Critism to the Europaen Commision´s- SCENIHR - Paper on the Safety of Dental Amalgam

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The following section reflect the personally opinion of the author, which must not fit with the one of the University Hospital Freiburg

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Running head: Amalgam and adverse health effects

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Table of Contents

1. Abstract

It was proposed by SCENIHR in a Premliminary Report to the EU-Commission (29.11.2007) that ***"….no risks of adverse systemic effects exist and the current use of dental amalgam does not pose a risk of systemic disease…".*** This statement is based on (i) unsystematicly selected studies, (ii) the comparison with occupationally mercury exposed workers which is not allowed, (iii) the mercury levels in blood or urine, which do not exceed "safety limits" in humans with dental amalgams.

But, a simple Medline search results in thousands scientific literature which confirms that mercury is extremely toxic even in very low levels and the WHO have repeatedly stated that amalgam is the major contributor to human body burden.

Furthermore, SCENIHR disregard the basic toxicology of mercury and, unfortunately, did not include many important scientific studies in their review. The scientific data provided here shows, in contrast to the study selection done by SCENIHR, that:

(a) dental amalgam is by far **the main source** of human total mercury body burden. This is proofed by many autopsy studies which found **2-12 times more mercury** in the 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. It is hard to explain, why exactly SCENIHR did not cite any autopsy study. This same methodicology is normaly used only in studies and reviews, performed by dentists and their advocates, for underplaying the importance of dental amalgam for the human mercury body burden.

(b) there exists no correlation between mercury levels in blood or urine, and the levels in body tissues or severity of clinical symptoms. SCENIHR only use levels in urine or blood. As expected, they found only levels below safety levels in amalgam bearers and concluded that this as a proof of the safety of dental amalgam.

(c) There exists no "safety level", below adverse effects are excluded (WHO 2005). But SCENIHR again insist on the unscientific assumption that no adverse effects occur below established "safety limits", which, furthermore, was never adopted for mercury vapour exposure.

(d) autopsy studies have shown consistently that, despite of mercury levels below "safety limits" in urine or blood, a significant proportion of individuals have very high mercury levels in their brains, kidneys or glands, derived from dental amalgam. **These mercury levels are far above toxic levels**, which easely cause damage in human- and animal cells in scientific experiments. SCENIHR neglect this data completely.

(e) the half-life of mercury in the brain could last from several years to decades, thus mercury accumulates over time of amalgam exposure in body tissues to toxic levels. But SCENIHR states that the half live of mercury in the body is only *"20-90 days"*.

(f) mercury, in particular mercury vapor is known to be the most toxic non-radioactive elelement, about ten times more toxic than lead on human neurons and with synergistic toxicity to other metals. Most studies cited by SCENIHR, which concludes that amalgam fillings are safe for humans have profound methodological flaws which makes them invaluable for assessing the safety of amalgam. Some of them were also granted by dental organisation. The SCENIHR report was neither performed by physicans nor by experts in environmental medicine, but mostly by dentists and their advocates which: (i) have conflict of interests regarding the use of dental amalgam, (ii) have no expertise in the pathogenesis, diagnosis, and treatment of most human diseases, possibly triggered by amalgam.

2. Dental amalgam is the main source of mercury in human tissues

SCENIHR write on page 17 (Section 3.3.2.2.)*: "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."*

It is not explainable, why SCENIHR did not cite any autopsy studies, which are the most reliable studies for assessing mercury levels in tissues. Levels in urine or blood are not important, important are the mercury levels in body tissues like brain or kidney.

Furthermore SCENIHR did not mention that dental amalgam is by far the **main source** of human mercury load in body tissues. An approx. 2-5-fold increase of mercury levels in blood und urine as well as a **2-12 fold** increase of the mercury concentration in several body tissues was observed in people with dental amalgam compared to those without amalgam (Barregard et al., 1999; Becker et al., 2002, 2003; Drasch et al., 1992, 1994; 1997; Egglestone & Nylander, 1987; Gottwald et al., 2001, Guzzi et al., 2002, 2006, Levey et al., 2004: Lorscheider et al., 1995; Kingmann et al., 1998; Mortada et al., 2002, Nylander 1986, 1991, Nylander et al., 1987; Pizzichini et al., 2003, Weiner & Nylander, 1993, Zimmer et al., 2002). Additionally, experiments with animals have confirmed the fact that dental amalgam lead to significantly increased levels in the tissues (Danscher et al., 1990; Galic et al., 1999, Galic et al., 2001, Hahn et al., 1989, 1990; Lorscheider et al., 1995; Lorscheider and Vimy, 1991; Vimy et al., 1990)

Therfore mercury exposure through dental amalgam exceeds the exposure by fish consumption by far. Dental amalgam is, according to the autopsy studies, responsible for at least 60-95% of mercury deposits in human tissues. This was not mentioned by SCENIHR.

2.1. Methyl-mercury through dental amalgam ?

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

This statement is somewhat weakly founded: Mercury (Hg) from dental amalgam is in fact transformed into organic mercury compounds by microorganisms in the gastrointestinal tract (Leistevuo et al., 2001, Heintze et al., 1983, Yannai et al., 1991). Leistevuo et al. (2001) found three times increased methyl mercury levels in the saliva from 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 (Leistevuo et al. 2001). The form of Methyl-mercury derived from dental amalgam is much more toxic (up to 20 times) than the form of methyl mercury found in fish (see section "toxixity of mercury").

2.2. Toxic mercury levels in humans through dental amalgam?

SCENIHR only use studies which assess inorganic mercury levels in urine or blood for the estimation of mercury body burden or severity of clinical symptoms. Because they found only urine levels below the safety levels for mercury in amalgam bearers, they concluded this as the proof of the safety of dental amalgam.

This argument need to be explained in detail. In a recent study on italian cadavers, 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, which have only 0-3 amalgam fillings (Guzzi et al. 2006).

- Guzzi G, Grandi M, Cattaneo C et al. Dental amalgam and mercury levels in autopsy tissues. Food for thought. Am J Forensic Med Pathol 2006; 27: 42-45.

The average mercury level in the brain of people with more than **12 amalgam fillings** was **300 ng Hg/g** brain tissue (Guzzi et al. 2006), **which is well above toxic mercury levels (see below)**. In another study, the levels of inorganic mercury (which correlates significantly with the number of amalgam fillings) in the occipital cortex was in average **12 ng Hg/g ± 29 ng Hg/g** (Bjorkmann et al. 2007). Mercury levels in thyroid- and pituitary gland were **55 ng Hg/g and 200ng Hg/g** respectively and again, these levels correlate significantly with the numbers of dental amalgam and are above toxic levels (see section 2.3.) (Bjorkmann et al. 2007).

Individuals with more than 10 amalgams have **504 ng Hg/ g** in their kidneys (0-2 amalgams: 54 ng Hg/ g); **83,3 ng Hg/ g** in the liver (0-2 amalgams: 17,68 ng Hg/g) (Drasch et al. 1992).

These levels, which are **far above toxic levels**, are only average levels. Therfore, a significant portion of individuals with dental amalgam have more than twice of this mercury levels in their body tissues. Additionaly, it must be considered that mercury levels found in subcellular fractions like mikrosomes, mitochondria and other cell- compartiments even exceed the average toxic mercury levels of the whole brain tissues by far (Wenstrup et al. 1990)

- Wenstrup D, Ehmann WD, Markesbery WR**.** Trace element imbalances in isolated subcellular fractions of Alzheimer's disease brains. Brain Research 1990; 533: 125-31.

2.3. Toxic mercury levels in vitro and in vivo

Inorganic mercury levels of **0,02 ng Hg/g** (2µl 0,1 µMolar Hg in 2 ml substrate) led to the total destruction of intracellular mircrotubuli and to the degeneration of axons (Leong et al., 2001). In other experiments inorganic mercury concentrations of **36 ng Hg/g** (0,18 µMol Hg) led to increased **oxidative stress** as a prerequesite for further cell damage (Olivieri et al, 2000, 2002).

Mercury vapour inhalation in doses, which also occur in humans with many amalgam fillings and chewing, lead to pathological changes in the brains of animals after 14 days (Pendergrass et al. 1995, 1997).

- Pendergrass JC, Haley BE. Mercury-EDTA Complex Specifically Blocks Brain-Tubulin-GTP Interactions: Similarity to Observations in Alzheimer´s Disease. In: Friberg LT, Schrauzer GN (eds.): Status Quo and Perspective of Amalgam and Other Dental Materials. International Symposium Proceedings. Thieme Verlag, Stuttgart- New-York, 1995, pp 98-105.
- Pendergrass JC, Haley BE, Vimy MJ, Winfield SA, Lorscheider FL. Mercury vapor inhalation inhibits binding of GTP to tubulin in rat brain: similarity to a molecular lesion in Alzheimer diseased brain. Neurotoxicology 1997;18: 315-324.

2.4. Toxic mercury levels in Alzheimer´s disease

The average mercury load in the brain of individuals with Alzheimer`s disease was **20 to 178 ng Hg/g**, in some cases the load exceeds up to (**236- 698 ng Hg/g**). **In 15% of the human brain samples** the mercury load was above **100 ng Hg/g** (Ehmann et al. 1986, Thompson et al. 1988, Saxe et al., 1999). The average mercury load in the pituitary gland was in mean **400 ng Hg/g** (Cornett et al., 1998). **These levels are again well above established toxic levels (see section 2.3.)**.

2.5. Mercury triggered pathological changes in german human brains

About 20% of people 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 have **for mercury typical**, pathological changes in their brains (Braak et al. 1997). This coverage of pathological brain chances in people from Germany, which is caused by very low levels of mercury in experiments and **not** by low levels of other metals like lead, iron, aluminum, copper, mangan, chrom. cadmium) (Leong et al. 2001, Pendergrass & Haley 1997) resembles the frequency of dental amalgam fillings implanted in human mouth: About 80-90% of people living in Germany had have dental amalgam implanted for decades in their mouth. It must be noted that about 30-50% of german people over the age of 85 years have Alzheimer´s disease (AD) and there are many hints that mercury plays the major pathogenetic role in AD (Mutter et al. 2004).

2.6. 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 (Drasch et al., 1994). Furthermore, placental, fetal and infant mercury body burden correlates with the numbers of dental amalgam fillings of the mothers. (Ask et al., 2002, Drasch et al., 1994, Holmes et al., 2003, Morgan et al., 2002; Takahashi et al., 2001, 2003; Vather et al., 2000; Yoshida et al., 2002, 2004).

Mercury levels in amniotic fluid (Luglie et al., 2003) and breast milk (Drasch et al., 1998, Oskarsson et al., 1996, Vimy et al., 1997) are also significantly correlated with the number of maternal amalgam fillings.

2.7. Mercury in infant tissues: Increased risk of neurodevelopmental disorders?

Especially fetal and infant neurons have an increased susceptibility to mercury exposure compared with adult brain cells. Drasch et al. (1994) found mercury levels of up to **20 ng Hg/g in infant brain tissues from Germany**, which were mainly caused by dental amalgam fillings of their mothers. As decribed above, mercury levels **of 0,02 ng Hg/g** led to degeneration of axons (Leong et al., 2001) and **36ng Hg/g led** to an increase of oxidative stress as a prerequesite for cell damage (Olivieri et al, 2000, 2002). Furthermore, the mercury levels found in the infant brains of mothers with dental amalgam are sufficient enough to inhibit the function of the important enzyme methionin syntethase (Waly et al., 2004, Deth, 2004). Methionin synthetase is crucial for methylation, a central step for most important metabolic reactions in the body, including the development of the brain, the maturation of nerve cells, synthesis of neurotransmitters and for production of the antioxidans glutathione.

Maternal amalgam fillings increases significantly mercury levels in **cord blood** (Palkovicova et al. 2007, Unuvar et al., 2007) and in fetal or infant tissues (Drasch et al., 1994).
The risk for delayed neurodevelopment of children was **3,58-** times increased, when mercury levels in **cord blood** were higher then **0,8 ng Hg/ml** (Jedrychowski et al, 2005). In Germany, mercury levels of **0,2 – 5 ng** Hg/ ml cord blood are considered as ***"normal"*** (Stoz et al., 1995), thus leaving many infants to mercury levels, which may cause neurodevelopmental deficits.

- Palkovicova L, Ursinyova M, Masanova V, Yu Z, Hertz-Picciotto I. Maternal amalgam dental fillings as the source of mercuri exposure in developing fetus and newborn. J Expo Sci Environ Epidemiol 2007; in print.

3. No correlation between mercury in urine or blood, and in body tissues

SCENIHR rely their report on studies, which have measured mercury levels in biomarkers, like urine, for the assessment of clinical symptoms or mercury body burden.

Even the WHO states (1991)

> "*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 is not explainable, why SENIHR neclect the following scientific studies:
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 like brain and kidney (Danscher et al., 1990; Drasch, 1997; Hahn et al. 1989, 1990, Hargeaves et al., 1988; Holmes et al., 2003; Lorscheider et al., 1995; Opitz et al., 1996; Vimy et al., 1990; Weiner & Nylander, 1993).
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 (Björkman et al. 2007).

Drasch et al. (2001, 2002, 2004) showed, that 64% of individuals, who were 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 Effekt Level (NOAEL). The same results were found for mercury levels in blood and hair (Drasch et al., 2001, 2002, 2004).

3.1. Paradoxical association between mercury levels in urine and clinical symptoms

Even a paradoxical correlation between mercury levels in urine, blood or hair and clinical symptoms exists:

Sudies on cadavers are known to be the gold standard for detecting mercury body burden. Deceased subjects, who showed only **0,3 ng** mercury per ml urine had up to **350 ng** mercury per g kidney tissue (wet weight) in kidney specimens. On the other hand, subjects with high urine levels of mercury (above **2ng/ml**) had only **150 ng** mercury per g in their kidney tissues. (Drasch et al, 1997).

1. Drasch, G., Wanghofer, E., and Roider, G. (1997). Are blood, urine, hair, and muscle valid bio-monitoring parameters for the internal burden of men with the heavy metals mercury, lead and cadmium? Trace Elem. Electrolyt. 14:116-123.

Subjects with highest urine levels of mercury showed best recovery rates from neuropsychological complaints after removing their amalgam fillings (Stenman& Grans, 1997). Also children with highest mercury levels in hair showed better performance in developmental tests (Grandjean et al., 1995)

Another study indicates that autistic children had up to 15-times lower mercury levels in their infant hair than healthy children, despite of significantly higher exposure to mercury in the womb (Holmes et al. 2003). Furthermore, the lower the mercury levels in infant hair, the higher was the severity of autism. (Holmes et al., 2003).

Despite higher mercury body burden, amalgam hyersensitives showed slightly lower levels of mercury in their saliva, blood and urine [Köhler et al. 2007]. Even after provocation with the mercury chelator DMPS, the amalgam hypersensitive group excrete in mean **only 7,77 µg Hg** via urine in 24 h whereas healthy amalgam bearers excrete **12,69 µg Hg/ 24h** [Köhler et al. 2007].

- Köhler W. et al. Prognos in the diagnosos of amalgam hypersensitivity: adiagnostic case control study. Forsch Komplement Med 2007; 14: 18-24.

The same tendency was found by Zimmer et al. (2002): Individuals with dental amalgam, who reported amalgam-derived-complaints showed partly lower mercury levels than individuals with dental amalgam, but without complaints. If this study were adequately powered, these differences would have reached statistical significance (Walach et al., 2003).

- Walach, H., Naumann, J., Mutter, J., and Daschner, F.D. (2003). No difference between self-reportedly amalgam sensitives and non-sensitives? Listen carefully to the data. In. J. Hyg. Environ. Health 206:139-141.

Furthermore, studies confirm that the ratio of fecal to urine excretion is 12 to 1 (Lorscheider et al. 1995). 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 total mercury exposure.

Conclusion: Given the same exposure to mercury, individuals with high levels of mercury in urine, blood or hair may have a better excretion capacity for mercury. Presumably, this leads to a lower mercury body burden and to fewer mercury derived complaints compared to individuals with low levels of mercury in urine or hair. Therefore, the preliminary report of SCENIHR, which rely only on the mercury-levels in urine or blood lead to completely distorted conclusions.

3.2. No safety level for mercury?

Taken together the data present above (and this was also confirmed by the WHO 2005): It is not possible to determine any safety levels for mercury, below adverse effects are excluded (WHO 2005).

SCENIHR also use safety limits for mercury which were deduced from studies with workers occupationally exposed to mercury. But this cannot be applied to individuals with amalgam fillings and must be critically evaluated:

1. Frequently, mercury exposure of workers in the chlorine-alkali industry are compared although the simultaneous exposure to chlorine considerably diminishes the absorption of Hg into the organs of animals (50-100%) [Viola & Cassano 1968].
2. Workers exposed to mercury usually represent a group, whose Hg-exposure begins as adults only (during about 8 hours, 5 days a week), while amalgam bearers can be exposed to mercury in the womb through maternal amalgam fillings, in childhood and up to death, at a rate of 24 hours per day, 7 days per week.
3. Workers are a selected healthy group, while pregnant women, infants, children and individuals with illness (like multiple sclerosis, autoimmunity, cancer, psychiatric diseases) do not start working at all either due to industrial safety regulations or to early health problems.
4. Despite mercury exposure below “safety limits”, significant adverse health effects were found in most studies in occupationally mercury exposed workers, even several years after exposure has ceased (Mathiesen et al. 1999, Meyer_Baron et al. 2002, Smith et al. 1983, Kishi et al. 1993, Piikivi et al. 1984, Roel et al. 1985, Soleo et al. 1990, Williamson et al. 1982, . Zavariz & Glina 1992).

- Mathiesen T, Ellingsen DG, Kjuus H (1999) Neuropsychological effects associated with exposure to mercury vapor among former chloralkali workers. Scandinavian Journal of Work, Environment & Health 25:(4)342-50
- Meyer-Baron M, Schaeper M, Seeber A (2002) A meta-analysis for neurobehavioural results due to occupational mercury exposure. Arch Toxicol. Apr;76(3):127-36
- Smith PJ, Langolf GD, Goldberg J (1983) Effects of occupational exposure to elemental mercury on short term memory. BR. J. IND. MED.; 40:(4)413-419
- Kishi R, Doi R, Fukuchi Y, Satoh H, Satoh T, Ono A et al (1993) Subjective symptoms and neurobehavioral performances of ex-mercury miners at an average of 18 years after the cessation of chronic exposure to mercury vapor. Mercury Workers Study Group. Environmental Research 62:(2)289-302
- Piikivi L, Hanninen H, Martelin T, Mantere P (1984) Psychological performance and long-term exposure to mercury vapors. Scand J Work Environ Health Feb;10(1):35-41
- Roels H, Gennart JP, Lauwerys R, Buchet JP, Malchaire J, Bernard A (1985) Surveillance of workers exposed to mercury vapour: validation of a previously proposed biological threshold limit value for mercury concentration in urine. American Journal of Industrial Medicine 7:(1)45-71
- Soleo L, Urbano ML, Petrera V, Ambrosi L (1990) Effects of low exposure to inorganic mercury on psychological performance. British Journal of Industrial Medicine 47:(2)105-9
- Williamson AM, Teo RK, Sanderson J (1982) Occupational mercury exposure and its consequences for behaviour. International Archives of Occupational & Environmental Health 50:(3)273-86
- Zavariz C, Glina DM (1992) [Clinico-neuro-psychological evaluation of workers exposed to metallic mercury in the electric lamp industry]. [Portuguese]. Revista de Saude Publica 26:(5)356-65

4. 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 much longer half-time. There is, for example, the case of a healthy worker who was shortly accidently exposed to mercury vapor. Four weeks afterwards, mercury levels in urine decreased to “normal levels” due to chelation. After the accident, he suffered for 16 years from severe fatigue, irritabily, burning stomach and diabetes. But these complaints were diagnosed as an “organic psycho syndrome” not caused by mercury because mercury levels in urine were found to be “normal”. He was never able to work again. 16 years after mercury exposure he died of lung cancer. Autopsy revealed very high mercury levels in his cerebellum (2190 ng Hg/g), occipital lobe (1090 ng Hg/g), thalamus (1010 ng Hg/g), kidneys (1650 ng Hg/g), lungs (600 ng Hg/g) and in thyroid glands (250 ng Hg/g) (Opitz et al, 1996). Interestingly most of the mercury was found to be intracellulary near to cell nuclei. Mercury was also acummulated in motoneurons and the basal ganglia (see also section 2.3.).

During 16 years after mercury exposure, these extraordinary high mercury levels in his body tissues were not excreted, neither naturally, nor through frequently applied chelation therapy.

According to SCENIHR even 99% of the mercury body load should be excreted after two years of mercury exposure. 16 years after exposure, no mercury should be detectable in the tissues.
Other authors also report about the extremly long half time or long lasting effect of mercury in body tissues (Hargreaves 1988; Takahata N 1970;Sugita M 1978, Kishi R, 1994, He FS 1984, Kobal et al., 2004, Letz et al., 2000).

5. Toxicity of Mercury

SCENIHR did not mention the specific toxicity of mercury vapour coming of dental amalgam fillings. This should be completed:

Mercury (Hg) has been shown to be 10- times more toxic than lead (Pb) in vitro (Thier et al., 2003, Stoiber et al, 2004a, 2004b). 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 is probably due to the efficient partitioning of vaporous mercury into certain body organs (e.g. Central Nervous system (CNS), kidney) and into specific cellular organelles (e.g. the mitochondria) based on mercury vapor's ability to easily penetrate cell membranes and the blood brain barrier. Thes extraordinary toxicity is also determined by the following properties:

1. It is the only metal representing a volatile gas at room temperature, which is is readily absorbed (80%) by the respiratory system.
2. Mercury vapors, which escape amalgam continuosly. Penetrate in tissues with great ease, because of his monopolar atomic configuration.
3. Once inside the cells, mercury vapor is oxidized to Hg^{2+}, the toxic form of mercury, which binds covalently to thiol groups of proteins inhibiting their biological activity.
4. Hg^{2+} is more toxic than Pb^{2+}, Cadmium (Cd^{2+}) and other metals because it has an extremely high affinity due to "covalent bond" formation with thiol groups (cysteines in proteins) causing irreversible inhibition (binding-constant 10^{30-40}). Other metals form reversible bonds with proteins and are therefore less toxic. This might explain the exceptionally long half-life of mercury in not renewing tissue (e.g. brain) from several years to decades (Hargreaves et al., 1988; Opitz et al., 1996; Sugita 1978).
5. Hg^{2+} does not bind tightly enough to the carboxylate groups of natural organic acids (natural chelators like citrate) to prevent its toxicity.
6. 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 (Duhr et al., 1993; Pendergrass & Haley, 1996). Other chelating agents (DMPS and DMSA) inhibit the toxic effect of Cd^{2+} and $Pb^{2+,}$ but not of Hg^{2+} (Soares et al., 2003). DMPS, DMSA or natural chelators like vitamin C, glutathione or alpha-lipoic acid are not able to remove mercury from nervous tissues. (Aposhian et al., 2003). DMPS or DMSA may even increase the inhibitory activity of Hg^{2+} and Cd^{2+}on enzymes but not by Pb^{2+} (Nogueira et al., 2003). Furthermore, DMPS in animals led to an increase of Hg concentrations in spinal cord (Ewan & Pamphlett, 1996).

The toxicity of methyl mercury (Me-Hg), which is bound to cysteine in fish, seems to be far lower (only approx. 1/20) than Me-Hg-compounds usually used in experiments [Harris et al. 2003].

- Harris HH, Pickering IJ, George GN. The chemical form of mercury in fish. Science 2003; 301: 1203.

Furthermore, marine fish represents a significant source of selenium and essential omega-3-fatty acids, which protect effectively against mercury toxicity. Nevertheless, Me-Hg-Cl, which proved to be more toxic than Me-Hg in fish, showed less neurotoxicity for the growing nervous system in vivo than did mercury vapor [Frederikson et al. 1996].

Investigations by Drasch et al. [2001] shows similar correlations: A 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 methyl-Hg from fish consumption, despite their Hg levels in hair and plasma were higher compared to the individuals exposed to mercury vapor [Drasch et al. 2001, 2002]. Another study also points to smaller neurotoxicity of Me-Hg from fish compared to iatrogenic Hg-sources (Amalgam, Thiomersal) [Holmes et al. 2003]. 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.

Taken together, mercury vapour coming off dental amalgam or methyl mercury derived from amalgam in the gastrointestinal tract has not reacted with anything yet and has the full toxic potential. Mercury vapour is easily absorbed by body tissues (like brain) and then did react to cellular structures, which are in turn damaged. On the other side, methylmercury in fish has already reacted with fish proteins and other protective molecules or atoms in fish tissues, like Glutathione or Selenium, which are enriched in fish and make the methylmercury less toxic.

5.1. 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, humans are exposed to many other toxins simultaneously, thus the effects add up or are even **synergistic**. (Schubert et al. 1978, Haley, 2002). For example, it has been proofen that the combination of one tens of the Letal Dosis 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: 1/10 LD1 (Hg) + LD1 (Pb) = LD 100 (Schubert et al. 1978).

In this context, it must be considered that modern humans have more mercury- and between 10-1000- fold more lead in their body tissues than ancient humans

- Ericson JE et al. Skeletal concentrations of lead in ancient Peruvians. N Engl J Med 1979; 300: 946-951.
- Ericson JE et al. Skeletal concentrations of lead, cadmium, zinc, and silver in ancient North American Pecos Indians. Environ Health Perspect 1991; 93:217-223
- Drasch G. Lead burden in prehistorical, historical and modern human bones. Sci Total Environ 1982; 24: 199-231.
- Patterson CC et al. Lead in ancient human bones and the relevance to historical developments of social problems with lead. Sci Total Environ 1987; 61: 167-200.
- Patterson C et al. Natural skeletal levels of lead in Homo sapiens sapiens uncontaminated by technological lead. Sci Total Environ 1991; 107: 205-236.

Lead levels well below the safety limits causes increased mortality through stroke and myocardial incarction (Menke et al. 2006)

- Menke A et al.: Blood lead below 0.48 µmol/L (10 µg/dL) and mortality among US adults. Circulation 2006; 114: 1388-94.

"Normal" lead levels in the bones correlates with brain and bone diseases and cancer.

- Yoshinaga J et al. Trace elements in ribs of elderly people and elemental variation in the presence of chronic disease. Sci Total Environ 1995; 162: 239-252.

Thus neither for lead nor for mercury exist any safety limits.

In other experiments the addition of aluminium, antibiotics, thimerosal (sometimes in vaccines) and testosterone increased the toxicity of mercury significantly [Haley 2005, 2006].

- Haley B & Small T. Biomarkers supporting mercury toxicity as the major exacerbator of neurological illness, recent evidence via the urine prophyrin tests. Medical Veritas 2006; 3: 1-14.
- Haley B. Mercury toxicity: Genetic susceptibilities and synergistic effects. Medical Veritas 2005; 2: 535-542.

6. 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 appearently neclect many scientific studies, which finds significant adverse health effects from dental amlgam:

6.1. Cytotoxicity from amalgam in comparison to composites

SCENIHR compare the toxicity of amalgam with composite and find about the same. But in most experiments, even inorganic mercury, which is less toxic than mercury vapor from amalgam (because inorganic mercury is not able to easely penetrate into the cells), was proofed to be much more toxic than any dental composites: Mercury was shown to be 100-800 fold more toxic than composite components for cells (Kehe et al. 2001, Walther et al. 2002, Reichl et al. 2001, 2006a, 2006b)

- Reichl FX, Walther UI, Durner K. et al. Cytotoxicity of dental composite components and mercury compounds in lung cells. Dent Mater 2001; 17: 95-101.
- Kehe K, Reichl FX, Durner J, Walther U, Hickel R, Forth W. Cytotoxicity of dental composite components and mercury compounds in pulmonary cells. Biomaterials 2001; 22: 317-322.
- Walther UI, Walther SC, Liebl B, Reichl FX, Kehe K, Nilius M, Hickel R. Cytotoxicity of ingredients of various dental materials and related compounds in L2- and A549 cells. J Biomed Mater Res 2002; 63: 643-9.
- Reichl FX, Simon S, Esters M, Seiss M, Kehe K, Kleinsasser N, Hickel R. Cytotoxicity of dental composite (co)monomers and the amalgam component Hg(2+) in human gingival fibroblasts. Arch Toxicol. 2006; 80:465-72.
- Reichl FX, Esters M, Simon S, Seiss M, Kehe K, Kleinsasser N, Folwaczny M, Glas J, Hickel R. Cell death effects of resin-based dental material compounds and mercurials in human gingival fibroblast. Arch Toxicol 2006; 80: 370-7.

6.2. Genotoxicity, oxidative Stress, cancer

In humans, DNA damage in blood was caused by their dental amalgam fillings (Di Pietro et al. 2008). Low levels of inorganic mercury lead to significant DNA damage in human tissue cells and lymphocytes (Schmid et al. 2007). This effect, which may trigger cancer, was seen below mercury levels which normally caused cytotoxicity and cell death. Aberrations of chromosomes can be provoked through amalgam in cell cultures (Akiyama et al., 2001). Amalgam bearers show significantly increased oxidative stress in saliva (Pizzichini et al., 2000, 2002) and blood (Pizzichini et al., 2001, 2003), which correlates with the numbers of amalgam fillings. Mercury levels, which are frequently seen in tissues of many people with dental amalgam fillings, lead to increased oxidative stress und reduction of glutathione levels, which lead to cellular damage (Olivieri et al., 2000, 2002). Significantly elevated mercury levels were also observed in breast cancer tissues (Ionescu et al. 2006)

- Di Pietro A, Vidalli G, La Maestra S et al. Biomonitoring of DNA damage in peripheral blood lymphocytes of subjects with dental restorative fillings. Mutat Res 2008; 650: 115-122.

- Schmid K, Saasen A, Staudenmaier R et al. Mercury dichloride induces DNA-damage in human salivary gland tissue calls and lymphocytes. Arch Toxicol 2007; 1: 759-767.
- Ionescu JG, Novitny J, Stejskal V et al. Increased levels of transition metals in breast cancer tissue. Neuro Endocrinol Lett 2006; 27: 36-9.

Mercury deposited in the tissue is mostly bound to selenium, which means, that this selenium is not longer available for the body. Therfore, amalgam may aggravate a latent deficiency of selenium, particularly in countries with suboptimal selenium supply (e.g. in Central Europe) (Drasch et al., 2000).

6.3.Antibiotica Resistence

It has been shown, that mercury from dental amalgam can induce mercury resistant bacteria (Liebert et al. 1997; Lorscheider et al. 1995b, Summers et al. 1993). This lead to a general antibiotica resistence in oral bacteria and in other body sites (Summers et al. 1993). This is particularly true when the antibiotic resistance genes are contained within the same mobile element as the mercury resistence operon [Davis et al. 2005]. Mercury resistance is common in human oral bacteria [Edlund et al, 1996, Leistevuo et al. 2000, Pike et al. 2002]. Monkeys with dental amalgam also showed an increase in antibiotic resistent bacteria in their stools [Summers et al. 1993; Wiremann et al. 1997].

- Wireman J, Liebert CA, Smith T, Summers AO. Association of mercury resistance with antibiotic resistance in the gram-negative fecal bacteria of primates. Appl Environ Microbiol. 1997 Nov;63(11):4494-503.
- Liebert CA, Wireman J, Smith T, Summers AO. The impact of mercury released from dental "silver" fillings on antibiotic resistances in the primate oral and intestinal bacterial flora. Met Ions Biol Syst. 1997;34:441-60.
- Lorscheider FL, Vimy MJ, Summers AO, Zwiers H. The dental amalgam mercury controversy--inorganic mercury and the CNS; genetic linkage of mercury and antibiotic resistances in intestinal bacteria. Toxicology. 1995b Mar 31;97(1-3):19-22.
- Summers AO, Wireman J, Vimy MJ, Lorscheider FL, Marshall B, Levy SB, Bennett S, Billard L. Mercury released from dental "silver" fillings provokes an increase in mercury- and antibiotic-resistant bacteria in oral and intestinal floras of primates. Antimicrob Agents Chemother. 1993 Apr;37(4):825-34.
- Davis IJ, Roberts AP, Ready D, Richards H, Wilson M, Mullany P. Linkage of a novel mercury resistance operon with streptomycin resistance on a conjugative plasmid in Enterococcus faecium. Plasmid. 2005 Jul;54(1):26-38
- Pike R, Lucas V, Stapleton P, Gilthorpe MS, Roberts G, Rowbury R, Richards H, Mullany P, Wilson M. Prevalence and antibiotic resistance profile of mercury-resistant oral bacteria from children with and without mercury amalgam fillings. J Antimicrob Chemother. 2002 May;49(5):777-83.

- Leistevuo J, Jarvinen H, Osterblad M, Leistevuo T, Huovinen P, Tenovuo J. Resistance to mercury and antimicrobial agents in Streptococcus mutans isolates from human subjects in relation to exposure to dental amalgam fillings. Antimicrob Agents Chemother. 2000 Feb;44(2):456-7.

6.4. Penetration of amalgam in tooth bone and jaw

Experiments on monkeys and sheeps have shown that mercury form amalgam penetrates into the dentin roots and jaw bone (Hahn et al. 1989, 1990). This was also shown for humans (Harris et al. 2008), which confirm an alternative route of mercury exposure through amalgam.

- Harris HH, Vogt S, Eastgate H, Legnini DG, Hornberger B, Cai Z, Lai B, Lav PA. Migration of mercury from dental amalgam through human teeth. J Synchrotron Radiat 2008; 15: 123-8.

6.5. Skin

There is a correlation between atopic eczema and IgE-levels and the body burden of mercury (Weidinger et al., 2004). Amalgam fillings can induce lichenoid reactions (Berlin, 2003; Dunsche et al., 2003a, 2003b; Martin et al., 2003; Wong & Freeman, 2003). In more than 90% of the cases, these lesions have been found to recover by removal of amalgam, no matter whether an allergy patch test was positive or not. Granulomatosis improved likewise (Guttman-Yassky et al., 2003). Also, other forms of dermatitis seem to be related with dental amalgams (Guarneri &Marini 2008, Pigatteo et al. 2008).

- Guarneri F, Marini H. Perioral dermatitis after dental filling in a 12-year-old girl: involvement of cholinergic system in skin neuroinflammation? ScientificWorldJournal. 2008 Feb 6;8:157-63.
- Pigatto PD, Brambilla L, Guzzi G. Mercury pink exanthem after dental amalgam placement. J Eur Acad Dermatol Venereol. 2008 Mar;22(3):377-8

6.6. Autoimmune Disorders and Sensitivity

Constant low-dose mercury exposure, as is common in amalgam bearers, has been considered as a possible cause for certain autoimmune diseases, e.g. multiple sclerosis, rheumatoid arthritis or systemic lupus erythematosis (SLE) (Bartova et al., 2003, Berlin, 2003, Hultmann et al., 1994, 1998; Pollard et al., 2001; Prochazkova et al., 2004, Stejskal & Stejskal, 1999; Stejskal et al., 1999, Sterzl et al., 1999, Via et al., 2003, Sterzl et al., 2006). These effects may occur with exposure below mercury safety limits (Kazantzis, 2002).

According to several reviews the frequency of amalgam sensitive individuals is considered to be between 1%-25%. (Berlin, 2003, Kommission Human-Biomonitoring des Umweltbundesamtes, 1999, Marcusson, 1999, Richardson, 1995).

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 (Rampersad et al. 2005). This shows that mercury exposures quite below the average exposure through amalgam exposure can cause disruption of the immune system at all ages.

- Rampersad et al. Transfusion 2005; 45: 384-93.

6.4.1. Only “rare cases of proven allergic reactions”?

SCENIHR only accept the old “proof” of allergic reactions to amalgam, which is a positive cutaneous patch test. But it has been shown that in more than 90% of the cases, these lesions have been found to recover by removal of amalgam, no matter whether a cutaneous patch test was positive or not.

- Dunsche A, Kastel I, Terheyden H, Springer IN, Christophers E, Brasch J. Oral lichenoid reactions associated with amalgam: improvement after amalgam removal. Br J Dermatol 2003b;148:70-76.
- Guttman-Yassky E, Weltfriend S, Bergman R. Resolution of orofacial granulomatosis with amalgam removal. J Eur Acad Dermatol Venereol 2003;17:344-347.
- Wong L, Freeman S. Oral lichenoid lesions (OLL) and mercury in amalgam fillings. Contact Dermatitis 2003;48:74-79.

Therfore the relevance of the cutaneous patch test in detecting sensitivity or allergy to mercury which are implanted in the oral cavity without any epicutaneous contact, was severly questioned.

- Bartram et al. Significance of the patch test and the lymphocyte transformation test in the diagnostic of type IV-sensitazion. J Lab Med 2006; 30: 101-106.

The results with another, validated test system, reveal that there exists more than only “rare cases” who suffers from immunological complaints through dental amalgam.

- Venclikova et al. In vivo effects of dental casting alloys. Neuro Endocrinol Lett. 2006; 27: Suppl 1. in print.
- Valentine-Thon E et al. Metallsensibilisierung: Nachweis, Validierung und Verlaufskontrolle mittels Lymphozyten-Test. Zs f Orthomol Med 2005; 1:12-15.
- Yaqob A, Danersund A, Stejskal VD, Lindvall A, Hudecek R, Lindh U. Metal-specific lymphocyte reactivity is downregulated after dental metal replacement. Neuro Endocrinol Lett. 2006 Apr 25;27(1-2):189-197
- Valentine-Thon E, Schiwara HW. Validity of MELISA for metal sensitivity testing. Neuro Endocrinol Lett. 2003 Feb-Apr;24(1-2):57-64.
- Valentine-Thon et al. LTT-MELISA(R) is clinically relevant for detecting and monitoring metal sensitivity. Neuro Endocrinol Lett. 2006; 27: in print
- Lindh, U., Hudecek, R., Dandersund, A., Eriksson, S., and Lindvall, A. (2002). Removal of dental amalgam and other metal alloys supported by antioxidant therapy alleviates symptoms and improves quality of life in patients with amalgam-associated ill health. Neuroendocrinol. Lett. 23:459-482.
- Stejskal VD et al. Diagnosis and treatment of metal-induced side effects. Neuro Endocrinol Lett. 2006; 27: Suppl 1. in print
- Stejskal VD, Danersund A, Lindvall A, Hudecek R, Nordman V, Yaqob A, Mayer W, Bieger W, Lindh U. Metal-specific lymphocytes: biomarkers of sensitivity in man. Neuroendocrinol Lett. 1999;20(5):289-298.
- Sterzl I, Prochazkova J, Hrda P, Bartova J, Matucha P, Stejskal VD. Mercury and nickel allergy: risk factors in fatigue and autoimmunity. Neuroendocrinol Lett. 1999;20(3-4):221-228
- Sterzl I, Prochazkova J, Hrda P, Matucha P, Bartova J, Stejskal VD. Removal of dental amalgam decreases anti-TPO and anti-Tg autoantibodies in patients with autoimmune thyroiditis. Neuro Endocrinol Lett. 2006;27(Suppl1) in print]

There may also be a correlation between atopic eczema, IgE-levels and the body burden of mercury, which is also not detected with cutaneus patch tests.

- Weidinger, S., Kramer, U., Dunemann, L., Mohrenschlager, M., Ring, J., and Behrendt, H. (2004). Body burden of mercury is associated with acute atopic eczema and total IgE in children from southern Germany. J. Allergy. Clin. Immunol. 114:457-459.

Because mercury from maternal dental amalgam is one of the main source of mercury body burden in fetal and and infant tissues, postnatal atopic eccema disappear after mercury detoxification of the infants (Wortberg 1997).

- Wortberg W. Intrauterine Fruchtschädigung durch Schwermetallbelastung der Mutter. Umwelt Medizin Gesellschaft 2006; 19:274-280].

6.7. Heart diseases

Mercury may cause hypertension and myocardial infarction (for review see Houston 2007).

- Houston MC. The role of mercury and cadmium heavy metals in vascular disease, hypertension, coronary heart disease, and myocardial infarction. Altern Ther Health Med 2007; 13: S128-S133],

Also, mercur accumulation was described in a form of heart insufficiency (Frustraci et al. 1999).

- Frustaci, A., Magnavita, N., Chimenti, C., Cladarulo, M., Sabbioni, E., Pietra, R., Cellini, C., Possati, G.F. and Maseri, A. J. American College of Cardiology V33(6), 1578-1583, 1999.

6.8. Urinary system

SCENIHR only cite one review, performed by a dentist, published in a dental trade journal (Dodes 2001) and 5-7 year studies on initlly iahealthy children, also performed mainly by dentists, for their argument that *"there is no evidence that dental amalgam fillings affect kidney function in human"*. But there are many studies which suggest the opposite:

In animal experiments, an impairment of renal functions due to amalgam fillings has been observed (Boyd et al., 1991, Galic et al., 2001; Pollard et al., 2001). Humans with amalgam fillings show more signs of tubular and glomerular damage when compared to individuals without dental amalgams (Mortada et al., 2002). The often cited children amalgam trail study found, even after 5 year of amalgam exposure, first signs of kidney damage (Microalbuminuria) (Trachtenberg & Barregard 2007).

- Trachtenberg F, Barregård L.The effect of age, sex, and race on urinary markers of kidney damage in children. Am J Kidney Dis. 2007 Dec;50(6):938-45.

6.9. Alzheimer's Desease (AD)

SCENIHR question that mercury may contribute to the development AD. As a proof of this statement, they cite only one study, mainly performed by dentists (Saxe et al. 1999), again published in the trade journal (JADA) of the world leading Dental association (ADA see also Section 9)), which have severe limits (Haley 2002). In contrast, some studies have shown that mercury may play a pathogenetic role in AD (Mutter et al. 2004, Mutter et al 2007):

a. no other metal in very low levels is capable to produce <u>every single</u> pathological change in the brains of animals and in cells, which is typical for AD including the increase of ß-Amyloid and the formation of neurofibrillar tangles (NFT).
b. If aluminium, lead or other metals are present in the body together with mercury, it is higly likely that synergistic toxic effects occur (Haley 2005, 2006, Schubert et al. 1978).
c. Several studies found elevated mercury levels in brain tissues or body fluids of individuals with AD.
d. The development of AD takes up to 30-50 years (Braak et al., 1997). Since about 95% of all AD cases are triggered by exogenic factors and the disease is now pandemic in developed countries, the main exogenic factor should be present since about 50 years in many

people, both in rural and in urban sites. This matches with the rised use of dental amalgam after the world war II 50 years ago.

e. The risk of AD increases with the incidence of dental decay. Therfore, edentulistic old people have earlier in their live cariotic teeth and thus a higher amalgam exposure, than old individuals with their own teeth.

f. It is also well known that the genetic inheritance of the APO-E4 form of apolipoprotein-E greatly increases the risk of early onset AD whereas inheritance of the APO-E2 form appears to be protective against AD ((Farrer et al., 1997; Ritchie and Dupuy, 1999). Both of these forms appear to do their biological functions adequately, and one of these functions is to remove oxidized cholesterol from the brain, into the cerebrospinal fluid, across the blood brain barrier and into the blood for removal by the liver. The second highest concentration of APO-E protein is in the cerebrospinal fluid. The one definite difference between APO-E4 and APO-E2 is the presence of two cysteines in the APO-E2 that are capable of mercury binding and therefore mercury removal from the central nervous system. APO-E4 differs from APO-E2 in that these two cysteines have been genetically replaced by arginines that have no mercury binding capacity. Therefore, as previously reported, one of the most logical explanations of the different protective effects of the widely accepted, differential risk for AD based on APO-E geneotype can be explained by the loss of mercury binding capacity in the cerebrospinal fluid and brain of the proteins expressed by these genes. Therfore individuals with APO-E4 are more sensitive to mercury exposure through dental amalgam (Godfrey et al., 2003; Pendergrass & Haley, 1996, Woijik et al. 2006) and lead (Stewart et al., 2002).

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- MUTTER J, NAUMANN J, SCHNEIDER R, WALACH H. Quecksilber und die Alzheimer-Erkrankung. *Fortschr Neuro Psychiat* **2007**;75:528-538.

In Alzheimer's disease (AD) the aberrant biochemical events and the pathological hallmarks are well described. So is the research that shows that mercury, and only mercury, will produce the aberrant biochemistry and produce most of the pathological hallmarks in appropriate test systems.

- Pendergrass, J.C. and Haley, B.E. Inhibition of Brain Tubulin-Guanosine 5'-Triphosphate Interactions by Mercury: Similarity to Observations in Alzheimer's Diseased Brain. In Metal Ions in Biological Systems V34, pp 461-478. Mercury and Its Effects on Environment and Biology, Chapter 16. Edited by H. Sigel and A. Sigel. Marcel Dekker, Inc. 270 Madison Ave., N.Y., N.Y. 10016 (1996).
- Pendergrass, J. C., Haley, B.E., Vimy, M. J., Winfield, S.A. and Lorscheider, F.L. Mercury Vapor Inhalation Inhibits Binding of GTP to Tubulin in Rat Brain: Similarity to a Molecular Lesion in Alzheimer's Diseased Brain. Neurotoxicology 18(2), 315-324 (1997).
- Haley, B. Mercury toxicity: Genetic susceptibility and synergistic effects. Medical Veritas 2 (2005) 535-542.

Also, a recent study has indicated that the increase in brain amyloid protein is due to an aberrant brain heme level and the heme synthetic pathway is one known to be extremely sensitive to mercury (Atamna & Frey 2004).

- Atamna, H. and Frey, W.H. A Role for heme in Alzheimer's disease: Heme binds amyolid β and has altered metabolism. PNAS 101:30 11153-58, 2004.

6.10. Parkinson´s disease (PD)

Heavy metals have long been suspected as a cause of PD, with several studies showing a relation, including epidemiological studies (Miller et al. 2003, Finkelstein et al. 1996, Dantzig 2006, Ngim &Devathasan 1989, Seidler et al. 1996, Rybicki et al. 1993, Gorell et al. 1999, Ohlson et al. 1981, Uversky et al. 2001, Carpenter 2001). Elemental mercury has induced PD (Miller et al. 2003), and the condition of a separate patient's PD substantially improved, after treatment with a mercury chelator (Finkelstein et al. 1996). The patient's neurological status remained the same in a 5-year follow-up period, after the initial improvement from treatment (Finkelstein et al. 1996). Significantly elevated blood mercury levels were found in 13 of 14 patients with PD compared to healthy controls in a study (Dantzig 2006). This supports the conclusion of a previous study which found a correlation between blood mercury levels and PD (Ngim & Devathasan 1989). Another study found significantly higher amalgam exposure in individuals with PD compared to healthy controls (Seidler et al. 1996).

- "Parkinsonism in chronic occupational metallic mercury intoxication." Miller K, OchudÅ‚o S, Opala G, Smolicha W, Siuda J. Neurol Neurochir Pol. 37 Suppl 5:31-8. 2003
- "The enigma of parkinsonism in chronic borderline mercury intoxication, resolved by challenge with penicillamine." Finkelstein Y, Vardi J, Kesten MM, Hod I. Neurotoxicology. 17(1):291-5. 1996 Spring
- "Parkinson's disease, macular degeneration and cutaneous signs of mercury toxicity." Dantzig PI. J Occup Environ Med. 2006 Jul;48(7):656.
- "Epidemiologic study on the association between body burden mercury level and idiopathic Parkinson's disease." Ngim CH, Devathasan G. Neuroepidemiology. 8(3):128-41. 1989
- "Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany." Seidler A, Hellenbrand W, Robra BP, Vieregge P, Nischan P, Joerg J, Oertel WH, Ulm G, Schneider E. Neurology. 46(5):1275-84. 1996 May
- "Occupational metal exposures and the risk of Parkinson's disease." Gorell JM, Rybicki BA, Cole Johnson C, Peterson EL. Neuroepidemiology. 18(6):303-8. 1999
- "Parkinson's disease mortality and the industrial use of heavy metals in Michigan." Rybicki BA, Johnson CC, Uman J, Gorell JM. Mov Disord. 8(1):87-92. 1993
- "Parkinson's disease and occupational exposure to organic solvents, agricultural chemicals and mercury--a case-referent study." Ohlson CG, Hogstedt C. Scand J Work Environ Health. 7(4):252-6. 1981 Dec

- "Metal-triggered structural transformations, aggregation, and fibrillation of human alpha-synuclein. A possible molecular NK between Parkinson's disease and heavy metal exposure." Uversky VN, Li J, Fink AL. J Biol Chem. 276(47):44284-96. 2001 Nov 23
- "Effects of metals on the nervous system of humans and animals." Carpenter DO. Int J Occup Med Environ Health. 14(3):209-18. 2001

Genetic susceptibility parameters, which lead to decreased mercury excretion seem to increase the risk for PD (see section XXX)

6.11. Adverse health effects in dental staff

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

A simple literature research reveal the opposite picture: Dentists working with amalgam have an increased Hg exposure (Harakeh et al., 2003; Tezel et al., 2001, Nylander & Weiner, 1991).

In most studies available, mercury exposure in dental clinics, **which is considered to be far below "safety limits"**, resulted in significant adverse health effects in dental workers (Aydin et al., 2003, Bittner et al., 1998; Echeverria et al., 1995;, 1998; Heyer et al., 2004, Echeverria et al., 2005, 2006, Gonzalez-Ramirez et al. 1995, Langworth et al. 1997, Ngim et al. 1992, Ritchie et al. 1995, 2002, Uzzell et al 1986).

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. But this is a unscientific conclusion (see section 3.). Low level mercury vapor exposure vapor lead also to behavioral changes in adult mice (Yoshida et al., 2004) and to the impairment of color discrimination in humans (Urban et al., 2003).

Visual evoked potentials in Hg exposed dental staff show significant changes when compared to controls (Urban et al., 1999) or pathological muscle biopsies (Nadorfy-Lopez et al., 2000). Rowland et al. (1994) found an increased incidence of infertility in female dental staff. 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 as to exposure to acrylate compounds, disinfectants or organic solvents (Lindbohm et al. 2007).

Even after 30 years after mercury exposure have stopped, dental nurses showed significant adverse health effects (Jones et al. 2007). 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 increased mercury induced neurological deficits with polymorphism of the CPOX4 gene (Echeverria et al., 2005, 2006; Heyer et al., 2006), SCENIHR still maintain that amalgams do not cause any significant medical problems in dental workers, because urine and blood levels are below "safety limits". Again, SCENIHR miss the point that it is

the mercury body burden, not the blood or urine levels that defines toxicity, and it has to take into account genetic susceptibility parameters.

- Lindbohm ML, Ylöstalo P, Sallmen M et al. Occupational exposure in dentistry and miscarriage. Occup Environ Med 2007; 64: 127-133.
- Jones L, Bunnell J, Stillman J. A 30-year follow-up of residual effects on New Zealand School Dental Nurses, from occupational mercury exposure. Hum Exp Toxicol 2007; 26:367-374.
- Langworth S, Sallsten G, Barregard L, Cynkier I, Lind ML, Soderman E (1997) Exposure to mercury vapor and impact on health in the dental profession in Sweden. J Dent Res Jul;76(7):1397-404
- Uzzell BP, Oler J (1986) Chronic low-level mercury exposure and neuropsychological functioning. J Clin Exp Neuropsychol. Oct;8(5):581-93
- Ritchie KA, Gilmour WH, Macdonald EB, Burke FJ, McGowan DA, Dale IM et al (2002) Health and neuropsychological functioning of dentists exposed to mercury. Occupational & Environmental Medicine 59:(5)287-93
- Ritchie KA, Macdonald EB, Hammersley R, O'Neil JM, McGowan DA, Dale IM et al (1995) A pilot study of the effect of low level exposure to mercury on the health of dental surgeons. Occupational & Environmental Medicine 52:(12)813-7
- Gonzalez-Ramirez D, Maiorino RM, Zuniga-Charles M, Xu Z, Hurlbut KM, Junco-Munoz P, Aposhian MM, Dart RC, Diaz Gama JH, Echeverria D (1995) Sodium 2,3-dimercaptopropane-1-sulfonate challenge test for mercury in humans : II. Urinary mercury, porphyrins and neurobehavioral changes of dental workers in Monterrey, Mexico. J Pharmacol Exp Ther. Jan;272(1):264-74

6.12. Infertility

SCENIHR states *"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 cite only one study, which examine only semen parameters in men. But others points to an opposite direction, especially in females:

Female dental assistants, who were exposed to amalgam, had a higher rate of infertility (Rowland et al., 1994).

Women with more amalgam fillings or increased mercury levels in urine (after mobilization with DMPS), have a higher incidence of infertility (Gerhard et al., 1998a, 1998b; Gerhard & Runnebaum, 1992). Heavy metal detoxification led to spontaneous pregnancies in a considerable part of the infertile patients (Gerhard et al., 1998b). Exposure to mercury may also lead to

decreased male fertility (Sheiner et al., 2003, Podzimek et al., 2003, 2005). The Norwegian study which is often cited as a proof that mercury exposure in dental clinics do not cause infertility, suffers from methodological flaws insofar, as only women were included who had already born 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.

6.13. Multiple Sclerosis (MS)

A 7, 5-fold increased level of mercury was found in the cerebrospinal fluid (CSF) of MS-patients (Ahlrot-Westerlund 1989). 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 neurological disease. The prevalence of MS has been shown to be correlated with the prevalence of caries (Craelius 1978; McGrotheret al., 1999) and the prevalence of amalgam (Baasch 1968; Ingalls 1983). Several MS-epidemics occurred after acute exposure to mercury vapor or lead (Ingalls 1986). In animal models inorganic mercury caused a loss of Schwann cells which build the myelin sheaths and stabilize the axons of neurons (Issa et al., 2003). Autoimmune pathogenesis, including antibodies against myelin basic protein (MBP), can be provoked by mercury and by other heavy metals (Stejskal & Stejskal, 1999).

MS-patients, who had their amalgam fillings removed, showed fewer depressions, and less aggressions and psychotic and compulsory behaviors when compared to a group of MS-patients with amalgam fillings (Siblerud, 1992). They also had significantly lower levels of mercury in blood (Siblerud & Kienholz, 1994). After the removal of the amalgam fillings, pathological oligoclonal bands in the CSF disappeared in MS patients (Huggins et al., 1998). Removal of dental amalgam led also to a recovery in a significant proportion of MS patients (Prochazkowa et al., 2004). A retrospective study on 20,000 military individuals revealed a significantly higher risk for MS in individuals with more amalgam-fillings (Bates et al., 2004). This risk was underestimated, because the study cohort consisted primary of healthy persons at the time of entrance to military, which was selected by the process of military scrutiny (Bates et al., 2004). Another problem in some studies regarding this topic is, that the dental status before or at the time of the onset of multiple sclerosis was not documented. Despite of this limitations Bates (2006) found a reanalysis, a 3.9- fold increased risk for multiple sclerosis in individuals with amalgam compared with individuals with no amalgams. A recent systematic review also found an increased risk for MS through dental amalgam in spite of the fact that most studies did not used proper amalgam free controls (Aminzadeh & Etminan 2007).

- Bates MN. Mercury amalgam dental fillings: an epidemiologic assessment. Int J Hyg Environ Health. 2006 Jul;209(4):309-16.
- Aminzadeh KK, Etminan M. Dental amalgam and multiple sclerosis: a systematic review and meta-analysis. J Public Health Dent. 2007;67(1):64-6.

6.14. Amyotrophic Lateral Sclerosis (ALS)

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

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

Mercury vapor is absorbed by motor neurons (Pamphlett R & Coote P, 1998) where it leads to increased oxidative stress. Mercury vapor is also suggested to promote motor neuron diseases like ALS (Pamphlett et al., 1998, Pamphlett & Waley, 1996, Stankovic, 2006).

It is proposed that mercury enhances glutamate toxicity in neurons, which is one factor in ALS (Albrecht and Matyja, 1996). Case reports show a correlation between accidental mercury exposure and ALS (Adams et al. 1983; Schwarz et al., 1996). 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 completely recovered (Rehde & Pleva, 1994). A retrospective study reported a statistically significant association between increased amalgam fillings and the risk of motoneurone diseases (Bates et al, 2004).

6.15. Frequently reported symptoms and markers of sensitivity

Among the most frequently reported symptoms due to amalgam fillings in amalgam-sensitive subjects 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 dysregulation, mood disorders and many more (Engel, 1998; Godfrey et al., 2003; Lindh et al., 2002; Siblerud 1989, 1992; Siblerud et al., 1993, 1994, Wojcik et al., 2006).

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) (Gottwald et al., 2001, Zimmer et al., 2002). But 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 (Marcusson, 1996). In addition, neutrophil granulocytes in amalgam-sensitive subjects react differently compared to those in amalgam-resistant subjects (Marcusson & Jarstrand, 1998) and different activities of the superoxide dismutase could be found (Marcusson et al., 2000).

6.13.1. High susceptibility to mercury and amalgam

SCENIHR did not mention 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

For example, it is known that mercury exposure lead to aberrant urine porphyrine profiles in dentists (Woods et al. 1993) and autistic children and that this aberrancy was reversed by treating these children with a mercury chelator (Nataf et al. 2006, Geier & Geier 2006).

2. Woods, J. Martin, MD, Naleway, CA and Echeverria, D. Urinary porphyrin profiles as a biomarker of mercury exposure: studies on dentists with occupational exposure to mercury vapor. J. Toxicol. Environ. Health 1993 40(2-3) 235-46.
3. Geier DA, Geier MR. A prospective assessment of porphyrins in autistic disorders: a potential marker for heavy metal exposure. Neurotox Res 2006; 10: 57-64.
4. Nataf R, Skorupka C, Amet L, Lam A, Springbett A, Lathe R. Porphyinuria in childhood autistic disorder: implications for environmental toxicity. Toxicol Appl Pharmacol 2006; 214: 99-108.

A genetic polymorphism of Coproporphyrinoxidase (CPOX4) (Woods et al. 2005, Heyer et al. 2006] lead to increased susceptibility to mercury and thus to a higher risk for neurobehavioral complaints [Echeverria et al. 2006].

5. Heyer NJ, Bittner AC Jr, Echeverria D, Woods JS. A cascade analysis of the interaction of mercury and coproporphyrinogen oxidase (CPOX) polymorphism on the heme biosynthetic pathway and porphyrin production. Toxicol Lett. 2006 Feb 20;161(2):159-66.
6. Echeverria D, Woods JS, Heyer NJ, Rohlman D, Farin FM, Li T, Garabedian CE. The association between a genetic polymorphism of coproporphyrinogen oxidase, dental mercury exposure and neurobehavioral response in humans. Neurotoxicol Teratol. 2006;28:39-48.
7. Woods JS, Echeverria D, Heyer NJ, Simmonds PL, Wilkerson J, Farin FM. The association between genetic polymorphisms of coproporphyrinogen oxidase and an atypical porphyrinogenic response to mercury exposure in humans. Toxicol Appl Pharmacol. 2005 Aug 7;206(2):113-20.

The critical question is the effect of mercury vapor exposure on brain porphyrins profiles since an aberrancy has been reported in brain heme that has been associated with the inability to remove beta-amyloid protein from brain cells, which may lead to Alzheimers disease.

8. Atamna, H. and Frey, W.H. A Role for heme in Alzheimer's disease: Heme binds amyolid β and has altered metabolism. PNAS 101:30 11153-58, 2004.

It should be noted that porphyrins lead to heme and heme is critical for several biochemical mechanisms:

1. First, heme is the oxygen carrying cofactor for haemoglobin
2. heme is a critical cofactor for the P450 class of enzymes that are responsible for detoxifying organic type of toxins from the body
3. 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 that cause 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 increased 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 (see section 3).

B. Brain derived neurotropic factor

Another genetic polymorphism of the Brain derived neurotropic factor (BNDF) increases also the susceptibility to low level mercury exposure [Echeverria et al. 2005, Heyer et al. 2004].

9. Echeverria D, Woods JS, Heyer NJ, Rohlman DS, Farin FM, Bittner AC Jr, Li T, Garabedian C. Chronic low-level mercury exposure, BDNF polymorphism, and associations with cognitive and motor function. Neurotoxicol Teratol 2005;27:781-796.
10. Heyer NJ, Echeverria D, Bittner AC Jr, Farin FM, Garabedian CC, Woods JS. Chronic low-level mercury exposure, BDNF polymorphism, and associations with self-reported symptoms and mood. Toxicol Sci 2004;81:354-363.

C. Apolipoprotein E diversity

It could also 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 are less likely to carry the APO-E2 (Godfrey et al., 2003, Wojcik et al., 2006). 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 caused through the difference in capacity to remove heavy metals from the Cerebrospinal fluid [Wojcek et al., 2006, Godfrey et al., 2003; Haley, 2002; Mutter et al., 2004, Pendergrass & Haley, 1996; Stewart et al., 2002). APO-E2 posses two Cysteine with metal binding Sulfhydryl-groups wheras APO-E4 did not have any Cysteine.

D. Glutathion metabolism

Glutathione (GSH) is the main natural chelator for heavy metals in the body due to his Sulfhydryl-containing Cysteine. Mainly mercury, which is bound to glutathione is capable to leaving the body via urine or biliary excretion. Thus, high levels of glutathione is crucial for mercury metabolism. It has been described that polymorphisms in genes leading to impaired GSH production lead higher retention of inorganic and organic mercury in the body

11. Custodio HM et al. Genetic influences of retention of inorganic mercury. Arch Environ Occup Health 2005; 60:17-22.
12. Custodio HM et al. Polymorphisms in glutathione-related genes affect methylmercury retention. Arch Environ Occup Health 2004; 59:588-595.

Genetic depletion of glutathione S-transferase (GST) and/or reduced glutathione (GSH) are known risk factors for Parkinson disease (PD) [37-42]. In a study of 349 patients with idiopathic PD and 611 controls, the frequency of the double deleted genotype (-/-) of GSTM1 was statistically significant in PD patients [37]. This relation was found to be the strongest among patients with an earlier onset of PD.

1. Association of GST M1 null polymorphism with Parkinson's disease in a Chilean population with a strong Amerindian genetic component." Perez-Pastene C, Graumann R, Díaz-Grez F, Miranda M, Venegas P, Godoy OT, Layson L, Villagra R, Matamala JM, Herrera L, Segura-Aguilar J. Neurosci Lett. 418(2):181-5. 2007 May 17
2. "Characterization of intracellular elevation of glutathione (GSH) with glutathione monoethyl ester and GSH in brain and neuronal cultures: relevance to Parkinson's disease." Zeevalk GD, Manzino L, Sonsalla PK, Bernard LP. Exp Neurol. 203(2):512-20. 2007 Feb
3. "Reversible inhibition of mitochondrial complex I activity following chronic dopaminergic glutathione depletion in vitro: implications for Parkinson's disease." Chinta SJ, Andersen JK. Free Radic Biol Med. 41(9):1442-8. 2006 Nov 1
4. "A functional transsulfuration pathway in the brain links to glutathione homeostasis." Vitvitsky V, Thomas M, Ghorpade A, Gendelman HE, Banerjee R. J Biol Chem. 281(47):35785-93. 2006 Nov 24
5. "Brain-derived growth factor and glial cell line-derived growth factor use distinct intracellular signaling pathways to protect PD cybrids from H2O2-induced neuronal death." Onyango IG, Tuttle JB, Bennett JP Jr. Neurobiol Dis. 20(1):141-54. 2005 Oct
6. "Glutathione depletion resulting in selective mitochondrial complex I inhibition in dopaminergic cells is via an NO-mediated pathway not involving peroxynitrite: implications for Parkinson's disease." Hsu M, Srinivas B, Kumar J, Subramanian R, Andersen J. J Neurochem. 92(5):1091-103. 2005 Mar

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), which lead to decrased mercury protecting agents, like S-Adenyl-methionine, Cysteine, Glutathione and metallothionine [For overview see Mutter et al. 2004, 2005].

13. Mutter J, Naumann J, Schneider R, Walach H, Haley B. Mercury and autism: Accelerating Evidence? Neuro Endocrinol Lett 2005; 26: 431-437.
14. Mutter J, Naumann J, Walach H., Daschner, F. Amalgam: Eine Risikobewertung unter Berücksichtigung der neuen Literatur bis 2005. Gesundheitswesen 2005, 67:204-216.

6.16. 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, also in studies with high case numbers (in most of the cases with elaborate protective measures to minimize mercury exposure) (Kidd, 2000, Lindh et al., 2002, Lygre et al. 2004, 2005,2007, Lindforss et al. 1994, Stenman & Grans 1997, Engel, 1998, Huggins et al., 1998, Prochazkova et al., 2004, Siblerud & Kienholz, 1994; Stejskal et al., 1999; Sterzl et al., 1999, 2006, Stromberg & Langworth, 1998, Valentine-Thon et al., 2006; Wojcik et al., 2006).

- Lygre GB, Gjerdet NR, Bjorkman L. A follow-up study of patients with subjective symptoms related to dental materials. Community Dent Oral Epidemiol 2005; 33(3):227-234.
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- Lygre GB, Gjerdet NR, Bjorkman L. Patients' choice of dental treatment following examination at a specialty unit for adverse reactions to dental materials. Acta Odontol Scand 2004; 62(5):258-263.

6.17. No neurodevelopmental disorders through mercury?

SCENIHR states *"There is no eveidence of a causal relationship between dental amalgam and autism"* and *"… that no link has been yet established between vaccines, thimerosal and autism"*

But 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)." (Faustmann et al. 2000)

The following studies, which indicates to mercury as a significant cause of neurodevelopmental disorders, was completely neclected by SCENIHR:

a. Cheuk and Wong (2006) in patients diagnosed with attention-deficit hyperactivity disorder and Desoto and Hitlan (2007) in patients diagnosed with autistic disorders founds significant elevations in blood mercury levels in comparison with controls. Adams et al. (2007) observed significant increases in the mercury levels of baby teeth in infants with autistic disorders in comparison with controls. 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 (Evans et al. 2008; Lopez-Hurtado & Prieto, 2008; Sajdel-Sulkowska et al. 2008).
b. The levels of mercury in urine of autistic children is increased by 3-5-fold after appropriate treatment with the mercury chelator DMSA compared to healthy children (Bradstreet et al, 2003). Autistic children also excrete higher concentrations of coproporphyrine which is exactly specific for mercury intoxication (Nataf et al. 2006; Geier & Geier 2006b; 2007a-b). This was also seen in mercury exposed dentists (Echeverria et al, 2005, 2006, Heyer et al, 2006). Detoxification of mercury with DMSA normalized the abnormal coproporphyrin levels in autistic children (Geier & Geier, 2006, Nataf et al., 2006). Therfore the increased level of coproporphyrin in autistic children could only be explained by mercury exposure.
c. Experimental as well as epidemiological studies indicate that mercury exposure could be responsible for autism or deterioration of the disease. Prenatal exposure through maternal amalgam (Holmes et al. 2003), maternal thimerosal (Holmes et al. 2003, Geier

et al. 2008) and postnatal sources (mercury from vaccines of the child) (Geier & Geier 2003, 2004, 2005) together with a geneticly sensitivity may trigger autism.

d. In animal experiments vaccination with thimerosal led to autistic symptoms (Hornig et al, 2004).
e. Epidemiological studies confirms that there was a significant association between low-dose mercury exposure and neurodevelopmental disorders (Amin-Zaki et al. 1981; Counter et al. 2002; Debes et al. 2006; Geier & Geier 2006a; Jedrychowski et al. 2006; Palmer et al. 2006; Rury, 2006; Windham et al. 2006).
f. Autistic children show decreased levels of the natural mercury chelator glutathione (James et al., 2004) and mercury is able to cause this phenomen (James et al, 2005).
g. In some therapy studies chelation therapy led to the improvement of symptoms in up to 60-80% of the cases. The Autism Research Institute therefore lists chelation as the most effective therapeutic approach among 88 therapies including 53 medications. (Autism Research Institute, 2005).
h. Some studies, which found no associations between mercury exposure and autism have severe methodical flaws (Mutter et al. 2005).

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 children are more susceptible towards mercury toxicity. Mothers consuming diet containing mercury pass the toxicant to fetus 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."*

It was shown that administration of prenatal Thimerosal to animals at less than 1 part-per-million (ppm) can induce significant fetal lethality and teratogenicity (Digar et al. 1987; Gasset et al. 1975; Itoi et al. 1972). Heinonen et al. (1977) examined 2,277 children with birth defects among 50,282 mother-child pairs and determined that Thimerosal exposure during the first 4 months of pregnancy was associated with a significantly increased risk.

The concentrations of inorganic mercury remained the same (in the thalamus) or doubled (in the pituitary) six months after mercury dosing had ended (Vahter et al. 1994; 1995). Studies on the brains of monkeys indicated that the persistence of inorganic mercury in the brain was associated with a significant increase in the number of microglia in the brain, whereas the number of astrocytes declined (Charleston et al., 1994; 1995; 1996). These observations are important because "an active neuroinflammatory process" including a marked activation of microglia was shown in pathological examinations of the brains of some with neurodevelopmental disorders (Vargas et al. 2005).

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7. Severe Methodical flaws in studies cited by SCENIHR as an proof of the safety of dental amalgam

For studying 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 which was never exposed to dental amalgam. Even when comparing samples with and without dental fillings, the sample without the dental fillings probably was exposed to dental amalgam earlier in life.

The studies cited frequently as a proof of the putative harmlessness of amalgam, do not use "proper" non-amalgam control groups. We would like to describe a prominent example:

The Swedish twin study (Björkmann et al., 1996) actually only compared 57 twin-pairs in a co-twin analysis, and not 587. 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 dental 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 dental materials other than amalgam had probably had dental amalgam previously. As Hg accumulates in organs, this “amalgam free group” might have been equally, or even have been more exposed to mercury than the “amalgam group” with currently existing amalgam fillings.

SCENIHR also cite Zimmer et al. (2002) as an proof of the safety of amalgam. But this studie 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 fillings) 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 Hg levels in both amalgam groups.
Zimmer et al. (2002: p. 210) conclude: “Thus, mercury released from amalgam fillings was not a likely cause of complaints reported by the amalgam sensitive subjects“.
It is not clear why these authors come to such a conclusion.
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.

7.1. “Childrens amalgam trails”

SCENIHR based their statement of the safety of dental amalgam mainly on two childrens amalgam trails. These studies was performed by dentists (see section 9) and show severe methodical flaws:

In two randomised trails on children (Children amalgam trails) it was evaluated whether mercury-containing dental amalgam had adverse neuropsychological or renal effects. [Bellinger et al. 2006, DeRouen et al. 2006]. Healthy children were randomised to either amalgam or composite surface restoration. Two children in the amalgam group die (one possible per suicide) and were excluded from the studie.

Power calculation [binomial - adverse event vs. 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” [Bellinger et al 2006] and "dental amalgam ---emits small amounts of mercury vapor" [DeRouen et al. 2006].

The conclusion is a classic type II (beta-) 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 profils and markers of oxidative stress [Chauhan & Chauhan 2006 in press], which are elevated in individuals with dental amalgam [Pizichini et al. 2002,2003] were not measured. Also, genetic polymorphism, which increase the suceptibility to mercury, like BDNF-Polymorphism [Echeverria et al 2005, Heyer et al. 2005] and Glutathion-S-Transferase gene polymorphism [Buyske et al. 2006] were not measured. Also the real exposure level of mercury (mercury vapor emitted in the oral cavitity) was not determined, which question the ethics of such a study. Research done in the laboratory of Prof. Boyd Haley have demonstrated that the emission of mercury vapor were much higher than what has been “estimated” by dentists. Further, Chew et al. [1991] showed that that 43.5 microgram/cm^2/day Hg was released from a “non-mercury releasing amalgam” and this remained constant over the study period of 2 years.

Mean mercury urine levels were significantly higher in the amalgam groups [Bellinger et al 2006, De Rouen et al 2006], despite on years 3 to 7 the level of mercury in the urine of the

amalgam bearer continuously drop until they near the levels of the amalgam free children [DeRouen et al 2006]. But restorative treatment was used in years 6 and, 7 which should increase, or at least maintain the urine mercury levels. This needed explaining. In the Chew study above [Chew 1991], the amount of mercury released was steady for 2 years (the length of the study). Amalgams do not stop releasing mercury vapor within 7 years. So, what caused the drop after year 2? Urine mercury levels are a measure of the amount of mercury being excreted by 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 it own excretion. It has been published and verified that over 90% of mercury excreted by humans leaves through the bilary transport system of the liver and is excreted in the feces, not the urine [Lorscheider et al. 1995].

The conclusion of Bellinger et al. (2006) 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 [Mutter et al. 2004 AD].

One of the inclusion criteria for the two studies was “no interfering health conditions” including neurodevolopmental disorders. The CDC reports that 1 in 6 American children have a neurodevelopmental disorder. However, these papers conclude that amalgams should remain a viable clinical option in dental restorative treatment [DeRouen et al 2006] and they did not exclude use on children with neurodevelopmental disorders, exactly the type of child they excluded from their studies. As mercury exposure during pregnancy may be the prime cause of neurodevelopmental disorders [Holmes et al. 2003, Mutter et al.

2005 autism, Jedrychowski et al. 2005], this conclusions from the children amalgam trails seem to be dangerous for the public.

- Chew et al. Clinical Preventive Dentistry 13(3) 5-7, 1991. In a study of long term dissolution of mercury from an non-mercury releasing amalgam it was determined that 43.5 microgram/cm2/day Hg was released and this remained constant for 2 years.

8. Amalgam and mercury in the environment

There was an alarmingly rising increase of mercury in our environment during the last decades. The UNEP (UNEP, 2002) reports on a 3-5 fold increase over the last 25 years.

In the Europaen Union (EU) the usage of amalgam amounts to 70 tons yearly. Dentist are the 2nd most user in the EU (Hylander & Godsite 2006, Hylander et al., 2006).

Recent calculations done by Hylander (2005a, 2006) show that there are 40 tons of mercury in teeth with dental amlagam 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 the citizens of the EU (Hylander et al, 2005b), and for USA the respective figures are about 1000 tons. In the US, dental amalgam is the 3rd significant source of environmental mercury (Bender, 2005). In contrast to the EU, removed amalgam is not separated from the wastewater of dental clinics in the US. But even in the EU, where such separators are in use, parts of the dental amalgam leaks into the environment (Hylander, 2005a).

As this mercury from dental amalgam (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) will enter into the environment. Hylander and Godsite (2006) showed that amalgam is the most costly material for dental fillings, if environmental costs are included into the economic calculation.

9. The role of dentistry in SCENIHR and in defending amalgam

SCENIHR consists of one engineer (chairman), four dentists, a toxicologist and two veterinarians.

The chairman has strong contacts to the industry. No experts for medicine or environmental medicine were included. One must wonder why exactly dentists were the strongest party in SCENIHR.

Due to their education and their limited clinical experience, they are not able to judge about possible adverse side effects from dental amalgam, like multiple sclerosis, autism, autoimmunity, Alzheimer´s disease, psychiatric diseases etc. Usage of dental amalgam is actually increasing worldwide (increasing caries

epidemic in undeveloped countries, where most of the world populations live). Today, Dental organisations are the only trade groups of health professionals, who endorse the use of a product that is primarily mercury. Every amalgam patent that has been awarded for decades has been produced according to Dental organisations specifications

This may be indeed a critical point, because organized dentistry, which proclamates the use of dental amalgam for decades, are responsible for the world-wide usage of thousands tons of mercury in dental amalgam and for their possible side effects, and posseses patents for dental amalgam mixtures.Therefore, the strategies of organisized dentistry to influence science and politics in the last decades, seem to be analogues to other well known topics, were conflicts of interests exist and effective measures for influencing the science and politics was used.

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In 1859, an enterprising group of dentists formed the up to date, the world most powerfull American Dental Association (ADA), which dictate until now dental organisations worldwide— not to advance the science of dentistry, but for the specific purpose of promoting the commercial use of "silver amalgam-mercury use in dentistry."

Since then, the ADA has marched with mercury producers and amalgam manufacturers, marketing the fillings as "silver" to an unsuspecting public. For 150 years, the existence of organized dentistry has depended on suppressing any suggestion that implanting mercury in the mouth might create health problems. Despite mounting scientific evidence to the contrary, it has continued to insist that mercury fillings are safe, based on the length of use – the same argument that enabled the tobacco industry to keep Federal regulators at bay for decades.

In 1988, in a move that protected the power of its existing patents on amalgam, the ADA promulgated within its "Code of Ethics" the infamous gag rule, forbidding dentists from volunteering information to patients about the toxicity of mercury. Today, all Federal government-funded research on the health risks of amalgam is run by dentists or other representatives of

organized dentistry. The Dental Devices Branch at US-FDA routinely collaborates with the National Institute of Dental and Craniofacial Research at NIH. Some Members of Congress have voiced strong criticism, pointing out that research and regulation of amalgam's toxicity is controlled by dentists – professionals whose training does not qualify them to determine the impact of mercury on the body and who have an inherent conflict of interest due to the ADA's endorsement of amalgam. The pro-amalgam dentists at NIH run the research, and the pro-amalgam dentists at FDA make the rules.It should come as no surprise that all government literature reviews on amalgam's toxicity have been managed by groups composed mainly of dentists. For example, a multimillion dollar grant to study amalgam was given to a dentist sitting on the ADA's Council of Scientific Affairs; that person chose a defenseless group – institutionalized Portuguese orphans – on which to experiment with mercury, without disclosures of health risks. The Secretary's Office of Human Research Protections, the watchdog charged with stopping unethical medical experimentation, found that this experiment denied the children and their guardians the basic disclosures of risks required in all research on human beings – making it both unethical and immoral.

10. Conclusion

Amalgam cannot be called a safe dental filling material as it was proposed by SCENIHR, neither with regard to medicine and occupational medicine, nor to ecology.

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