Consultation Response Form

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

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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.

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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.

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Question 3: Is there scientific evidence that supports a link between alternative materials and allergic reactions, neurological disorders or other health disorders?

YOUR COMMENTS
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?

YOUR COMMENTS
Do you agree with the response given?

Yes (non metallic restorations)
No (gold, nickel and titanium alloys).

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

Regarding 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.

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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 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.**

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