EUROPEAN COMMISSION

Health & Consumer Protection
Directorate-General

Scientific Committee on Emerging and Newly Identified Health Risks

SCENIHR

The safety of dental amalgam and alternative dental restoration materials for patients and users

Scientific Committees
on consumer products
on emerging and newly identified health risks
on health and environmental risk

The SCENIHR adopted this opinion via written procedure on 6 May 2008

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Products (SCCP), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Evaluation Agency (EMEA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCENIHR

Questions concerning emerging or newly-identified risks and on broad, complex or multi-disciplinary issues requiring a comprehensive assessment of risks to consumer safety or public health and related issues not covered by other Community risk- assessment bodies.

In particular, the Committee addresses questions related to potential risks associated with interaction of risk factors, synergic effects, cumulative effects, antimicrobial resistance, new technologies such as nanotechnologies, medical devices, tissue engineering, blood products, fertility reduction, cancer of endocrine organs, physical hazards such as noise and electromagnetic fields and methodologies for assessing new risks.

Scientific Committee members

Anders Ahlbom, James Bridges, Wim De Jong, Jana Hajslová, Philippe Hartemann, Thomas Jung, Mats-Olof Mattsson, Jean-Marie Pagès, Konrad Rydzynski, Dorothea Stahl, Mogens Thomsen, David Williams

Contact:

European Commission
Health & Consumer Protection DG
Directorate C: Public Health and Risk Assessment
Unit C7 - Risk Assessment
Office: B232 B-1049 Brussels

Sanco-Sc1-Secretariat@ec.europa.eu

(ISSN)

ACKNOWLEDGMENTS

Members of the working group are acknowledged for their valuable contribution to this opinion. The members of the working group are:

SCENIHR members:

Prof. David Williams (*Chair and Rapporteur)*

Dr. Wim De Jong

External experts:

Prof. Wolfgang Dekant[1], Scientific Committee on Health and Environmental Risks (SCHER)

Prof. Arne Hensten[1], Institute of Clinical Dentistry, Medical Faculty, University of Tromsø, Norway

Prof. Michel Goldberg[1], University Paris Descartes, Montrouge, France

Prof. John A. Jansen, Department of Periodontology and Biomaterials, Radboud University Nijmegen Medical Center, The Netherlands

Dr. Ole Ladefoged, Scientific Committee on Health and Environmental Risks (SCHER)

Prof. Nairn Wilson[1], King's College London Dental Institute at Guy's, King's College and St Thomas' Hospitals, London, United Kingdom

[1] Declared interest (see the minutes of the SCENIHR Plenary http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_mi_016.pdf)

ABSTRACT

In order to reconcile oral health and the aim of the Community Strategy concerning mercury, it has become necessary to review the safety and performance of both dental amalgam and their alternatives, such as composite resins, glass ionomer cements, ceramics and gold alloys. This Opinion concerns the scientific evidence about any links that may exist between either amalgam or these alternatives and allergies, neurological disorders or other health disorders.

SCENIHR recognises that dental amalgam is an effective restorative material and may be considered the material of choice for some restorations, but because it is neither tooth-coloured nor adhesive to remaining tooth tissues, its use has been decreasing in recent years and the alternative tooth-coloured filling materials have become increasingly more popular. Independent of risk management decisions, a sustained reduction in the use of dental amalgam in oral health care provision is expected across the European Union, the rate of which is dependant on trends in dental education towards the increasing use of alternative materials in place of amalgam and the possible reduced availability of mercury products in general.

Mercury is the major metallic element used in dental amalgam. In general it does constitute a toxicological hazard, with reasonably well defined characteristics for the major forms of exposure. Some local adverse effects are seen with amalgam fillings but the incidence is low and normally readily managed. There have been claims of causation with respect to a variety of systemic conditions, particularly neurological and psychological/psychiatric effects. It is concluded however, that there is no scientific evidence for risks of adverse systemic effects exist and the current use of dental amalgam does not pose a risk of systemic disease. The main exposure to mercury in individuals with amalgam restorations occurs during placement or removal of the fillings. The removal of amalgam restorations will transiently increase the exposure of individual patients to relatively high levels of mercury and there is no clinical justification for removing clinically satisfactory amalgam restorations, except in patients suspected of having allergic reactions to amalgam constituents. The mercury release during placement and removal also results in exposure to the dental personnel. However, this may be minimized by the use of appropriate clinical techniques. No studies have shown that dental personnel suffer classical signs of mercury intoxication.

The alternative materials are not without clinical limitations and toxicological hazards. They frequently contain a variety of organic substances and undergo chemical reactions within the tooth cavity and adjacent soft tissues during placement, and some of the monomers used are cytotoxic to pulp and gingival cells in vitro. There is evidence that some of these are also mutagenic in vitro although it is far from clear whether this has any clinical significance. Allergies to some of these substances have been reported, both in patients and in dental personnel. There are very limited scientific data available concerning exposure to these substances and, although the pervasiveness of some of the low molecular weight species throughout dental clinics is apparent, their use has revealed little evidence of clinically significant adverse events.

We conclude that dental health can be adequately ensured by both types of material. All the materials are considered safe to use and they are all associated with very low rates of local adverse effects with no evidence of systemic disease. There is, obviously, a greater level of aesthetic appeal with those alternatives that are tooth coloured compared to the metallic amalgam. Furthermore, these alternatives allow the use of minimally interventional adhesive techniques. These clinical trends themselves ensure that there will continue to be a sustained reduction in the use of dental amalgams in clinical practice across the European Union.

Keywords : Dental amalgam, mercury, toxicology, exposure, composite resins, glass ionomer cements, allergy, systemic health effects, SCENIHR.

Opinion to be cited as: SCENIHR (Scientific Committee on Emerging and Newly-Identified Health Risks), Scientific opinion on the Safety of Dental Amalgam and Alternative Dental Restoration Materials for Patients and Users, 6 May 2008.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This Opinion concerns one of the oldest controversies in medicine, that is whether there is a causal relationship between mercury-containing amalgams for the restoration of teeth and the aetiology of a variety of diseases in individuals with amalgam restorations.

In order to reconcile oral health and the aim of the Community Strategy concerning mercury, it has become necessary to review the safety and performance of both dental amalgam and their alternatives, such as composite resins, glass ionomer cements, ceramics and gold alloys. SCENIHR has therefore been asked to provide an Opinion on whether there is scientific evidence that supports a link between either amalgam or these alternative materials and allergies, neurological disorders or other health disorders.

In coming to their Opinion, SCENIHR recognises that dental amalgam is an effective restorative material and, from the perspectives of longevity, the mechanical performance and health economics, may be considered the material of choice for some restorations in posterior teeth, including replacement therapy for existing amalgam fillings. However, because dental amalgam is neither tooth-coloured nor adhesive to remaining tooth tissues, its use has been decreasing in recent years and the alternative tooth-coloured filling materials have become increasingly more popular. This is consistent with the trend towards minimal interventional, adhesive, techniques in dentistry. This trend towards non-amalgam restorations is emphasized by the significant reduction of training in the placement of dental amalgam restorations, and the corresponding increase in training in the use of amalgam alternatives in many dental schools in European countries.

Independent of risk management decisions and of the economic considerations in restorative dentistry, a sustained reduction in the use of dental amalgam in oral health care provision is expected across the European Union, the rate of which is dependant on trends in dental education towards the increasing use of alternative materials in place of amalgam and the possible reduced availability of mercury products in general.

Mercury is the major metallic element used in dental amalgam. It is recognized that mercury in general does constitute a toxicological hazard, with reasonably well defined characteristics for the major forms of exposure, involving elemental mercury, organic and inorganic mercury compounds. It is accepted that the reduction in use of mercury in human activity would be beneficial both for the decrease in indirect human exposure and environmental considerations.

It is recognized that some local adverse effects are occasionally seen with dental amalgam fillings, including allergic reactions and an association with clinical features characteristic of lichen planus, but the incidence is low and normally readily managed. There have been claims of causation with respect to a variety of systemic conditions, particularly neurological and psychological/psychiatric effects, including Alzheimer's, Parkinson's Disease, Multiple Sclerosis and also kidney disease. However, several major epidemiological studies have failed to reveal such effects. These studies have included assessments in children and in pregnant and lactating women. The most recent studies have failed to find any association between the use of amalgam and neuropsychological development in children. It is generally concluded that no increased risks of adverse systemic effects exist and we do not therefore consider that the current use of dental amalgam poses a risk of systemic disease.

The main exposure to mercury in individuals with amalgam restorations occurs during placement or removal of the fillings. The transient mercury release during placement and removal will result in exposure to the patients and also to the dental personnel. It should be noted that the removal of amalgam restorations will increase the exposure of the individual patient to relatively high levels of mercury compared to leaving the amalgam filling intact and there is no clinical justification for removing clinically satisfactory amalgam restorations, except in those patients suspected of having allergic reactions to one of the amalgam constituents.

We note that the alternative materials, which may be very complex chemically, are not without certain clinical limitations and toxicological hazards. They contain a variety of organic substances and undergo chemical reactions within the tooth cavity and adjacent soft tissues during placement. Therefore, it should not be assumed that non-mercury containing alternatives are free from any concerns about adverse effects. With respect to dental composite restorative materials and hybrid systems that incorporate polymerisable resins, it is known that some of the monomers used are highly cytotoxic to pulp and gingival cells in vitro. There is also evidence that some of these are mutagenic in vitro although it is far from clear whether this has any clinical significance. Allergies to some of these substances have been reported, both in patients and in dental personnel.

It is noted that there are very limited scientific data available concerning exposure of patients and dental personnel to these substances that are used in alternative restorative materials. It is recognised that such data are very difficult to obtain.

These alternative materials have now been in clinical use for well over thirty years, initially in anterior teeth and more recently also for restorations in posterior teeth. This clinical use has revealed little evidence of clinically significant adverse events. It is also important to note that the commercially available materials have either changed substantially or been improved considerably over this time, with reduced bioavailability of harmful components through improved polymerisation processes.

We note that the full chemical specification of these alternative restorative materials is not always divulged and it may be difficult to ascertain exactly what they contain. As a result, there is limited toxicological data publicly available for these materials. All dental restorative materials are defined as medical devices according to EU-Directive 93/42/EEC, within which a derogation clause states that when such medical devices are used in teeth they will be in class 2a. When regulatory approval is sought it is not necessary to include a design dossier and therefore the chemical specification does not have to be revealed. In view of the lack of information on the toxicity of the constituents of the materials and relevant exposure data it may not be possible to provide a scientifically sound statement on the generic safety of these materials.

As a general principle, the relative risks and benefits of using dental amalgam or the various alternatives should be explained to patients to assist them to make informed decisions. In view of the controversial nature of this subject, it would also be beneficial for the community in general to be better informed of the recognized benefits and risks.

In the light of the above comments we conclude that dental amalgam is a safe material to use in restorative dentistry with respect to patients. With respect to populations at risk, there is a lack of information about effects in pregnant women. There is no evidence to suggest that pre-existing amalgam restorations pose any risk as far as the health of such women and the developing foetus is concerned, and certainly any removal of restorations during this time would present a greater exposure to mercury. As with any other medical or pharmaceutical intervention, however, caution should be exercised when considering the placement of any dental restorative material in pregnant women. There is no evidence that infants or children are at risk of adverse effects arising from the use of dental amalgam. As far as dental personnel are concerned, it is recognised that they may be at greater risk with respect to mercury exposure than the general population, although the incidence of reported adverse effects is very low.

Far less information is available concerning exposure, toxicity and clinical outcomes for alternative materials. There is some evidence that certain of the low molecular weight substances used in their preparation are associated with local allergic reactions, although the incidence is very low. There is no evidence that there is any association between these materials, as used clinically, and any neurological disorders or any other health disorders. We do emphasise, however, that data is sparse and the continuing evolution of these materials suggests that caution should be exercised before new variations are introduced into the market. As far as dental personnel are concerned, again there is

evidence of limited numbers of cases of allergies to these materials. The pervasiveness of some of the low molecular weight species throughout dental clinics should be noted.

We conclude that dental health can be adequately ensured by both types of material. All the materials are considered safe to use and they are all associated with very low rates of local adverse effects with no evidence of systemic disease. There is, obviously, a greater level of aesthetic appeal with those alternatives that are tooth coloured compared to the metallic amalgam. Furthermore, the use of these alternatives allows the use of minimally interventional adhesive techniques. On a historical basis, amalgam restorations have in general been found to last longer, as restorations using alternatives have had a higher incidence of secondary caries. There are indications, however, that the longevity of restorations of alternative materials in posterior teeth has improved with the continuing development of these materials and the practitioner's familiarity of effective replacement techniques. The alternative materials were originally introduced for the restoration of anterior teeth but their use has now extended towards lesions of all sizes in posterior teeth. Dental amalgam may for the foreseeable future continue to find application in the restoration of large lesions and in the replacement of failed amalgam restorations, but the clinical trends themselves towards the use of adhesive alternatives imply that there will continue to be a sustained reduction in the use of dental amalgams in clinical practice across the European Union.

1. BACKGROUND

Dental amalgam has been used for over 150 years for the treatment of dental cavities and is still used, in particular in large cavities due to its excellent mechanical properties and durability. Dental amalgam is a combination of alloy particles and mercury that contains about 50% of mercury in the elemental form.

Overall, the use of alternative materials such as composite resins, glass ionomer cements, ceramics and gold alloys, is increasing, either due to their aesthetic properties or alleged health concerns related to the use of dental amalgam.

Whereas the toxicity of mercury has been extensively researched, relatively little is known about the safety of alternative materials, possibly because some alternatives are relatively new materials.

In January 2005, the Commission adopted a proposal for a Community Strategy concerning Mercury[2] in order to reduce mercury levels in the environment and human exposure. Pursuant to Action 6 of the Strategy, the use of dental amalgam should be evaluated with a view to considering whether additional regulatory measures are appropriate.

Dental amalgam and its substitutes are regulated under Council Directive 93/42/EEC[3] concerning medical devices, according to which they must comply with the essential requirements laid out in the directive, in particular in relation to the health and safety of the patients.

An Expert Report mandated by the European Commission's DG III and published in 1998[4] concluded that no proven adverse effects could be associated with the presence, placement or removal of dental amalgam fillings in patients and users, based on available science and when used according to manufacturer's instructions.

Subsequently, several Member States have adopted recommendations according to which dental amalgam should not be used in certain patient groups such as pregnant women or young children.

In view of the above and in order to reconcile patients' oral health and the global aim of the Community Strategy concerning mercury, it is necessary to review the safety and performance of dental amalgam and of their substitutes for the treatment of dental cavities.

[2] COM (2005) 20 final

[3] OJ L 00042, 20.11.2003, p.2

[4] Dental Amalgam. A report with reference to the Medical Devices Directive 93/42/EEC from an AD Hoc Working Group mandated by DG III of the European Commission. 1998.

2. TERMS OF REFERENCE

2.1. Human safety

2.1.1. Dental amalgam

In view of mercury exposure level due to the presence, the placing or the removal of dental amalgam, the Scientific Committee is requested to consider the following questions:

1. is there scientific evidence that supports a link between amalgam and allergic reactions, neurological disorders or other health disorders?
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?

2.1.2. Alternative materials

Overall, alternative materials such as composite resins, glass ionomer cements, ceramics and gold alloys, are increasingly used for the restorative treatment of dental cavities. The Scientific Committee is requested to evaluate the safety of these materials when used for dental restorative treatment and to consider the following questions:

1. is there scientific evidence that supports a link between alternative materials and allergic reactions, neurological disorders or other health disorders?
2. 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?

2.2. Oral health and safety

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?

3. SCIENTIFIC RATIONALE

3.1. Introduction

This Opinion concerns one of the oldest unresolved controversies in medicine, that is whether there is a causal relationship between the use of mercury-containing amalgams for the restoration of teeth and the aetiology of a variety of diseases in individuals with amalgam restorations, in dental professionals and in the general population.

Dental amalgam has been used in various forms for the reconstruction of carious teeth for more than 150 years and became common, especially in the USA, in the latter part of the nineteenth century, its formulation and clinical use being rationalised by G V Black at the end of that century. The use of amalgam was almost wholly predicated on the fact that mercury is one of the very few metallic elements that is liquid at room temperature. As a consequence of this it is able to undergo an alloying reaction with other elements at ambient temperatures to form, in a clinically acceptable time, a customised mass that can be adapted to the size and shape of a tooth cavity, where it should be strong enough to resist the forces of occlusion for many years. At the time of the introduction of amalgam into dentistry, gold could be used in some types of dental restoration, but its cost prohibited widespread use. There were no other synthetic materials that had the combination of the required mechanical properties and ease of intra-oral manipulation. As a metallic alloy, amalgam did not have any aesthetic appeal, but the increasing prevalence of dental caries in the late eighteenth and early nineteenth centuries meant that this was a minor consideration. The even more profound increase in caries throughout the early and middle twentieth century, through the ubiquitous use of refined carbohydrates in foodstuffs, resulted in the increased use of dental amalgam fillings.

The essential metallurgical principles of dental amalgam, discussed in detail below in section 3.3, are fairly straightforward. Liquid mercury is able to react with many other metallic elements to produce a series of multi-phase alloys that are solid at room temperature. The key development was to find an element, or a combination of elements, that would allow the amalgamation reaction to occur in a short space of time, with a rapid rate of solidification and development of strength. Although several metallic elements were tried, it was soon realised that an alloy of silver and tin, essentially Ag_3Sn, reacts with liquid mercury to produce a clinically acceptable alloy that would solidify in a few minutes and gradually harden over a few hours.

It had been recognised for a long time that certain forms of mercury and its compounds have toxicological characteristics, and the potential for neurotoxicity had already been discussed at the same time that amalgam was introduced into dentistry. Throughout the twentieth century and even more now at the beginning of the twenty-first century, the potential role of dental amalgam in the causation of disease has been a matter of considerable controversy. The focus has been on the mercury contained within the amalgam, and the potential for it to induce local intra-oral reactions to the amalgam restorations and to cause systemic or remote-site diseases associated with its systemic distribution and accumulation. Both governmental and non-governmental organisations have considered this possibility and many reports have been written on the subject. Many academic studies have been published, including some very recent epidemiological studies, which have attempted to prove conclusively, one way or the other, whether the mercury in amalgam has a causative role in disease, but until now, no clear unequivocal conclusion has been forthcoming. This is of immense importance since, during the last forty years, several types of alternative to amalgam for dental restorations have been developed such that the overall risk – benefit assessments for dental restorations in general have had to be changed. However, it is far from clear whether the use of such alternatives, involving, as they do, their own potentially toxic components, reduces the risk of disease associated with dental restorations.

This Opinion therefore takes into account currently available scientific and clinical evidence concerning mercury and other elements contained within dental amalgam, and

also the components of the alternative materials. These alternatives include resin based composite materials, glass ionomer cements and a variety of hybrid structures. In addition, restorations made of gold-based and other alloys are possible alternatives to dental amalgam. These latter types of restoration are considered as custom-made devices in the context of the Medical Device Directive of the European Commission and are produced by indirect techniques in dental laboratories, which are clearly more time consuming and expensive. With each of the different types of alternative material, it is necessary to consider the chemistry and toxicology of all of the components, including monomers, acids, glasses and ions, taking into account the physico-chemical aspects of the setting process, the techniques for promoting adhesion to the tooth substance and the energies of any light sources used in photo-polymerisation. The clinical and epidemiological evidence has to be analysed in relation both to the patients themselves and to dental personnel, taking into account the phases of use, including placement of the filling, corrosion, degradation or wear in clinical service, and the release of materials during the removal of restorations. With respect to amalgam, it is also necessary to consider the exposure of the general population to mercury derived from the use of dental amalgam, placing this in the context of environmental exposure in general, and the contribution that amalgams make over their whole life cycle, including aspects of waste water treatment in dental offices and the release of mercury into the atmosphere in crematoria. With respect to alternatives to dental amalgam, it is also relevant to consider the life cycle of these materials, although very little data is available.

It is also important to examine the pattern of usage of amalgams and alternatives in dental clinics, since perceived benefits and risks, and the trends in these perceptions may change and this should be taken into account in making recommendations for future usage. For example, in some countries, general environmental considerations and public attitudes and expectations have contributed to a decline (sometimes a very substantial decline) in amalgam use and to a reduction in the use of mercury-containing products in general. Furthermore, dental schools are either reducing or have discontinued teaching the use of amalgams in view of the changing attitudes to restorative dentistry (Roeters et al. 2004). These trends must be placed in the context of the overall performance and longevity of amalgam and non-amalgam restorations, taking into account the size and location of the restorations. It is also important to recognise that the perception of patients may differ to some extent from the views of health care professionals.

3.2. Methodology

This Opinion of SCENIHR is concerned with the analysis of the evidence for the potential for either amalgam or alternatives to amalgam to have adverse effects on human health, from the perspectives of both scientific plausibility and clinical and epidemiological data, and to make observations about the future uses of these materials in dentistry.

The Working Group has considered evidence derived from a wide variety of sources, including peer-reviewed scientific and medical literature and published reports of institutional, professional, governmental and non-governmental organisations. In common with the usual practice of SCENIHR Working Groups, no reliance has been made on unpublished work or publicly available opinions that are not scientifically based. Due to the availability of extensive peer reviewed epidemiological and large scale clinical studies with respect to dental amalgam, it has not been necessary to rely on single case or anecdotal reports in establishing this Opinion. The Working Group has been careful, however, to review as much evidence as possible and, especially where the available data on alternatives is limited, attention has been given to some less rigorous studies where no other information was available. During the course of the deliberations of the Working Group, a Call for Information was issued by the Commission and the replies have all been considered.

In a major review of the evidence for or against causation of disease, it is necessary to take into account the generally accepted criteria for causation. The Working Group has therefore been mindful of such criteria, particularly the Bradford Hill Criteria of Causation

(Bradford Hill 1965). The main features of these criteria are the paramount need to establish a temporal relationship between exposure and outcome, the strength of any effect or association determined statistically, the evidence of a dose-response relationship, the plausibility and specificity of any association, and the coherence of any putative association with existing knowledge. It will become obvious with respect to both dental amalgam and the alternative restorative materials, that some of these questions are difficult to analyse, for example because of the uncertainty over the exposure of individuals to mercury derived from amalgams compared to their exposure to mercury from other sources. Nevertheless, the Working Group is confident that it has been possible to take all factors into account in producing an Opinion that is consistent with these criteria for causation.

3.3. Dental Amalgam

In this Chapter, the essential and relevant characteristics of dental amalgam and the evidence concerning the general exposure and toxicity of mercury based substances are explained and discussed. This is followed by an assessment of the reported adverse effects in individuals with amalgam restorations, the epidemiological and clinical evidence concerning adverse effects in dental personnel, and general observations about the clinical usefulness of dental amalgam restorations.

3.3.1. Metallurgical principles and physical-chemical properties

An amalgam is an alloy of mercury with one or more other metals. Most dental amalgams are called silver amalgams since silver is the principal constituent that reacts with mercury. The kinetics of reactions between mercury and silver are not appropriate for clinical use, so that the silver is provided as an alloy with other elements. This alloy is often referred to as a dental amalgam alloy or, collectively, they are known as 'alloys for dental amalgam' (ISO 1995). There are several types of dental amalgam alloy, all involving tin and most having some copper and, to a lesser extent, zinc. Some of the dental amalgam alloys themselves contain a little mercury to facilitate the amalgamation reaction. A conventional dental amalgam alloy will contain between 67% and 74% silver, with 25-28% tin, and up to 6% copper, 2% zinc and 3% mercury. The so-called dispersion type amalgam alloys have around 70% silver, 16% tin and 13% copper. A further, quite different, group of amalgam alloys may contain up to 30% copper, and are known as high-copper content amalgam alloys. In addition, again being very different, so-called copper amalgams which contained approximately 30% copper and 70% mercury were once used, but these are no longer recommended.

The amalgam alloys are mixed with mercury before clinical placement at a 1 to 1 weight-ratio. The mercury content of a finished dental amalgam restoration is therefore approximately 50% by weight.

In the conventional dental amalgam alloys, the ratio of silver to tin results in a crystal structure that is essentially the intermetallic compound Ag_3Sn, referred to as the gamma (γ) phase. The exact percentage of this phase controls the kinetics of the amalgamation reaction and many properties of the resulting amalgam structure. With the higher copper dispersion alloys, the microstructure is usually a mixture of the gamma phase with the eutectic silver-copper phase.

Different manufacturers present the amalgam alloy in different formats, although they are usually made available as fine particles, either spherical or irregular in shape, with particle sizes around 25-35 microns. Although there are also several different ways of dispensing the liquid mercury and the solid amalgam alloy, this is usually achieved by means of a sealed, compartmentalised capsule, with the alloy in one part and the mercury in the other, the membrane between the two being broken during the process of mixing in a mechanical amalgamator. This is an important point since a major route for exposure to metallic mercury during hand mixing, as carried out until a few decades ago, is eliminated during this process. Nevertheless, exposure certainly does occur during the

next phases of placement, where the setting amalgam is placed into the prepared tooth cavity and condensed, or compressed, firmly within the cavity. During this process, the structure of the amalgam is optimised by this compression, causing excess mercury to rise to the surface, from where it is removed. The properties of the amalgam restoration will depend on the perfection of this technique, the elimination of as much excess mercury as possible being essential.

The metallurgical characteristics of the amalgamation process are very important. With the conventional amalgam alloy, the reaction between the Ag_3Sn (γ) phase and the mercury results in the formation of the γ_1 phase, which is a body-centred cubic mercury - silver phase with a mercury – silver ratio between 3:2 and 8:5, and the γ_2 phase, a hexagonal tin-mercury phase of mercury - tin ratio between 1:6 and 1:8. The reaction does not go to completion and some 30% of the set amalgam consists of un-reacted Ag_3Sn (γ) phase. There will be, as noted above, some retained mercury, the majority of which is removed by the dentist during condensation; much of the remainder continues to react, very slowly, with the Ag_3Sn (γ) phase. It is emphasised that the set amalgam contains about 50% mercury and it will be seen that the majority of this mercury in the amalgam is contained in the γ_1 phase, with a minority in the γ_2. These metallurgical principles of dental amalgam are well established and have been discussed in detail in standard dental textbooks and reference documents (for example, Anusavice 2003).

The mercury in the set amalgam is in a very different form to that in the liquid mercury. According to Okabe (1987), mercury has a vapour pressure of 1.20×10^{-3} Torr at 20°C. It is difficult to compare directly the vapour pressure of liquids and solids, and indeed it is difficult to obtain good and reproducible measurements of very low vapour pressures such as those found with amalgams (Halbach and Welz 2004), but best estimates of the vapour pressure for amalgam surfaces range from 10^{-6} to 10^{-10} Torr (Wieliczka et al. 1996). This implies that the release of mercury vapour from a set amalgam restoration will be many orders of magnitude lower than that from liquid mercury, and the availability of mercury from a solid alloy structure should not be equated with that from the liquid. This subject is considered further in the following sections on exposure levels.

An amalgam restoration will be susceptible to tarnish and corrosion. Tarnish is a process that involves the deposition of substances from the oral environment, especially sulphides, such that the surface loses its metallic lustre, but without any significant chemical reaction involving the underlying alloy. In fact, tarnished alloys have greater protection from corrosion because of the passivating effect of the deposited layer. Nevertheless, the amalgam itself will corrode over time, even though mercury and silver are intrinsically corrosion resistant elements. The main cause is that the γ_2 is significantly more electronegative than either the γ or γ_1 phases so that galvanic corrosion occurs, with the release of the constituents of the γ_2, namely tin and mercury. The corrosion of the higher copper based amalgams is less because little or no γ_2 forms. It is anticipated that the corrosion rate of amalgams will decrease with time as the surface becomes progressively more noble, but this appears to take place more slowly in restorations than predicted by in vitro tests on amalgam samples (Sutow et al. 2007). This latter paper typifies the problems with the assessment of the corrosion rate of amalgams, as most estimates are based on electrochemical tests in vitro, from which it is extremely difficult to extrapolate to reliable, clinically relevant data on the rate of release of mercury from amalgam restorations by corrosion process within the mouth. With respect to this Opinion, it may be stated that corrosion of restorations will occur at a very low rate, which may contribute to overall exposure, but the exact contribution that this makes is unknown.

3.3.2. Exposure to Mercury

Mercury is a metallic element that occurs naturally and also in the form of several types of ore, the mercury burden of the environment being derived predominantly from natural sources. Input into the earth's atmosphere occurs regularly through emissions from volcanoes, soil erosion and the combustion of fossil fuels. Widespread utilisation of

mercury and its compounds in a number of industries over the last several centuries has resulted in the release of large amounts of mercury into the atmosphere, increasing the total amount in the ecosphere. Of special importance has been the accumulation of some mercury compounds in the aquatic food chain and the use of mercury compounds in a variety of medical and cosmetic products including dental amalgam. It is clear that exposure to mercury by individuals will be controlled by several factors, including ambient mercury levels (determined by geographical location and life-style choices), the diet, especially in relation to fish consumption, the possibility of occupational exposure for those who work in mercury-related industries and practices, and the use of mercury containing medical or cosmetic products, including amalgam. The exposure of individuals with amalgam restorations and dental personnel has to be considered in the context of this broader exposure scenario.

3.3.2.1. Major Forms of Mercury

It is also important to note that there are several different forms of mercury. First there is elemental mercury itself, a volatile form of the liquid metal, referred to as Hg^0. Secondly, mercury is stable in two other oxidation states (Hg^{1+} and Hg^{2+}) and is able to form inorganic compounds, of either monovalent or divalent form, including mercuric chloride ($HgCl_2$), mercurous chloride (Hg_2Cl_2), mercuric sulphide (HgS), and mercuric selenide (HgSe). Thirdly, mercury is able to form a variety of organic compounds, including methylmercury. There is a clear connectivity between these forms with respect to the global cycle of mercury (Nielsen et al. 2006). Elemental mercury may be converted to soluble inorganic forms, which may be methylated in water, especially by microorganisms, which enter the food-chain and accumulate in the tissues of large predatory fish. The ratio of methylmercury in these fish to the mercury concentration in the water can be as high as 10^5.

Each form of mercury has its own toxicological profile, although, in general terms, the toxicity of these forms is highest with the organic mercury compounds, followed by elemental mercury and inorganic mercury compounds. This is important when considering different exposure routes to these forms.

3.3.2.2. Evidence of exposure to mercury from dental amalgam restorations

Exposure to Mercury in Adults

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. Autopsy/post-mortem studies give an indication of the overall exposure of individuals during their whole lifetime due to all kinds of mercury sources, including dental amalgam. As such, these studies suffer certain unquantifiable limitations. Therefore, data dealing with blood and urine mercury determination were considered more relevant as they reflect actual exposure.

Mercury is distributed ubiquitously in the environment and can therefore be taken up by the general population via food, water and air, potential sources of exposure including the inhalation of mercury vapors in ambient air, the ingestion of drinking water and food, and exposure to mercury through dental and medical treatments. Dietary intake is the most important source of non-occupational exposure to methylmercury, with fish and other seafood products being the dominant source of this highly absorbable form in the diet. Intake of elemental mercury from dental amalgams is another source contributing to the total mercury burden in humans in the general population (WHO 1990, WHO 1991). Tolerable limits for methylmercury content of fish and human consumption have been set by various organisations. In the USA, the Environmental Protection Agency set a limit, the so-called Tissue Residue Criterion, of 0.3 mg methylmercury / kg fish (EPA 2001). In Europe, the 2005 Opinion of the Scientific Panel of the EFSA on contaminants

in the food chain (EFSA 2005) contained detailed reference to methylmercury in fish. In practice, levels range from under 0.1 mg/kg fish up to 0.5 mg/kg. The provisional tolerable weekly intake (PTWI) has been established at 1.6 µg/kg body weight, implying that a high consumption of a predatory fish such as bluefin tuna, which may have a methylmercury level around 0.5 mg/kg, gives up to twice the recommended intake.

Because the two major sources of mercury body burden include dietary intake of methylmercury and intake of elemental mercury from dental amalgams, mercury is inevitably present at low concentrations in human tissues. Mercury has been detected in blood, urine, human milk, and hair in individuals in the general population. The mercury concentrations in whole blood of individuals with or without amalgam fillings are usually below 5 µg/l blood, but these concentrations do depend on dietary habits and the number of amalgam fillings (ATSDR 1999, BAT 1997).

In a study on the influence of fish consumption and number of amalgam fillings, (Schweinsberg 1994), blood mercury concentrations in individuals without fish consumption and dental amalgams were in the range of 0.2 – 0.4 µg/l. Blood mercury concentrations were raised the least in individuals without fish consumption but with more than 6 amalgam fillings, followed by high fish consumers with no amalgam restorations, and highest in high fish consumers with more than six fillings, at 1.5 to 4 µg/l. Average blood mercury levels below 3 µg/l in individuals with amalgam fillings are also reported in several other studies. Barany et al. (2003) studies 245 17-year-old Swedish individuals and found a geometric mean level of 1.1 µg/l in their blood, which were positively correlated with fish consumption and serum mercury was influenced by the number of fillings as well as fish consumption. Dye et al. (2005) found that the average urinary mercury level in women of childbearing age was 1.34 µg/l and it was estimated that an increase of 1.8 µg/l would be seen in the urinary levels for each ten dental surfaces restored with amalgam. Zimmer et al. (2002) reported median mercury levels in blood of 2.35 µg/l in 40 females who had claimed to suffer from serious health damage due to amalgam fillings and 2.40 µg/l in a series of 43 control female subjects.

The mercury concentrations in the urine of persons not occupationally exposed to mercury are usually below 5 µg/l. Again, the urinary excretion may vary considerably depending on non-occupational sources of mercury, such as fish consumption and amalgam fillings. In one study with 380 Italians without occupational exposure to mercury, a mean value of 3.5 µg/l urine was observed, with a range from 0.1 to 6.9 µg/l (BAT 1997). Median values between 1.5 and 1.8 µg/l urine have been reported (Zimmer et al. 2002). In a study of 1127 healthy males, Kingman et al. (1998) found an average total mercury urinary concentration of 2.55 µg/l with a significant correlation between this level and amalgam exposure equivalent to an increase of 1 µg/l of urine for each 10 amalgam surfaces.

As discussed by Barregard (2005) and Barregard et al. (2006) values of urinary mercury expressed in relation to creatinine vary between countries, especially with reference to different food habits and national health care systems. Median levels in subjects with dental amalgams were 1.2 µg/g creatinine in Italy but 0.6 µg/g creatinine in Sweden, corresponding figures for those without amalgams being 0.9 and 0.2 µg/g creatinine respectively. Elevated levels, approximately five times higher than controls are found in individuals who regularly use nicotine chewing gums as a smoking replacement therapy (Sallsten et al. 1996).

In a population of 245 German children, mercury concentrations in urine ranged between <0.1 and 5.3 µg/l, with a mean of 0.25 µg/g creatinine, with some correlation with the number of teeth with amalgam fillings and also the number of defective amalgam fillings (Pesch et al. 2002). Differences were noted between mercury in plasma and erythrocytes by Halbach et al. (2000, 2007). The authors conclude that the integrated daily mercury dose of 7.4 µg for a high amalgam load is well below the tolerable dose of 30 µg (WHO 2003, ATSDR 1999). A recent paper indicated that there may be difference in mercury excretion between boys and girls 8-18 years of age, treated with dental amalgam (Woods 2007).

Exposure during pregnancy and breast-feeding

Mercury is normally present in amniotic fluid. In one study of 72 pregnant women, (Luglie et al. 2005) there was an overall mean mercury concentration in amniotic fluid of 0.37 +/- 0.49 ng/ml. The women were divided into those with a low concentration of less than 0.08 ng/ml (26.4% of the subjects) and those with a high concentration of greater than 0.08 ng/ml, mean 0.49 +/- 0.52 ng/ml (73.6% of subjects). The amniotic fluid concentration was dependent of the number of amalgam fillings and fish consumption; the low concentration group having an average of 2.26 amalgam fillings and the high concentration group having an average of 5.32 fillings. However, no adverse effects were observed throughout pregnancies and in the newborn. Only a small fraction of divalent inorganic mercury is transferred to the fetus, whereas placental transfer of methyl mercury and elemental mercury occurs easily.

Bjornberg et al. (2005) report that infant blood inorganic mercury is similar to maternal blood mercury at delivery but decreases until 13 weeks of age. In breast milk inorganic mercury decreased from day 4 to 6 weeks after delivery, and remained unchanged thereafter. Total mercury in breast-milk was associated with maternal but not infant inorganic mercury. The exposure to both methylmercury and inorganic mercury was low, being higher before birth than during the breast-feeding period. Methylmercury contributes more than inorganic mercury to infant exposure post-natal via breast milk. The median value for methylmercury in maternal blood at delivery is 0.99µg/l, decreasing to 0.38 µg/l by 13 weeks after birth. The median for inorganic mercury concentration was 0.09µg/l in maternal blood at delivery and 13 weeks. The same values were found in infant blood at delivery, reducing to 0.05µg/l at 13 weeks. The child's exposure to methylmercury and inorganic mercury is much greater before birth than during breast-feeding. In breast milk, the mercury level correlated significantly to maternal blood inorganic mercury (0.29µg/l). Gundacker et al. (2002) indicate that the mean concentration of total mercury in human breast milk is 1.59µg/l, which they considered to pose no risk to infants.

Intake estimates for mercury from dental amalgams

Mercury vapour is released from silver amalgam restorations during chewing, tooth brushing, and parafunctional activities including bruxism. The parameters of this release of mercury vapour by amalgam depends of the number of fillings, the filling size and placement, chewing habits, food texture, grinding and brushing teeth, nose-mouth breathing ration, inhalation-absorption, ingestion and body weight, and the surface, composition and age of the amalgam restorations. Therefore, there are large variations in the estimation of daily mercury absorption and release.

Mercury released from dental amalgam distributes in the oral cavity as inhalable mercury vapour, or is dissolved in saliva after oxidation or suspended in it as amalgam particles. There is no evidence that biotransformation of amalgam-derived mercury takes place intra-orally in association with bacterial activity. With respect to systemic exposure assessment, only the inhaled fraction is relevant since elemental mercury and inorganic mercury are poorly absorbed from the GI-tract and therefore have only a very minor contribution to systemic exposure. The daily uptake of mercury from amalgam fillings is estimated to be up to 27 µg/day in individuals with large numbers of fillings. One study shows an intake from 1 to 5 µg/day from dental amalgam for people with 7-10 fillings. The World Health Organization reported a consensus average estimate of 10 µg/day of amalgam derived mercury (range: 3-17 µg/day) (WHO 1991). Weiner and Nylander (1995) estimated the average uptake of mercury from amalgam fillings in Swedish subjects to be within the range of 4-19 µg/day. Skare and Engqvist (1994) estimated that the systemic uptake of mercury from amalgams in middle - aged Swedish individuals with a moderate amalgam load (30 surfaces) was, on average, 12 µg/day.

3.3.2.3. Exposure to mercury in dental personnel

The mercury body burden of dental personnel is normally higher than in the general population. The mean urine mercury levels in dental personnel has been variously reported to range from 3 µg/l to 22 µg/l, compared to 1-5 µg/l as the normal range for non-occupational groups (Hörsted-Bindslev 2004). This increased body burden is attributed to dental personnel mixing and applying dental amalgam and removing amalgam restorations; Ritchie et al. (2004) showed that dentists had, on average, urinary mercury levels over 4 times that of control subjects although all but one dentist had urinary mercury below the UK Health and Safety Executive health guidance value. Dentists were significantly more likely than control subjects to have suffered from disorders of the kidney but these symptoms were not significantly associated with their level of mercury exposure as measured in urine. Over 67% of the 180 surgeries visited had environmental mercury measurements in one or more areas above the Occupational Exposure Standard (OES) set by that Executive. In the majority of these surgeries the high levels of mercury were found at the skirting and around the base of the dental chair. In 45 surgeries (25%) the personal dosimetry measurement (i.e. in the breathing zone of dental staff) was above the OES.

Dental personnel may now be exposed to much less mercury than in the past, in view of the increased use of encapsulated dental amalgam, improvements in amalgam capsule design, the heightened awareness and practice of appropriate dental mercury hygiene measures, and the increasing use of alternative, non-mercury-containing materials (ADA 2003, Hörsted-Bindslev 2004). However, despite trends to reduce exposure to mercury, large, highly statistically significant differences ($P<0.0001$) may be found between dental personnel (in particular dentists) and controls, with respect of mean urinary, hair (head and pubic) and nail (finger and toe) mercury levels, with the reasons for such differences being considered to be multifactorial (Morton et al. 2004)

Since most dental chairside personnel do not touch dental amalgam during mixing and placement, it is considered that the main sources of mercury exposure are aerosols, created in the immediate working environment during and in particular, the removal of restorations of dental amalgam, and the exhaust air from dental vacuum systems. These mercury vapour releases can be substantial and well in excess of human exposure limits (Stone et al. 2007). Immediate working environment aerosols and exhaust air from dental vacuum systems will be inhaled despite the wearing of face masks, which may provide little, if any, barrier to mercury vapour entering the lungs and being absorbed.

Correlations have been found amongst dentists between urinary mercury levels and the number of hours worked in the surgery ($r=0.22$, $P=0.006$) and the number of amalgam restorations placed ($r=0.38$, $P<0.001$) and removed ($r=0.29$, $P<0.001$) in a week, with urine mercury levels in dentists ranging from 0.02 to 20.90 (mean 2.58) nmol mercury per nmol creatinine. A confounding factor in such investigations is the number of amalgam surfaces dentists have in their own mouths (Ritchie et al. 2002, Ritchie et al. 2004).

3.3.2.4. Metrology

While the analytical instruments for the determination of mercury concentrations in biological samples are well developed and sufficiently sensitive, a number of problems with sampling, the determination of mercury speciation, and the interpretation of results are evident. For the determination of total mercury in occupation exposures, the German BAT-commission (which sets limit values for occupational exposures to chemicals and develops and validates analytical methodology) recommended a specific sampling procedure and analytical methods to determine mercury in blood or urine. Sampling procedures for mercury determination are also described by the "Humanbiomonitoring Kommission" of the German UBA (Umweltbundesamt, Federal Environment Agency, Dessau-Rosslau, Germany). These authorities also concluded that the often proclaimed exposure assessment for mercury release from dental amalgams, "dimercaptopropane sulfonate (DMPS) mobilisation test" for mercury, does not provide additional important

information. This mobilisation test uses DMPS to chelate mercury, which results in an increased elimination of mercury with urine for a short time after DMPS-application (BAT 1997, UBA 1999).

Rapid and reliable detection of mercury in blood and urine resulting from environmental and occupational exposure may be carried out in most analytical laboratories, using, for example, atomic fluorescence spectrophotometry (Berglund et al. 2005). Measurements of total mercury in the urine tend to reflect inorganic mercury exposure and total mercury levels in whole blood are more indicative of methylmercury exposure. However other fluids, such as saliva, hairs or nails or faeces have been proposed and used. Total mercury in red blood cells may be a suitable proxy for methylmercury exposure. The mercury concentration in saliva and scalp hair is more controversial. According to Pesch et al. (2002), hairs reflect fish consumption, the age of a child and the smoking habits of parents, with a low correlation between the hair and urine mercury content. Mercury content in saliva ranged between 0.32 and 4.5 µg/l and below the limit of quantification for more than 70% of the samples. Pesch et al. (2002) concluded that saliva does not seem to be a suitable tool to monitor the mercury burden. Although in general no correlation was found between elemental concentration in hairs and internal organs (Yoshinaga et al. 1990) a hair-organ relationship was found by Suzuki et al. (1993) for mercury concentration. More recently, the total mercury levels in hair, toenail and urine were shown to result from fish consumption, but the method was applicable neither to occupational exposure nor to dental filling mercury release (Ohno et al. 2007).

Mercury levels in saliva determined by cold vapour atomic absorption spectrometry did not correlate with the concentration in blood and urine, and therefore is not recommended for a biological monitoring (Zimmer et al. 2002). Faeces reflect the elimination of metallic mercury by abrasion and therefore do not present any usefulness in the context of a potential burden. Generally blood and urine are preferred for the assessment of mercury exposure.

3.3.3. Mercury toxicology

In general, the toxicology of mercury is highly dependent on the route of administration, the exposure conditions and the speciation of the mercury. Since human exposure to mercury from dental amalgams may occur by inhalation of mercury vapour released from the dental fillings into the oral cavity, by ingestion of the released elemental mercury, or swallowing small pieces of amalgam releasing elemental mercury in the alimentary tract, this discussion focuses on the toxicology of elemental mercury.

3.3.3.1. Toxicokinetics

Oral ingestion of elemental mercury results only in a very limited absorption, typically < 0.01 % of the dose (ATSDR 1999, MAK 1999, Klaassen 2001). Dermal absorption of liquid elemental mercury is also very limited. In contrast, approximately 80 % of the inhaled elemental mercury is absorbed in the lungs. Due to the high lipid solubility, elemental mercury rapidly penetrates alveolar membranes and is then distributed to all tissues of the body. Elemental mercury is slowly oxidized in the blood in a saturable process to give Hg^{2+}, probably by catalases. Due to the ease of saturation of the enzymatic oxidation of elemental mercury to Hg^{2+}, the proportion of elemental mercury in blood increases with increasing dose of elemental mercury. A small part of the elemental mercury dose received is also eliminated by exhalation and a small part of the dose is also delivered to the central nervous system. Oxidation of elemental mercury may also occur in the central nervous system and result in an accumulation of Hg^{2+} in the central nervous system since Hg^{2+} is unable to cross the blood-brain barrier and diffuse out of the brain. Hg^{2+} is tightly bound to sulphydryl groups in proteins which represents the principal mode of action for its toxicity and is responsible for the slow elimination from the organism. It may be eliminated by excretion within urine and/or faeces. The elimination of elemental mercury or Hg^{2+} follows complex kinetics with half-lives in the range of 20 – 90 days. Usually, the kidney contains the highest concentration

of mercury following exposure to elemental mercury and Hg^{2+}. After repeated exposures, a steady state level of blood mercury is reached, this being influenced by the average intake of mercury. At the end of the exposure, mercury levels slowly decline.

3.3.3.2. Toxicity of Elemental Mercury

Due to the very low absorption of elemental mercury after oral intake, this section focuses on toxic effects observed after inhalation of elemental mercury. Due to the widespread use of mercury in industrial settings, a large and detailed database on human effects of elemental mercury inhalation is available. A number of reviews addressing the toxicity of elemental mercury have been published (MAK 1999, BAT 1997, UNEP 2002, ATSDR 1999, IRIS 2002)

The assessment of elemental mercury toxicity is mainly based on observations in occupationally exposed humans. Inhalation of extremely high concentrations of elemental mercury, in excess of 10 mg/m^3, may produce bronchitis and pneumonia, in addition to symptoms of the central nervous system. However, such concentrations are many orders of magnitude above those encountered through the release of elemental mercury from dental fillings. After long-term elemental mercury exposure in occupational settings, and under occupational hygiene conditions considered as poor by present standards, the major effects of elemental mercury reported are on the central nervous system. The major manifestations of mercury poisoning from inhalation of elemental mercury are increased excitability and tremors. Characteristic symptoms after long-term high dose exposures (the inhalation of concentrations above 0.5 mg/m^3 for many years) are muscle tremors in fingers, eye lids and lips, which may progress to chronic spasms of the extremities. Early signs of toxicity after inhalation of mercury are less specific and the early phase of toxicity is often referred to as "micromercurialism". Clinical findings in this condition are tremor, enlargement of the thyroid, increased uptake iodine in the thyroid, tachycardia, gingivitis and haematological changes. For diagnosis of the early phase of elemental mercury intoxications, at least three of these findings should be present along with increased mercury concentrations in blood or increased mercury excretion with urine. After chronic occupational exposure to mercury vapour, proteinuria and even a nephritic syndrome have been described in humans. The glomerular damage may progress to an interstitial immune-complex nephritis. Gingivitis and hypersalivation with a strong metallic taste are considered to be further symptoms of chronic inhalation exposure to elemental mercury.

Quantitative data on elemental mercury inhalation exposure, mercury concentrations in blood and urine and early effects of mercury toxicity have been established. The non-specific symptoms of micromercurialism are observed at long term exposures to elemental mercury air concentrations of 0.05 mg/m^3, or at concentrations of mercury of 35 µg/l in blood or 150 µg/l in urine. Overt neurotoxicity (tremor) occurs after long term inhalation of elemental mercury at concentrations between 0.1 and 0.2 mg/m^3 with resulting blood mercury concentrations between 70 – 140 µg/l and urinary mercury in the range of 300 – 600 µg/l (MAK 1999, BAT 1997, UNEP 2002, ATSDR 1999, IRIS 2002).

Occupational allergies to mercury were rare in the past, even with widespread exposures to elemental mercury at the workplace and the use of mercury in medicinal preparations (including the use of Hg^{2+} due to its bactericidal activity) and consumer products (Kanerva et al. 1993).

Regarding animal toxicity studies, no adequately performed studies with elemental mercury inhalation are available for evaluation. However, long term oral administration of Hg^{2+} to rodents causes glomerulonephritis, which was found to have an immune basis, thus being similar to the human disease described after long term elemental mercury inhalation (Bigazzi 1999, Havarinasab and Hultman 2005, Havarinasab et al. 2007).

Mercury compounds are well known for their immunosuppressive activity (Havarinasab and Hultman 2005). Organic mercury compounds such as methylmercury and

ethylmercury are much more potent suppressors of the immune system than inorganic mercury or elemental mercury. In a susceptible genotype of mice, inorganic mercury interacts with the immune system inducing immunostimulation, antinuclear antibodies and systemic immune-complex deposits, a syndrome designated as mercury-induced autoimmunity (Hultman et al. 1989, Reuter et al. 1989). In mice a similar effect was observed for mercury vapour (Warfvinge et al. 1995). In a genetically modified mercury susceptible rat model for autoimmune diseases, the Brown Norway (BN) rat, dental restorations with amalgam induced immune activation with an increase in IgE plasma concentrations, and immune complex deposits in systemic organs including the kidney, whereas this was not observed in BN rats receiving composite resin restorations, or mercury resistant Lewis rats (Hultman et al. 1998). Another model for studying mercury induced autoimmunity is the New Zealand White rabbit in which mercuric chloride treatment results in immune deposits in kidneys and other organs (Roman-Franco et al. 1978).

3.3.4. Toxicology of other metallic elements in amalgam

3.3.4.1. Toxicology of silver

Despite the widespread use of silver and silver ions in industry and for medicinal purposes, only limited information on silver toxicity is available. Silver exposure is ubiquitous in the general population and dietary intake is estimated at 70 – 90 µg/day. Silver ions may be absorbed from the gastrointestinal tract after oral uptake or after inhalation of silver containing dusts. At higher local concentrations, silver ions may produce skin and gastrointestinal tract irritation. The critical effect of excessive silver absorption is argyria, a deposit of silver sulphide resulting in local or generalized impregnation of tissues. Other specific toxic effects of silver in humans or in experimental animals have not been described. Silver does have antimicrobial activity (Drake and Hazelwood 2005).

3.3.4.2. Toxicology of copper

Copper is an essential nutrient that is incorporated into a number of metalloenzymes. Symptoms associated with copper deficiency in humans include anaemia and leucopoenia. Copper released from dental amalgams may be readily absorbed from the stomach and small intestine. After nutritional requirements at the recommended daily intake are met (2 mg/person), excess copper (well above TDI of 0.5 mg/kg bw/day) is absorbed into gastrointestinal mucosal cells and into the liver induces the synthesis of and binds to metallothionein. Bound copper is excreted when the cell is sloughed off or released into bile and excreted in the faeces. Exposure to excessive levels of copper can result in a number of adverse health effects including liver and kidney damage, anaemia, immunotoxicity, and developmental toxicity. One of the most commonly reported adverse health effect of copper in humans is nausea, vomiting, and/or abdominal pain. The observed effects are not usually persistent and gastrointestinal effects have not been linked with other health effects. The liver is also a target of toxicity. Liver damage has been reported in individuals ingesting lethal doses of copper sulphate. Liver effects have also been observed in sensitive subpopulations such as individuals diagnosed with Wilson's disease or Indian childhood cirrhosis, or idiopathic copper toxicosis. These syndromes are genetic disorders that result in an accumulation of copper in the liver or with excessive copper exposure. Inflammation, necrosis, and altered serum markers of liver damage were observed in rats fed diets with copper sulphate levels that are at least 100 times higher than the nutritional requirements (Klaassen 2001).

3.3.4.3. Toxicology of tin

Humans chronically exposed to inorganic tin (e.g., stannic oxide dust or fumes) manifest a benign form of pneumoconiosis known as stannosis, which mainly involves the lower respiratory system. Gastrointestinal effects, such as nausea, vomiting, and diarrhoea

have been reported in subjects ingesting food items containing inorganic tin. Based on the available studies in humans, there is no evidence that inorganic tin affects reproduction or development in humans or that it is neurotoxic, mutagenic, or carcinogenic. Studies in animals have not clearly established potential target organs for inorganic tin toxicity. Of the effects described, signs of anaemia and gastrointestinal distension appear to be tin-related. No adverse reproductive or developmental effects of inorganic tin were reported. Studies in animals have shown that excess dietary tin reduces serum iron and copper levels. Excess doses of tin affects the metabolism of other metals such as copper, zinc, and iron. Due to the altered disposition of these metals, it is difficult to ascertain whether an effect is specific to tin itself or is due to fluctuations in tissue levels of other metals. Feeding a diet with excess tin to rats produced signs of anaemia and individuals with low levels of iron or copper may be at risk of developing signs of anaemia if they consume excessive amounts of tin. (Klaasen 2001).

3.3.4.4. Toxicology of zinc

Zinc is an essential nutrient and zinc deficiency has been associated with dermatitis, anorexia, growth retardation, poor wound healing, impaired reproductive capacity, and depressed mental function; an increased incidence of congenital malformations in infants has also been associated with zinc deficiency in the mothers. Nausea has been reported in humans exposed orally to high doses of zinc chloride. Other gastrointestinal symptoms reported in cases of excess zinc exposure include vomiting, abdominal cramps, and diarrhoea. The limited data suggest that single-dose exposures in the range of 140–560 mg zinc are sufficient to cause these effects, which are consistent with gastrointestinal irritation. Following longer-term exposure to doses of 0.5–2 mg zinc/kg/day, the observed symptoms are indicative of copper deficiency. The most noticeable manifestation of the decreased copper levels due to the interaction with zinc is anaemia, manifesting as decreased erythrocyte number. Long-term consumption of excess zinc may also result in decreased iron stores. Effects of zinc on reproductive or developmental end points have been noted in oral-exposure animal studies, but generally only at very high doses (>200 mg/kg/day) (Klaasen 2001).

3.3.4.5. Conclusions

The elements other than mercury contained with dental amalgam all have their own, different profiles in terms of essentiality and/or toxicology. There is no scientific evidence that any of those elements currently used in dental amalgam restorations constitute a risk of adverse health effects in individuals apart from allergic reactions to the individual elements.

3.3.5. General conclusions concerning correlation between exposure and toxicology (risk assessment)

A number of regulatory limits for mercury exposures have been set by various organisations. When using these regulatory limits describing safe intakes of mercury (safe as defined to be without toxic effects after lifetime exposure) it should be recognised that many of the values are recommended for dietary intake of mercury ions and methyl mercury. Therefore, these limits have only limited use for the assessment of mercury emissions from dental amalgams since the exposure in this case is inhalation or ingestion of elemental mercury. Due to the differences in toxicokinetics as outlined above, the assessment for mercury exposure from dental amalgams therefore should be based on resulting blood levels of mercury and/or urinary excretion of mercury. Toxicologically based limits for both of these media have been developed.

Due to the small dose received by inhalation of mercury from amalgams, a direct comparison of maximal mercury air concentration in the oral cavity of individuals with amalgam fillings and occupational limits for air concentrations of mercury requires consideration of absorbed dose. As shown in table 1, inhalation of mercury at the

occupational exposure limit results in an uptake of more then 300 µg of Hg per day, whereas inhalation of mercury from dental amalgams gives body burdens which are at least 20 fold lower then those resulting from occupational exposures at present limits for air concentrations.

Based on the evaluation of several longitudinal studies involving blood samples to determine mercury content over a prolonged time period, the German MAK-Commission (tasked to set occupational exposure limits which are without health risks) concluded that even many years of mercury exposure to concentrations that result in urinary mercury levels of 100 µg/l or even higher do not cause objective adverse effects. The urinary mercury levels were equivalent to mercury concentrations in blood of approximately 23 µg/l. The BAT-value (maximal permissible concentration of hazardous compounds or their metabolites in body fluids) was therefore set at 100 µg/l of urine or 25 µg/l of blood and is considered a No-adverse-effect-concentration for mercury in humans.

For the general population, the Federal Environment Agency (Umweltbundesamt (UBA)) derived reference values including general background exposure to mercury from various sources (fish and seafood consumption, mercury in other foods) of 1.4 µg/l of urine and of 2 µg mercury/L of blood in adults without amalgam fillings and with low seafood consumption. According to UBA, no adverse effects of mercury are observed at blood levels lower than 5 µg/l (including pregnant women) and urinary mercury concentrations lower than 0.7 µg/l. These assessments included both inorganic mercury and the more toxic methyl mercury (UBA 1999).

Table 1 Estimated average daily intake and retention of total mercury and mercury compounds in the general population.

Sources of exposure	Elemental mercury vapour	Inorganic mercury compounds	Methylmercury
Air	0.030 (0.024)	0.002 (0.001)	0.008 (0.0064)
Food			
Fish	0	0.600 (0.042)	2.4 (2.3)
Non-fish	0	3.6 (0.25)	0
Drinking water	0	0.050 (0.0035)	0
Dental amalgams	3.8 – 21 (3 – 17)	0	0
Total	3.9 – 21 (3 – 17)	4.3 (0.3)	2.41 (2.31)

Note: Values given are the estimated average daily intake (µg/day) for adults in the general population who are not occupationally exposed to mercury; the figures in parentheses represent the estimated amount retained in the body of an adult. In Europe, the intake of total mercury with food was estimated to be below 1 µg/kg body weight/week in adults (1 to 9 µg/person/day), depending on fish consumption (EFSA 2004)

Source: WHO 1990, WHO 1991

Table 2 gives respiratory air concentrations, blood levels and urinary excretion of mercury in individuals with amalgam fillings and compares these to levels of mercury considered safe for occupational exposures. It is clear that, although exposure to individuals with amalgam restorations does occur, the levels of exposure encountered as between 5 and 30 times lower than those permitted for occupational exposure.

Table 2 Respiratory air concentrations, blood levels and urinary excretion of mercury in individuals with amalgam fillings compared to levels of mercury considered safe for occupational exposures.

Medium	Individual with typical number of fillings	Occupational limit
Respiratory air concentration	3 – 17 µg Hg/day	346 µg Hg/day*
Urinary concentration of mercury	3.5 µg Hg/l	100 µg Hg/l
Blood concentration	3 – 5 µg Hg/l	25 µg Hg/l

*Based on an alveolar ventilation of 9 l/min, a retention of 0.8 for elemental mercury. The MAK-value was 0.1 mg/m^3 and 8h of occupational exposure.

3.3.6. Adverse effects in individuals with amalgam restorations

Mercury toxicity associated with methylmercury, elemental and inorganic mercury is well documented (see above). The question remains, however, whether metallic mercury exposure from dental amalgams is the cause of adverse health effects, including multiple sclerosis, autism, CNS and renal damage, chronic fatigue, memory impairment and depression. These conditions and their etiology have been studied extensively and risk factors are well defined (see the review article by Brownawell et al. 2005).

The parameters of the adverse effects may be toxicological, allergic and/or psychological.

3.3.6.1. Localized mucosal reactions

The possibility that restorative dental materials could be responsible for lesions within the mouth associated with direct contact between the material and the oral mucosa is obviously of importance. Such localised reactions are often discussed in the context of allergies and hypersensitivity.

In the dental clinic two reaction patterns are relevant: the delayed reaction (Type IV) and the immediate reaction (Type I). In the type IV reaction, the incomplete allergens (haptens) are brought in contact with tissue proteins by way of the oral mucosa to form complete allergens. Provided that previous sensitisation has taken place, specialised T-lymphocytes now produce inflammatory mediators causing tissue damage, seen as contact mucositis, i.e. intra-oral diffuse, red zones, blisters, or ulceration with pain and burning sensation. The inflammation is not always limited to the exposure site. Contact dermatitis may be observed in the face or more distant locations as urticarial or eczematous reactions. A suspected Type IV reaction may be confirmed with an epidermal patch test (see standard textbook such as Roitt and Delves 2006)

An immediate type (Type I) allergic reaction is based on the release of vasoactive humoral mediators from mast cells or basophilic granulocytes. These mediators are released from the cells upon contact with antigens binding to the IgE antibodies on their surface. The antigen specific IgE antibodies provide the specificity of the allergic response. The released mediators lead to increased capillary permeability and contraction of smooth muscles. The symptoms may consist of urticaria, asthmatic seizures, swelling of the mucosa of throat and eyes and even result in anaphylaxis, all seen within minutes. This immediate type hypersensitivity is in general associated with allergic responses to protein allergens. Potential full allergens encountered in restorative dentistry are mainly limited to the accessories used, including residual proteins from natural rubber latex in gloves, rubber dam, polishing remedies or parts of anaesthetic cartridges.

A chronic inflammatory response of the gingival tissue around restorations may be present, which appears as chronic gingivitis, recurrent necrotic gingivitis and periodontal pockets. When patients with self-diagnosed oral problems (142 women and 76 men)

were examined, the mean concentration of mercury in the whole blood was 17.3 nmol/l and no value exceeded 50 nmol/l. Mental disorder was diagnosed in 93 cases (42.7%), including 41 cases of generalized anxiety disorder and 12 cases of panic disorder. A total of 82 patients (40%) did not work because of medical reasons or unemployment (Herrstrom and Hogstedt 1993). However, no correlation could be demonstrated between the oral symptoms and a generalized toxic effect of amalgam fillings.

Amalgam tattoos, which are occasionally observed, are associated with the iatrogenic introduction of small particles of dental amalgam, inadvertently implanted into oral soft tissues during dental procedures. Tattoos are resistant to protracted conventional therapies. Most of the foreign bodies examined by light and EDAX methods contained amalgam (amalgam dusts) that appears either as fine granular or larger globular structures implanted in gingival tissues. There is no free mercury, but large globular pieces of amalgam, which induce metallothionein expression in adjacent histiocytes. There is no consequence to the presence of tattoo, except the unpleasant dark blue staining of the gingiva (Lau et al. 2001) and currently there is no indication for the surgical removal of these tattoos.

Metals in close contact with skin and mucosa are well-recognized causes of contact dermatitis including mercury (Garner 2004). Oral lichen planus is associated with dental restorations and one of the causes may be contact allergy to constituents of dental amalgam. Khamaysi et al. (2006) examined 134 patients presenting with mucosal reactions, where the most frequent oral manifestations were cheilitis, peri-oral dermatitis, burning mouth, lichenoid reactions and orofacial granulomatosis. Patch testing showed several allergens in this group, including metals such as gold, cobalt, platinum, nickel and mercury. No specific association between any one metal and a specific clinical manifestation was found but mercury was not a significant factor contributing to the pathogenesis of oral lichenoid reactions.

When dental amalgam was removed in a subgroup of patients suspected of amalgam contact hypersensitivity lesions, considerable improvement was seen (Thornhill et al. 2003) Seventy percent of these patients also showed a positive skin patch test for amalgam or mercury. Total or partial replacement of amalgam fillings following a positive skin patch test reaction to ammoniated mercury, metallic mercury, or amalgam is followed by significant improvement, when the lesions are confined to areas in close contact with amalgam fillings. Even if there is no topographic relationship, improvement occurs in nearly all patch test-positive patients (Laeijendecker et al. 2004). If mercury is the allergen, the removal of the filling should lead to complete remission after about 3 months. A total of 51 patients who had oral lichenoid lesions suspected to be related to the dental restorations were investigated. Fifty three per cent (n= 27) of the patients had positive patch test reactions, 24 of them for one or more mercury compounds. Nine months after the removal of the fillings, 42% of the patients were completely healed. Improvement was found in 47% especially when lesions were in close contact with restorations (Issa et al. 2005). This possible adverse effect of dental amalgam is widely recognized and reflected in contemporary contra-indications for the use of this material.

Burning Mouth Syndrome can occasionally be associated with a change in the appearance of the clinically normal oral mucosa. In some case it may be associated with a strong allergy to mercury and a positive patch test supports the removal of the amalgam filling. Full recovery and complete remission of systemic dermatitis may occur after removal of a mercury-containing filling (Pigatto et al. 2004). Patch-test analysis for the determination of mercury allergies was carried out by Wong & Freeman (2003) on a group of 84 patients with reticulate, lacy, plaque-like or erosive oral lichenoid lesions. Thirty three (39%) of the patients had positive patch test findings. The amalgam fillings were removed for thirty of these, and an improvement was seen within 3 months in 28 of these (87%).

3.3.6.2. Systemic reactions

General

There are some epidemiological studies on the health effects of mercury released by dental amalgam fillings. The effects reported may affect the nervous and renal system, and also the immune, respiratory, cardiovascular, gastro-intestinal, haematological, and reproductive systems. Bates (2006) reviewed these studies and concluded that the available studies show little evidence of effects on general chronic disease incidence or mortality.

Reports of effects caused by amalgams have involved many diseases. A few data suggest that the mercury from amalgam reduces lymphocytes responses, compromising immune functions. As a consequence, amalgam has been implicated in the development of Alzheimer‘s disease and there is a long list of heterogeneous diseases that might be due to the accumulation of mercury in the body. However, for many of the claims, scientific investigations have tended to provide either refutation or evidence of a lack of correlation. There is usually little evidence of general chronic disease incidence or mortality associated with dental amalgams. In one New Zealand retrospective cohort study of 20.000 military personnel (84% males) followed up for 20 years, data on dental history was linked with national mortality, hospital discharge and cancer incidence databases. There was no association between dental amalgams and chronic fatigue syndrome or kidney diseases. The number of cases for investigation of Alzheimer’s or Parkinson‘s diseases was insufficient to draw any conclusion (Bates et al. 2004).

No link has been detected between mercury exposure and negative health effects with respect to dentist mortality, although the mercury blood level is higher in dentists than in a control population. The life span of dentists was shown to be three years greater than that for a control non-dentist group. The same type of effect was seen with many other parameters, indicating that the general health of dentists is good (McComb 1997).

In several situations, such as with Alzheimer’s and Parkinson’s diseases, there is no definitive answer concerning causation and caution has to be expressed, bearing in mind that this collection of diseases possibly associated with amalgam restorations bears little comparison with the known characteristics of the occupational toxicology of mercury.

The available evidence is discussed here in relation to specific organ systems.

Urinary system

A few studies have investigated the relation between amalgam and kidney function. Except for a small increase in N-acetyl-β-glucosaminidase, which is not considered to have any clinical significance, no parameters suggest that there is an association between amalgam fillings and kidney diseases. Evidence of renal disease was investigated among dentists, who are exposed to greater levels of mercury vapour than other populations, but no kidney dysfunction has been found. During on-site screening of dentists at annual American Dental Association meetings in 1985 and 1986, the mean urinary values were of mercury were 5.8- 7.6 µg /l , showing that dentists have a much higher mean urinary mercury, but there was no evidence that they exhibited any higher levels of morbidity, mortality and kidney dysfunctions (see for review: Dodes 2001). It is recognized that mercury does induce antinuclear antibodies and the induction of metal-associated autoimmunity in general, with some effects in the renal system (Bigazzi 1999).

Bellinger et al. (2006), in a comprehensive neurophysiological and urological analysis of 534 children followed for five years in a randomized clinical trial, comparing groups with amalgam restorations and alternative composite resins. There were no statistically significant differences between these two groups in renal glomerular function as measured by creatinine adjusted albumin levels.

The overall conclusion of the epidemiological studies suggests that there is no evidence that dental amalgam fillings affect kidney function in human.

Neurological System

Alzheimer's Disease

Inorganic mercury is a neurotoxin at high doses and it has therefore been suspected to play a role in the pathogenesis of neurodegenerative diseases such as Alzheimer's disease. Mercury vapour released by dental amalgam has been suspected of being one of the potential factors relating to this disease. However, when autopsies of subjects with and without Alzheimer's disease were carried out, no significant association of the disease with the number, the surface area or history of dental restorations was found. Retrospective cohort studies provide limited evidence of an association between amalgam and this disease (Bates et al. 2004). There was no significant difference in brain mercury levels between Alzheimer's disease and control subjects (Saxe et al. 1999).

Multiple Sclerosis

Although a few articles have concluded that there is some suggestion of a possible association between amalgam and multiple sclerosis, the evidence is inconclusive. A systematic review and meta-analysis suggests that there is a non-statistically significant difference in the risk of multiple sclerosis between individuals with and without amalgam restorations. However, the small number of subjects, inadequate exposure data, and inadequate control recruitment methods constitute limitations of the available studies. Without any knowledge on the size of the restoration, the surface area, the duration of the exposure, it is not possible to confirm or to rule out any link between amalgam and multiple sclerosis (Aminzadeh and Etminan 2007).

One case control comparison between 132 multiple sclerosis patients and 423 controls failed to demonstrate an association between the number of dental fillings, the duration of the exposure to dental amalgam and the condition (Casetta et al. 2001). However, in one further study a correlation was found between the number of amalgam restorations in the a multiple sclerosis group of 39 females compared to matched 62 controls, although it is impossible to establish any temporal relationship concerning cause and effect in such a situation; in other words it may not be possible to determine whether patients with such a neurological condition are more likely to need dental restorations because of difficulty with oral hygiene (McGrother et al. 1999). In another case-control study (Bangsi et al. 1998) a comparison was made between 143 multiple sclerosis patients and 128 controls, where neither the number nor the duration of exposure to amalgam fillings supported an increased risk of multiple sclerosis.

Parkinson's Disease

Parkinson's disease involves the aggregation of alpha-synuclein forming fibrils, the major constituent of intracellular protein inclusions (Lewy bodies and Lewy neurites) in dopaminergic neurons of the substantia nigra. Aluminium, copper, iron, cobalt and manganese are effective di- and trivalent metals that may be involved in this process; however mercury is also included as a risk factor. Even low concentrations of some metals can directly induce alpha-synuclein formation (Uversky et al. 2001). An analysis of 130 patients with confirmed disease versus matched controls support the view that the disease has a multifactorial etiology, involving genetic, environmental, trauma, and possibly other factors (Semchuk et al. 1993). Consequently, it is very difficult to establish any causal link with a putative agent such as dental amalgam. In one study, occupational mercury exposure was related to an eightfold increase in risk of Parkinson's disease (Schulte et al. 1996), but this is still a matter of debate and there is no scientifically sound report establishing a direct relation with dental fillings.

Paresthesia

Paresthesia is considered to be the most sensitive neurological effect, and is produced by blood mercury concentration in the range of 34 to 97µg/l. A deficit in neurocognitive functions may result from doses below those considered to be the threshold for general clinical effects. Accentuated postural tremor, impaired coordination, positive Romberg sign, and reduced distal sensation suggesting peripheral neuropathy have been reported especially among those occupationally exposed to mercury. Low-dose, long-term exposure to mercury vapour from dental amalgam has been suggested as a risk factor. However, Kingman et al. investigated the relation between amalgam exposure and neurological functions in a cohort of 2038 participants (Kingman et al. 2005). No significant trends between neurological signs (tremor, alternate motion rate, coordination, vibrotactile threshold deficit, proximal and distal strength and station) and the presence of dental amalgam were detected. Therefore, no link could be established between peripheral neuropathy and amalgam exposure.

Autism

Mercury and an infectious agent such as the measles virus may contribute to the immunopathogenesis of autism (Cohly and Panja 2005). Studies showing elevated brain specific antibodies support an autoimmune mechanism. A virus may initiate the process but subsequent activation of cytokines is the damaging factor associated with the disease. Environmental exposure to mercury is suggested to modulate immune homeostasis. These hypotheses have not yet been demonstrated, but their involvement in autism cannot be ruled out (Cohly and Panja 2005). Some data are related to the possible effects of the mercury-containing Thimerosal, included in certain vaccines to protect from bacterial and fungal contamination. One retrospective cohort study did not support the possibility that Thimerosal exposure causes neurodevelopmental disorders (Andrews et al. 2004). The systematic critical review of the articles published between 1966 and 2004 does not support any relationship between the mercury-containing vaccine and clinical findings (Parker et al. 2004). A report for the Food and Drug Administration by the Institute of Medicine (IOM 2004) confirms that no link has been yet established between vaccines, Thimerosal and autism. There is no evidence of a causal relationship between dental amalgam and autism.

Amyotrophic Lateral Sclerosis

There is no evidence for a relationship between Amyotrophic Lateral Sclerosis (ALS) and mercury. A retrospective case-control study was conducted on 66 ALS patients and 66 age- and sex-matched control patients. No association was found between heavy metal exposure and the pathogenesis of ALS (Gresham et al. 1986).

Psychological Conditions

During the past two decades, mercury and heavy metals have been claimed to be responsible for a series of mental health problems, with a variety of symptoms. Between 1978 and 2007, a total of 53 publications in international journals were published and listed in MedLine, with an increased tendency to take into account the psychological and psychiatric aspects of these patients. However, evidence is lacking for a causal link between mercury and human mental health problems or psychological conditions.

A series of self-assessed patients were referred to the Dental Biomaterials Adverse Reaction Unit in Bergen, Norway (Lygre et al. 2005). Patient's complaints were heterogeneous. Many individuals displayed multiple subjective symptoms associated with several organ systems. The most common were fatigue, muscle and joint pain, dizziness and headache. Intra-oral symptoms were related to burning sensations, taste disturbances and dry mouth. After removal of the mercury-containing fillings, a small decrease in the intensity of different symptoms was noted. Intra-oral symptoms were decreased and the decrease was statistically significant for taste disturbances ($p=0.001$),

dry mouth (p=0.034), and stiffness/paresthesia (p=0.05). However, the symptoms were still higher than in a reference group sampled from the general population in Norway.

A psychiatric diagnosis was established in 70% of the patients referred for self-reported complaints, which they had attributed to amalgam restorations; this compared to 14% in the control group. The prevailing symptoms were anxiety, asthenia and depression. Mercury levels were similar in the two groups, and far below the critical levels of mercury intoxication. No positive patch test was found in any of the two groups. As the number of fillings and the mercury level were similar in the two groups, the authors concluded that mercury was not the cause of the impaired health reported by the patients, and that the reported symptoms were parts of a broad spectrum of mental disorders (Bratel et al. 1997a,b).

The psychological/psychiatric, odontological and medical aspects of patients with symptoms attributed to the side effects of mercury-containing dental filings were studied in a total of 67 patients and 64 controls matched for age, sex, and residential area. The high prevalence of psychiatric disorders (89% in the patient group) compared to the control group (6%) seems to constitute the main characteristic of the patients. The clinic and medical data did not provide any explanation on the occurrence of the symptoms (Bagedahl-Strindlund et al. 1997).

General neuropsychological and neurophysiological functions

One epidemiologic study showed no evidence of deterioration of performance associated with amalgam exposure. The evaluation of relationships between amalgam fillings and any decrease of peripheral neurological function did not allow any correlation to be established. The mouths of 2038 US military personnel were examined, the number of oral fillings scored and neurological function assessed (Kingman et al. 2005). Consistent with other studies, no evidence of effects of amalgam fillings on neurological functions was found.

Another study (Factor-Litvak et al. 2003) was carried out on 550 adults, aged between 30 and 49 years. Urinary mercury was 1.7µg/gC (range 0.09-17.8), the mean number of amalgam surfaces was 10.6 (range 0-19). It was concluded that mercury exposure derived from dental amalgam was not associated with any detectable deficit in cognitive or fine motor functioning.

While many individuals consider that their neuropsychological conditions are related to exposure to dental amalgam the literature contains no credible supportive data

Psychological Development

Two randomized, controlled clinical trials have been carried out on the neuropsychological and renal effects of dental amalgam in children (Bellinger et al. 2006 and 2007, DeRouen et al. 2006). In the first study 534 children aged 6 to 10 years living in New England area (USA), were randomly assigned to receive dental restorations using either amalgam (n=267) or resin composites (n=267). They were examined after a 5-year period. No difference appeared in full-scale IQ. No difference was found in the general memory index. Over the 5-year period, a significantly higher mean urinary mercury level was noted, but no renal effect was observed (Bellinger et al. 2006). The latest publication from this group (Bellinger et al. 2006), concludes that the exposure to mercury from dental amalgam was not associated with any adverse neuropsychological effects over a five year period and that the use of dental amalgam is not associated with an increase in children's risk of experiencing neuropsychological dysfunction. Another randomized clinical trial with annual follow-up for 7 years was carried out on 507 children in Lisbon, Portugal. The children received either amalgam restorations (n=253) or resin composites (n=254). The creatinine-adjusted urinary mercury levels were 1.8µg/g in the amalgam group, and 1.9µg/g in the composite group. No statistically significant difference was found in measures of memory, attention, visual function, or nerve conduction velocities over all the 7 years of follow-up. The authors noticed also that the

need for additional restorative treatment was approximately 50% higher in the composite group. These data suggest that exposure to dental amalgam restorations within this age range has no effect on psychological development, with the superior performance of the amalgams compared to alternatives being noteworthy, although of course each procedure with a non-amalgam alternative would normally be less invasive.

As noted above, epidemiological evidence supports the view that low-level mercury exposure is not a cause of autism. Based on a recent meta-analysis, from all the published data, the risk of neurodevelopmental disabilities from low-level methylmercury exposure has not been established (Ng et al. 2007).

There is evidence of *in utero* exposure of mercury to the fetus, or in infancy through the breast milk transfer. The relationship between mercury exposure from dental filling placement during pregnancy and low birth weight risk was investigated on a cohort of 1117 women with low-birth weight infants (< 2.500 g) compared with 4468 women with infants weighting 2.500g or more. The study found no evidence that the mercury-containing dental fillings placed during pregnancy increased low-birth-weight risk (Hujoel et al. 2005).

Immune System

It has already been noted that mercury is able to induce autoimmunity in susceptible strains of rodents and so the question arises as to whether such effects are seen in humans with respect to amalgam related mercury exposure. In man a correlation between plasma mercury and IgE levels has not been demonstrated, while contradictory results have been seen with other immunoglobulins (Langworth et al. 1993, Queiroz et al. 1994, Herrström et al. 1994, 1997). No association was found between the number of fillings in individuals and Henoch-Schönlein purpura and acute glomerulonephritis, which are all autoimmune diseases. With respect to the reduced lymphocyte responses, Mackert et al. (1991) showed no indication that amalgam affects the human immune system. Epidemiologic studies have shown that occupational exposure to mercury does not usually result in autoimmunity.

Mercury does induce antinuclear antibodies, scleroderma-like diseases, lichen planus, or membranous nephropathy in some individuals. Immunogenetic and pharmacogenetic factors are responsible for the induction of metal-associated autoimmunity in general (Bigazzi 1999). In addition to estrogen replacement therapy, other factors including mercuric chloride are putative risk factors for the development of lupus, scleroderma, and Reynaud disease. Mercuric chloride causes complex glomerulonephritis and autoantibodies recognizing a nucleolar protein, fibrillarin. Antibodies directed against fibrillarin are higher in scleroderma patients. Urinary mercury excretion has been reported to be higher in scleroderma patients who are positive for antifibrillarin antibodies. However this level is still in the normal and unexposed ranges, and these patients never develop immune complex glomerulonephritis (Mayes 1999).

Another epidemiological study established that the effects of mercury occur at high doses which are above the levels to which humans would be exposed through fish consumption. The hypothesis was tested that mercury exposure does not cause autoimmune disease directly, but rather interacts with genetic predisposition, or with exposure to antigens or infection, and consequently exacerbates the disease, acting as a co-factor (Silbergeld et al. 2005).

As mentioned above, mercury like other metals is well known for its potency to induce allergic contact dermatitis (Garner 2004, Khamaysi et al. 2006). Indeed a high percentage of patients with localized mucosal reactions (oral lichen planus) shows a positive skin patch test for amalgam or mercury and removal of dental amalgam restorations can result in clinical improvement and even complete remission (see 3.3.6.1).

Reproductive system

Although reproductive effects have been addressed in several of the studies discussed in this Opinion, there is very little data available on this subject. There is no evidence of any association between amalgam restorations and either male of female fertility or obstetric parameters. One study that attempted to examine the question of fertility in detail failed to show any correlation between the mercury burden from amalgam restorations and male fertility disorders (Hanf et al. 1996). No evidence can be found for any relationship between amalgam restorations and birth defects.

Miscellaneous effects

The risk of coronary heart disease in man was studied in 470 cases of coronary heart disease (coronary and artery surgery, non fatal myocardial infarction, and fatal coronary heart disease). The mercury level was significantly correlated with fish consumption, and the level of mercury higher in dentists than in non-dentists. However, the mercury level was not associated with the risk of coronary heart disease (Yoshizawa et al. 2002). However, in a further study of a birth cohort, methylmercury exposure was associated with decreased sympathetic and parasympathetic modulation of the heart rate variability (Grandjean et al. 2004).

Long-term parenteral exposure to mercury may occur in patients with hypogammaglobulinaemia. The patients receive regular long-term replacement therapy with a concentrate of pooled human immunoglobulin G containing an organic mercury compound (Thiomersal) as a preservative. In 26 such patients, the urinary mercury level ranged from 4 to 734mg (mean 152mg) over treatment periods of 6 months to 17 years (mean 6.5 years). The urine concentration was raised in 73%, but without any correlation between urine mercury and the age of the patient, the IgG dose, or the duration of the treatment. No clinical evidence of toxicity was apparent (Haeney et al. 1979).

At the present time we may conclude that there is no epidemiological evidence to support the contention that mercury released by dental amalgam fillings contributes to the etiology of systemic diseases.

3.3.7. Epidemiological and clinical evidence concerning adverse effects of dental amalgam in dental personnel

As with individuals with amalgam restorations, adverse effects of mercury exposure in dental personnel have been the subject of numerous investigations (Hörsted-Bindslev 2004). These investigations have focussed on general reactions to chronic low-level exposure to mercury and atypical mercury body burden.

Jones et al. (2007) reported possible residual adverse effects from occupational mercury exposure in dentistry, Thirty years ago, the all-women exposed group worked with both silver and copper amalgam filling material without protective gloves or a ventilation system, resulting in chronic mercury exposure. The aim of the study was to test the null hypothesis in a survey of general and reproductive health, and a battery of nine neurobehavioral tests. The population was the 115 graduates of one school for dental nurses from 1968 to 1971. The sample was 43 mercury-exposed women and 32 matched controls. Statistical comparisons revealed that the two groups were equivalent on cognitive tasks and four of the six mood subscales. Significant between-group differences were found in current health symptom experience and reproductive health, especially early hysterectomy experience.

Concerning neurobehavioral studies, the review of Hörsted-Bindslev (2004) determined that it was justified to conclude that a risk of subtle neurotoxic changes may occur in dental personnel, who show a urine concentration of mercury below that which is seen when operating within the accepted threshold limit. However, they stressed that other

factors such as the daily exposure to high frequency vibrations (Åkesson et al. 1995) and stress may be equally important for the subtle behavioural changes. Also none of the studies referred to had shown the dental personnel to suffer the classical signs of mercury intoxication. This conclusion is mirrored by others: for example the principal conclusion of Ritchie et al. (2002) indicated that although differences in health and cognitive functioning between dentists and controls could be found, these differences could not be directly attributed to their exposure to mercury. They further recommended that environmental monitoring of dental surgeries should be regularly conducted to ensure that dental personnel were not exposed to mercury concentrations above the occupational exposure standard. The need for such measures will diminish with further reductions in the use of dental amalgam and fewer amalgam restorations being removed in everyday clinical practice. The possible exception may be dental personnel with a brain-derived neutrotrophic factor (BDNF) polymorphism which may be associated with abnormal intracellular trafficking in hippocampal neurons which, in turn, may be associated with episodic memory impairment, as described by Echeverria et al. (2005).

Non-neurological adverse effects of occupational exposure to mercury have been claimed to be many and varied, in a similar fashion to those alleged to occur in patients. Of particular concern to dental personnel have been the possible reproductive effects of occupational exposure to mercury. In contrast to the work of Rowland et al. (1994) which reported that chair-side assistants with a high occupational exposure to mercury were less fertile than unexposed controls, a substantial study in Norway by Dahl et al. (1999) found no difference in fertility between high school teachers and dental surgeons, of whom one-third placed more than 50 restorations of dental amalgam a week. Work by Lindbohm et al. (2007) found a slightly increased risk of miscarriage amongst "dental workers" with occupational exposure to dental amalgam, but no pattern of dose-response was found. Lindbohm et al. (2007) concluded that no strong association or clear dose-response relationship could be observed between occupational exposure to chemical agents or restorative materials (including dental amalgam) and the risk of miscarriage amongst dental personnel. It was acknowledged, however, that the possibility of a slightly increased risk of miscarriage among exposed workers could not be excluded. Concerning cytogenetic damage in dentists exposed to mercury, Atesagaoglu et al. (2006) found that examination of leukocytes from dentists exposed to mercury vapour below concentrations of 0.1mg/m^3 failed to reveal cytogenetic damage.

3.3.8. Life-cycle of mercury in relation to dental amalgam

This Opinion is concerned with the possible direct effects on human health arising from the use of amalgams, relating both to patients and dental personnel. There is an obvious life cycle for the mercury used in these amalgams. This starts with the opening of a packaged amalgam product in the dental clinic, followed by its clinical handling during placement and possible subsequent manipulation or removal, the possible excretion or exhalation of mercury from recipients throughout their lifetime, and culminates with the disposal of the body. Implicit in this life cycle is the exposure of the environment in general and the possibility of indirect effects on human health in general. The detailed discussion of these life cycle factors and environmental effects is outside the scope of this Opinion. It is noted, however, that amalgam waste management, including the disposal of packaging materials and surplus amalgam is take seriously in the dental profession with respect to dental clinics and offices (Jokstad and Fan 2006) and detailed studies have recently been performed on the mercury generation from dental waste amalgam and its potential for both recycling and environmental exposure (Drummond et al. 2003). With respect to disposal of amalgam-containing bodies, no significant information can be found about contamination at burial sites, but it is known that cremation process will yield mercury emissions (Santarsiero et al. 2006). These have been estimated to range from 0.036 to 2.140 g mercury per corpse, with mercury concentrations ranging from 0.005 to 0.300 mg/m^3.

3.3.9. Experience with non mercury-based fillings / amalgams

Mercury is not the only element that is liquid at room temperature and some others have also been considered for use in dentistry. As reported by Hero and Okabe (1994), gallium has been in use, in limited amounts, since 1956, but they did note problems with corrosion resistance and overall biocompatibility. Dunne et al. (2005) have recently published a longitudinal controlled clinical study of a commercially available gallium based restorative material and found the clinical performance so grossly inferior to a control amalgam that its continued clinical use could not be justified. Indium has also been considered, but mostly as an adjunct to mercury, possibly replacing up to 10% of the mercury, but there is little evidence about either performance or safety (Johnson et al. 1992) and its use is not considered significant.

3.3.10. General Observations on Amalgam Efficacy

The efficacy, longevity and general performance of amalgam restorations has been assessed on many occasions in the past, and it is not necessary to review these studies here. Whatever the material chosen, direct restorations may fail, primarily through secondary caries, fracture of the restoration or tooth, marginal deficiencies or wear. The rates at which these failures occur are difficult to compare since they will vary with clinical technique and patient characteristics, and since there have been improvements to the quality of all materials over time. It remains the view, however, that from mechanical functionality and longevity perspectives and resistance to secondary caries, possibly through anti-bacterial activity, amalgam will outlast alternative materials under many circumstances (Mitchell RJ et al. 2007). From such perspectives, it may still be the material of choice with many dental practitioners for large restorations and the replacement of large restorations. It is with respect to their aesthetics and non-adhesive character, which means that larger cavities have to be prepared, often with excessive tooth tissue removal, that amalgams may be seen to be inferior to the alternatives, and it is this, and not overall longevity, that is driving a change to these alternatives.

3.3.11. Conclusions on Dental Amalgam

We emphasise that dental amalgam remains an effective restorative material and, from the several perspectives of performance and economics, may be considered the material of choice for some restorations in posterior teeth. However, because dental amalgam is not tooth-coloured nor does it adhere to remaining tooth tissues, its use has been decreasing in recent years and tooth-coloured filling materials have become increasingly more popular, consistent with the general trend towards more minimal intervention techniques in dentistry. There has been for some years a move towards non-amalgam, adhesive, tooth coloured restorations. This trend shows some variations within and between countries, and is emphasized by the significant reduction of training in the placement of dental amalgam restorations and the corresponding increase in training in the use of amalgam alternatives in a growing number of dental schools. We anticipate there to be a continued and sustained reduction in the use of dental amalgam in oral health care provision across the European Union, the rate of which is dependant on trends in dental education towards the increasing use of alternative materials in place of amalgam and the possible reduced availability of mercury products in general.

It is recognized that mercury which is the major metallic element used in dental amalgam, does constitute a toxicological hazard in general, with reasonably well defined characteristics for the major forms of exposure. It is accepted that the reduction in use of mercury in human activity would be beneficial, both for the general decrease in human exposure and from environmental considerations.

However, with respect to the debate about the possibility of causal relationships between the use of mercury containing amalgam and a wide variety of adverse systemic health effects and taking into account many studies and investigations into this putative causal link, there is no unequivocal evidence to support this possibility. These studies have

included assessments in children and in pregnant and lactating women. It is generally concluded that no increased risks on adverse systemic effects exist and we do not consider that the current use of dental amalgam poses a risk of systemic disease. It is recognized that some local adverse effects are occasionally seen with dental amalgam fillings, but the incidence is low and normally readily managed. It is also recognised that there have been reports of reactions to dental amalgam, which are not supported by scientific evidence, but indicate that very occasionally an individual may have unexplained atypical physical or other reactions attributed to mercury.

The main exposure to mercury in individuals with amalgam restorations occurs during placement or removal of the fillings. The transient mercury release during placement and removal will result in exposure to the patients and also to the dental personnel. It should be noted that the removal of amalgam restorations will result in an acute relatively high exposure of the individual patient to mercury, compared to leaving the amalgam filling intact. We find no evidence of clinical justification to remove clinically satisfactory amalgam restorations with the exception of those patients which are suspected to have allergic reactions and positive patch tests.

3.4. Alternatives

3.4.1. Classification of alternatives according to chemical composition

Increasing use is made of tooth-coloured materials in restorative dentistry. Currently, most attention is focused on direct restorative materials, such as composites, glass ionomer cement, compomers, giomers and sealants, and less on indirect materials, such as dental porcelain. The reason is that the use of indirect materials is costly and time consuming (in terms of procedure) even though these materials show excellent biocompatibility properties and durability, particularly a high resistance to wear and distortion.

A composite is generally defined as a material composed of two or more distinct phases (O'Brien 2002). Dental composites consist of a polymerisable resin base containing a ceramic filler. They may be classified in a number of ways, the normal method being based on the size, distribution, and volume percentage of the ceramic particles. With respect to their size, this classification yields the so-called macrofill, midifill, minifill, microfill and nanofill composites. Macrofill composites contain ceramic particles ranging in size form 10-100 µm, midifill in the range from 1-10 µm, minifill in the range from 0.1-1 µm, microfill in the range from 0.01-1 µm and nanofill in the range from 0.005-0.01 µm. Hybrid composites contain a mix of two particles size fraction of fillers, e.g. midi-hybrids consist of mix of microfillers and midifillers, mini-hybrids or micro-hybrids consist of a mix of microfillers and minifillers and nanohybrids consist of a mix of nanofillers and minifillers.

Filler loading varies significantly between the different composite materials. For example in a macrofill and hybrid composite, the filler material occupies 50-80% of the composite by weight, while in a microfill composite the filler loading is limited to about 35-50% by weight.

Currently, almost all composites are supplied as a pre-packed single-paste system, the curing of the resins occurring by light activation. Different types of commercially available curing units have different light intensities and utilise different light sources. Light-curing units use halogen-based, light-emitting diode (LED), plasma-arc, or laser technology. The energy levels range from 300 to more than 3,000 milliwatts/cm^2.

Glass ionomer cements were introduced in 1972 by Wilson and Kent (1972) and may be considered as a combination of silicate and polyacrylate cement system. Glass ionomer cements bind to dental hard tissues. Polyalkenoate chains enter the molecular surface of dental apatite, replacing phosphate ions, which leads to the development of an ion-enriched layer of cement that is firmly attached to the tooth (Wilson et al. 1983). In

addition to the original concept of glass ionomer cement, certain resin modified cements are now used in order to improve functionality.

Compomers were introduced in the 1990's and combine some of the benefits of composites and glass-ionomer cements. However, compomers do not bond to hard dental tissue. Giomers have been recently introduced and feature the hybridization of glass-ionomer and composite resins. They contain an adhesive promoting monomer and a bonding polymer catalyst, which allow bonding to hard tooth tissues.

Sealants are flowable resins and high viscous glass ionomers that are applied to seal pits and fissures in permanent teeth in order to prevent the occurrence of caries.

3.4.2. Chemical characterisation of alternative materials

3.4.2.1. Composites

Dental composites are composed of a wide variety of components with different chemical composition (O'Brien 2002, Powers and Wataha 2007, Roeters and de Kloet 1998). There is inadequate data on the composition and leachables of these materials, which is sometimes reflected in the material safety data sheets (MSDS) (Henriks-Eckerman and Kanerva, 1997)

Filler material

The filler materials are of inorganic composition, such as silica glass (SiO_2), alumina glass (Al_2O_3), and combinations of glass and sodium fluoride. Silica glass is made of beach sand and ordinary glass, but also of crystalline quartz, pyrolytic silica and specially engineered aluminium silicates (e.g. barium, strontium or lithium aluminium silicate glass). Alumina glass is made of crystalline corundum, while sodium-calcium-alumina-fluorosilicate glass is an example of a combination glass. A combination glass has to be considered as an engineered mixture of various glasses, which can serve as a source of fluoride ions. The radiopacity of composites is obtained by the addition of barium, strontium, lithium or ytterbium fluoride (YF3) to the filler particles.

Matrix material

The matrix is of organic composition. A large group of different aromatic and diacrylate monomers and oligomers is used, such as bisphenol A-glycidylmethacrylate (Bis-GMA), ethoxylated bisphenol A-methacrylate (Bis-EMA), triethyleneglycoldimethacrylate (TEGDMA) and urethane dimethacrylate (UDMA).

Filler particle incorporation

Coating of the filler particles with silane coupling agents (such as trialkoxysilane) ensures covalent coupling between filler and resin matrix. The carbon-carbon bond on silane molecules binds to the filler particles as well as resin monomer during polymerization of the composite.

Composite curing

Chemical agents (self or auto-cure) or, most commonly, light energy (ultraviolet or visible light) ensures polymerization of dental composites. Dual curing, i.e. a combination of chemical and light curing is also possible. For most composite systems in current use, visible light polymerization at 470 ± 20 nm wavelength is used. Depending on the curing method, various polymerisation initiators and accelerators are required. Initiators for chemical curing are usually benzoyl peroxide and benzene sulphinic acid which initiate polymerisation in the presence of an aromatic tertiary amine. For light curing systems,

camphorquinone is normally used in conjunction with an aliphatic tertiary amine as accelerator.

Additional components

Inorganic oxides and organic compounds are pigments that are added to create a range of various composite shades.

Bonding to enamel and dentine

Bonding of the composite material to hard tooth tissues is achieved by use of a bonding system may that incorporates etchants, primers and resins. Chemical etching solutions, such as phosphoric acid, citric acid, and maleic acid are used to demineralise the tooth surface and increase the surface area. Subsequently, after rinsing and drying, a primer solution, composed of a low viscosity resin such as hydroxyethylmethacrylate may be applied to obtain optimal wetting of the surface for the bonding agent. In addition to water based primers, use is also made of acetone based primers, and primers without the addition of resins. Final bonding of the composite material is achieved by the application of a very thin resin layer. Classical bonding agents are composed of unfilled resin of similar composition as the resin matrix of the composite material. Newer bonding systems are composed of two components, one consisting of a resin and the other containing ethanol and a catalyst. Currently, there is a trend to simplify the bonding procedure by combining the etchant and primer and by supplying primer and bonding as one component.

3.4.2.2. Glass ionomer cements

In the original form, the powder component of these cements is a sodium-calcium-alumino-fluoro-silicate glass. The liquid component is composed of polyacrylic acid and tartaric acid. When the powder and liquid are mixed together, a three phase acid-base reaction occurs, involving calcium and aluminium ions leaching as the acid attacks the glass particles, hydrogel formation as the polyacrylic acid molecules crosslink, and polyalkenoate salt gelation as the polyalkenoate salt captures un-reacted glass.

In the resin modified cements, methacrylate monomers have been added to improve functionality with respect to higher strength and water resistance. The materials have been further modified by the addition of photo initiators so that light-curing can occur, but they maintain their ability to set by an acid-base reaction. The setting of resin modified glass ionomer cement is identical to the polymerization of composite resin. During this process, free radical species are generated.

3.4.2.3. Compomers

The main components of compomers are polymerisable dimethacrylate resins, such as urethane dimethacrylate and TCB, which is a reaction product of butane tetracarboxylic acid and hydroxyethylmethacrylate, and ion-leachable glass filler particles such as strontium fluorosilicate glass. The glass particles are partially silanised to achieve bonding with the resin matrix. The setting reaction is based on free radical polymerization using photoinitiators. During the setting reaction HEMA is released while fluoride release occurs after setting. Since compomers do not bind to enamel and dentine directly, a specific priming and bonding system has had to be developed, which includes the use of a tooth conditioner (34% phosphoric acid) and a light curing adhesive consisting of di- and trimethacrylate resins, functionalized amorphous silicon dioxide, dipentaerythritol penta acrylate monophosphate, photoinitiators, stabilizers, cetylamine hydrofluoride and acetone.

3.4.2.4. Giomers

Giomers are based on the technology of a reaction between fluoride containing glass and a liquid polyacid. The reacted glass particles are mixed with resin such as urethane dimethacrylate and hydroxyethylmethacrylate, and a catalyst to initiate polymerization. Bonding of the material is achieved through the use of self-etching primers that modify the smear layer and allow the penetration of the bonding agent into the dentine. The bonding agent releases fluoride. This group of materials may be used for restoration of small cavities, and also for pit and fissure sealing.

3.4.3. Toxicology of components of alternative materials

Clearly these alternative restorative materials are complex chemically, with many different components, setting reaction mechanisms and opportunities to interact with tissues of the individuals in whom they are placed. However, characteristics of exposure are very difficult to determine, bearing in mind that volumes of the materials used are very small, the residence time within the body of chemicals that take part in setting reactions is usually very short and the chemical and toxicological profiles of the set material are usually very different to those of the starting materials. In evaluating the possibilities for adverse effects arising from the clinical use of these materials, it is necessary to consider the evidence about the inherent toxicity of the chemicals used and the performance and behaviour of the restorations over time. Of interest to most investigations here have been the monomers used in polymerisation reactions, which may remain unreacted and therefore present in the set material, the acids used in various phases of the setting and etching processes and ions released from glasses. An extensive evaluation of the acute and chronic toxicity of materials used in various alternatives to dental amalgam was published by IARC (1999).

3.4.3.1. Short-term release of monomers during polymerisation

Unbound monomers and/or additives are eluted within the first hours of placement in the tooth cavity. The very nature of the polymerisation processes, that involve the absorption of light energy by the material, which will vary with depth within the restoration, and the subsequent conversion of monomer molecules into cross-linked macromolecules, inevitably means that some monomer molecules do not have the opportunity to take part because of diffusion limitations. The completeness of the polymerisation process is reflected by the degree of conversion. Between 15 and 50% of the methacrylate groups may remain un-reacted according to Ferracane (1994). Improvements in the material formulations has resulted in increasingly superior degrees of conversion in recent years and currently only 1.5 - 5% of groups should remain un-reacted. However, this is may be enough to contribute to major cytotoxic effects in vitro (Stanislawski et al. 1999). The effects may also be dependent on dentine permeability and residual dentine thickness (Bouillaguet et al. 1998) since dentine may absorb unbound monomers and therefore contributes to decrease the cytotoxicity of the material. This is not directly under the control of the dental surgeon although the formation of reactionary dentine may be stimulated by preparative steps. Dentine permeability may also be modified by calcium phosphate precipitation in the lumen of the tubules leading to sclerotic dentine formation. It has also been shown that the surface of composite resins exposed to oxygen during curing produces a non-polymerized surface layer rich in formaldehyde, which by itself is an additional factor of cell toxicity (Schmalz 1998).

Monomers have been identified in dental composites eluates by gas and liquid chromatography/mass spectrometry. A considerable concentration of the co-monomer triethyleneglycoldimethacrylate and minor concentrations of the basic monomers Bis-GMA and UDMA as well as the co-monomer HDDMA have been detected with these methods (Geurtsen 1998, Spahl et al. 1998). TEGDMA and the photostabiliser 2-hydro-4-

methoxybenzophenone (HMBP) are cytotoxic and inhibit cell growth (Geurtsen and Leyhausen 2001). The intracellular glutathione level may be decreased by 85% by TEGDMA (Stanislawski et al. 1999, Stanislawski et al 2000, Stanislawski et al 2003, Engelmann et al. 2001, Engelmann et al 2002).

An i*n vitro* evaluation of the cytotoxicity of 35 dental resin composite monomers and additives indicated moderate to severe cytotoxic effects (Geurtsen et al. 1998). The effects vary according to the material tested, but also they are strongly depending on the cells used for testing. For example, human periodontal ligament and pulp fibroblasts are more sensitive than 3T3 and gingival fibroblasts (Geurtsen et al. 1998). With the exception of a very few reports, there is a general consensus that resin-containing restorative materials are cytotoxic (Geurtsen et al 1998, Geurtsen 2000, Schmalz 1998), greater effects generally been seen at early intervals after preparation.

3.4.3.2. Leachable substances generated by erosion and degradation

Leachable components are released due to degradation or erosion over time, the leaching process being determined not only by the degradation process itself but also diffusivity through the material. Chemical degradation is caused by hydrolysis or enzymatic catalysis. Non-specific esterases, human saliva derived esterase and pseudocholinesterase may catalyze the biodegradation of composite resins (Geurtsen 2000, Jaffer et al. 2002, Finer et al. 2004). Incubated *in vitro* with cholesterol esterase, the composites may release 2,2-bis [4(2,3-hydroxypropoxy)-phenyl]propane (bis-HPPP) and TEGDMA for up to 32 days, the amount depending on the matrix/filler ratio (Shajii and Santerre, 1999).

It is also assumed that bonds in the pendant side chains of the macromolecule are attacked through the effect of thermal, mechanical and photochemical factors.

Water or other solvents may diffuse into the polymer, facilitating the release of degradation products, including oligomers and monomers. The leaching process is influenced by size and polarity and by hydrophilic and lipophilic characteristics of the released components (Geurtsen 1998). Softening of the Bis-GMA matrix allows the solvents to penetrate more easily and expand the polymer network, a process that facilitates the long-term diffusion of unbound monomers (Finer and Santerre 2004). Differences in the toxicity of monomers leached out in the short-term and long-term are not yet documented.

3.4.3.3. Release of ions

Many of the alternative materials release ions such as fluoride, strontium and aluminium ions. The fluoride is expected to be beneficial and reduce the development of secondary caries. Presumably, the fluoride content of toothpastes and nutriments reload the material so that the resins or resin modified glass ionomer cements do not become porous. Other ions are implicated in the colour of the restorative material, and these metal elements may interfere with the biocompatibility of the resin because they are implicated in the Fenton reaction producing reactive oxygen species that are cytotoxic. The concentration of fluoride and strontium is considered to be too low to produce cytotoxicity. In contrast, however, copper, aluminium and iron may be present in toxic concentrations. The cytotoxic cascade has been shown to be enhanced by metals such as aluminium and iron present in various amounts in some of these materials (Stanislawski et al. 1999, Stanislawski et al.2000, Stanislawski et al.2003).

3.4.3.4. Toxicity of composite resin monomers

Only limited toxicity data for the monomers used for in dental composite systems are available. Major differences in the degrees of cytotoxicity of various composite materials have been found (Schedle et al. 1998, Franz et al. 2003, Franz et al. 2007). Most tested

materials showed only mild cytotoxicity comparable to amalgam or less than amalgam but there were a few exceptions. Most of the available toxicity data have been generated in in-vitro systems that focus on genetic toxicity of the compounds in standard test systems such as the Ames-test, and on cytotoxicity in gingival fibroblasts. TEGDMA, UDMA and HEMA have all been shown to be positive in the COMET assay indicating induction of DNA-damage in mammalian cells. HEMA, BisGMA and TEGDMA also induced gene mutations in mammalian cells by a clastogenic mechanism.

The monomers also caused cytotoxicity in cultured cells with ED_{50} in the low millimolar to submillimolar concentrations (Kleinsasser et al. 2006, Schweikl et al. 2005, Schweikl and Schmalz 1996a, Schweikl and Schmalz 1997, Schweikl et al. 1998a, Schweikl et al. 1996b, Schweikl et al. 1998b, Schweikl et al. 2006). In an in vitro embryotoxicity screening study, BisGMA induced effects at low, non-cytotoxic concentrations suggesting a potential for embryotoxicity or teratogenicity (Schwengberg et al. 2005).

The limited data on these monomers in experimental animals include studies on absorption, distribution, metabolism and elimination (ADME) on HEMA and TEGDMA after oral application of radiolabelled compounds. A rapid absorption of these compounds from the gastrointestinal tract and rapid catabolism by physiological pathways to carbon dioxide, which is exhaled (Reichl et al. 2001a, Reichl et al. 2002a, Reichl et al. 2002b, Reichl et al. 2001b, Reichl et al. 2002c).

No direct data on toxic effects of resin monomers in animals are available from publicly accessible sources. However, since the materials used as a basis for resin generation are derivatives of methacrylic acids and glycidyl ethers, the well studied toxicology of methacrylate and its esters may be used as a basis for structure activity relationships to predict major toxicities.

Methylmethacrylate, as a relevant resin monomer, is rapidly absorbed after oral administration in experimental animals and is rapidly catabolised by physiological pathways to carbon dioxide. The major toxic effects of methylmethacrylate in animals are skin irritation and dermal sensitization. In repeated dose-inhalation studies, local effects on respiratory tissue were noted after methylmethacrylate inhalation. Neurotoxicity and liver toxicity were observed as systemic effects after inhalation of methylmethacrylate in rats and in mice to concentrations above 3000 ppm for 14 weeks. For developmental toxicity of methylmethacrylate a NOAEC > 2000 ppm was observed. Methylmethacrylate is also clastogenic at toxic concentrations (EU-RAR 2002).

A detailed overview of the toxicity of glycidyl ethers compounds is available (Gardiner et al. 1992), although it is based mainly on unpublished study reports. Skin irritation and sensitization were the major toxicities observed. In addition, positive effects in genetic toxicity testing were seen with many glycidyl ethers at comparatively high concentrations.

3.4.4. Exposure

As noted earlier there are very limited data on exposure levels to the components of alternative dental restorative materials. Unlike the situation with amalgam, there are no obvious markers for exposure. Moreover, there are significant limitations to the determination of these exposure levels. The molecules used in any setting reaction, whether that is a polymerisation or an acid – base reaction, are by definition chemically reactive with a potential to exert toxic effects in humans. However, the reaction involves a small amount of material and usually takes place very quickly, following which many of these molecules have been irreversibly changed into far less reactive species or trapped within a solid mass with very limited capacity to diffuse and leach out. It is therefore expected that there will be a low but detectable level of exposure to many of these molecules during placement of the restoration. This is followed by a very much reduced level, possibly an infinitesimally low level, during the lifetime of the restoration. It is difficult to see how such low levels could be measured in a clinical setting.

The monomers used in dental resin-based materials are volatile and it is usually possible to smell them in dental clinics. The exposure of dental personnel to airborne methacrylates was studied during the placing of composite resin restorations in six dental clinics in Finland by Henriks-Eckermann et al. (2001). Both area and personal sampling were performed, and special attention was paid to measurement of short-term emissions from the patient's mouth. The median concentration of HEMA was 0.004 mg/m^3 close to the dental nurse's work-desk and 0.003 mg/m^3 in the breathing zone of the nurse with a maximum concentration of 0.033 mg/m^3. Above the patient's mouth the concentration of 2-HEMA was about 0.01 mg/m^3 during both working stages, i.e., during application of adhesive and composite resins and during finishing and polishing of the fillings. Maximum concentrations of 3-5 times higher than median concentrations were also measured. TEGDMA was released into the air during the removal of old composite resin restorations (0.05 mg/m^3) but only to a minor extent during finishing and polishing procedures. The results showed that, except for short-term emissions from the patient's mouth, the exposure of dental personnel to methacrylates is very low. Measures to reduce exposure were discussed, as the airborne concentrations of methacrylates should be kept as low as possible in order to reduce the risk of hypersensitivity. Except for the data from this paper, there seems to be very limited information about the actual level of exposure to volatile monomers in a clinical situation.

Polymerised resin based materials contain various amounts of residual monomers and polymerisation additives that may leach from restorations. The release may remain on a high level for some days (Polydorou et al. 2007). In addition, as noted above, chemical, microbiological and wear impacts are observed over time, and occlusal or approximal degradation of composites restorations occurs (Groger et al. 2006, Söderholm 2003). Most information on the release of material components is based on laboratory models with solvents such as ethanol, water, saline, artificial saliva or culture media. Gas chromatography and mass spectrometry of the solutes from composites, compomers and resin based glass-ionomers have demonstrated the presence of a number of organic leachables such as monomers, co-monomers, initiators, stabilizers, decomposition products and contaminants Some of them have been identified as the low viscosity monomers EDGMA, TEGDMA and HEMA together with initiator and co-initiators such as hydroquinone, camphorquinone, and DMABEE and an ultraviolet absorber, Tinuvin P (Lygre et al. 1999, Michelsen et al. 2003). Attempts at quantification have shown that elution from different materials differs significantly (Michelsen et al. 2006) and the data are contradictory. Bis-GMA, Bis-EMA, UDMA and various additives have been shown to leach (Rogalewicz et al. 2006), although others have failed to demonstrate BisGMA and UDMA in aqueous extracts, even though TEGDMA-based composites released high amounts of monomers (Moharamzadeh et al. 2007).

It is reasonable to assume that similar leaching reactions take place in patients, depending on the composition of the material, the effectiveness of the polymerisation process and the chemical impact of the oral environment, although limited information is available on the concentration of components from amalgam alternatives in patient saliva or other body fluids. There are some exceptions, such as acrylic monomers from soft liners and phthalates from denture base materials (Lygre et al. 1993, Lygre 2002). In addition, bisphenol A has been indicated in leachables from composites and sealants (Olea et al. 1996, Sasaki et al. 2005).

3.4.5. Potential adverse effects in patients

On the basis of the above comments on the composition of the alternatives to amalgam, the possible exposure levels associated with their components and known in vitro data on their toxicity, a general assessment of potential adverse effects in patients may be made.

3.4.5.1. General

The components released from dental restorative materials comprise a long list of xenobiotic organic substances and metallic elements (Schmalz 2005, Wataha and

Schmalz 2005). The components are subject to oral mucosal, pulpal and gastrointestinal absorption, and, for aerosols, pulmonary absorption, the passive diffusion through cell membranes being guided by factors such as the concentration gradient, molecular size, polarity, lipophilicity, and hydrophilicity.

Toxic effects after inadvertent contact with chemicals associated with restorative dentistry may appear as acute soft tissue injuries among dental patients. Local chronic reactions of irritation, or of combined irritation and hypersensitivity, appear as lichenoid reactions of the gingiva or mucosa. It is generally accepted that the amount of potentially toxic substances absorbed from alternatives to amalgam is too small to cause systemic reactions by dose dependent mechanisms in target organs. However, this statement does not deny that adverse reactions may occur, elicited by minute quantities of released substances, including allergies and genotoxicity. Of these, only allergy has been confirmed among dental patients.

The cytotoxicity and genotoxicity of substances leached from resin based materials and metallic elements have been the subject of extensive studies using cell culture techniques and bacterial mutation test (Ames test). Substances such as TEGDMA and HEMA cause gene mutations in vitro. Studies on the intracellular biochemical mechanisms have clarified various effects such as cell membrane damage, inhibition of enzyme activities, protein or nucleic acid synthesis etc. (Schweikl et al. 2006). At present, the clinical relevance of these in vitro studies is uncertain.

The release of Bisphenol A from Bis-GMA based materials such as fissure sealants and composites into saliva has been of special interest because of its potential estrogenic effect (Joskow et al. 2006). The concentration of released Bis-GMA from certain types of sealants has been reported to be within the range at which estrogen receptor-mediated effects were seen in rodents (Schmalz et al. 1999). However, the release from resin based restoratives is much lower. The conversion of Bis-GMA to Bis-MA is minimal in resin based materials if pure base monomers are used (Arenholt-Bindslev and Kanerva 2005). However, the minute concentration in resin based amalgam alternatives is not considered to be a problem.

It must be noted that there are other alternatives to amalgams in addition to these resin and cement based materials. These primarily include gold alloys and ceramics used for indirect restorations. These, however, do not represent clinically relevant options for the treatment of the vast majority of teeth and are only used when direct restorations are contra-indicated. Although idiosyncratic responses may be encountered with most materials (Ahlgren et al. 2002), and there may be exposure even to gold from such restorations (Ahlgren et al. 2007), there are very few indications that such materials have the potential for adverse effects and they are not considered further in this Opinion.

3.4.5.2. Allergy

Potential allergens among amalgam alternatives

There is limited possibility to predict the allergenic potential for a foreign substance on the basis of chemical composition using Quantitative Structure-Activity Relationship (QSAR) analysis. However, experimental testing such as the Guinea Pig Maximisation Tests or the murine Local Lymph Node Assay, and empirical results after years of testing substances causing allergies, have given some leads: the strongest allergens are often low molecular weight, aromatic, lipid soluble substances, or otherwise chemically active substances that react with proteins. Metal and metal salts are also high ranking haptens. On this basis, monomers, cross-linking agents, chemicals associated with the polymerisation process, and degradation products, all associated with resin based materials, are important candidates for allergic responses among users of these alternatives, including dental patients and professionals. A short list of allergens relevant to resin based amalgam alternatives is presented in Table 3.

Although an allergic reaction may be provoked by haptens derived from dental materials, the sensitisation process may be caused by substances unrelated to dentistry. Plastics are met with in everyday life and in occupations such as construction work and printing. For anatomical reasons both the allergic sensitisation and the allergic response are more easily obtained on skin than in the oral tissues. Epidermal tests are therefore adequate also for observations of intraoral adverse effects. A positive patch test is an indication of a causal relationship between the substance and the suspected allergic reaction, but does not provide definitive evidence without other criteria of causality, which often cannot be performed for practical and ethical reasons.

Table 3 Some allergens in resin based amalgam alternatives (primers, bonding agents, composites, glass ionomers, resin modified glass-ionomers, compomers etc).

Methacrylate monomers
2-hydroxy ethyl methacrylate
Triethylene glycol dimethacrylate
Pyromelilitic acid dimethylmethacrylate
Bisphenol-A glycidyl methacrylate
Urethane dimethacrylate
Bis-phenol-A polyethylene glycol diether dimethacrylate
Ethylene glycol dimethacrylate (EGMDA)
Other substances
Benzoyl peroxide, camphoroquinone (initiators)
Tertiary aromatic amine (activator)
Methylhydroquinone (inhibitor)
2-hydroxy-4-methoxy benzophenones, (UV absorber)
2-(2-hydroxy-5 methylphenyl) benzotriazole (Tinuvin P)

3.4.5.3. The role of bacteria

The presence of bacteria located at the interface between composite materials and dental tissues may be important (Hansel et al. 1998). EGDMA and TEGDMA promote the proliferation of cariogenic microorganisms such as *Lactobacillus acidophilus* and *Streptococcus sobrinus*; TEGDMA stimulates the growth of *S mutans* and *S salivarius* in a pH dependent manner (Khalichi et al. 2004). This provides one explanation for caries that develops beneath restorations of resin-containing materials. In addition, bacterial exotoxins have harmful effects on pulp cells after diffusion throughout dentine tubules.

It is also important to note that effects on dental pulp associated with restorations may be caused by bacterial contamination rather than the materials themselves (Bergenholtz et al. 1982, Bergenholtz 2000). This is still a matter of controversy and a few reports still consider that the pulp reaction to adhesive systems is generally minimal (Murray et al. 2002, Murray et al. 2003). Improvements of resin-containing materials and bonding agents and techniques have reduced the significance of shrinkage and gaps at the interface, which may be less than 1µm (Hashimoto et al. 2004). However this is still a large gap for many microorganisms such as lactobacilli that are less than 0.1µm in diameter, and therefore the microbial parameter cannot be ignored.

3.4.6. Epidemiological and clinical evidence concerning adverse effects of alternatives in patients

3.4.6.1. Case reports

Several cases of confirmed allergic reactions caused by tooth coloured restorative materials have been published. For example, an early case report described a female patient who developed a rash and hives on her chest, arms and legs after treatment with a composite (Nathanson and Lockhart 1979). Patch testing indicated that Bis-GMA was the provoking agent, whereas the sensitisation might have taken place by contact with a cross-reacting epoxy product. Patch tests also indicated Bis-GMA in a case of peri-oral erythema and crusting of cheeks following the application of a bonding agent for composite and glass ionomer fillings (Carmichael et al. 1997). Moreover, stomatitis and peri-oral dermatitis was attributed to Bis-GMA in a filling material (Kanerva and Alanko 1998). Local lichenoid reactions similar to those described for amalgam, have also been attributed to composite fillings. In one case patch testing indicated EGDMA as the allergen (Auzeerie et al. 2002), other cases indicated formaldehyde derived from the resin (Lind 1988). Ulcerating gingivitis localised to composite fillings was explained as a delayed reaction to the UV-absorber Tinuvin P (Björkner and Niklasson 1979).

3.4.6.2. Reports from adverse reaction registry units

In the years 1999-2002 the Norwegian Dental Biomaterials Adverse Reaction Unit received an increasing number of reports of adverse reactions associated with composite materials, although these were still outnumbered by reactions to amalgam and other alloys (Lygre et al. 2003, Vamnes et al. 2004). Swedish data showed a similar tendency. Patch testing of referred patients demonstrated positive reactions to methacrylates and additives relevant to resin based materials, although the most frequent allergens were nickel, gold, cobalt, palladium, mercury, and chromium. A survey by the UK registry indicated that the number of adverse reactions caused by resin based materials, amalgam alternatives included, was about 14 % of the total number of patient reactions (Scott et al. 2004).

Since all dental materials pose a potential risk to patients and members of the dental team, the post-market monitoring of adverse reactions caused by dental materials should be considered essential. Van Noort et al. (2004) reviewed the current status of post-market monitoring of adverse reactions to dental materials and highlights some of the issues that arise in trying to establish an evidence base on the characteristics of adverse reactions to dental materials. Norway, Sweden and the UK have sought to monitor adverse reactions to dental materials systematically and proactively in an effort to add to the evidence base on the safety of dental materials. Their experience in undertaking post-market surveillance was combined. The Norwegian, Swedish and the UK projects had received 1268 reports over 11 years, 848 reports over 5.5 years and 1117 reports over 3 years, respectively, relating to adverse reactions seen or experienced by dental personnel and patients. There are no harmonized criteria for what can be classified as an adverse reaction related to dental materials. Under-reporting was a recognised problem and lack of awareness and lack of clarity as to what constitutes an adverse reaction may be contributory factors. A pro-active reporting system takes a considerable time to become established, but can generate a lot of potentially useful information. Van Noort et al. (2004) concluded that there is a need to raise the awareness among dental professionals of the potential for adverse reactions due to dental materials and to develop an internationally accepted system of data gathering that can produce the evidence that reflect the extent, severity and incidence of adverse reactions to dental materials.

3.4.6.3. Reports from dermatological units

A Finnish multicentre study based on dental screening allergens on 4000 patients concluded that methacrylates, particularly HEMA, were responsible for 2.8 % of

reactions, which were otherwise dominated by metal salts (Kanerva et al. 2001). A Swedish investigation showed positive patch tests to methacrylate allergens in 2.3 % of the patients (Goon et al.2006). The most common of these allergens was HEMA, followed by EDGMA, TEGDMA, and MMA. Simultaneous positive reactions were frequent. Only one patient reacted to Bis-GMA, whereas reactions to HEMA alone were seen in most patients. Data from Israel after testing of patients with oral manifestations such as cheilitis, burning mouth, lichenoids, and orofacial granulomatosis also ranked HEMA as the most frequent dental allergen after the metal salts (Khamaysi et al. 2006).

3.4.6.4. Questionnaire studies

A few attempts have been made to estimate the incidence of adverse effects of dental materials among dental patients. However, no studies have focussed specifically on alternatives to amalgam. After about 10 000 dental treatments, one fifth of which were composite restorations, 22 adverse reactions were observed, none of them being related to tooth coloured restorative materials. Thirty-one dentists, representing a collective practice time 387 years, recollected 70 cases of adverse effects, of which two were attributed to temporary resin based and denture base materials, and 5 to copper cement, but none to alternatives to amalgam (Kallus and Mjør 1991).

Other questionnaire studies have aimed at obtaining incidence rates of materials related side effects in dental specialty practices such as paedodontics, orthodontics, and prosthodontics. Data from paedodontics indicated one reaction in 2400 patients, but only a minimal part was attributed to alternatives to amalgam (Jacobsen et al. 1991). Orthodontics and prosthodontics do not regularly include the placement of restorative amalgam alternatives, but resin based materials of similar composition are used. In orthodontics, only one of 41 000 patients showed an intra-oral reaction to an orthodontic composite, but 9 others reacted to resin based removable appliances, retention appliances, activators, and polymeric brackets (Jacobsen and Hensten-Pettersen 2003). However, some of these appliances are often made by chemically polymerised methacrylates, containing relatively higher concentration of potentially allergenic residual monomers as compared to well-cured restorative composites. Questionnaire data from prosthodontics could be interpreted to indicate a reaction rate of one per 600 patients for resin-based prosthodontic materials (Hensten-Pettersen and Jacobsen 1991).

3.4.6.5. General Comments

Case reports and reports from dermatological units highlight the possibility of adverse effects related to identified dental materials. Information from these sources is helpful in a field where these events are infrequent. The adverse reaction registry units in some countries contribute data on the relative frequency of the different adverse reactions, including those to amalgam alternatives. However, since participation by dental personnel is voluntary, the amount of under-reporting of patient reactions is unknown. The existing epidemiological studies offer an impression of the different materials related adverse effects as perceived by dental personnel. However, none of these studies are well suited as a basis for estimation of the prevalence of reactions caused by specific allergens associated with amalgam alternatives or other materials.

In spite of these drawbacks, an attempt to rationalise the risk of materials related adverse effects in dentistry on the basis of published reports has appeared recently (Schedle et al. 2007). Large variations were found, ranging between 1:10 000 and 1:100 for dental patients. A recent FDI-report also points to the fact that the vast majority of patients have encountered no adverse reactions, but dentists were advised to be aware of the possibility of reactions to resin based materials (Fan and Meyer 2007). The importance of satisfactory curing of these materials was specifically underlined. It is assumed that the most frequent potential allergens associated with resin based amalgam alternatives are found in Table 3.

3.4.7. Epidemiological and clinical evidence concerning adverse effects of alternatives in dental personnel

The potential for adverse effects to alternative restorative materials amongst dental personnel is widely recognised (Hume and Gerzina 1996). Most of the evidence of adverse effects takes the form of case reports, findings from surveys (Örtengren 2000) and reports from national reporting systems (van Noort et al. 2004). Given the extent of the use of alternative restorative materials, hundred of millions of restorations annually, and the possibility that <7% of dental personnel may report skin symptoms when working (Örtengren 2000), it is surprising that the reported incidence of adverse effects to alternative restorative materials is low (van Noort et al. 2004). The prevalence of verified allergic contact dermatitis amongst dental personnel (<1%) is much lower than the prevalence of self-reported skin symptoms (<7%) (Örtengren 2000).

Most of the adverse reactions reported take the form of contact dermatitis, which in severe cases may be associated with paresthesia of the finger tips (Kanerva et al. 1998). Reactions around the eyes, generalised skin itching and bronchial problems have been reported, but these are rare (Hume and Gerzina 1996).

HEMA appears to be a common sensitizer, although a small minority of dental personnel may have positive patch-tests to BisGMA and/or TEGDMA (Kanerva et al. 2001). It is relevant that relatively low molecular weight resin monomers, including HEMA and TEGDMA take only a few minutes to diffuse through latex gloves of the type worn by dental personnel, while higher molecular weight monomers, such as BisGMA, take a little longer to pass through the relatively thin latex of treatment gloves (Jensen et al. 1991, Munksgaard 1992). These findings emphasise the importance of a "no-touch" technique when handling resin-based restorative materials, even when wearing gloves. This approach to the handling of resin-based restorative materials is highlighted in manufacturers' directions for use.

Regarding the lower incidence of allergic responses to resin-containing alternative restorative materials in patients relative to dental personnel, Kallus and Mjör (1991) and Hensten-Pettersen and Jacobsen (1991) suggest that this may be related to the fact that the principal exposure of dental personnel is to methacrylates as monomers during the handling of uncured materials. Adverse effects of alternative restorative materials in dental personnel may, as a consequence, be minimised by the avoidance of contact with, in particular, low molecular weight monomer during the handling and placement of uncured materials. The effects may be further reduced by the use of effective face protection, water cooling and suction, as appropriate, in all operative procedures involving both cured and uncured resin-based materials and associated systems.

Between 1995 and 1998, 174 dental personnel were referred as patients to the Department of Occupational and Environmental Dermatology, Stockholm (Wrangsjö et al. 2001). After clinical examination, 131 were patch tested with the Swedish standard series and 109 with a dental screening series. Furthermore, 137 were tested for IgE-mediated allergy to natural rubber latex. Hand eczema was diagnosed in 109/174 (63%), 73 (67%) being classified as irritant contact dermatitis and 36 (33%) as allergic. Further diagnoses included other eczemas, urticaria, rosacea, psoriasis, tinea pedis, bullous pemphigoid or no skin disease. 77/131 (59%) had positive reactions to substances in the standard series and 44/109 (40%) to substances exclusive to the dental series. 24/109 (22%) patients had positive reactions to (meth)acrylates, the majority with reactions to several test preparations. Reactions to HEMA, EGDMA and MMA were most frequent. Nine of the 24 were positive only to (meth)acrylates, the remaining 15 also had reactions to allergens in the standard series. Irritant hand dermatitis was the dominant diagnosis. Contact allergy to (meth)acrylate was seen in 22% of the patch tested patients, with reactions to 3 predominant test substances. In one third of these cases the (meth)acrylate allergy was seen together with atopy and/or further contact allergies.

Also less severe allergic skin reactions among dental personnel have been diagnosed as caused by methacrylates, secondary in frequency only to chemicals related to natural

rubber latex (Alanko et al. 2004). Hand dermatoses, together with eye-, nose-, and airways reactions are consistent findings among dental personnel, although the role played by amalgam alternatives is undecided (Sinclair and Thomson 2004, Andreasson et al. 2001).

The Finnish Register of Occupational Diseases diagnosed 24 cases of occupational asthma or rhinitis caused by methacrylates during the years 1990-98 .The incidence rate of occupational respiratory disease was considered greater than in the whole population (Piirilä et al. 2002)

Preventive actions such as change in hygiene factors, use of no-touch techniques when working with methacrylates, less use of latex and awareness of risk factors seems to keep the prevalence of skin and respiratory symptoms low among dental personnel (Schedle et al. 2007).

3.4.8. Potential adverse effects of ancillary items and equipment

3.4.8.1. Photopolymerisation energy sources

Light sources are used to activate photoinitiators, by absorption of photons, in order to initiate polymerisation in many restorative materials (Small 2001). The applied energy depends on the light source used. Photoinitiator activation occurs at specific wavelengths. The most common photoinitiator is camphoroquinone, the activity of which peaks between 470 and 480 nm. The main advantages of light-cured composites compared to chemically cured products are based on the fact that mixing of components in the clinic is not required, resulting principally in less porosity and increased strength.

Types of curing lamps

Dental curing systems use light sources such as quartz-tungsten-halogen lamps (QTH), light-emitting diodes (LEDs), xenon-plasma arcs and lasers. The lamps are discussed here in the conventional order of lowest to highest intensity, although this has changed recently since some of the LED lamps now claim to have much higher energy output than the QTH lamps.

LED dental curing lamps, using a solid-state, electronic process emit radiation only in the blue part of the visible spectrum, between 435 and 495 nm and do not require filters. The irradiance of 13 products measured in the 400 to 515 nm range varied from 454 - 1456 mW/cm^2 (Bruzell and Wellendorf 2007). Some LED lamps marketed in 2007 claim irradiance values up to 3000 mW/cm^2.

QTH lamps with halogen inside quartz bulbs generate light through the heating of a tungsten filament to high temperatures. A small percentage (less than 1 %) of the energy is given off as light, most of the energy being in the form of heat. A drawback of halogen bulbs is that the generation of heat causes a degradation of the components of the curing unit over time. The result can be a decline in the irradiance, which compromises the curing ability of the unit. The light is filtered to remove heat and all wavelengths except those in the violet-blue range (400-515 nm). The irradiance varies from 366 to 1360 mW/cm^2, depending on the product.

Plasma-arc lights are made up of two electrodes in a xenon-filled bulb. The plasma is heated to several thousand degrees Celsius and gives off light (less than 1 percent of the energy) and heat. The high intensity white light is filtered to remove heat and to allow blue light (400-500 nm) to be emitted.

Lasers can emit light at specific wavelengths as a result of the excitation of atoms of suitable gases/liquids/solids to specific energy levels. Argon lasers currently available emit at 488 nm and have the highest energy output of the dental curing units, up to 5 W. Lasers are reported to require less time to adequately polymerise composites although these units are large, expensive and not widely used.

Light-curing of composites

The dental curing lights initiate polymerization of resin-based dental restorative materials by transmission of light through a fibre optic tip into to the material. For maximum curing, a radiant energy influx of about 16 J/cm^2 is required for a 2 mm thick layer of resin. This can be delivered by a 40 second exposure from a lamp emitting 400 mW/cm^2 or by using higher intensity energy output and shorter exposure times. Curing depths equivalent to that of a 500 mW/cm^2 QTH lamp have been demonstrated using an exposure time of 10 seconds with certain PAC lamps and 5 seconds with an argon laser (Rawls and Esquivel-Upshaw 2003).

Hazards

The light intensity and energy output may be hazardous per se. The light emitted by curing lamps can cause retinal damage if a person looks directly at the beam. Laser light sources require the use of special protective glasses.

Exposure of the eyes

The eyes of the lamp operators are at risk from acute and cumulative effects, mainly due to back-reflection of the blue light. Exposure to intense visible light radiation sources in a dental clinic necessitates the use of eye protective filters to avoid blue-light photochemical retinal damage. Bruzell et al. (2007) measured the visible light transmittance of protective filters; nine of the 18 tested filters had adequate filtering capacity.

Exposure of the eyes of patients and professional persons with ocular diseases

Most manufacturers state in the instructions for use that the exposure to light from dental curing units should be avoided in persons who have undergone cataract surgery, with other cataract problems or who have other types of impaired eyesight.

Exposure of skin

The visible light wavelengths and intensity of the dental curing lights do not appear to cause damage to healthy skin. The quartz-halogen lamps may emit some radiation in the UV-region. Chadwick et al. (1994) assessed the level of UVA-I (340 to 400 nm) emitted from three commonly used QTH-radiation sources and assessed the level of protection afforded by six brands of surgical gloves. It was concluded that the risk of initiating adverse dermatological consequences as a result of exposure to UVA-I, is minimal in normal usage. Irradiation with a QTH dental curing light on human stratified epithelium in heterotransplanted skin on nude mice showed that 72 hours after exposure, there was epithelial hyperplasia and reduced reactivity for OKT6 cells. After 4 min of exposure OKT6 positive cells were completely absent from the epithelium after 72 hours. The results indicated that emission from dental light curing units can affect Langerhans cells and could thus modify the local immunological response (Bonding et al. 1987). There does not seem to be any scientific studies on the possibility of adverse reactions in the oral mucosa after exposure to high intensity visible blue light.

Exposure of teeth

The curing lamps with high energy output intensity may cause local thermal emission. Laboratory studies show temperature rises, at 3 mm distance from the light source, from 4.1°C to 12.9°C, and from 17.4°C to 46.4°C for LED and QTH lamps, respectively (Yap and Soh 2003). In vitro studies with thermocouples placed in pulp chambers of extracted teeth show a moderate rise in pulpal temperature. In a vital tooth this does not seem to be a problem, possibly due to the effects of the blood circulation. However, the recent introduction of the high-intensity LED-lights might change this situation.

Light as cofactor in photobiological reactions

Most manufacturers state in the instructions for use that dental curing lights should not be used in patients with a history of photobiological reactions – or who are currently on photosensitising medication, including 8-methoxypsoralen or dimethylchlorotetracycline. Phototoxic and photoallergic reactions are potential problems, but there does not seem to be any case reports on this issue. The dose or output from the high intensity lights are in the same range of what is used for dermatological skin testing of photobiological reactions. Phototoxic or photoallergic reactions have not been documented in the context of oral medicine. The possibility of photo-related reactions should be taken into account in evaluation of dermatological conditions in dental personnel.

Electromagnetic compatibility (LED, QTH)

The instructions for use for some QTH and LED lights warn that the devices must not be used in patients, or by users, with heart pacemaker implants, who have been advised to be cautious about their exposure to small electrical devices. A 59-year-old male with Parkinson's disease had stimulator electrodes implanted in the brain. During curing of composites with a LED curing unit the patient felt immediate headache which he associated with the use of the curing light. Although the cause-and-effect relationship was questionable, an incidence report was submitted to the Norwegian Board of Health (Vangstein 2003).

Cross-contamination

The routines for infection control procedures as written in the instructions for use for the dental curing light units vary greatly. Some have no recommendations, one states that it should be sterilized before using it the first time, many have elaborate descriptions for cleaning and disinfection procedures.

Ineffective treatment/inferior quality of restoration

Most of the dental curing lights have an integrated photometer to check that the energy output is sufficient for the intended use. Others recommend the use of a separate photometer or to use a device for checking that the depth of cure for the various composites is sufficient. The latter method checks both the quality of the light source and the quality of the composite material. This is an important aspect, since the resin-based materials have a limited shelf life. It is also an issue with some of the very light shades of tooth-coloured resin-based materials that use phenyl propanedione as photo-activator, which requires radiation in the lower part of the spectrum of lower wavelengths than does camphorquinone (absorption peak at about 390 nm).

Overall risk assessment

There are inherent problems in the assessment of adverse effects of light exposure from dental curing lamps. Spectral characteristics vary among the different products, tissues treat radiation differently and the repair mechanisms for photo-induced damage may mask any adverse effect.

The dental curing lights, when used according to the manufacturer's instructions and with proper eye protection, seem to be safe for use in most patients and users. However, the potential for adverse reactions to occur are definitely present and the manufacturer's cautionary statements about not using them in specific situations should be heeded (Bruzell Roll et al. 2004).

3.4.8.2. Glove use

The wearing of gloves, often of latex, but increasingly of non-latex alternatives, has become routine in the everyday dental practice. Although not advised, should alternative resin-based filling materials be handled during use, low molecular weight components

may quickly pass through the glove (Jensen et al. 1991, Munksgaard 1992) and will remain in contact with the moist skin of the clinician until the gloves are removed and the hands washed at the conclusion of the treatment. With practitioners who are sensitive to such constituents, or in the presence of skin conditions, cuts or abrasions, an adverse reaction may occur. Such reactions may be avoided by strict adherence to the no-touch techniques recommended by manufacturers of alternative restorative materials.

3.4.9. General Observations on Efficacy of Alternatives

The general observations on the efficacy of amalgam restorations (Section 3.3.10) may be reinforced here. Alternatives to amalgam have been in clinical use for well over 30 years. They have not only addressed the issues on the aesthetics of amalgams but have facilitated a radical change in the concepts of restorative dentistry through the introduction of more minimally invasive techniques and the associated retention of more tooth substance when treating caries. This has been achieved through the use of tooth coloured materials that are themselves adhesive to tooth substances or that can achieve adhesion through the use of intermediary agents. It is recognised that their use may be technique sensitive and that the procedures for their placement may take longer and therefore be more expensive. It is also true that they may be more susceptible to secondary caries and, in some situations, have less longevity than amalgams. In general therefore these tooth coloured alternatives offer an effective modality for the treatment of dental caries in most situations.

3.4.10. Conclusions on Alternatives

We note that the materials used as alternatives to dental amalgam for direct restorations are usually very complex chemically, and are not without certain clinical limitations or toxicological hazards. They frequently contain a variety of organic substances and they undergo chemical reactions within the tooth cavity and adjacent soft tissues during placement. It should not be assumed that non-mercury containing alternatives are free from any concerns about adverse effects (Goldberg 2007).

With respect to those materials that incorporate polymerisable resins, it is known that some of the monomers involved in their intra-oral placement and polymerisation are highly cytotoxic to pulp and gingival cells in vitro and there is also evidence that some of them are mutagenic, although it is far from clear whether this has any clinical significance. Some of these substances are irritants when used by themselves in various situations and the occupational hazards associated with their use are similar to those hazards found in the printing and automotive industries. Allergies to a few of these substances have been reported, both in patients and in dental personnel. We note that the full chemical specification of these alternative restorative materials is not always divulged and it may be difficult to ascertain exactly what they contain. In the absence of data, it may not be possible to provide a scientifically sound statement on the safety of individual products. It is also noted, however, that there are very limited scientific data available concerning exposure of patients and dental personnel to these substances.

Nevertheless, these alternative materials have now been in clinical use for well over thirty years, and this use has revealed little evidence of clinically significant adverse events. The commercially available materials have either changed substantially or been improved considerably during this time, with reduced bioavailability of harmful components through improved polymerisation processes. It is recognised that many of the new forms of these alternative materials lack long-term clinical data and as such, need to be monitored for possible risks to patients and dental personnel.

As a separate issue, it should be borne in mind that these photo-polymerisable systems require activation and that the powerful light sources now used for this purpose may constitute an additional risk for adverse effects, both to patients and dental personnel. Eye protection is extremely important.

4. OPINION

We discuss here the general observations that constitute the scientific opinions concerning the safety of dental amalgams and alternative dental restorative materials and then provide answers to the questions posed in the mandate.

4.1. The scientific and clinical evidence

Dental amalgam remains an effective restorative material and, from the perspectives of longevity, the mechanical performance and economics, may be considered the material of choice for some restorations in posterior teeth, including the replacement therapy for existing amalgam fillings.

However, because dental amalgam is not tooth-coloured nor does it adhere to remaining tooth tissues, its use has been decreasing in recent years and tooth-coloured filling materials have become increasingly more popular. This is consistent with the significant trend towards more minimal intervention techniques in dentistry, especially those that involve materials with adhesive properties.

There is an increasing trend towards non-amalgam restorations, which shows some variations within and between countries, and is emphasized by the significant reduction of training in the placement of dental amalgam restorations and the corresponding increase in training in the use of amalgam alternatives in a growing number of dental schools in European countries.

Independent of risk management decisions, and of the economic considerations in restorative dentistry, a sustained reduction in the use of dental amalgam in oral health care provision is expected across the European Union, the rate of which is dependant on trends in dental education towards the increasing use of alternative materials in place of amalgam and the possible reduced availability of mercury products in general.

Mercury is the major metallic element used in dental amalgam. It is recognized that mercury in general does constitute a toxicological hazard, with reasonably well defined characteristics for the major forms of exposure, involving elemental mercury, organic and inorganic mercury compounds. It is accepted that the reduction in use of mercury in human activity would be beneficial, both for the decrease in indirect human exposure and environmental considerations.

For many decades, going back to the introduction of amalgam into clinical practice over 150 years ago, there has been a debate about the possibility of causal relationships between the use of mercury containing amalgam and a wide variety of adverse systemic health effects. In spite of many studies and investigations into this putative causal link, there is no unequivocal evidence to support this possibility.

It is recognized that some local adverse effects are occasionally seen with dental amalgam fillings, including allergic reactions and an association with clinical features characteristic of lichen planus, but the incidence is low and normally readily managed. There have been claims of causation with respect to a variety of systemic conditions, particularly neurological and psychological/psychiatric effects, including Alzheimer's, Parkinson Disease, Multiple Sclerosis and also kidney disease. However, several major epidemiological studies have failed to reveal such effects. These studies have included assessments in children and in pregnant and lactating women. It is generally concluded that no increased risks on adverse systemic effects exist, and indeed the most recent studies have failed to find any association between the use of amalgam and neuropsychological development in children. We do not therefore consider that the current use of dental amalgam poses a risk of systemic disease.

The main exposure to mercury in individuals with amalgam restorations occurs during placement or removal of the fillings. Exposure does occur through the lifetime of a restoration, but the rates of mercury release are extremely low. The transient mercury release during placement and removal will result in exposure to the patients and also to

the dental personnel. However, this may be minimized by the use of appropriate clinical techniques. In particular it should be noted that the removal of amalgam restorations will increase the exposure of the individual patient to relatively high levels of mercury compared to leaving the amalgam filling intact. Although there is the possibility of some alleviation of subjective symptoms such as burning or dry mouth and taste disturbance, we find no evidence of clinical justification to remove clinically satisfactory amalgam restorations with the exception of those patients which are suspected to have allergic reactions and positive patch tests.

The use of dental amalgam results in environmental exposure to mercury, primarily through its release during amalgam placement and removal, and the handling and disposal of amalgam waste products in general. Improvements in the treatment of waste water from dental clinics and amalgam waste has generally reduced this exposure. A further source of environmental exposure occurs through the burial or cremation of individuals with dental amalgam fillings. It should be noted that a significant increase in amalgam usage occurred between 1950 and 1990 that may result in a rise in environmental exposure over the next few decades as these individuals die.

The general reduction in the use of dental amalgam in clinical practice has been coincident with an increasing use of alternative restorative materials, usually referred to as tooth-coloured materials, principally composites, cements and their hybrids. We note that these materials, which may be very complex chemically, are not without certain clinical limitations and toxicological hazards. They frequently contain a variety of organic substances and they undergo chemical reactions within the tooth cavity and adjacent soft tissues during placement.

It should not be assumed that non-mercury containing alternatives are free from any concerns about adverse effects. With respect to dental composite restorative materials and hybrid systems that incorporate polymerisable resins, it is known that some of the monomers involved in their intra-oral placement and polymerisation are highly cytotoxic to pulp and gingival cells in vitro. There is clear evidence that some of these substances are mutagenic in vitro although it is far from clear whether this has any clinical significance. Some of these substances are irritants when used by themselves in various situations and the occupational hazards associated with their use are similar to those hazards found in the printing and automotive industries. Allergies to a few of these substances have been reported, both in patients and in dental personnel.

It is noted that there are very limited scientific data available concerning exposure of patients and dental personnel to those substances that are used in alternative restorative materials. It is recognised that such data are very difficult to obtain.

These alternative materials have now been in clinical use for well over thirty years, initially in anterior teeth and more recently also for restorations in posterior teeth. This use has revealed little evidence of clinically significant adverse events, even taking into account the fact that the quality of evidence concerning clinical outcomes is limited, with a reliance on case reports. It is also important to note that the commercially available materials have either changed substantially or been improved considerably during this time, with reduced bioavailability of harmful components through improved polymerisation processes.

As a separate issue, it should be borne in mind that these photo-polymerisable systems require activation and that the powerful light sources now used for this purpose may constitute an additional risk for adverse effects, both to patients and dental personnel. Eye protection is extremely important.

We note that the full chemical specification of these alternative restorative materials is not always divulged and it may be difficult to ascertain exactly what they contain. As a result, there is limited toxicological data publicly available for these materials. All dental restorative materials are defined as medical devices according to EU-Directive 93/42/EEC. They are surgically invasive medical devices intended for long-term use which according to rule 8 defines them as class 2b medical devices. However, the

directive has a derogation clause which states that when such medical devices are used in teeth they will be in class 2a. As such when regulatory approval is sought from a notified body it is not necessary to reveal a design dossier including a risk analysis and therefore the chemical specification does not have to be revealed. In view of the lack of information on the toxicity of the constituents of the alternatives and relevant exposure data it is not possible to provide a scientifically sound statement on the safety of these materials.

As a general principle, the relative risks and benefits of using dental amalgam or the various alternatives should be explained to patients to assist them to make informed decisions. This may have implications concerning the provision of product information. In view of the controversial nature of this subject, which has existed for very many years, it would also be beneficial for the community in general to be better informed of the recognized benefits and risks.

It is noted that indirect restorative techniques, involving the use of gold alloys and ceramics may also be used when direct restorations are contra-indicated. Their use, which is both time-consuming and expensive, has remained at a comparatively low level in recent years. This use is not seen as a health concern.

4.2. Human Safety of Dental Amalgam

4.2.1. Is there scientific evidence that supports a link between amalgam and allergic reactions, neurological disorders or other health disorders?

With respect to allergic reactions, many metals in close contact with the skin or mucosal surfaces can be the cause of contact dermatitis and equivalent conditions, and mercury is no exception. Oral lichen planus is sometimes associated with dental amalgam restorations, and one of the possible causes is allergy to constituents of dental amalgam. Whilst the incidence is low, it is recognised that many of the patients affected will show a positive skin patch test for either amalgam or mercury, and removal of restorations from patients with such conditions and positive patch tests often results in the alleviation of symptoms.

With respect to all other putative links between dental amalgam and health disorders in recipients of amalgam restorations, there is no scientific evidence to support such links. It is accepted that elemental mercury does have a specific toxicological profile and that the presence of amalgam restorations in an individual is likely to lead to raised blood and urine mercury levels. However these raised levels appear to be lower than those necessary to cause adverse effects in general, and the overwhelming clinical and epidemiological evidence does not support any causal link between mercury and any of the diseases that have been suggested as being associated with dental amalgam. This analysis has taken into account the possibilities of effects within the urinary, neurological, reproductive and immune systems and also associations with psychological conditions.

4.2.2. 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?

In the light of the above comments we conclude that dental amalgam is a safe material to use in restorative dentistry with respect to patients. Dental health is an extremely important component of general health care and the benefits of amalgam to individuals presenting with dental caries far outweigh the very low level of risk associated with allergies. With respect to populations at risk, there is a lack of information about effects in pregnant women. There is no evidence to suggest that pre-existing amalgam restorations pose any risk as far as the health of such women and the developing foetus

is concerned, and certainly any removal of restorations during this time would present a greater exposure to mercury. As with any other medical or pharmaceutical intervention, however, caution should be exercised when considering the placement of any dental restorative material in pregnant women. There is no evidence that infants or children are at risk of adverse effects arising from the use of dental amalgam, the most recent studies failing to find any association between the use of amalgam and neuropsychological development in children. We emphasise that we find no evidence of clinical justification 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. It should be noted that the removal of amalgam restorations will result in an acute relatively high exposure of the individual patient to mercury, compared to leaving the amalgam filling intact.

As far as dental personnel are concerned, it is recognised that they may be at greater risk with respect to mercury exposure than the general population. However, the incidence of reported adverse effects is very low and this possibility has decreased substantially with improvements to dental amalgam delivery and amalgam hygiene practices in general.

4.3. Human Safety of Alternatives

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

Far less information is available concerning exposure, toxicity and clinical outcomes for alternative materials compared with dental amalgam. The materials themselves are far more complex chemically and there are no simple surrogates as markers for either exposure or toxicity, equivalent to the mercury in amalgams.

There is some evidence that certain of the low molecular weight substances used in the preparation of these alternatives are associated with local allergic reactions, although the incidence is very low.

There is no evidence that there is any association between these materials as used clinically and any neurological disorders or any other health disorders.

4.3.2. 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?

Although there are well recognised cytotoxicity and mutagenicity profiles for some of the chemical substances used in alternative materials, there is no evidence of any adverse clinical effects associated with such substances, apart from a very low incidence of allergies. Notwithstanding the observation that complete chemical compositions and risk analyses do not have to be revealed during the regulatory approval process so that some uncertainties may exist, these materials can be considered safe for patients. Since there is no evidence of any systemic bioavailability of these substances in the body, there would be no expectation that any particular population would be at risk. Again, as with any other medical or pharmaceutical intervention caution should be exercised when considering the placement of any dental restorative material in pregnant women. We do emphasise, however, that data is sparse and the continuing evolution of these materials suggests that caution should be exercised before new variations are introduced into the market.

As far as dental personnel are concerned, again there is evidence of limited numbers of cases of allergies to these materials. The pervasiveness of some of the low molecular weight species throughout dental clinics should be noted.

4.4. Oral Health and Safety - 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?

It is difficult to make direct comparisons between dental amalgam and the alternative materials since they are not used in the same way. Dental health can be adequately ensured by both types of material. All the materials are considered safe to use and they are all associated with very low rates of local adverse effects with no evidence of systemic disease. There is, obviously, a greater level of aesthetic appeal with those alternatives that are tooth coloured compared to the metallic amalgam. Furthermore, the use of these alternatives allows the use of minimally interventional adhesive techniques.

In clinical practice, amalgams usually require more extensive cavity preparation, with the removal of more tooth substance, than is necessary with the adhesive alternative systems. The composite resins, cements and various hybrids are associated with more minimally invasive operative techniques, and this trend in dental practice is seen to be very important and valuable as far as patients are concerned, being consistent with the general principles of contemporary dentistry. It is true, nevertheless that on a historical basis amalgam restorations have in general been found to last longer, as restorations using alternatives have had a higher incidence of secondary caries. This may change with continuing improvements to the alternative materials. Patients in general have had needed more frequent interventions when treated with alternatives, but each intervention involves much less tooth removal than required for amalgam restorations. Although the alternative materials were originally introduced for the restoration of anterior teeth, primarily with small and moderate size initial lesions, in recent years their use has extended towards lesions of all sizes in posterior teeth. Dental amalgam may still be used for large lesions, and for the replacement of failed existing amalgam restorations, especially those associated with secondary caries. It is recognised that there are alternative indirect restorative materials, including gold alloys and ceramics, which are used in situations where direct restorative treatments are contra-indicated.

As a general principle, the relative risks and benefits of using dental amalgam or the various alternatives should be explained to patients to assist them to make informed decisions. This may have implications concerning the provision of product information. In view of the controversial nature of this subject, which has existed for very many years, it would also be beneficial for the community in general to be better informed of the recognized benefits and risks.

Finally, independent of risk management decisions and of the economic considerations in restorative dentistry, a reduction in the use of dental amalgam in oral health care provision is expected across the European Union. The rate at which this takes place is dependent on the trends in dental education towards the increasing use of alternative materials in place of amalgam, and the possible reduced availability of mercury products in general. This is a process that can be readily managed by the dental profession with no detriment to patient oral health. In view of the opinions expressed above, we see few if any advantages to carrying out further research on aspects of the safety of dental amalgam restorations. The lack of data on the toxicity, exposure and health effects of the alternative materials does imply, however, that more experimental, clinical and epidemiological research is required to guarantee patient safety in the future.

5. Comments received from the Public Consultation

Information about the public consultation has been broadly communicated to national authorities, international organisations, and other stakeholders. The relevant web site was opened for comments on 14 January 2008 and the deadline for submission was 22 February 2008. In total, 26 contributions were received from which 14 were from organisations and 12 from individuals. Of the organisations, 6 were non governmental, 4 public authorities and 4 other institutions, including dental associations.

In evaluating the responses from the consultation, submitted material has only been considered for revision of the opinion if

1. it is directly referring to the content of the report and relating to the issues that the report addresses,
2. it contains specific comments and suggestions on the scientific basis of the opinion,
3. it refers to peer-reviewed literature published in English, the working language of the SCENIHR and the working group,
4. it has the potential to add to the preliminary opinion of SCENIHR.

Each submission which meets these criteria has been carefully considered by the Working Group. Overall, many of the comments were of good quality. The scientific rationale of the report has been revised to take account of relevant comments. The literature has been updated with relevant publications. The Opinion, however, remained essentially unchanged, but was, in certain respects, clarified by the amendments to the scientific rationale.

Epidemiological studies on dental amalgam do not indicate that this material induces systemic adverse effects in patients, other than the recognised local irritation and allergic responses. However, it is recognised that very occasionally an individual may have unexplained atypical physical or other reactions attributed to mercury.

As indicated in the opinion, the information on adverse effects on alternatives is limited. During the public consultation, limited additional information became available regarding the alternative restorative materials.

6. MINORITY OPINION

none

7. LIST OF ABBREVIATIONS

ADME	Absorption, distribution, metabolism and elimination
ALS	Amyotrophic Lateral Sclerosis
ATSDR	Agency for Toxic Substances Disease Registry
BAT	Biologischer Arbeitsplatz Toleranzwert (biological tolerance value at the workplace)
BDNF	Brain derived neurotrophic factor
Bis-EMA	Ethoxylated bisphenol A-methacrylate
Bis-GMA	Bisphenol A - glycidylmethacrylate
Bis-HPPP	2,2-bis[4(2,3-hydroxypropoxy)-phenyl]propane
DMABEE	4-N,N-Dimethyl amino benzoic acid ethylester
DPMS	Dimercaptopropane sulfonate
EFSA	European Food Standards Agency
EGDMA	Ethyleneglycoldimethacrylate
EPA	Environmental Protection Agency
HDDMA	Hexanediol dimethacrylate
HEMA	Hydroxyethylmethacrylate
HMBP	2-Hydroxy-4-methoxybenzophenone
IRIS	Integrated Risk Information System
ISO	International Standards Organisation
LED	Light-emitting diode
MAK	Maximale Arbeitsplatz Konzentration (maximum concentration at the workplace
MMA	Methylmethacrylate
MRL	Minimal Risk Level
MS	Multiple Sclerosis
NOAEL	No Observable Adverse Effect Level
OES	Occupational Exposure Standard
PTWI	Provisional Tolerable Weekly Intake
QTH	Quartz – tungsten – halogen
TEGDMA	Triethyleneglycoldimethacrylate
UBA	Umweltbundesamt (German Federal Environment Agency)
UDMA	Urethane dimethacrylate
UNEP	United Nations Environment Programme
WHO	World Health Organisation

8. REFERENCES

ADA (American Dental Association Council on Scientific Affairs). Dental mercury hygiene recommendations. J Am Dent Assoc 2003; 134:1498-9.

Ahlgren C, Ahnlider I, Bjorkner B, Bruze M, Liedholm R, Moller H, et al. Contact allergy to gold – correlation with dental gold, Acta Dermat Venerol 2002; 82:41-4.

Ahlgren C, Molin M, Lundh T, Nilner K. Levels of gold in plasma after dental gold insertion. Acta Odont Scand 2007; 65(6):331-4.

Åkesson I, Lundborg G, Horstmann V, Skerfving S. Neuropathy in female dental personnel exposed to high frequency vibrations. Occup Environment Med 1995; 52:116-23.

Alanko K, Susitaival P, Jolanki R, Kanerva L. Occupational skin diseases among dental nurses. Contact Dermatitis 2004; 50:77-82.

Aminzadeh KK, Etminan M. Dental amalgam and multiple sclerosis: a systematic review and meta-analysis. J Publ Health Dent 2007; 67(1):64-66.

Andreasson H, Örtengren U, Barregård L, Karlsson S. Work-related skin and airway symptoms among Swedish dentists rarely cause sick leave or change of professional career. Acta Odontol Scand 2001; 59: 267-72.

Andrews N, Miller E, Grant A, Stowe J, Osborne V, Taylor B. Thimerosal exposure in infants and developmental disorders: a retrospective cohort study in the United Kingdom does not support a casual association. Paediatrics 2004; 114:584-91.

Anusavice KJ. Phillips' Science of Dental Materials, Philadelphia: Saunders, 2003.

Arenholt-Bindslev D, Kanerva L. Die Diagnose von Nebewirkungen. In: Schmalz G, Arenholt-Bindslev D, editors. Biokompatibilität zahnarztlicher Werkstoffe. München: Elsevier GmbH; 2005. p.337-68.

ATSDR (Agency for Toxic Substances Disease Registry). Toxicological profile for mercury. Update. Atlanta-GA: 1999. http://www.atsdr.cdc.gov/toxprofiles/tp46.html (accessed 11 January 2008)

Atesagaoglu A, Omurlu H, Ozcagli E, Sardas S, Ertas N. Mercury exposure in dental practice. Op Dent 2006; 31-6:666-9.

Auzeerie V, Mahé, Marck Y, Auffret N, Descamps V, Crickx B. Oral lichenoid eruption due to methacrylate allergy. Contact Dermatitis 2002; 45:241.

Bagedahl-Strindlund M, Ilie M, Furhoff AK, Tomson Y, Larsson KS, Sandborgh-Englund G, et al. A multidisciplinary clinical study of patients suffering from illness associated with mercury release from dental restorations: psychiatric aspects. Acta Psychiatr Scand 1997; 96(6):475-482.

Bangsi D, Ghadirian P, Ducle S, Morisset R, Ciccocioppo S, McMulien E, et al. Dental amalgam and multiple sclerosis: a case-control study in Montreal, Canada. Int J Epidemiol 1998; 27:667-71.

Barany E, Bergdahl IA, Bratteby LE, Lundh T, Samuelson G, Skerfving S, et al. Mercury and selenium in whole blood and serum in relation to fish consumption and amalgam fillings in adolescents. J Trace Element Med Biol 2003; 17:165-70.

Barregard L. Mercury from dental amalgam: looking beyond the average. Occup Environ Med 2005; 62:352-353.

Barregard L, Horvat M, Mazzolai B, Sallsten G, Gibicar D, Fajon V, et al. Urinary mercury in people living near point sources of mercury emissions. Sci Total Environ 2006; 368:326-34.

BAT Kommission der Deutschen Forschungsgemeinschaft (DFG). Mercury, metallic mercury and inorganic mercury compounds. In: G Triebig, K-H Schaller, editors. Analyses of hazardous substances in biological material. München: Wiley-VCH; 1997. Vol. 3, p.123-142.

Bates MN, Fawcett J, Garrett N, Curtess T, Kjeilstrom T. Health effects of dental amalgam exposure: a retrospective cohort study. Int J Epidemiol 2004; 33:894-902

Bates MN. Mercury amalgam dental fillings: an epidemiological assessment. Int J Hyg Environ Health 2006; 209(4):309-316.

Bellinger DC, Trachtenberg F, Barregard L, Tavares M, Cernichiari E, Daniel D. Neuropsychological and renal effects of dental amalgam in children. A randomized clinical trial JAMA 2006; 295:1775-1783.

Bellinger DC, Tracgtenberg F, Daniel D, Zhang A, Tavares MA, McKinlay S. A dose-effect analysis of children's exposure to dental amalgam and neuropsychological function. J Amer Dent Assoc 2007; 138:1210-6.

Bergenholtz G, Cox CF, Loesche WJ. Bacterial leakage around dental restorations and bacterial growth in cavities. J Oral Pathol 1982; 11:439-50.

Bergenholtz G. Evidence for bacterial causation of adverse pulpal responses in resin-based dental restorations. Crit Rev Oral Biol Med 2000; 11:467-80.

Berglund M, Lind B, Björnberg KA, Palm B, Einarsson O, Vahter M. Inter-individual variations of human mercury exposure biomarkers: a cross-sectional assessment. Environ Health 2005; 4:20:1-11.

Bigazzi PE. Metal and kidney autoimmunity. Environ Health Perspect 1999; 107(suppl 5):753-65.

Björkner B, Niklasson B. Contact Allergy to the UV Absorber Tinuvin P in a dental restorative Material. Am J Contact Derm 1979; 8:6-7.

Bjornberg KA, Vahter M, Berglund B, Niklasson B, Blennow M, Sandborgh-Englund G. Transport of methylmercury and inorganic mercury to the fetus and breast-fed infant. Environ Health Perspect 2005; 113:1381-5.

Bonding N, Graem N, Rygaard J, Dabelsteen E. Effects of irradiation with dental light curing units on Langerhans cells in human stratified epithelium in heterotransplanted skin. Scan J Dent Res 1987; 95:463-6.

Bouilliaguet S, Virgillito M, Wataha J, Ciucchi B, Holz J. The influence of dentine permeability on cytotoxicity of four dentine bonding systems, *in vitro*. J Oral Rehab 1998; 25:45-51.

Bradford Hill A. The environment and disease: association or causation? Proc Royal Soc Med 1965; 58:295-300.

Bratel J, Haraldsson T, Meding B, Yontchev E, Ohman SC, Ottosson JO. Potential side effects of dental amalgam restorations. (I). An oral and medical investigation. Eur J Oral Sci 1997a; 105(3):234-43.

Bratel J, Haraldson T, Ottosson JO. Potential side effects of dental amalgam restorations. (II). No relation between mercury levels in the body and mental disorders. Eur J Oral Sci 1997b; 105(3):244-50.

Brownawell AM, Berent S, Brent RL, Bruckner JV, Doull J, Gerschwin EM, et al. The potential adverse health effects of dental amalgam. Toxicol Rev 2005; 24(1):1-10.

Bruzell E, Wellendorf H. LED (Light Emitting Diodes) – lampor för ljushärdning av dentala material.http://www.socialstyrelsen.se/Publicerat/2007/9656/2007-123-25.htm

Brunel Roll EM, Jacobsen N, Hensten-Pettersen A. Health hazards associated with curing light in the dental clinic. Clin Oral Invest 2004; 8:113-7.

Carmichael AJ, Gibson JJ, Walls WG. Allergic contact dermatitis to bisphenol-A-glycidylmethacrylate (BIS-GMA) dental resin associated with sensitivity to epoxy resin. Br Dent J 1997; 183:297-8.

Casetta I, Invernizzi M, Granieri E. Multiple sclerosis and dental amalgam: case control study in Ferrara, Italy. Neuroepidemiology 2001; 20:134-37.

Chadwick RG, Traynor N, Moseley H, Gibbs N. Blue light curing units – a dermatological hazard. Brit Dent J 1994; 176:17-31.

Cohly HH, Panja A. Immunological findings in autism. Int Rev Neurobiol 2005; 71:317-41.

Dahl JE, Sundby J, Hensten-Pettersen A, Jacobsen N. Dental workplace exposure and effect on fertility. Scand J Work Environ Health 1999; 25:285-90.

DeRouen TA, Martin MD, Leroux BG, Townes BD, Wood JS, Leitao J, et al. Neurobehavioral effects of dental amalgam in children- A randomized clinical trial. JAMA 2006; 295:1784-92.

Dodes JE. The amalgam controversy - an evidence-based analysis. JADA 2001; 132:348-56.

Drake PL, Hazelwood KT. Exposure related health effects of silver and silver compounds: a review. Ann Occup Hyg 2005; 49:575-85.

Drummond JL, Cailas MD, Croke K. Mercury generation potential from dental waste amalgam. J Dent 2003; 31:493-501.

Dunne SM, Abraham R, Pankhurst CL. A 3-year longitudinal controlled clinical study of a gallium-based restorative material. Brit Dent J 2005; 198:355-9.

Dye BA, Schober SE, Dillon CF, Jones RL, Fryar C, McDowell M, et al. Urinary mercury concentrations associated with dental restorations in adult women aged 16-49 years. Occ Environ Med 2005; 62:368-75.

Echeverria D, Woods JS, Heyer NJ, Rohlman DS, Farin FM, Bittner AC, et al. Chronic low-level mercury exposure, BDNF polymorphism, and associations with cognitive and motor function. Neurotox Teratol 2005; 27:781-96.

EFSA (European Food Safety Authority). Opinion of the Scientific Panel on Contaminants in the Food Chain on a request from the Commission related to mercury and methylmercury in food. The EFSA Journal 2004; 34:1-14.

EFSA (European Food Safety Authority). Opinion of the Scientific Panel on contaminants in the food chain on a request from the European Parliament related to the safety assessment of wild and farmed fish. The EFSA Journal 2005; 236:1-118.

Engelmann J, Leyhausen G, Leibfritz D, Geurtsen W. Metabolic effects of dental resin components *in vitro* detected by NMR spectroscopy. J Dent Res 2001; 80:869-75.

Engelmann J, Leyhausen G, Leibfritz D, Geurtsen W. Effects of TEGDMA on the intracellular glutathione concentration of human gingival fibroblasts. J Biomed Mater Res 2002; 63:746-51.

EPA (Environmental Protection Agency, US). Water quality criterion for the protection of human health Report EPA-823-R-01-001. Washington DC, USA: Environmental Protection Agency; January 2001.

EU-RAR (European Union Risk Assessment Report). Methyl methacrylate, CAS No: 80-62-6, EINECS-No. 201-297-1. Institute for Health and Consumer Protection, European Chemicals Bureau, European Commission Joint Research Centre, 1st Priority List, Luxembourg: Office for Official Publications of the European Communities; 2002.

Factor-Litvak P, Hasselgren G, Jacobs D, Begg M, Kline J, Geier J, et al. Mercury derived from dental amalgam and neuropsychologic function. Environ Health Perspect 2003; 111:719-23.

Fan PL, Meyer DM. FDI report on adverse reactions to resin based materials. Int Dent J 2007; 57:9-12.

Ferracane JL. Elution of leachable components from composites. J Oral Rehabil 1994; 21:441-52.

Finer Y, Jaffer F, Santerre JP. Mutual influence of cholesterol esterase and pseudocholinesterase on the biodegradation of dental composites. Biomaterials 2004; 25:1787-93.

Finer Y, Santerre JP. The influence of resin chemistry on a dental composite's biodegradation. J Biomed Mater Res 2004; 69A:233-46.

Franz A, König F, Anglmayer M, Rausch-Fan X, Gille G, Rausch WD, et al. Cytotoxic effects of packable and nonpackable dental composites. Dental Mat 2003; 19:382–392.

Franz A, König F, Skolka A, Sperr W, Bauer P, Lucas T, et al. Cytotoxicity of resin composites as a function of interface area. Dental Mat 2007; 23:1438–1446.

Gardiner TH, Waechter JM, Wiedow MA, Solomon WT. Glycidyloxy compounds used in epoxy resin systems: a toxicology review. Regul Toxicol Pharmacol 1992; 15:S1-77.

Garner LA. Contact dermatitis to metals. Dermatol Ther 2004; 17:321-27.

Geurtsen W. Substances released from dental resins composites and glass ionomer cements. Eur J Oral Sci 1998; 106:687-95.

Geurtsen W. Biological Interactions of Non-Metallic Restorative Materials with Oral Tissues. Acad Dent Mater Trans 1999; 13:75-93.

Geurtsen W. Biocompatibility of resin-modified filling materials. Crit Rev Oral Biol Med 2000; 11:333-55.

Geurtsen W, Leyhausen G. Chemical-biological interaction of the resin monomer triethyleneglycoldimethacrylate (TEGDMA). J Dent Res 2001; 80:2046-50.

Goldberg M. In vitro and in vivo studies on the toxicity of dental resin components: a review. Clin Oral Invest 2007 [Epub ahead of print].

Goon AT, Isaksson M, Zimerson E, Goh CL, Bruze M. Contact allergy to (meth)acrylates in the dental series in southern Sweden: simultaneous positive patch test reaction patterns and possible screening allergens. Contact Dermatitis 2006; 55:219-26.

Grandjean P, Budtz-Jørgensen E, Weihe P. Cardiac autonomic activity in methylmercury neurotoxicity: 14-year follow-up of a Farose birth cohort. J Pediatr 2004; 144:169-76.

Gresham LS, Molgaard CA, Golbeck AL, Smith R. Amyotrophic lateral sclerosis and occupational heavy metal exposure: a case-control study. Neuroepidemiology 1986; 5:29-38.

Groger G, Rosentritt M, Behr M, Schroder J, Handel G. Dental resin materials in vivo – TEM results after one year: a pilot study. J Mater Sci Mater Med 2006; 17:825-8.

Gundacker C, Pietschning B, Wittmann KJ, Lischka A, Salzer H, Hohenauer L, et al. Lead and mercury in breast milk. Pediatrics 2002; 110(3):873-878.

Haeney MR, Carter GF, Yeoman WB, Thompson RA. Long-term parenteral exposure to mercury in patient with hypogammaglobulinaemia. Br Med J 1979; 2(6181):12-4.

Halbach S, Welzl G, Kremers L, Willruth H, Mehl A, Wack FZ, et al. Steady-state transfer and depletion kinetics of mercury from amalgam fillings. Sci Total Environ 2000; 259:13-21.

Halbach S, Welz G. In situ measurements of low level mercury vapor exposure from dental amalgam with Zeeman atomic absorption spectroscopy. Toxicol Mech Methods 2004; 14:293-9.

Halbach S, Vogt S, Köhler W, Felgenhauer N, Welzl G, Kremers L, et al. Blood and urine mercury levels in adult amalgam patients of a randomized controlled trial: interaction of Hg species in erythrocytes. Environ Res 2008; 107(1):69-78 [Epub ahead of print].

Hanf V, Forstman A, Costea JE, Schieferstein G, Fischer I, Schweinsberg F. Mercury in urine and ejaculate in husbands of barren couples. Toxicol Lett 1996; 88:227-31.

Hansel C, Leyhausen G, Mai UE, Geurtsen W. Effects of various resin composite (co)monomers and extracts on two caries-associated micro-organisms *in vitro.* J Dent Res 1998; 77:60-7.

Hashimoto M, Ito S, Tay FR, Svizero NR, Sano H, Kaga M, et al. Fluid movement across the resin-dentine interface during and after bonding. J Dent Res 2004; 83:843-48.

Havarinasab S and Hultman P. Organic mercury compounds and autoimmunity. Autoimmunity Rev 2005; 4:270-5.

Havarinasab S, Björn E, Nielsen JB, Hultman P. Mercury species in lymphoid and non-lymphoid tissues after exposure to methyl mercury: correlation with autoimmune parameters during and after treatment in susceptible mice. Toxicol Appl Pharmacol 2007; 221:21-8.

Henriks-Eckerman ML and Kanerva L. Product analysis of acrylic resins compared to information given in material safety data sheets. Contact Dermatitis 1997; 36:164-5.

Henriks-Eckerman ML, Alanko K, Jolanki R, Kerusuo H, Kanerva L. Exposure to airborne methacrylates and natural rubber latex allergens in dental clinics. J Environ Monit 2001; 3:302-5.

Hensten-Pettersen A, Jacobsen N. Perceived side effects of biomaterials in prosthetic dentistry. J Prosthet Dent 1991; 65:138-44.

Hero H, Okabe T. Gallium alloys as dental restorative materials; a research review. Cells Mater 1994; 4:409-18.

Herrstrom P, Hogstedt B. Clinical study of oral galvanism: no evidence of toxic mercury exposure but anxiety disorder an important background factor. Scand J Dent Res 1993; 101(4):232-237.

Herrström P, Holmén A, Karlsson A, Raihle G, Schütz A, Högstedt B. Immune factors, dental amalgam, and low dose exposure to mercury tin Swedish adolescents. Arch Environ Health 1994; 49:160-4.

Herrström P, Högstedt B, Holthuis N, Schütz A, Rastam L. Allergic disease, immunoglobulins, exposure to mercury and dental amalgam in Swedish adolescents. Int Arch Occup Environ Health 1997; 69:339-42.

Hörsted-Bindslev P. Amalgam toxicity – environmental and occupational hazards. J Dent 2004; 32:359-365.

Hujoel PP, Lydon-Rochelle M, Bollen AM, Woods JS, Geurtsen W, del Aguila MA. Mercury exposure from dental filling placement during pregnancy and low birth weight risk. Am J Epidemiol 2005; 161:734-40.

Hultman P, Enestrom S, Pollard KM, Tan EM. Anti-fibrillarin autoantibodies in mercury treated mice. Clin Exp Immunol 1989; 78:470-7.

Hultman P, Lindh U, Horsted-Bindslev P. Activation of the immune system and systemic immune complex deposits in Brown Norway rats with dental amalgam restorations. J Dent Res 1998; 77:1415-25.

Hume WR, Gerzina TM. Bioavailability of components of resin-based materials which are applied to teeth. Crit Rev Oral Biol Med 1996; 7:172-179.

IARC (International Agency for Research on Cancer). Mercury and mercury compounds. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemical to Humans: Volume 58. IARC Press; 1993. p.239-345.

IARC (International Agency for Research on Cancer). Surgical implants and other foreign bodies: Volume 74. IARC Press; 1999. p.268-277.

IMO (Institute of Medicine). Immunization Safety Review: Vaccines and Autism. Washington DC: Institute of Medicine; 2004.

IRIS, Methylmercury. In: Integrated Risk Information System. Database quest, last revised: 12/03/2002. US-EPA.

ISO (International Standards Organisation). Standard ISO 1559, Dental materials – alloys for dental amalgam; 1995.

Issa Y, Duxbury AJ, Macfarlane TV, Brunton PA. Oral lichenoid lesions related to dental restorative materials. Br Dent J 2005; 198:361-6.

Jacobsen N, Aasenden R, Hensten-Pettersen A. Occupational health complaints and adverse patient reactions as perceived by personnel in public dentistry. Community Dent Oral Epidemiol 1991; 19:155-9.

Jacobsen N, Hensten-Pettersen A. Changes in occupational health problems and adverse patient reactions in orthodontics from 1987 to 2000. Eur J Orthod 2003; 25:591-8.

Jaffer F, Finer Y, Santerre JP. Interactions between resin monomers and commercial composite resins with human saliva derived esterases. Biomaterials 2002; 23:1707-19.

Jensen JS, Trap B., Skydsgaardk. Delayed contact hypersensitivity and surgical glove penetration with acrylic bone cements. Acta Orthop Scand 1991; 62:24-28.

Johnson GH, Bales DJ, Powell LV. Clinical evaluation of high copper dental amalgams with and without admixed indium. Amer J Dent 1992; 5:39-41.

Jokstad A, Fan PL. Amalgam waste management. Int Dent J 2006; 56:147-53.

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; 26:367-74.

Joskow R, Boyd Barr D, Barr RR, Calafet AM, Needham LL, Rubin C. Exposure to bisphenol A from bis-glycidyl dimethacrylate-based dental sealants. J Amer Dent Assn 2006; 137:353-62.

Kallus T, Mjör IA. Incidence of adverse effects of dental materials. Scand J Dent Res 1991; 99:236-40

Kanerva L, Komulainen M, Estlander T, Jolanki R. Occupational allergic contact dermatitis from mercury. Contact Dermatitis 1993; 28:26-8.

Kanerva L, Alanko K. Stomatitis and perioral dermatitis caused by epoxy diacrylates in dental composite resins. J Am Acad Dermatol 1998; 38:116-20.

Kanerva L, Rantanen T, Aalto-Korte K. A multicenter study of patch test reactions with dental screening series. Am J Contact Dermatol 2001; 12:83-7.

Khalichi P, Cvitkovitch DG, Santerre JP. Effect of composite resin biodegradation products on oral streptococcal growth. Biomaterials 2004; 25:5467-72.

Khamaysi Z, Bergman R, Weltfriend S. Positive patch test reactions to allergens of the dental series and the relation to clinical presentations. Contact Dermatitis 2006; 55:216-8.

Kingman A, Albertini T, Brown LJ. Mercury concentrations in urine and whole blood associated with amalgam exposure in a US military population. J Dent Res 1998; 77:461-71.

Kingman A, Albers JW, Arezzo JC, Garabant DH, Michalek JE. Amalgam exposure and neurological function. Neurotoxicology 2005; 26:241-55.

Klaassen, CD. editor. Casarett and Doull's toxicology. The basic science of poisons. New York: McGraw-Hill Medical Publishing Division; 2001.

Kleinsasser NH, Schmid K, Sassen AW, Harreus UA, Staudenmaier R, Folwaczny M, et al. Cytotoxic and genotoxic effects of resin monomers in human salivary gland tissue and lymphocytes as assessed by the single cell microgel electrophoresis (Comet) assay. Biomaterials 2006; 27:1762-70.

Laeijendecker R, Dekker SK, Burger PM, Mulder PG, Van Joost T, Neumann MH. Oral lichen planus and allergy to dental amalgam restorations. Arch Dermatol 2004; 140:1434-38.

Langworth S, Elinder CG, Sundqvist KG. Minor effects of low exposure to inorganic mercury on the human immune system. Scand J Work Environ Health 1993; 19:405-13.

Lau JC, Jacksin-Boeters L, Daley TD, Wysocki GP, Cherian MG. Metallothionein in human gingival amalgam tattoos. Arch Oral Biol 2001; 46:1015-20.

Lind PO. Oral lichenoid reactions related to composite restorations. Preliminary report. Acta Odontol Scand 1988; 46:63-5.

Lindbohm ML, Ylöstalo P, Sallmén M. Occupational exposures in dentistry and miscarriage. Occup Environ Med 2007; 64:127-33.

Luglie PF, Campus G, Chessa G, Spano G, Capobianco G, Fadda GM, et al. Effects of amalgam fillings on the mercury concentration in human amniotic fluid. Arch Gynecol Obstet 2005; 271:138-142.

Lygre GB, Gjerdet NR, Grönningsaeter AG, Björkman L. Reporting on adverse reactions to dental materials – intraoral observations at a clinical follow-up. Community Dent Oral Epidemiol 2003; 31:200-6.

Lygre GB, Gjerdet NR, Björkman I. A follow-up study of patients with subjective symptoms related to dental materials. Community Dent Oral Epidemiol 2005; 33:227-34.

Lygre H, Solheim E, Gjerdet NR, Berg E. Leaching of organic additives from dentures in vivo. Acta Odontol Scand 1993; 51:45-51.

Lygre H, Hol PJ, Moe G. Organic leachables from polymer-based dental filling materials. Eur J Oral Sci 1999; 107:378-83.

Lygre H. Prosthodontic biomaterials and adverse reactions: a clinical review of the clinical and research literature. Acta Odontol Scand 2002; 60:1-9.

Mackert JR, Leffel MS, Wagner DA, Powell BJ. Lymphocyte levels in subjects with and without amalgam restorations. JADA 1991; 122(3):49-53.

MAK Kommission der Deutschen Forschungsgemeinschaft (DFG). Mercury and inorganic mercury compounds. In: Greim H, editor. Occupational Toxicants - Critical data evaluation for MAK values and classification of carcinogens by the commission for the investigation of health hazards of chemical compounds in the work area. München: Wiley-VCH; 1999. Volume 15: p.81-122.

Mayes MD. Epidemiological studies of environmental agents and systemic autoimmune diseases. Environ Health Perspect 1999; 107(suppl 5):743-8.

McComb D. Occupational exposure to mercury in dentistry and dentist mortality. J Can Dent Assoc 1997; 63:372-76.

McGrother CW, Dugmore C, Phillips MJ, Raymond NT, Garrick P, Baird WD. Multiple sclerosis, dental caries and fillings: a case-control study. Br Dent J 1999; 187:261-4.

Michelsen VB, Lygre H, Skalevik R, Tveit AB, Solheim E. Identification of eluates from four polymer-based dental filling materials. Eur J Oral Sci 2003; 111:263-71.

Michelsen VB, Moe G, Skalevik R, Jensen E, Lygre H. Quantification of organic eluates from polymerised resin-based dental restorative materials by use of GC/MS. J Chromatogr Analyt Technol Biomed Life Sci 2007; 850(issues 1-2):83-91. (Available online 28 November 2006)

Mitchell RJ, Koike M, Okabe T, Posterior amalgam restorations – usage, regulation and longevity. Dent Clin N Amer 2007; 51:573-89.

Moharamzadeh K, Van Noort R, Brook IM, Scutt AM. HPLC analysis of composites with different resin compositions using different extraction media. J Mater Sci Mater Med 2007; 18:133-7.

Morton J., Mason HJ., Ritchie KA., White M. Comparison of hair, nails and urine for biological monitoring of low level inorganic mercury exposure in dental workers. Biomarkers 2004; 9:47-55.

Munksgaard EC. Toxicology versus allergy in restorative dentistry. Adv Dent Res 1992; 6:17-21.

Murray PE, Windsor LJ, Smyth TW, Hafez AA, Cox CF. Analysis of pulpal reaction to restorative procedures, materials, pulp capping and future therapies. Crit Rev Oral Biol Med 2002; 13(6):504-20.

Murray PE, Smith AJ, Windsor LJ, Mjor IA. Remaining dentine thickness and human pulp responses. Int Endo J 2003; 36(1):33-43.

Nathanson D, Lockhart P. Delayed extra-oral hypersensitivity to dental composite material. Oral Surg Oral Med Oral Pathol 1979; 47:329-33.

Ng DK, Chan CH, Soo MT, Lee RS. Low-level chronic mercury exposure in children and adolescents: meta-analysis. Pediatr Int 2007; 49(1):80-87.

Nielsen E, Larsen JC, Ladefoged O. Risk assessment of contaminant intake from traditional food items. Danmarks Fødevareforskning; 2006.

Nylander M, Weiner J. Mercury and selenium concentrations and their interrelations in organs from dental staff and the general population. Br J Ind Med 1991; 48:729-34.

O'Brien WJ. Dental materials and their selection, Chicago: Quintessence Publishing Co., Inc.; 2002.

Ohno T, Sakamoto M, Kurosawa T, Dakeishi M, Iwata T, Murata K. Total mercury levels in hair, toenail, and urine among women free from occupational exposure and their relations to renal tubular function. Environ Res 2007; 103(2):191-7.

Okabe T. Mercury in the structure of dental amalgam. Dent Mater. 1987; 3:1-8.

Olea N, Pulgar R, Perez P, Olea-Serrano F, Rivas A, Novillo-Fertrell A, et al. Estrogenicity of resin based composites and sealants used in dentistry. Env Health Perspec 1996; 104:298-305.

Örtengren U. On composite resin materials. Degradation, erosion and possible adverse effects in dentists. Swed Dent J 2000; Suppl 141:1-61.

Parker SK, Schwartz B, Todd J, Pickering LK. Thimerosal-containing vaccines and autistic spectrum disorders: a critical review of published original data. Pediatrics 2004; 114:793-804.

Pelletier L, Tournade H, Druet P. Immunologically mediated manifestations of metals. In: Dayan AD, Hertel RF, Heseltine E, Kazantis G, Smith EM, Van Der Venne MT, editors. Immunotoxicity of metals and immunotoxicology. New York and London: Plenum Press; 1990.

Pesch A, Wilhelm M, Rostek U, Schmitz N, Weishoff-Houben M, Ranft U, et al. Mercury concentrations in urine, scalp hair, and saliva in children from Germany. J Expo Anal Environ Epidemiol 2002; 12:252-8.

Pigatto PD, Guzzi G, Persichini P, Barbadillo S. Recovery from mercury-induced burning mouth syndrome due to mercury allergy. Dermatitis 2004; 15:75-77.

Piirilä P, Hodgson U, Estlander T, Keskinen H, Saalo A, Voutilainen R, et al. Occupational respiratory hypersensitivity in dental personnel. Int Arch Occup Environ Health 2002; 75:209-16.

Polydorou O, Trittler R, Hellwig E, Kümmerer K. Elution of monomers from two conventional dental composite materials. Dent Mater 2007; 23(12):1535-41.

Powers J, Wataha J. Dental Materials: Properties and Manipulation. New York: Mosby; 2007.

Queiroz M, Perlingeiro R, Dantas D, Bizzacchi J, DeCapitani E. Immunoglobulin levels in workers exposed to inorganic mercury. Pharmacol Toxicol 1994; 74:72-5.

Rawls HR, Esquivel-Upshaw JF. Restorative resins. In: Anusavice KJ, editor. Phillips' Science of Dental Materials; 2003. p.399-442.

Reichl FX, Durner J, Hickel R, Kunzelmann KH, Jewett A, Wang M Y, et al. Distribution and excretion of TEGDMA in guinea pigs and mice. J Dent Res 2001a; 80:1412-5.

Reichl FX, Durner J, Kunzelmann KH, Hickel R, Spahl W, Hume WR, et al. Biological clearance of TEGDMA in guinea pigs. Arch Toxicol 2001b; 75:22-7.

Reichl FX, Durner J, Hickel R, Spahl W, Kehe K, Walther U, et al. Uptake, clearance and metabolism of TEGDMA in guinea pigs. Dent Mater 2002a; 18:581-9.

Reichl FX, Durner J, Kehe K, Manhart J, Folwaczny M, Kleinsasser N, et al. Toxicokinetic of HEMA in guinea pigs. J Dent 2002b; 30:353-8.

Reichl FX, Durner J, Manhart J, Spahl W, Gempel K, Kehe K, et al. Biological clearance of HEMA in guinea pigs. Biomaterials 2002c; 23:2135-41.

Reuter R, Tessars G, Vihr HW, Gleichmann E, Luhrmann R. Mercuric chloride induces autoantibodies against U3 small nuclear ribonucleoprotein in susceptible mice. Proc Nat Acad Sci USA 1989; 86:237-41.

Ritchie KA, Gilmour WH, Macdonald EB, Burke FTJ, McGowan RD, Dale IM et al. Health and neuropsychological functioning of dentists exposed to mercury. Occupat Environ Med 2002; 59:287-93.

Ritchie KA, Burke FJT, Gilmour WH. MacDonald RD, Dale IM, Hamilton RM, et al. Mercury vapour levels in dental practices and body mercury levels of dentists and controls. Br Dent J 2004; 197:625-32.

Roeters J, de Kloet H. Handboek voor Esthetische Tandheelkunde. Nijmegen: STI; 1998.

Roeters FJM, Opdam NJM, Loomers BA. The amalgam-free dental school. J Dent 2004; 32:371-7.

Rogalewicz R, Batco K, Voelkel A. Identificaton of organic extractables from commercial resin modified glass-ionomers using HPLC-MS. J Environ Monit 2006; 8:750-8.

Roitt IM, Delves PT. Roitts Essential Immunology. London: Blackwells; 2006.

Roman-Franco AA, Turiello M, Albini B, Ossi E, Milgrom F, Andres GA. Anti-basement membrane antibodies and antigen-antibody complexes in rabbits injected with mercuric chloride. Clin Immunol Immunopathol 1978; 9:464-81.

Rowland AS, Baird DD, Weinberg CR, Shore DL, Shy CM, Wilcox AJ. The effect of occupational exposure to mercury vapour on the fertility of female dental assistants. Occupat. Environment Med. 1994; 51:28-34.

Sallsten G, Thoren J, Barregard L, Schutz A, Skarping G. Long term use of nicotine chewing gum and mercury exposure from dental amalgam fillings. J Dent Res 1996; 75:594-8.

Santarsiero A, Settimo G, Dell'Andrea E. Mercury emissions from crematoria. Annali dell'Istituto Superiore di Santa 2006; 42:369-73.

Sasaki N, Okuda K, Kato T, Kakishima H, Okuma H, Abe K, et al. Salivary bisphenol-A levels detected by ELISA after restoration with composite resin. J Mater Sci Mater Med 2005; 16:297-300.

Saxe SR, Wekstein MW, Kryscio RJ, Henry RG, Cornett CR, Snowdon DA, et al. Alzheimer's disease, dental amalgam and mercury. J Am Dent Assoc 1999; 130:191-199.

Schedle A, Franz A, Rausch-Fan X, Spittler A, Lucas T, Samorapoompichit P, et al. Cytotoxic effects of dental composites, adhesive substances, compomers and cements. Dent Mater 1998; 14:429–440.

Schedle A, Örtengren U, Eidler N, Gabauer M, Hensten A. Do adverse effects of dental materials exist? What are the consequences, and how can they be diagnosed and treated? Clin Oral Impl Res 2007; 18(suppl3):232-56.

Schmalz G. The biocompatibility of non-amalgam dental filling materials. Eur J Oral Sci 1998; 106:696-706.

Schmalz G, Preiss A, Arenholt-Bindslev D. Bisphenol-A content of resin monomers and related degradation products. Clin Oral Invest 1999; 3:114-9.

Schmalz G. Kompositt-Kunststoffe. In: Schmalz G, Arenholt-Bindslev D, editors. Biokompatibilität zahnarztlicher Werkstoffe. München: Elsevier GmbH; 2005. p.99-132.

Schulte PA, Burnett CA, Boeniger MF, Johnson J. Neurodegenerative diseases: occupational occurrence and potential risk factors, 1982 through 1991. Am J Public Health 1996; 86:1281-8.

Schweikl H, Schmalz G. Toxicity parameters for cytotoxicity testing of dental materials in two different mammalian cell lines. Eur J Oral Sci 1996a; 104:292-9.

Schweikl H, Schmalz G, Gottke C. Mutagenic activity of various dentine bonding agents. Biomaterials 1996b: 17:1451-6.

Schweikl H, Schmalz G. Glutaraldehyde-containing dentine bonding agents are mutagens in mammalian cells in vitro. J Biomed Mater Res 1997; 36:284-8.

Schweikl H., Schmalz G, Federlin M. Mutagenicity of the root canal sealer AHPlus in the Ames test. Clin Oral Invest 1998a; 2:125-9.

Schweikl H, Schmalz G, Rackebrandt K. The mutagenic activity of unpolymerized resin monomers in Salmonella typhimurium and V79 cells. Mutat Res 1998b; 415:119-30.

Schweikl H, Hiller KA, Bolay C, Kreissl M, Kreismann W, Nusser A, et al. Cytotoxic and mutagenic effects of dental composite materials. Biomaterials 2005; 26:1713-9.

Schweikl H, Spagnuolo G, Schmalz G. Genetic and cellular toxicology of dental resin monomers. J Dent Res 2006; 85:870-7.

Schweinsberg F. Risk estimation of mercury intake from different sources. Toxicol Lett 1994; 72:345-51.

Schwengberg S, Bohlen H, Kleinsasser N, Kehe K, Seiss M, Walther UI, et al. In vitro embryotoxicity assessment with dental restorative materials. J Dent 2005; 33:49-55.

Scott A, Egner W, Gawkrodger DJ, Hatton PV, Hatton PV, Sherrif M, et al. The national survey of adverse reactions to dental materials in the UK: a preliminary survey by the UK Adverse Reactions Reporting Project. Br Dent J 2004; 196:471-7.

Semchuk KM, Love EJ, Lee RG. Parkinson's disease: a test of the multifactorial etiologic hypothesis. Neurology 1993; 43:1173-80.

Shajii l, Santerre JP. Effect of filler content on the profile of released biodegradation products in microfilled bis-gma/tegdma dental composite resins. Biomaterials 1999; 20:1897-1908.

Silbergeld EK, Silva IA, Nyland JF. Mercury and autoimmunity: implications for occupational and environmental health. Toxicol Appl Pharmacol 2005; 207(suppl 2): 282-92.

Sinclair NA, Thomson WH. Prevalence of self-reported dermatoses in New Zealand dentists. N Z Dent J 2004; 100:38-41.

Skare I, Engqvist A. Human exposure to mercury and silver released from dental amalgams. Arch Environ Health 1994; 49:384-94.

Small BW. A review of devices used for photocuring resin-based composites. Gen Dent 2001; 49:457-60.

Söderholm KJ. Degradation mechanisms of dental resin composites. In: Eliades G, Eliades T, Brantley W.A, Watts DC, editors. Dental Materials In Vivo. Aging and Related Phenomena. Chicago: Quintessence Publishing co, Inc; 2003. p.99-122.

Spahl W, Budzikiewicz H, Geursten W. Determination of leachable components from four commercial dental composites by gas and liquid chromatography/mass spectrometry. J Dent 1998; 26:137-45.

Stanislawski L, Daniau X, Lauti A, Goldberg M. Factors responsible for pulp cell cytotoxicity induced by resin-modified glass ionomer cements. J Biomed Mater Res 1999; 48:277-88.

Stanislawski L, Soheili-Majd E, Perianin A, Goldberg M. Dental restorative biomaterials induce glutathione depletion in cultured human gingival fibroblast: protective effect of N-acetyl cysteine. J Biomed Mater Res 2000; 51:469-74.

Stanislawski L, Lefeuvre M, Bourd K, Soheili-Majd E, Goldberg M, Perianin A. TEGDMA-induced toxicity in human fibroblasts is associated with early and drastic glutathione depletion with subsequent production of oxygen reactive species. J Biomed Mater Res A 2003; 66:476-82.

Stone ME, Cohen ME, Stone Debban, BA. Mercury vapour levels in exhaust air from dental vacuum systems. Dent. Mater. 2007; 23:527-32.

Sutow EJ, Maillet WA, Taylor JC, Hall GC, Millar M, Time-dependent corrosion potential of newly-placed admixed dental amalgam restorations. Dent Mater 2007; 23:644-7.

Suzuki T, Hongo T, Yoshinaga J, Imai H, Nakazawa M, Akagi H. The hair-organ relationship in mercury concentration in contemporary Japanese. Arch Environ Health 1993; 48(4):222-9.

Thornhill MH, Pemberton MN, Simmons RK, Theaker ED. Amalgam contact hypersensitivity lesions and oral lichen planus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003; 95:291-99.

UBA (Umweltbundesamt). Kommission "Human-Biomonitoring des Umweltbundesamtes, Berlin: Stoffmonographie Quecksilber - Referenz- und Human-Biomonitoring-(HBM)-Werte. Bundesgesundheitsbl. Gesundheitsforsch Gesundheitsschutz. 1999; 42:522-32.

UNEP (United Nations Environment Programme). Global mercury assessment. United Nations Environment Programme – Chemicals. Geneva; 2002.

Uversky VN, Li J, Fink AL. Metal-triggered structural transformations, aggregation, and fibrillation of human alpha-synuclein. A possible molecular link between Parkinson's disease and heavy metal exposure. J Biol Chem 2001; 276:44284-96.

Vamnes JS, Lygre GB, Grönningsaeter AG, Gjerdet NR. Four years of clinical experience with an adverse reaction unit for dental biomaterials. Community Dent Oral Epidemiol 2004; 32:150-7.

van Noort, R., Gjerdet, NR., Schedle, A., et al. An overview of the current status of national reporting systems for adverse reactions to dental materials. J. Dent. 2004; 32:351-358.

Vangstein A. Case report: Dental light-curing unit and brain stimulator electrodes - a risk? Nor Tannlegeforen Tid 2003; 113:337.

Warfvinge K, Hansson H, Hultman P. Systemic autoimmunity due to mercury vapour exposure in genetically susceptible mice: dose response studies. Toxicol Appl Pharmacol 1995; 132:299-309.

Wataha JC, Schmalz G. Dentalegierungen. In: Schmalz G, Arenholt-Bindslev D, editors. Biokompatibilität zahnarztlicher Werkstoffe. München: Elsevier GmbH; 2005. p.212-44.

Weiner JA, Nylander M. An estimation of the uptake of mercury from amalgam fillings based on urinary excretion of mercury in Swedish subjects. Sci Total Environ 1995; 168:255-65.

WHO (World Health Organisation). Environmental Health Criteria 101, Methylmercury. Geneva: World Health Organisation, International Programme on Chemical Safety; 1990.

WHO (World Health Organisation). Environmental Health Criteria 118, Inorganic mercury. Geneva: World Health Organisation, International Programme on Chemical Safety; 1991.

WHO (World Health Organisation). Concise International Chemical Assessment Document 50. Elemental mercury and inorganic mercury compounds: human health aspects. Geneva: World Health Organization; 2003.

Wieliczka DM, Spencer P, Moffitt CE, Wagner ES, Wandera A. Equilibrium vapor pressure of mercury from dental amalgam *in vitro*. Dent Mater 1996; 12:179-84.

Wilson AD, Kent BE. A new translucent cement for dentistry. The glass ionomer cement. Br Dent J 1972; 132:133-5.

Wilson AD, Prosser HJ, Powis DM. Mechanism of adhesion of polyelectrolyte cements to hydroxyapatite. J Dent Res 1983; 62:590-2.

Wong L, Freeman S. Oral lichenoid lesion (OLL) and mercury in amalgam fillings. Contact Dermatitis 2003; 48:74-79.

Woods JS, Martin MD, Leroux BG, DeRouen TA, Leitão JG, Bernardo MF, et al. The Contribution of Dental Amalgam to Urinary Mercury Excretion in Children. Env Health Perspec 2007; 115(10): 1527- 1531.

Wrangsjö K, Swartling C, Meding B. Occupational dermatitis in dental personnel: contact dermatitis with special reference to (meth)acrylates in 174 patients. Contact Dermatitis 2001; 45:158-63.

Yap AU, Soh MS. Thermal emission by different light-curing units. Oper Dent 2003; 28:260-6.

Yoshinaga J, Imai H, Nakazawa M, Suzuki T, Morita M. Lack of significantly positive correlations between elemental concentrations in hair and in organs. Sci Total Environ 1990; 99:125-35.

Yoshizawa K, Rimm EB, Morris JS, Spate VL, Hsieh C-C, Spiegelman D, et al. Mercury and the risk of coronary heart disease in men. N Eng J Med 2002; 347:1755-60.

Zimmer H, Ludwig H, Bader M, Bailer J, Eickholz P, Staehle HJ, et al. Determination of mercury in blood, urine and saliva for the biological monitoring of an exposure from amalgam fillings in a group with self reported adverse effects. Int J Hyg Environ Health 2002; 205:205-11.