 53 medications [274].

Zahir et al. (2005) described that the access of mercury

> "...to man through multiple pathways air, water, food, cosmetic products and even vaccines increase the exposure. Fetuses and infants are more susceptible to mercury toxicity. Mothers consuming diet containing mercury pass the toxicant to fetuses and to infants through breast milk. Decreased performance in the areas of motor function and memory has been reported among children exposed to presumably safe mercury levels [...] Mercury has been found to be a causative agent of various sorts of disorders, including neurological, nephrological, immunological, cardiac, motor, reproductive and even genetic. Recently heavy metal mediated toxicity has been linked to diseases like Alzheimer's, Parkinson's, Autism, Lupus, Amyotrophic lateral sclerosis, etc."[275].

Some studies which found no associations between mercury exposure and autism have severe methodical flaws [245].

Severe methodical flaws in studies cited by SCENIHR as a proof of the safety of dental amalgam

In order to study toxic effects it is necessary to compare at least two samples: one that was exposed to the substance in question and one that was not. One of the main problems in most of the amalgam studies is that the vast majority did not incorporate a true control group that had never been exposed to dental amalgam. Even when comparing samples with and without dental fillings, the sample without dental fillings had been exposed to dental amalgam earlier in life. The studies cited frequently not only by SCENIHR as a proof of the putative harmlessness of amalgam do not use "proper" non-amalgam control groups. There is a prominent example to describe:

The Swedish twin study [276] actually only compared 57 twin-pairs in a co-twin analysis, and not 587 as mentioned by the authors and many governmental institutions. As the average age of the sample was 66 years, 25% had no teeth at the time of investigation, many had missing teeth and an unknown number had crowns using other dental materials. Root fillings with amalgam and amalgam fillings under crowns were not calculated. As an allegedly "non-amalgam" group, they were compared with individuals who still had teeth with amalgam fillings. The authors found that individuals with more amalgam fillings (which means also more own teeth) had a better health status. It is fair to assume that individuals with few or no teeth or teeth that have been restored with crowns or bridges had probably had dental amalgam previously. As mercury accumulates in body tissues, this "amalgam free group" might have a higher mercury body burden than the "amalgam group" with currently existing amalgam fillings.

SCENIHR also cited Zimmer et al. (2002) as a proof of the safety of amalgam. But this study compared two groups exposed to amalgam (all female, one group of patients who claimed to be suffering from symptoms they related to their amalgam fillings and the other group which did not report any association between complaints and their amalgam) in terms of mercury levels in body fluids and psychometric tests. The mean number of amalgam fillings was identical in both groups. They found equal mercury levels in both amalgam groups. Zimmer et al. (p. 210) conclude: "Thus, mercury released from amalgam fillings was not a likely cause of complaints reported by the amalgam sensitive subjects" [21]. It is not clear why these authors come to such a conclusion. Furthermore it is known from animal experiments and pharmacological studies that individuals given equal amounts of a toxin might react differently. An example for this is that not every smoker develops lung cancer, although smoking is now accepted as a main cause for cancer.

"Children amalgam trials"

SCENIHR based their statement about the safety of dental amalgam also on two children amalgam trials. These studies show severe methodical flaws:

In two randomised trials on children it was evaluated whether mercury containing dental amalgam had adverse neuropsychological or renal effects [277,278]. Healthy children were randomised to either amalgam or composite surface restoration. Two children in the amalgam group died (one possibly by committing suicide) and were excluded from the study.

Power calculation (binomial - adverse event versus no event) indicates that psychological illness, having prevalence of 6.7% in the composite-treated children, would have to have had a prevalence of at least 14.5% in the amalgam group to have an 80% chance of being proven statistically (observed was 9.0%). Similarly for neurological illness, observed prevalences in the composite group (0.4% composite, 1.5% amalgam) would have needed at least 4.5% prevalence in the amalgam group to be significant. From the authors it was concluded that "there is no reason to discontinue use of mercury amalgam" [277] and that "dental amalgam [...] emits small amounts of mercury vapor" [278].

The first conclusion is a classic error: Due to its lack of power, the study provides false reassurance that mercury is 'safe'. To effectively evaluate the effect sizes seen, the trial should have been much larger (1500-2500/group).

Urine porphyrin profiles and markers of oxidative stress, which are elevated in individuals with dental amalgam [19,119] were not measured. Also, genetic polymorphism, which increase the susceptibility to mercury, like BDNF-Polymorphism [186,188] and Glutathion-S-Transferase gene polymorphism [279] were not measured either. Furthermore, the real exposure level of mercury (mercury vapor emitted in the oral cavity) was not determined, which questions the ethics of such a study. Research has demonstrated that the emission of mercury vapor was much higher than what has been "estimated" by dentists. Chew et al. (1991) showed that 43.5 microgram/cm^2/day mercury was released from a "non-mercury releasing amalgam" and this remained constant over the study period of 2 years [280].

Mean mercury urine levels were significantly higher in the amalgam groups [277,278], although in years 3 to 7 the levels of mercury in the urine of the amalgam bearers continuously dropped until they approached the levels of the amalgam free children [278]. But restorative treatment was used in years 6 and 7, which should have increased or at least maintained the urine mercury levels. This needed explaining. In the Chew study above [280], the amount of mercury released was steady for 2 years (the length of the study). It is known that amalgam do not stop releasing mercury vapor within 7 years. The question therefore is what the drop was caused by after year 2? Urine mercury levels are a measure of the amount of mercury being excreted via this route. Therefore, after two years of mercury exposure the route of kidney excretion of mercury appears to be becoming less effective. This is consistent with the well-known fact that increased mercury exposure inhibits its own excretion. It has been published and verified that over 90% of mercury excreted by humans leaves through the biliary transport system of the liver and is excreted in the feces, not in the urine [13]. The conclusion of Bellinger et al. [277] that "there is no reason to discontinue use of mercury amalgam" is amazing, because possible adverse effects may need more than five years of mercury exposure to develop. If mercury is involved in the pathogenesis of Alzheimer's disease, the disease may need up to 50 years to be diagnosed clinically [44].

One of the included criteria for the two studies was "no interfering health conditions" including neurodevelopmental disorders. The Centers for Disease Control and Prevention (CDC) in Atlanta (USA) reports that 1 in 6 American children have a neurodevelopmental disorder. However, above mentined papers conclude that amalgams should remain a viable clinical option in dental restorative treatment [278] and they did not exclude use on children with neurodevelopmental disorders - exactly the type of child, however, which they excluded from their studies. As mercury exposure during pregnancy may be the prime cause of neurodevelopmental disorders [46,61,245], this conclusion from the children amalgam is unsafe for the public.

Amalgam for mercury pollution

There has been an alarmingly increase of mercury in our environment [281] and human bodies [282] over the last decades. The UNEP reports on a 3-5 fold increase over the last 25 years [281].

In the European Union (EU) the usage of amalgam amounts to 120 tons yearly. Dentists are the 2nd largest user group in the EU [283,284].

Recent calculations done by Hylander [284,285] show that there are 40 tons of mercury in teeth with dental amalgam of Swedish people, which results to the excretion of 100 kg of mercury per year in wastewater. 1300 to 2200 tons of mercury in dental amalgam is present in the teeth of citizens in the EU (27 countries) [284], and for the USA the respective figures are about 1000 tons. In the US, dental amalgam is the 3rd most significant source of environmental mercury [286]. In contrast to the EU, removed amalgam is not separated from the wastewater of dental clinics in the US. But even in most EU-countries, where such separators are in use, parts of the dental amalgam leaks into the environment [284].

This mercury from dental amalgam (i.e. mercury emissions from dental clinics in wastewater, excreted mercury emissions from amalgam in living individuals,

mercury emissions from elevated mercury deposits in tissues of deceased and cremated humans with dental amalgam) enter into the environment. When including environmental costs into the economic calculation (except costs from amalgam related diseases), amalgam is the most costly dental material as was shown by Hylander and Godsite [283].

The role of organized dentistry in SCENIHR and in defending amalgam

The SCENIHR amalgam expert group consisted of one engineer (chairman), four dentists, a toxicologist and two veterinarians. The chairman has tight contacts to the industry. No experts for medicine or environmental medicine were included. One must wonder why it were the dentists who represented the strongest party in SCENIHR.

Due to their education and clinical experience, dentist are not able to judge medical systemic adverse side effects caused by dental amalgam, like multiple sclerosis, autism, autoimmunity, Alzheimer's disease, psychiatric diseases etc. Usage of dental amalgam may increase worldwide (increasing caries epidemic in undeveloped countries which constitute the highest percentage of the world`s population). Today, dental organisations are the only trade group of health professionals who endorse the use of a product that is primarily made of mercury. Every amalgam patent has been produced according to dental organisations specifications [287,288]. This may indeed be a critical point, because organized dentistry, which has always support the use of dental amalgam, are responsible for adverse side effects [287,288]. Therefore, the strategies of organized dentistry used to influence science and politics over the last decades [287-290] may be analogous to other well known topics with existing conflicts of interest, where effective measures have been applied to influence science and politics regarding dangerous products [291-295].

Competing interests

The author declare that he have no competing interests.

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