Consultation Response to

SCENIHR preliminary report on "The safety of dental amalgam and alternative dental restoration materials for patients and users"

Comment by
Prof. Vera Stejskal
Associated Professor of Immunology
University of Stockholm, Sweden and
Department of Immunology and Microbiology
1st Medical Faculty, Charles University, Prague, Czech Republic

Co-signed by
Prof. Marie Grosman
Prof. Agrégée de Biologie,
Association Non au mercure dentaire, FRANCE

Prof. André Picot
Directeur honoraire de Recherche CNRS
Président de l`Assosication de Toxicologie - Chimie ATC, Paris, FRANCE

Dr Katalin Pasche-Vadnai, DDS, Forum Odontologicum of Lausanne, Switzerland, Université Pierre et Marie Curie, Paris VI, France

Submitted on 22 February 2008, Case number 446729220261605308
Please observe that an incomplete comment was submitted on the 21 February and we would appreciate if that comments is disregarded.

General observations: The scientific and clinical evidence.

Disagree

Metals affect the immune system in several ways (1). In the oral cavity, a high concentration of metal ions may be toxic and act as a local immunosuppressant. This may explain why the oral mucosa contains only few immunocompetent cells and why mucosal changes adjacent to amalgam or other metal fillings are infrequent (2).

Certain metals stimulate the immune system non-specifically as shown by increased levels of serum immunoglobulins and autoantibodies in workers professionally exposed to Hg (3,4). In the general population, anti-oxidant capacity of serum is inversely related to the number of amalgam fillings, as described by Pizzichini and coworkers (5). Interestingly, glutathione depletion inhibits TH1-associated cytokine production and/or favors TH2-associated responses (6). This might explain the TH1 to TH2 switch in animals treated with low concentrations of inorganic Hg (7, 8). In contrast, in some hereditarily predisposed individuals, metals may act as specific allergens (9-13).

The majority of metals including mercury belong to the group of transition metals in the periodic table. A general characteristic of these elements is the strong binding capacity to various groups of enzymes and cells in the body. Transition metals form strong complexes with both organic and inorganic ligands (14). Metals bind to sulfhydryl and other groups, thus altering the molecular structure of autologous proteins. T-lymphocytes mistakenly recognize metal-modified cells as foreign and start the autoimmune process (15). Largely of unknown etiology, autoimmune disorders affect approximately 3% of European and North American population (16).

Since clinical reactions to metals, such as local skin reactions or systemic reactions are not experienced by all exposed individuals, standard case-control studies with a small number of participants, who are not matched for the susceptible genotype, are of limited value (17). Instead, a suitable cohort should consist of patients suffering from the same symptoms but selected on the basis of susceptible phenotype (18-20). To evaluate the risk for susceptible populations such as children and adults with hypersensitive immune system (allergy and autoimmunity), one needs to study the effect of amalgam replacement in those groups. More research is also necessary to identify the biomarkers of susceptibility at the immunological and biochemical level.

The reason for the amalgam ban in some countries such as Norway and the decision for the same action in Denmark and Sweden is not that amalgam is non tooth coloured as postulated by the authors of Scenihr, but because of the toxic and allergenic effects of mercury and other parts of amalgam on the environment and health. According to a WHO policy paper from 2005, recent studies suggest that mercury may have no threshold level below which some adverse effects do not occur. This is also the reason why US Food and Drug administration recently started to phase out mercury.

References

1. Campbell A et al. mechanisms by which metals promote events connected to neurodegenerative diseases. Brain Res 2001;55:125-132
2. Magnusson B, Bergman M, Bergman B, Sörenmark R. Nickel allergy and nickel-containing dental alloys. Scand J Dent Res. 1982 Apr; 90:163– 5.
3. Bencko V, Wagner V, Wagnerova M, Ondrejcak V. Immunological profiles in workers occupationally exposed to inorganic mercury. J Hyg Epidemiol Microbiol Immunol. 1990;34:9-15.
4. El-Fawal HA et al. Neuroimmunotoxicology: humoral assessment of neurotoxicity and autoimmune mechanisms. Environ health Persp 1999;107 (Suppl 5):767-75
5. Pizzichini M, Fonzi M, Giannieri F, Mencarelli M, Gasparoni A, Rocchi G, et al. Influence of amalgam fillings on Hg levels and total antioxidant activity in plasma of healthy donors. Sci Total Environ. 2003;301:43–50.
6. Peterson JD, Herzenberg L, Vasques K, Waltenbauch C. Glutathione levels in antigen-presenting cells modulate Th1 versus Th2 response patterns. Proc Natl Acad Sci USA. 1998;95:301-6.
7. Goldman M, Druet P, Gleichmann E. TH2 cells in systemic autoimmunity: insights from allogeneic diseases and chemically-induced autoimmunity. Immunol Today. 1991;12:223
8. Prigent P, Saoudi A, Pannetier C, Graber P, Bonnefoy JY, Druet P, et al. Mercuric chloride, a chemical responsible for T helper cell (Th)2-mediated autoimmunity in brown Norway rats, directly triggers T cells to produce interleukin-4. Clin Invest 1995;96:1484-9.
9. Björkner B, Bruze M, Möller H. High frequency of contact allergy to gold sodium thiosulfate. An indication of gold allergy? Contact Dermatitis. 1994;30:144-51.
10. Everness KM, Gawkrodger DJ, Botham PA, Hunter JAA. The discrimination between nickel-sensitive and non nickel-sensitive subjects by an in vitro lymphocyte transformation test. Br J Dermatol. 1990;122:293–8.
11. Kazantis G. The role of hypersensitivity and the immune response in influencing susceptibility to metal toxicity. Environ Health Perspect. 1978;25:111–8.
12. Marcusson JA. Contact allergies to nickel sulfate, gold thiosulfate and palladium chloride in patients claiming side-effects from dental alloy components. Contact Dermatitis. 1996;34:320–3.

13. Prochazkova J, Bartova J, Ivaskova E, Kupkova L, Sterzl I, Stejskal VD. HLA-association in patients with intolerance to mercury and other metals in dental materials. Dis Markers. 2000;16:135-8.
14.Vallee BL, Ulmer DD. Biochemical effects of mercury, cadmium, and lead. Annu Rev Biochem. 1972;41:91-128.
15. Griem P, Gleichman E. Metal ion induced autoimmunity. Curr Opin Immunol. 1995;7:831–8.
16. Smith DA, Germolec DR. Introduction to immunology and autoimmunity. Environ Health Persp 1999;107(Suppl 5):661-5
17. Weiss NS, Liff JM. Accounting for the multicausal nature of disease in the design and analysis of epidemiologic studies. Am J Epidemiol. 1983;117:14-8.
18. Prochazkova J, Sterzl I, Kucerova H, Bartova J, Stejskal V. The beneficial effect of amalgam replacement on health in patients with autoimmunity. Neuro Endocrinol Lett. 2004;25:211–8.
19. Stejskal VD, Danersund A, Lindvall A, Hudecek R, Nordman V, Yaqob A et al. Metal-specific lymphocytes: biomarkers of sensitivity in man. Neuro Endocrinol Lett. 1999;20:289–298.
20. 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):25–30.

Question 1: Is there scientific evidence that supports a link between amalgam and allergic reactions, neurological disorders or other health disorders?
Do you agree with the response given?

Disagree.

1. Unsatisfactory conclusion from the scientific point of view
2. Relevant information missing from the analysis of the situation

In addition to toxic effects, mercury induces local and systemic allergic and autoimmune reactions. Many metals, including mercury, function as haptens and induce cellular type hypersensitivity. This type of allergy is mediated by white blood cells (T-cells).
Inorganic mercury, thimerosal and nickel are the most frequent allergens in children as shown by skin patch test. In 1094 children with skin disease, 10% reacted to thimerosal (ethyl mercury salt) and 6 % to mercury (1). In 96 Spanish children, skin test reactivity to thimerosal was 21% and to mercury 19%. Body burden of mercury is associated with atopic eczema and total IgE antibodies in German children (3).
Below is a selection from the many articles indicating a causal relationship between mercury-induced sensitization and autoimmune diseases (4). The majority of patients improved following the removal of amalgam and other sensitizing dental restorations such as gold. The mechanisms behind of metal-induced effects in multiple sclerosis, rheumatoid arthritis and amyotrophic lateral sclerosis has been published by Stejskal and Stejskal (5).
Pelcova (6) reported skin exposure to mercury-containing creams which induced neuropsychological problems and glomerulonephritis in patients with juvenile diabetes. After chelation of mercury, the symptoms disappeared confirming a causal relationship.
Prochazkova (7) studied the impact of amalgam replacement on the health of patients with autoimmune diseases (multiple sclerosis, rheumatoid arthritis, psoriasis) who showed increased mercury-specific proliferation *in vitro*. Patients with only amalgam in the oral

cavity were included in the study. Amalgam was replaced by composites and/or ceramics. Twenty out of 35 patients studied (71%) showed health improvement half a year later. Thus, amalgam replacement might be beneficial in autoimmune patients with hypersensitivity to mercury.
Cellular hypersensitivity and autoantibodies to thyroid antigens were studied in 39 patients with autoimmune thyroiditis (8). Patients were divided into two groups, those with positive mercury-specific response *in vitro* and those with no stimulation with mercury *in vitro*. Amalgam fillings were replaced in 15 patients with hypersensitivity to mercury and left in place in the remaining 12 patients (control group). Anti-thyroid peroxidase and anti-thyreoglobulin antibodies were also measured. Only patients with mercury hypersensitivity who replaced their amalgam showed a significant decrease of autoantibodies compared to levels prior treatment. Thus, removal of amalgam in patients with mercury hypersensitivity might improve treatment of autoimmune thyroiditis. These results confirm the previous data (9-11). To our knowledge this is the first time when a specific biomarker of mercury susceptibility was used to select patients for amalgam replacement. Any risk factor may be diluted if evaluated in a heterogeneous population. As suggested by Weiss (12), studies of phenotypic markers may be suitable for elucidation of causal pathways, and identification of specific risk factors. The limited power of epidemiological studies to detect minor susceptible populations such as those susceptible to mercury has been discussed by Wallach (13) and Barregård (14).
Patch test and LTT-MELISA® were used for the diagnosis of metal allergy in 15 patients who suffered from clinical metal sensitivity and allergic and autoimmune diseases (15). The concordance of the two tests was good but the *in vitro* test was more sensitive. The removal of allergy-inducing dental restorations (amalgam and gold) resulted in long-term health improvement (follow up to 15 years). The improvement related to the decrease of metal-specific lymphocyte responses *in vitro*. Thus, in susceptible patients, metal ions might activate T-cells and start the inflammatory cascade. Replacement of inflammation-inducing materials results in decreased systemic inflammation and improved health.

References

1. Seidenari S, Giusti F, Pepe P, Mantovani L. Contact sensitization in 1094 children undergoing patch testing over a 7-year period. Pediatr Dermatol 2005;22:1-5
2. Vozmediano JMF, Hita A. Allergic contact dermatitis in children. J European Academy Dermatol venerol 2005;19:42-46
3. Weldinger S, Krämer U, Dunemann L, Möhrenschklager M, Ring J et al. J Allergy Clin Immunol 2004;114:457-459
4. Cooper G, Germolec D, Heindel, Selgrade.Linking envrironmentgal agents and autoimmune diseases. Environ health Persp 1999;107 (Suppl 5): 659-660.
5. Stejskal J, Stejskal V. The role of metals in autoimmunity and the link to neuroendocrinology. Neuro Endocrinol Lett 1999;20:351-364
6. Pelcova D, Lukas E, Urban P, Preiss J, Rysava R et al. Mercury intoxication from skin ointment containing mercuric ammonium chloride. Int Arch Occup Environ Health 2002;75(Suppl): S54-S59
7. Prochazkova J, Sterzl I, Kucerova H, Bartova J, Stejskal V. The beneficial effect of amalgam replacement on health in patients with autoimmunity. Neuro Endocrinol Lett. 2004;25:211-8.
8. Sterzl I, Prochazkova J, Hrda P, Matucha P, Bartova J et al. Removal of dental amalgam decreases anti-TPO and anti-Tg autoantibodies in patients with autoimmune thyroiditis. Neuro Endocrinol Lett 2006;27:25-30

9. Sterzl I, Prochazkova J, Hrda P, Bartova J, Matucha P, Stejskal VDM. Mercury and nickel allergy: risk factors in fatigue and autoimmunity. Neuro Endocrinol Lett. 1999;20:221-228.
10. Lindkvist B, Mörnstad H. Effects of removing amalgam fillings from patients with diseases affecting the immune system. Med Sci Res 1996;34:355-356
11. Anneroth G, Ericson T, Johansson I,Mörnstad H, Ryberg M et al. Comprehensive medical examination of a group of patients with alleged adverse effects from dental amalgam. Acta Odont Scand 1992;50:101-111
12. Weiss NS, Liff JM. Accounting for the multicausal nature in disease in the design and analysis of epidemiological studies. Am Epidemiol 1983;117:14-18.
13. Wallach H, Nauman J, Mutter J, Daschner F. No difference between self-reportedly amalgam sensitivitie and non-sensitivites? Listen carefully to the data. Int J Hyg Environ Health 2003; 206:139-141
14. Barregård L, Eneström S, Ljunghusen O, Wieslander J, Hultman P. A study of autoantibodies and circulating immune complexes in mercury-exposed chloralkali workers. Int Arch Occup Environ Health 1997; 70:101-6
15. Stejskal V, Hudecek R, Stejskal J Sterzl I. Diagnosis and treatment of metal-induced side-effects Neuroendo Lett 2006;27(Suppl 1):7-16

More references on the subject not mentioned in the text due to limited space:

Balasz T. Immunogenetically controlled autoimmune reactions induced by mercury, gold and D-penicillamine in laboratory animals: a review from the vantage point of premarketing safety studies. Toxicol and Industrial health 1987;3:331-336
Bangsi D et al. Dental amalgam and multiple sclerosis: a case-control study in Montreal, Canada. Int J Epidemiol 1998;27:667-71
Bigazzi PE Autoimmunity and heavy metals. Lupus 1994;3:449-453
Bigazzi PE. Metals and kidney autoimmunity. Environ Health Persp 1999;107 (Suppl5):753-765
Campbell A et al. Mechanisms by which metals promote events connected to neurodegenerative diseases. Brain Res 2001;55:125-132
Cooper GS et al. Occupational risk factors for the development of systemic lupus erythematosus. J Rheumatol 2004;31:1928-33
Charpentier B et al. Fonctions lymphocytaires T au cours d'une glomerulonephrite extramembraneuse induite par une intoxication chronique au mercure. Nephrologie 1981;2:153-157
Druet P. Metal-induced autoimmunity. Human and Expt Toxicol 1995;14:120-121
El-Fawal HA et al. Neuroimmunotoxicology: humoral assessment of neurotoxicity and autoimmune mechanisms. Environ Health Persp 1999;107:767-75
El Safty IA et al. Nephrotic effects of mercury exposure and smoking among Egyptian workers in fluorescent lamp factory. Arch Med Res 2003;34:50-55
Hock C et al. Increased blood mercury levels in patients with Alzheimer's disease. J of Neural Trans 1998;105:59-68
KazantisG. Mercury exposure and early effects: an overview. Med Lav 2002; 93:139-46
Kosuda LL et al. Effects of $HgCl_2$ on the expression of autoimmune responses and disease in diabetes-prone (DP) BB rats. Autoimmunity 1997;26:173-187
Lindh U et al. Removal of dental amalgam and other metal alloys supported by antioxidant therapy alleviated symptoms and improves quality of life in patients with amalgam-associated ill health. Neuroendo Lett 2002;23:459-482
Mach E et al. Umweltgifte und multiple Sklerose. Der Allgemeinartz 1996;20:2216-2219
Queiroz R et al: Immunoglobulin levels in workers exposed to inorganic mercury. Pharmacol Toxicol 1994;74:72-75

Shenker BJ et al. Immunotoxic effects of mercuric compounds on human lymphocytes and monocytes III. Alterations in B-cell function and viability. Immunopharmacol Immunotoxicol 1993;15:87-112
Silbergeld EK et al. Mercury and autoimmunity: implications for eccupational and environmental health. Toxicol Appl Pharmacol 2005;207:282-92
Siblerud RL. A comparison of mental health of multiple sclerosis patients with silver/mercury fillings and those with fillings removed. Psychol Rep 1992;70:1139-51
Silva IA et al. Mercury exposure malaria and serum antinuclear/antinucleolar antibodies in Amazon populations in Brazil: a cross-sectional study. Environ Health 2004;3:11
Tubbs RR et al. Membranous glomerulonephritis associated with industrial mercury exposure. Study of pathogenic mechanisms. Am J Clin pathol 1982;77:409-13
Tchounwou PB, et al. Environmental exposure to mercury and its toxicopathologic implications for public health. Environ Toxicol 2003;18:149-75
Valentin-Thon E et al. Validity of MELISA® for metal sensitivity testing. Neuroendo Lett 2003; 24:57-64
Via Ch et al. Low-dose exposure to inorganic mercury accelerated disease and mortality in acquired murine lupus. Environ Health Perspectives 2003;111:1273-1277

Question 2: In view of the above, is the use of dental amalgam safe for patients and users, i.e. dental health professionals? Are certain populations particularly at risk, e.g. pregnant women or children?

Disagree

1. Unsatisfactory conclusion from the scientific point of view
2. Relevant information missing from the analysis of the situation

Heavy metals including mercury are biologically active substances and may in susceptible subjects affect many organs and cause health disturbances. Heavy metals are known to induce so called cellular type hypersensitivity (delayed type or Type 4 reaction) but humoral antibodies might be affected as well. Metal-induced reactions are influenced by genetic background in experimental animals and associated with certain HLA antigens in man (1). Patients with allergic and autoimmune diseases such as multiple sclerosis, collagenous diseases, and psoriasis might be particularly vulnerable (2).
Mercury has been documented to be a reproductive and developmental toxin in humans. The effects include male infertility (3,4), lowered sperm counts, defective sperm cells, menstrual disturbances, infertility, spontaneous abortions and birth effects. Mercury causes learning disabilities and impairment and reduction in IQ. Regarding children, amalgam-treated children exhibited significantly higher microalbuminuria compared to children without amalgam (5).
The assumption that mercury released from amalgam only rarely induces allergy is wrong and is based on the observations of oral mucosal problems which are less frequent due to lower sensitivity of oral mucosa. In the oral cavity, a high concentration of metal ions may be toxic to immuno-competent cells and act as a local immunosuppressant. Oral mucosa contains only a low number of dendritic cells, and mucosal changes adjacent to dental metal fillings are infrequent (6). Nielsen and Klaschka (7) have shown that a 5-12 times higher concentration of the allergen has to be applied on the oral mucosa than on the skin to elicit microscopic reactions.
The authors of the SCENIHR report claim that it is not necessary to remove clinically satisfactory amalgam restorations on the grounds of patient safety, with the exception of those

patients which have a positive patch test and local alterations of the oral mucosa or **systemic allergic reactions**. We agree with that. As mentioned in answer to Question 1, vulnerable groups includes children and adults with diseases of immune origin such as contact dermatitis and autoimmunity. By definition, in those patients, the immune system reacts aberrantly and might recognize mercury as a hapten and trigger allergic and autoimmune disease (8, 9). Therefore, amalgam has to be removed.

References

1. Prochazkova J, Bartova J, Ivaskova E, Kupka L, Sterzl I, HLA-association in patients with intolerance to mercury and other meals. Disease Markers 2001;16:135-138
2. Bartova J, Prochazkova J, Kratka Z, Benetkova K, Venclikova Z et al. Dental amalgam as a risk factor in autoimmune diseases. Neuroendo Lett 2003; 24:65-67
3. Choy CM Lam CV, Cheung LT, Briton-Jones CM et al. Infertility, blood mercury concentrations and dietary seafood consumption. BJOG 2002; 109:1121-1125
4. Hanf V, Forstman A, Costea JF, Schierferstein G, Fisher I et al. Mercury in urine and ejaculate in husbands of barren couples, Toxicol lett 1996;1-3:227-231
5 Barregard L, Trachtenberg F, Mc Kinlay S. Effects of Dental Amalgam in Children: The New England Children's Amalgam Trial Environ Health Perspect 2008;116:394–399
6. Magnusson B, Bergman M, Bergman B, Sörenmark R. Nickel allergy and nickel-containing dental alloys. Scand J Dent Res. 1982;90:163-65
7. Nielsen C, Klaschka F. Test studies on mouth mucosa in allergic eczema. Dtsh Zahn Mund Kieferheilkd Zentralbl Gesamte 1971;57:201-18
8. Stejskal V, Hudecek R, Stejskal J Sterzl I. Diagnosis and treatment of metal-induced side-effects. Neuroendo Lett 2006;27(Suppl 1):7-16
9. Stejskal J, Stejskal V. The role of metals in autoimmunity and the link to neuroendocrinology. Neuro Endocrinol Lett 1999;20:351-364

Question 3: Is there scientific evidence that supports a link between alternative materials and allergic reactions, neurological disorders or other health disorders?
Do you agree with the response given?

Mostly agree, regarding non-metallic materials.

Question 4: In view of the above, is the use of alternative dental restoration treatment safe for patients and dental health professionals? Are certain populations particularly at risk, e.g. pregnant women or children?
Do you agree with the response given?

Uncertain.

The use of non metallic restorations is safe for patients (including pregnant woman and children) and dental health professionals. However, the use of alternative metallic restorations such as gold, nickel and titanium alloys, may carry risks for children and adults which allergic and autoimmune diseases.
The authors of this study don't distinguish between different types of alternative dental restorations. Composites are completely different than the ceramic restorations which are electro-chemically and biologically stable. The authors seem to ignore the existence of specific national institutes of biomaterial testing, which guarantee the quality and inertness of new materials. The ISO norms are sometimes completed by national norms. The ISO norms require tests for cytotoxicity, mutagenicity in vivo and in vitro, and sometimes also clinical

tests on animals and humans before the commercialisation of a new material. In that way, these alternative materials are biologically safer than amalgam, which was never tested this way.
Regarding alternative metallic restorations for example gold alloys, nickel alloys and titanium alloys they contain transitional metals which may in susceptible subject trigger allergy and autoimmunity (1-12). Gold is now the second most common sensitizer in man after nickel. Palladium, as well as titanium, is a transition metal with the capacity to bind to proteins and cause sensitization (13-15). Regarding non metallic materials such as composites and ceramics, we agree with the response given by authors.

References:
1. Stejskal V, Hudecek R, Stejskal J, Sterzl I. Diagnosis and treatment of metal-induced side-effects. Neuroendo Lett 2006;27(Suppl 1):7-16
2. Magnusson B, Bergman M, Bergman B, Södermark R. Nickel allergy and nickel-containing dental alloys. Scand J Dent Res 1992;90:163-167
3. Samitz MH, Katz SA. Nickel dermatitis hazards from prostheses. British J Dermatol 1975;92:287-290
4. Bruce GJ. Nickel hypersensitivity-related periodontis. Compendium 1995;16:178-184
5. Marcusson JA Lindh G, Evengård B. Chronic fatigue syndrome and nickel allergy. Cont Derm 1999;40:269-272
6. Björkner B, Bruze M, Möller H. High frequency of contact allergy to gold thiosulfate. An indication of gold allergy? Contact Derm 1994;30:144-151
7. Marcusson JA. Contact allergies to nickel sulfate, gold sodium thiosulfate and palladium chloride in patients claiming side-effects from dental alloy components. Contact Derm 1996;34:320-323
8. Schlumpf, Meyer J, Ulrich, Friede RL. Neurologic complications induced by gold treatment. Arthritis Rheumat 1983;26:825-831
9. Agrup G. Sensitization induced by patch testing. Br J Derm 1968;80:631-634
10. Räsänen L, Tuomi ML. Diagnostic value of the lymphocyte proliferation test in nickel contact allergy and provocation in occupational coin dermatitis. Contact Derm 1992;27:250-2
11.Muris J, Feilzer A. Microanalysis of metals in dental restorations as part of diagnostic approach in metal allergies. Neuroendo Lett: 2006;27(Suppl1):49-52
12. Venclikova Z, Benada O, Bartova J, Joska L, Mrklas L et al. In vivo effects of dental casting alloys. Neurendo Lett; 2006;27(Suppl1):61-68
13.Aberer W, Holub H, Strohal L, Slavicek L. Palladium in dental alloys: the dermatologist's responsibility to warn? Contact Derm 1998;28:163-168
14.Valentine-Thon, Muller K, Guzzi G, Kreisel S, Ohnsorge P et al. LTT-MELISA® is clinically relevant for detecting and monitoring metal sensitivity. Neuroendo Lett; 2006;27(Suppl1):17-24
15. Muller K, Valentine-Thon E. Hypersensitivity to titanium: clinical and laboratory evidence. Neuroend Lett; 2006;27(Suppl1):31-35

Question 5: In view of the specific properties of dental amalgam and alternatives when used for dental restorative treatment, is dental health equally ensured by dental amalgam and alternatives?
Do you agree with the response given?

Disagree

1 Unsatisfactory conclusion from the scientific point of view

2. Relevant information missing from the analysis of the situation

The alternative materials are less invasive. The problem of secondary caries is mostly due to bad treatment and the wrong use of materials.
For big posterior restorations (essentially after removal of old amalgam) ceramic is the only possibility to guarantee a sufficient mechanical resistance.
Composites can be used for smaller (1 or 2 side) restorations. It is essential to use kofferdamm. The longevity of these restorations depends mainly on the skill of the dentist.
The authors of SCENIHR report claim that they see no advantages to carrying out further research on any aspects of the safety of dental amalgam restorations.
We disagree. More research is necessary, especially prospective longitudinal studies in susceptible subjects. Since it is not ethical to insert amalgams to children with already compromised immune systems (those with allergies and autoimmunity), longitudinal studies are necessary when careful replacement of amalgam with ceramic and composite materials will be performed and the health outcome monitored. Such treatment can be done in addition to standard therapeutic treatment for the disease in question and compared to the treatment without the replacement of amalgam (and other sensitizing metals in question).
More research is also necessary to identify the biomarkers of susceptibility at the immunological and biochemical level. For example, biomarkers of harmful effects of metals and other environmental pollutants include detoxification enzymes, such as apolipoprotein E, where the substitution of cystein with arginin – an amino acid lacking SH-groups – predisposes for increased risk for Alzheimer's disease (1) and increases vulnerability to chronic mercury toxicity (2). Other detoxification enzymes of importance are glutathione S transferase T1 (GSTT1) and glutathione S transferase M1 (GSTM1). As shown by Westphal's group (3), homozygous deletion of GSTT1 and combined deletion of GSTT1-/GSTM1- was markedly more frequent in patients sensitized by thimerosal, than in healthy controls.
Regarding metal susceptibility, measurement of beryllium specific memory cells in the blood of exposed workers is currently the golden standard for detection of beryllium susceptibility (4-6). We postulate that a similar approach should be used for screening of patients at risk for side-effects of dental material.
In conclusion, susceptible populations at risk due to mercury and other metals are children and adults with allergic and autoimmune diseases. Children with autistic and behavioral disorders belong with all probability to the susceptible group as well. Until now, epidemiological studies either excluded these groups (7) or had limited power to detect those risks (8,9).
In the future, the best way to study the possible role of metals in the pathogenesis of diseases seems to be:

1) **Selection of susceptible patients on the basis of phenotype and genotype from the heterogeneous cohort**
2) **Therapy based on the elimination of the exposure to putative allergen(s)**
3) **Long-term follow-up of patient's health combined with monitoring of improvement in relevant laboratory markers.**

References

1. Godfrey ME, Wojcik DP, Krone CA. Apolipoprotein E genotyping as a potential biomarker for mercury neurotoxicity. J Alzheimers Dis. 2003;5:189-95.
2. Wojcik DP, Godfrey ME, Christie D, Haley BE. Mercury toxicity presenting as chronic fatigue, memory impairment and depression: diagnosis, treatment, susceptibility, and

outcomes in a New Zealand general practice setting (1994-2006). Neuro Endocrinol Lett. 2006;27:415-23
3.Westphal GA, Schnuch A, Schulz TG, Reich K, Aberer W, Brasch J, et al. Homozygous gene deletions of the glutathione S-transferases M1 and T1 are associated with thimerosal sensitization. Int Arch Occup Environ Health. 2000;73:384–8)
4. Kreiss K, Newman LS, Mroz M, Campbell PA. Screening blood test identifies subclinical beryllium disease. J Occup Med. 1989;31:603–8,
5. Kreiss K, Miller F, Newman LS, Ojo-Amaze E, Rossman MD, Saltini C. Chronic beryllium disease – from the workplace to cellular immunology, molecular immunogenetics, and back. Clin Immunol Immunopathol. 1994;71:123-9
6. Newman LS. Significance of the blood beryllium lymphocyte proliferation test. Environ Health Perspect. 1996;104(Suppl 5):953-6
7. Bellinger DC, Trachtenberg F, Barregard L, Tavares M, Cernichiari E et al. Neuropsychological and renal effects of dental amalgam in children. A randomized clinical trial JAMA 2006;295:1775-1783
8. Wallach H, Nauman J, Mutter J, Daschner F. No difference between self-reportedly amalgam sensitivitie and non-sensitivites? Listen carefully to the data. Int J Hyg Environ Health 2003;206:139-141
9. Barregård L, Eneström S, Ljunghusen O, Wieslander J, Hultman P. A study of autoantibodies and circulating immune complexes in mercury-exposed chloralkali workers. Int Arch Occup Environ Health 1997;70:101-6