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1. Membership

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2. Introduction

Dental Amalgam is a combination of alloy particles and mercury, a liquid metal at room temperature, which is mixed to a paste and then inserted in this plastic state into prepared cavities in teeth where it sets hard. It is the most commonly used dental restorative material in the world, with many billions of such fillings having been placed following its use on a broad basis since the 19th century. It is a material whose widespread use by dentists owes much to its mechanical properties and to the relative ease with which it can be placed satisfactorily. Changes to the material since its introduction have concentrated on improving its physical properties in order to enhance its performance.

Controversy has followed the use of this material since its widespread introduction as a restorative material for teeth in the middle of the last century. In recent years there has been some public discussion, both within Europe and elsewhere, regarding its suitability as a filling material for human teeth. The controversy centres on the safety of the material and relates particularly to the mercury containing fraction within the mixed material. In several countries the use of dental amalgam has decreased in recent years.

Dental amalgam is a medical device within the meaning of Council Directive 93/42/EEC, (the Medical Devices Directive or MDD). As a direct result of the discussion on the safety of dental amalgam mentioned above and for other reasons relating to the environment, some Member States of the European Economic Area (EEA) have adopted, or intend to adopt, measures to restrict its use.

Since the primary aim of the Medical Devices Directive is the reduction of barriers to trade within the European Union (EU), the potential exists for a barrier to the free movement of these products to be erected; particularly given that this Directive was implemented on 1 January 1995 and the transition period for any parallel national regulatory arrangements related to it ended in June 1998.

In 1995 DGIII of the European Commission (the Commission) following advice from the EU Medical Devices Expert Group convened an Ad hoc working group of experts to explore matters in relation to regulatory issues and the use of dental amalgam as a filling material. All Member States of the EEA were invited to nominate appropriate participants. Members of the group were experts drawn from healthcare professionals including dentistry, public authorities including

government, the dental trade, industry, notified bodies and standards bodies. (A full membership list is at chapter 1).

This report is the result of the work of that group carried out over 9 meetings held from April 1995 to April 1997. A meeting took place in October 1998 to finalise the report following comments received on a draft presented to the Medical Devices Expert Group dated June 1997. A list of the comments considered can be found at **Annex 4.**

The mandate drafted for the group by the Commission can be found at chapter 3 of this report and sets out a number of tasks relating to an examination of regulatory policies in Member States, the analysis of adverse incidents, standardisation activities and available research data on the safety of dental amalgam. As the meetings progressed it became clear to the Commission and to the group that consideration of the use and safety of alternative dental restorative materials to dental amalgam would be necessary. However in the time available this could not be addressed to the same degree as for dental amalgam.

This report examines material related to the biocompatibility (including the toxicology) of modern formulations of dental amalgam and, to a lesser extent, alternative materials. This was the basis for analysing the risks to patients and users associated with these materials. We have not considered matters relating to dental amalgam formulations consisting of copper and mercury, so-called 'copper amalgam'. This has hardly been used in the EEA for a large number of years and was judged to be of historic interest only.

The group has analysed available information relating to adverse incidents to some extent and the results of research relating to the safety of dental amalgam as the mandate required. In carrying this out a wide body of published material has been drawn upon, principally from national and international reviews carried out in recent years. The group was aware that current, but unpublished, research may provide additional information on the matters under consideration. The drawing of conclusions from such data however was considered to be inappropriate by our group until they had been subjected to proper independent scientific scrutiny.

The mandate required an examination of standardisation activities in this area at national, European and international level and to consider whether, and to what extent, these activities need to be enlarged. It was judged more helpful to do this following a consideration of matters of risk.

In fulfilling the remaining elements of the tasks in the mandate, detailed consideration was given to the labelling of materials used to make dental amalgam. Relevant research topics, including those required to support further decision making have also been identified.

It was considered important to establish the nature of any existing prohibitions or restrictions on the use of dental amalgam in Member States of the EEA. To this end a questionnaire was devised. Replies to the questionnaire and comments on them are the subject of chapter 4 of this report.

It must be emphasised that this report is not a scientific investigation or treatise on the safety of dental amalgam in humans, but is a report based on the available scientific evidence. Also, the mandate was interpreted, following advice from the Commission, as excluding detailed consideration of the environmental impact of dental amalgam, however the working group recognised that the disposal of dental amalgam may have environmental consequences and this has resulted in regulatory interventions in a number of Member States. According to the mandate these have been addressed to a very limited extent only.

Currently there are no materials which are considered a complete substitute for sound healthy tooth tissue and consequently the group wished to emphasise, at the outset of this report, the importance of preventing the need for the restoration of teeth.

This report attempts to set up-to-date information on safety aspects of dental amalgam within the risk-benefit context of the Medical Devices Directive and the regulatory framework of Member States of the EEA. The conclusions have been drawn and recommendations made to the Commission with this in mind.

3. Mandate

In December 1994 the following draft mandate was made by the Medical Devices Expert Group, European Commission, Directorate-General III - Industry, D.2 Sector of the Medical Devices:

'Issues related to the safety of dental amalgam and the conditions of use of these products have been recently brought again into public discussion. These products will be governed from January 1995 by the Medical Devices Directive 93/42/ EEC. In view of the uniform application of the relevant directive it is important to establish a common understanding of current regulatory policies within EEA related to these products. Therefore, an Ad hoc working group will be established in order to examine the situation and to elaborate, if necessary, recommendations.

The tasks of the Ad hoc working group would be:

1. to examine regulatory policies and regulatory/administrative measures undertaken and envisaged by EEA Member States in relation to the placing on the market and use of dental amalgam

2. to analyse available information related to adverse incidents

3. to examine the activities of national/european/international standardization and to explore whether and to what extent these activities may need to be enlarged

4. to analyse available results of research relating to the safety of dental amalgam and to consider relevant research topics which may be required in order to support further decision making.

The working group will be composed of experts from public authorities, notified bodies, industry and health care professionals. It should deliver a comprehensive report including, if necessary, recommendations on measures to be taken, or to be further considered, by Autumn 1995.'

Our Ad hoc group was established during Spring 1995 and held its first meeting in Brussels, on 27 April 1995.

4. National Regulations and Policies

In order to find out the requirements which affect the placing on the market and the use of dental filling materials a questionnaire (**Annex 1**) was sent to the national authorities of the EEA countries in the summer of 1995. Answers were received from all countries. The following information is based on the replies to that questionnaire and additional information from the group members. It has not been subject to any critical review.

Legally binding restrictions on the use of dental amalgam are rare in the EEA. In the Nordic countries Denmark, Finland, Norway and Sweden, recommendations to restrict the use of dental amalgam are based on environmental concerns. In Austria and Germany restrictions are intended as a preventive health measure in order to reduce human exposure to mercury.

There are no regulations or guidance from national authorities in EEA countries which indicate that clinically satisfactory dental amalgam fillings should be removed.

4.1 Implementation of the Medical Devices Directive

All countries except Belgium, Ireland, Luxembourg and Spain state that they have implemented the MDD in their own national legislation.

4.2 National legislation/regulations during the transitional period (until June, 1998)

National legislation is most extensive in **Germany**. Before the regulations implementing the MDD (Medizinproduktegesetz), dental filling materials were considered to be pharmaceuticals and subject to pharmaceuticals legislation (Arzneimittelgesetz). After the MDD became active in Germany on 1 January 1995, dental filling materials, for a transitional period until June 1998, are to be regarded either as pharmaceuticals or as medical devices.

In 1995, the Federal Institute for Drugs and Medical Devices (BfArM) ordered the following measures:

- Dental amalgam fillings are not permitted to be used as materials for cores, fillings in or on metallic restorations.
- New dental amalgam fillings should not be placed in contact with existing metallic restorations.
- Dental amalgam fillings should not be placed in those who are pregnant.
- The indication to use dental amalgam for children up to 6 years of age shall be considered.

Dental amalgam is contra-indicated in patients with severe renal disorders and those allergic to one of the components of dental amalgam.

Alternative materials should be preferred whenever other materials are not indicated. Dental amalgam fillings are only allowed to be placed for stress bearing fillings in the posterior region (Class I and II), and only then if other plastic filling materials are not indicated and other restorative techniques are not appropriate. For reasons of preventive health care the number of dental amalgam fillings for each patient should be as low as possible, as each dental amalgam filling contributes to the body burden of the patient. There is, however, no need to have clinically satisfactory dental amalgam fillings removed.

The product information for dentists (Fachinformation) has been supplemented with further details about the pharmacological and toxicological properties of mercury released from dental amalgam.

In **Austria** an Ordinance on Dental Amalgam exists and only non-gamma 2 dental amalgam fillings may be used. A test certificate is obligatory for all filling materials and labelling is required.

In **Norway** dental restorative materials have to be NIOM (Scandinavian Institute for Dental Materials) certificated in accordance with international standards or programmes if not CE-marked.

In **Sweden** dental materials which form part of dental appliances have, from October 1996, to be in compliance with the law on medical devices to be reimbursed.

In **France** if dental materials are not CE-marked, they must conform with French Standards defined by AFNOR (Association Française de Normalisation).

4.3 Recommendations from national health authorities for health reasons

Belgium, Denmark, France, Greece, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain and the UK have neither recommendations nor restrictions on the use of dental amalgam or other filling materials.

In **Austria** the Federal Ministry of Health and Consumer Protection set up an Expert Group on dental materials to elaborate recommendations to dental practitioners and industry.

The group presented the following recommendations:

- Recommendation against the use of dental amalgam fillings in the deciduous (milk) teeth of children.
- Recommendation against the use and removal of dental amalgam fillings in pregnant and nursing women.
- Restrictions with regard to several medical and occupational conditions (impairment of renal function, progressive degenerative diseases of the peripheral and central nervous system).
- Improved information to patients and dental practitioners on the composition, safety, risks, performance of dental amalgam fillings and on correct procedures.
- In patients with adequately proven hypersensitivity, dental amalgam fillings should be replaced only in case of relevant classical symptoms. Suitable alternatives should be used for further restorations.

Steps to be taken in the medium term should be the avoidance of the use of dental amalgam fillings in juveniles and improvement of prophylactic measures.

In **Germany** a consensus was reached at the end of 1996 between the Ministry of Health, the BfArM and scientific organizations. The key element of this consensus are:

- A dental filling material in general is not to be used, if a patient has a confirmed diagnosis of allergy to any of the components of the respective filling material.
- No extensive filling therapy should be performed in pregnant women except for emergency therapy.
- Relative contra-indication for amalgam in patients with severe renal disease.
- The special situation with children should be considered when choosing the appropriate filling material. As amalgam increases the mercury level, its use should be considered carefully as well as the release of components from alternative filling materials.
- The choice of the appropriate filling material must be based upon the individual clinical situation. A general ranking of dental filling material is difficult. The patients have the right to participate in the choice of the material.

In **Norway** the Norwegian Board of Health's recommendations on the use of dental filling materials are as follows:

- Avoid extensive dental amalgam therapy in pregnant women.
- Avoid contact between dental amalgam and gold.
- Drilling, polishing and grinding of dental amalgam fillings should always be combined with watercooling and vacuum suction.
- Alternative restorative materials, for example composites, glass ionomers, are best suited to restore small carious defects. The alternative materials should be used to the greatest possible extent in treating small defects and in other cases when indicated. Dental amalgam, as one of many direct tooth restorative materials, can continue to be employed in the future.

In **Sweden** there are general recommendations from the National Board of Health and Welfare :

- Work with dental amalgam in pregnant women should be avoided as far as possible.

- Dental amalgam fillings should be avoided when repairing gold crowns. The number of different alloys in any oral cavity should be minimized. Gold crowns should not be cemented to dental amalgam cores. When the replacement of an existing dental amalgam core under a gold crown on a root-filled tooth is being considered, the risk of possible endodontic complications should be weighed against the possibility of not carrying out such a replacement.

- Alternatives such as composite materials or glass-ionomer cements should be used as far as possible when repairing teeth with small carious lesions and also in other cases where indicated and where other alternatives with more permanent properties cannot be used for various reasons.

- In patients who have developed hypersensitivity to mercury, existing dental amalgam restorations should be replaced with another material.

In **Norway and Sweden** any adverse effects that can be related to dental materials are to be reported by dentists and physicians to their National Board of Health and Welfare. This is true to some extent also in **Finland**.

4.4 Regulations/recommendations from national authorities for environmental reasons

Mercury from any source in the environment can accumulate in eco systems. There has been increasing pressure to take account of this by reducing the amount of mercury waste. For this reason alone this has resulted in some countries recommending the restriction of the use of dental amalgam.

In **Denmark** there is a legally binding Order (no 520 of 9 June 1994) on the prohibition of sale of mercury and mercury-containing products. Exceptions currently are made for certain devices including dental fillings. The sale of dental filling materials containing mercury generally was permitted until 1 January 1995. However, the order allows the sale, until 1 January 1999, of filling materials containing mercury for use in posterior teeth where the filling is stress bearing, or where oral conditions make it impossible to obtain a good result using other plastic

materials. According to the order the ban will only extend to dental filling materials when appropriate alternatives (to dental amalgam) have been developed.

In **Sweden** the Parliament has recommended that dental amalgam should not be used after 1 January 1997. This is a recommendation and is not legally binding. The National Chemicals Inspectorate has in consultation with the National Board of Health and Welfare presented to the Government an evaluation of progress on the discontinuation of the use of dental amalgam. The Government will decide on future measures during 1997. There is also an agreement between the Ministry of Health and Social Affairs and the Association of County Councils that dental amalgam should not be used in children and young people. Exemptions are allowed depending on the needs of the individual patient. For example, when dental treatment is given under general anaesthesia and when the use of other dental materials would require additional appointments, dental amalgam may be used. This agreement has been confirmed by the Government.

In **Finland** the Ministry of Social Affairs and Health in 1994 recommended to dentists that materials other than dental amalgam should be used in preference for dental care, due to environmental pollution.

In **France** the General Directorate for Health has set up a working group to study the environmental issues related to dental materials.

In **Belgium** special attention is to be paid to dental restorative materials which are sent directly by mail to dentists.

5. Biocompatibility and Dental Amalgam

5.1 General remarks

It was decided that in order to fulfil the mandated tasks an examination of the biological effects of dental amalgam was required. To carry this out we concentrated on the biocompatibility and consequently toxicological aspects of *inorganic* mercury released from dental amalgam, since these have formed the scientific basis for regulatory decisions on this material; a brief discussion of the other components of dental amalgam are described in chapter 7 together with a discussion of their risk. However it was not practicable with the time and resources available to evaluate every paper on this subject individually. This ground has been covered, to a large extent, by national and international reviews in the past few years. Therefore the reviews listed below and significant recent papers were the basis for our discussions.

The criteria used for selecting these reviews were that they should:

- cover the scientific literature comprehensively,
- be commissioned by an official body and,
- be publicly available.

On the basis of all these criteria, the following reviews were heavily drawn upon:

1. WHO (1991)
2. USA National Institutes of Health (1992)
3. Swedish Medical Research Council (1992)
4. US Public Health Service (1993)
5. Swedish National Board of Health and Welfare (1994).

More recent material, mostly published papers, was also considered. The main criteria used for selecting papers were that they should be peer reviewed in a scientific journal.

In assessing the toxicological aspects the basic dictum of Paracelsus was borne in mind that, potentially, all substances are poisons and that any adverse effect depends on the dose given. Considerations of biocompatibility were discussed in relation to the ability of the material to perform as a dental filling with a host tissue response which is tolerated rather than a more stringent requirement of being beneficial.

Under the Medical Devices Directive 93/42/EEC (MDD) safety aspects of mercury associated with dental amalgam have to be addressed in relation to both patients and health care providers.

Exposure of humans to mercury generally occurs by different routes and in different forms. There are three forms of inorganic mercury: Hg^0 (metallic), Hg_2^{++} (mercurous) and Hg^{++} (mercuric) mercury. The mercurous and mercuric states form numerous inorganic and organic compounds. Organic compounds of mercury are forms where mercury is attached covalently to at least one carbon atom, for example methylmercury. Whilst these mercury forms have some common properties, differences exist in their physicochemical properties, metabolism and toxicity.

The presence of mercury in the diet and dental amalgam are probably the most significant sources of exposure for the general population. Within the diet fish are a dominant source of organic mercury, whilst mercury derived from dental amalgam is inorganic or elemental.

The hazards (see **Annex 5**) of mercury toxicity generally can be established from available animal or human data in the literature. There are over 13.000 references describing the biological effects of mercury. A number of toxic effects can be identified with estimates of doses which produce these effects. Whilst these doses could not always be precisely defined they could be estimated for risk analysis.

5.2 Mercury, its release from dental amalgam and fate

The potential for dental amalgam to be a source of mercury exposure was shown by Stock (1939). Until about 15 years ago there was little interest in these findings since any adverse effects from this source were considered unlikely given the very small amounts of mercury involved (Frykholm 1957). Since then several studies

have been performed measuring mercury in intra oral air, tracheal air, expired air or saliva in humans with dental amalgam restorations. These studies established that the mercury concentrations in air and saliva from subjects with dental amalgam restorations are significantly higher than from subjects without (Hörsted-Bindslev et al 1991; Visser 1993). It has also been established that mercury vapour and dental amalgam particles are released during placement and removal (Arenholt-Bindslev and Schmalz 1995).

It has become clear therefore with improved analytical techniques over recent years that mercury is released from dental amalgam fillings, although it was recognised that the determination of the small amounts of mercury in tissues and fluids is associated with great difficulty (Swedish Medical Research Council, 1992) and may be prone to significant analytical errors.

Mercury may be released from dental amalgam fillings in several ways. These

include:

- Mercury vapour (Hg^0) from restoration surfaces.

- Corrosion products, considered to be mercuric ions (Hg^{++}).

- Particles worn, removed or broken containing mercury in amalgamated phases.

Since the form, routes and extent of absorption of the mercury released vary between these different mechanisms, so do the risks associated with these exposures. Different compositions and methods of manufacture may also result in products with different release rates for mercury *in vitro* (Ferracane et al 1995).

Changes to the composition of dental amalgam have, in recent years, concentrated on the improvement of physical properties. In recent years a major change by manufacturers has been to attempt to eliminate the most corrodible phase of dental amalgam, a tin-mercury compound (the gamma 2 phase), by increasing the amount of copper in the dental amalgam alloy powder. Dental amalgam restorations placed using these so-called 'non-gamma 2 dental amalgam alloys' have been shown clinically to last longer compared with gamma 2 containing dental amalgam (Osborne et al 1991). In some countries in the EEA, for example Germany, dentists are almost exclusively using such products because of clinical data showing that the benefits to the patient are greater and the restoration is more durable than a gamma 2 containing dental amalgam. Small amounts of gamma 2 phase, however, are

present in non-gamma 2 dental amalgam and one *in vitro* study (Ferracane et al 1995) indicates that such dental amalgam fillings are associated with slightly raised levels of mercury vapour release compared with gamma 2 containing dental amalgam fillings.

In vitro studies by Strietzel and Viohl (1992) and Fritz et al (1993) appear to confirm that copper and tin are released from dental amalgam fillings rather than silver or mercury and that the leaching rates of gamma 2 free and gamma 2 containing dental amalgam fillings in their corrosion experiments are not significantly different. In summary Strietzel and Viohl state that 'under the aggressive experimental conditions the release of mercury is very low, sometimes under the limit of sensitivity of the used analytical method and always under the WHO limits.'

5.2.1 Inhalation of mercury vapour

The main route of absorption for elemental mercury vapour is the lungs. When inhaled, about 80 % of mercury vapour is absorbed (Hursh et al 1976). Whilst rapid oxidation to mercuric ions in red blood cells and tissues follows, elemental mercury remains present in the circulation for several minutes allowing its distribution to many tissues and organs, including the brain and the kidneys. This is a rate limiting step in the retention of inhaled mercury vapour. Hg^{++} is distributed in roughly equal concentrations in plasma and red blood cells (WHO 1976). Hg^{++} cannot cross the blood-brain barrier. Elemental mercury is able to cross the placenta and the blood-brain barrier, however this is in proportion to both the dose and the rate of oxidation.

During dental treatment the patient is exposed to mercury vapour to a varying degree. A number of studies have however found that recommended limit values for short term and long term exposure to mercury vapour are far from being reached when water spray cooling and vacuum suction are used. (Brune et al 1980; Reinhardt et al 1983; Richards and Warren 1985; Pulsmeyer and Ott 1990).

Mercury release from dental amalgam is influenced by chewing, brushing, polishing and bruxing (Berglund 1990; Björkmann and Lind 1992; Barregard et al 1995; Sällsten et al 1996). Other components of dental amalgam are also released by these activities.

Calculations of the amount of human exposure to mercury from dental amalgam are based mainly on studies of the rate of mercury release into intra oral air.

A wide range of values, >1.3 - 19.8 µg Hg/day, has been reported (**Table 1**). These values tend to be highly model dependent and some of these assessments have been criticised as too high, if equated with amounts of mercury inhaled, because important modifying factors reflecting the distribution of amounts inspired, exhaled or swallowed have not been taken into account. Some have subsequently been revised downwards. The discrepancies can partly be attributable to variations in analytical methods, assumptions and methods of calculation, however, the results also imply considerable individual variation in mercury exposure from dental amalgam.

Recalculation by Olsson and Bergman (1992) using consistent assumptions of almost all the daily dose data resulted in a value of about 2 µg Hg/day (**Table 2**).

These figures can only estimate the actual bodily intake as they were based on different conditions and assumptions, which have a great influence on mercury release values (Björkmann and Lind 1992).

For evaluation and interpretation of these data with respect to the related risk see chapter 7.

5.2.2 Ingestion of mercury

The amount of mercury that reaches the systemic circulation from the ingestion of dental amalgam particles entering the gastrointestinal tract is minimal according to present limited knowledge (Visser 1993).

Almost all mercury vapour will be converted to Hg^{++} under the aerated conditions of the upper gastrointestinal tract.

Table 1

Estimates of daily intake of mercury from dental amalgam

Reference	Number of surfaces mean (range)	Mercury Intake (µg/day)
Vimy & Lorscheider 1985	1 - 16[1]	19.8
Vimy & Lorscheider 1990	- " -	9.8[2]
Langworth et al 1988	25 (8-54)	3
Snapp et al 1989	14 (4-12)	>1.3
Berglund 1990	27 (13-48)	1.7 (0.4-4.4)[3]
Jokstad et al 1992	24[4]	10
Jokstad et al 1992	>36	10-12
Skare & Engqvist 1994	39[4]	12
Halbach 1995	18 (5-42)[3]	4.8 (0.3-13.9)[3]
Richardson et al 1995	7	2.8

[1]Occlusal surfaces [2]recalculated data from 1985 [3]range [4]median

Table 2

Recalculations of daily intake of mercury

Reference	Recalculation based on reference	Number of surfaces mean (range)	Mercury Intake (µg/day)
Mackert 1987	Vimy and Lorsch. 1985	1-16	1.24
Clarkson 1988	Svare et al. 1981	not stated	17.5
	Abraham et al.1984	range 0.2-4.2 cm^2	8.0
	Patterson et al.1985	not stated	2.5
	Vimy and Lorsch. 1985	1-16	2.9
Olsson and Bergman 1992	Svare et al.1981	not stated	4.8
	Abraham et al.1984	range 0.2-4.2 cm^2	2.2
	Patterson et al.1985	not stated	0.8
	Vimy and Lorsch. 1985	1-16	0.9
	Aronsson et al.1989	43 (range 33-53)	2.2

Animal studies suggest that the absorption of mercuric ions in the gastrointestinal tract is 5 to 10 % (WHO 1991). Rahola et al (1973) reported that 4-5 days after ingestion of a single oral dose of protein-bound mercuric mercury, 75-92 % was recovered in the faeces. On average 0.3 % of the dose was apparent in whole-blood 24 hours after ingestion. This is in contrast to 90 % absorption, approximately, of methylmercury by this route.

Whilst it has been demonstrated *in vitro* that bacteria are capable of converting mercuric ions to methylmercury and vice versa, the *in vivo* situation is unclear. The balance of these two opposing actions should determine whether the potential for mercury toxicity is increased or decreased.

5.2.3 Other routes of mercury uptake

It has been suggested that mercury released from dental amalgam may be transferred to the oral mucosa, including the gingivae and enter the general blood circulation (Hahn et al 1989). These tissues are well supplied with blood and can contact dental amalgam directly (Rechmann 1993). Data are sparse however and the significance of low level mercury uptake through the oral mucosa is unclear.

Willershausen-Zönnchen et al (1992) reported a significantly elevated average mercury concentration in oral mucosal specimens from symptom-free dental amalgam bearers when compared with patients without dental amalgam fillings.

In contrast, Bolewska et al (1990) with a very sensitive histochemical autometallographic method found only very small traces of mercury in biopsies of normal oral mucosa in contact with dental amalgam fillings. In a study of mercury deposition in monkey molars, identical methodology (autometallography) was used to demonstrate a possible uptake of mercury via dentin tubules in relation to dental amalgam filled cavities (Hörsted-Bindslev et al 1991a).

When inserting dental amalgam directly into the tooth pulp of rat molars, Arvidsson et al (1994) showed with the same technique that traces of mercury may be transported from the pulp cavity to the trigeminal ganglion via nervous tissue. None of the studies on a possible pulpal mercury uptake reported any pathological findings. The significance of such low level mercury uptake is unclear.

5.2.4 Mercury in blood

Brune et al (1991) reviewed published data on normal mercury concentrations in whole blood and plasma. Several studies contained insufficient information on all sources of possible mercury exposure including fish consumption and number of dental amalgam fillings. Experimental design, analytical quality control and statistical treatment were inadequate in several investigations. Hence current knowledge of normal mercury concentrations in blood and plasma and the impact of dental amalgam fillings and fish consumption on those concentrations might be judged to be incomplete. In dental personnel who are exposed to mercury from the usual environmental sources such as air, food and their own dental amalgam fillings as well as occupational exposure, a slightly elevated blood mercury level has been shown (Åkesson et al 1991).

Fish consumption, however, rather than the presence of dental amalgam fillings was found by Möller-Madsen et al (1988) and Åkesson et al (1991) to be more significantly associated with whole blood mercury levels.

A number of studies have shown a correlation between the number of dental amalgam surfaces and the levels of mercury in plasma (Åkesson et al 1991; Molin et al 1991; Sandborgh-Englund et al 1994). Such correlations were not seen with whole blood (Stoz et al 1995a and 1995b).

Mercury levels in whole blood (Snapp et al 1989) and in plasma and urine (Molin et al 1990; Begerow et al 1994; Haikel et al 1995) were shown to decrease after removal of all dental amalgam fillings.

5.2.5 Mercury in saliva

It has been suggested that mercury vapour from dental amalgam fillings could be dissolved in saliva and reduce the amount of mercury vapour which could be inhaled and absorbed in the lungs. Ott et al (1984) reported median concentration values ranging from 6.3 to 8.3 µg/l with stimulated and unstimulated saliva samples. Measurements of mercury following chewing are usually higher. Berglund (1990) collected unstimulated saliva samples and found levels equivalent to 0.18 to 1.4 µg/day. Halbach (1995) found that release of mercury into saliva added

an average 1.1 μg Hg to the daily mercury uptake from dental amalgam fillings as estimated only from intra oral mercury vapour measurements.

5.2.6 Excretion of mercury

Excretion of mercury takes place via urine, faeces and, to some extent, exhalation, sweat and saliva. The rate of faecal excretion is about four times greater than urinary excretion in the first four days after exposure to elemental mercury (Hursh et al 1976). Quantitatively however, excretion via the kidney is considered to be dominant in the long run. The critical organ for the excretion of inorganic mercury is the kidney. Mercury exposure has been shown to give rise to different types of renal effects and these are set out at section 5.3.4.

There are a number of studies on urinary excretion of mercury in subjects with and without dental amalgam fillings. Values obtained ranged from 0.4 - 1.9 μg/day for those without dental amalgam fillings (Olstad et al 1987; Berglund 1990; Molin et al 1990; Jokstad et al 1992). The studies of those individuals with dental amalgam fillings were considered to be more difficult to evaluate; there were large discrepancies between investigators and there are several confounding factors, such as urinary flow, glomerular filtration rate, current and previous mercury exposure, number of dental amalgam fillings and marked differences between individuals. Nevertheless some studies (Nilsson and Nilsson 1986; Olstad et al 1987; Langworth et al 1991; Molin et al 1991; SandborghEnglund et al 1994) showed a correlation between the number of dental amalgam fillings and urinary output of mercury.

5.3 Toxicity, mercury and dental amalgam

The following review of the literature from sections 5.3.1 to 5.3.9 was based on conclusions from recent national and international reviews and significant recent scientific papers.

5.3.1 Mechanism of mercury toxicity

The mechanism of mercury toxicity involves the mercuric ion Hg^{++} as the chemical form causing damage on a molecular level. This is a sulphydryl poison and binds ligands with thiol groups such as structural proteins and enzymes. These may cause alterations in cellular function which may result in cell death. Such poisoning is not unique to mercury and a number of cellular defences to sulphydryl poisons exist. These comprise the endogenous sulphur compounds including methionine and cysteine and also glutathione which acts as a scavenger. The fate of glutathione conjugates is complex; they may be excreted with subsequent modifications prior to excretion.

A number of adverse effects are attributable to mercury exposure and include neurotoxicity, nephrotoxicity, reproductive toxicity, immunological effects, skin reactions and hypersensitivity (see **Annex 5**). Local effects to the dental pulp, gingivae and oral mucosa may also occur.

5.3.2 Neurological, neuromuscular and cardiovascular disease

Mercury is a known neurotoxicant and mercury levels in autopsied brain tissue have shown an apparent correlation with the number of dental amalgam fillings (Nylander et al 1987). Therefore hypotheses have been postulated of a link to various neurological or neuromuscular diseases.

There is little or no evidence to link mercury with these diseases. The most investigated hypothesis is the involvement of mercury in Alzheimer's disease. This theory is based on observations of increased brain mercury content in Alzheimer's disease patients and *in vitro* and animal data on the interference of mercury with a binding site on tubulin. There is no evidence to suggest these observations are causal effects rather than a consequence of the disease. Currently the weight of evidence is that there is no link between Alzheimer's disease and mercury (Edwardson 1995; Saxe et al 1995).

It has occasionally been claimed that multiple sclerosis (MS) may be related to mercury intoxication. To test this hypothesis Clausen (1993) compared the total mercury and the lipid soluble mercury fractions of brains at autopsy from diseased individuals with and without clinical signs of MS. He found no evidence that

mercury intoxication was a pathogenic factor for MS. In contrast he did find that the amount of lipid soluble mercury was significantly lower in those brains from individuals with clinical signs of MS.

In a Swedish epidemiological study (Ahlqwist et al 1993), 1462 women were followed for over 20 years. No correlation between dental amalgam fillings and cardiovacular disease, diabetes, cancer nor early death was found. In the same population dental amalgam fillings were found not to be associated with the impairment of kidney function or immunological status.

The 1992 US NIH report concluded that large population studies of patients and dental personnel have not provided convincing data linking any specific diseases to the body burden of mercury attributable to dental amalgam.

The 1992 Swedish report is quoted in the 1993 US report as concluding that: 'Neurological diseases such as multiple sclerosis and amyotrophic lateral sclerosis have also been alleged to be caused by mercury released from dental amalgam. However, it must be emphasised that there is no evidence for the existence of such relationship.

Epidemiological studies in Sweden have not revealed that amalgam fillings are a risk factor for cardiovascular disease, diabetes mellitus, cancer, or early death.'

The Swedish 1994 report concluded that the literature does not support an association between low-level exposure to mercury and the development of degenerative neurological diseases such as Alzheimer's disease, Parkinson's disease or amyotrophic lateral sclerosis. Also that scientific studies show that dental amalgam does not contribute to cardiovascular disease in women. There are no similar studies in men.

5.3.3 Neurotoxicity

The WHO (1991) report summarized that at exposures to mercury vapour above 80 $\mu g/m^3$, corresponding to a urine mercury level of 100 $\mu g/g$ creatinine, the probability of developing the classical neurological signs of mercury intoxication and proteinuria is high. Also that mercury vapour exposures between 25 and 80 $\mu g/m^3$, corresponding to a level of 30 to 100 $\mu g/g$ creatinine, have been associated

with increased incidence of certain less severe toxic effects such as objectively detectable tremor, and evidence of impaired nerve conduction velocity, without overt clinical impairment. These effects are present only in particularly sensitive individuals.

The occurrence of several subjective symptoms (for example fatigue, irritability) is also increased. In a few studies, tremor, recorded electrophysiologically, has been observed at low urine concentrations (down to 25 - 35 μg/g creatinine). Other studies did not show such an effect. Although the incidence of some signs was increased in this exposure range, most studies did not find a dose-response relationship.

The 1991 WHO report concluded that 'appropriate epidemiological data covering exposure levels corresponding to less than 30 - 50 μg mercury per g creatinine are not available. Since a specific no observed-effect level cannot be established and if larger populations are exposed to low concentrations of mercury, it cannot be excluded that mild adverse effects may occur in certain sensitive individuals'.

The NIH report (1992) concluded that 'except for dental personnel who have had excessive exposure to repeated mishandling, altered brain or kidney function have not been correlated with dental amalgam exposure.'

The US PHS report (1993) noted that signs and symptoms of neurotoxicity were seen following exposures greater than 50 $\mu g/m^3$ in air or urinary levels of 100 μg/l. Clinically significant adverse effects such as erethism (a mental disturbance, characterised by acute irritability, abnormal shyness, indecision and over reaction to criticism), intention tremor and gingivitis were not seen below 100 $\mu g/m^3$. Effects below this level were subclinical, for example slowed nerve conduction and short term memory loss.

The 1992 Swedish report noted that mercury levels were very similar in cases considered to be of neurotoxicity and caused by dental amalgam fillings and those of appropriate controls. These levels were far below those found in dental personnel and workers occupationally exposed to mercury. The levels of mercury found did not reach the critical level at which mental and other symptoms are invoked. There was no correlation between the reported mercury levels and the severity of mental distress. It was noted that many of these patients who had been diagnosed as having physical illnesses of anxiety and depression originally caused by adverse life situations, attributed the resulting symptoms to mercury intoxication.

The summary of the 1994 report of an expert group of the Swedish National Board of Health and Welfare stated 'In chronic exposure to mercury vapour the most vulnerable organ is the central nervous system' and that while dental amalgam fillings cause some exposure to mercury vapour, with subsequent uptake into the central nervous system 'normally the level of exposure is very low. The current scientific literature does not support an association between mercury exposure from dental amalgam and toxic effects on the central nervous system or the peripheral nerves'.

Also that psychic problems and symptoms attributed to dental amalgam fillings had not been shown to be due to direct damage either by mercury or other dental amalgam components. Such patients were considered to form a heterogeneous group of individuals who had not only dental and other oral diseases but also systemic diseases and dysfunction and a considerable proportion of psychic disturbances and psychosomatic overtones. Follow up of patients at medical centres showed that 'many, in some cases the majority of subjects', had persistent symptoms and discomfort, which were generally attributable to other causes and which remained even after the removal of amalgam fillings.

5.3.4 Nephrotoxicity

The nephrotoxicity of mercury can be divided into two distinct mechanisms: direct toxicity and an immunologically mediated mercury induced toxicity.

Direct renal toxicity involves both glomerular damage and selective necrosis of the proximal tubule which extends as the dose increases. Whilst the precise biochemical mechanism has not been fully elucidated, there is considerable information derived from animal models on the dose-response relationship.

Immunologically mediated mercury induced nephrotoxicity is poorly understood.

There are both species and strain differences in the mechanism by which this occurs. Brown Norway rats dosed with 1 mg/kg^{-1} mercuric chloride three times per week were unique in showing increased levels of immunoglobulin and antibodies (Hua et al 1993). The significance of this is not known. The group was unaware of any such findings in humans.

The 1992 US NIH report concluded that 'at present, no scientific evidence exists that mercury from dental amalgam contributes to renal disease in dental workers or their patients'. 'Except for dental personnel who have had excessive exposure due to repeated mishandling, altered brain or kidney function has not been correlated with dental amalgam exposure.'

The 1993 US PHS report found no clinical evidence of nephrotoxicity with mercury vapour in air below 100 $\mu g/m^3$. Mercury levels of up to 20 µg/l urine were found in individuals with no occupational exposure to mercury.

The 1994 Swedish report noted that there were increases in urinary mercury concentration in individuals with dental amalgam fillings compared with those without such restorations. These concentrations, however, were generally much lower than the threshold values for renal damage. Some individuals, with multiple dental amalgam fillings and who ground their teeth, had urinary levels at which some effects could be observed but these effects were of little or no importance for general health. There were no studies which indicated that there was a risk of serious renal dysfunction or renal damage due to mercury exposure from dental amalgam fillings.

Eti et al (1995) reported on the number of dental amalgam restorations or surfaces and various markers such as lysosomal enzyme, urinary mercury and proteinuria levels. They found no correlation between urinary mercury levels and the number of fillings or enzyme excretion and concluded that the small differences detected in urinary enzyme level excretion were insufficient to indicate renal injury. Herrström et al (1995) found no significant relationship between various proteins and the number of dental amalgam surfaces or urinary mercury levels. Their results suggest that dental amalgam fillings do not cause kidney dysfunction in humans.

In a kidney function study Sandborgh Englund et al (1996) followed 10 healthy subjects, one week before and 60 days after the removal of dental amalgam fillings. Blood, plasma and urine mercury were analysed as well as different kidney parameters including determination of the glomerular filtration rate and N-acetyl-ß-glucosamidase (NAG); the latter is an enzyme considered to be the most sensitive indicator of disturbance in the kidney tubules. Although plasma mercury concentration increased significantly one day after dental amalgam removal no signs of renal toxicity could be found.

5.3.5 Reproductive toxicity, fetotoxicity and fertility

Elemental mercury is able to cross the placenta. It has been implied therefore that mercury vapour released from dental amalgam represents a hazard to the fetus. There appear to be few controlled studies to establish this risk.

The WHO 1991 review states that 'some studies have found miscarriages and abortions after occupational exposure to mercury, but other studies did not confirm these effects'. It goes on to quote from a 1980 WHO document entitled 'Recommended Health-Based Limits in Occupational Exposure to Heavy Metals' that the occupational exposure of women of child-bearing age should be as low as possible.

As in 1980, the 1991 WHO group was not in a position to recommend a specific limit below which exposure to mercury has no effect until new data became available and stated that 'the standard of published epidemiological studies is such that it remains an open question whether mercury vapour can adversely affect the menstrual cycle or fetal development in the absence of the well-known signs of mercury intoxication'. In evaluating exposure levels and routes to inorganic mercury compounds this report states that 'mercuric mercury is to a great extent deposited in the placenta where it causes damage that may lead to adverse effects on the fetus'.

The 1992 Swedish report concluded that 'There are no data supporting that mercury released from dental amalgam gives rise to teratological effects'. It further stated that 'Restriction of dental amalgam therapy during pregnancy has been advocated on the grounds that the insertion or removal of dental amalgam fillings causes an acute peak exposure to mercury vapour. Available scientific data do not support such a restrictive policy'. The Swedish report particularly criticised work by Sikorski et al (1987), which indicated an association between mercury concentration found in hair and reproductive failure, for methodological weaknesses.

The 1992 US NIH report concluded that confirmed fetal effects from the use of dental amalgam have not been reported.

There is no specific mention made on this topic in the 1993 US PHS report.

The 1994 Swedish report summarised its findings in this area, which had included a consideration of the work, mentioned below, of Drasch et al (1994), by stating that

'According to the scientific literature, no adverse effects on foetal development or infant health have been shown to be associated with mercury vapour from amalgam fillings'.

Drasch et al (1994) determined the total mercury concentrations in the liver, kidney cortex and cerebral cortex of 108 children aged 1 day - 5 years and mercury concentrations in kidney cortex and liver of 46 foetuses. Mercury concentrations in kidney and liver of fetuses and kidney and cerebral cortex of older infants (11 - 50 weeks of life) were correlated significantly with the number of dental amalgam fillings of the mother. The mercury concentrations in the tissues of the newborn and young infants (0 - 10 weeks) were not well correlated. Also information on maternal occupational, domestic or medical mercury burden and dental status was only partially available. The authors concluded that infants may accumulate mercury apparently derived from maternal dental amalgam fillings. The authors recommended that the unrestricted application of dental amalgam for dental restorations in women before and during the child-bearing age should be reconsidered.

Stoz et al (1995a) followed 185 pregnant women until after delivery. Information on dental amalgam status and occupational and dietary mercury burden was available and concentrations of mercury in maternal blood before and after birth, umbilical cord blood and placenta were determined. All the women gave birth to healthy children. No correlation between the blood values of either the women or children and the area of the surfaces of the dental amalgam fillings was found. A slight correlation was found between placenta mercury levels and the surface area of the mother's dental amalgam fillings. The mean mercury level of placenta tissue was ten times higher than the mean mercury blood level of babies and mothers suggesting marked retention by the placenta. A highly significant correlation was found between blood mercury levels of umbilical cord and maternal blood. Higher mercury values were found in the umbilical cord blood of those children whose mothers had a high fish consumption, even when the latter had no dental amalgam fillings. The authors concluded that concerns regarding heavy metal contamination from tooth restoration during pregnancy seemed unjustified. Furthermore, no association between the placement of new dental amalgam fillings during pregnancy and the level of mercury in the full blood of infants and of placenta tissue was found (Stoz et al 1995 b).

Little work had been carried out to elucidate the effect (if any) of dental amalgam restorations on fertility. There was more material on mercury in this respect and conclusions could be extrapolated.

WHO in 1991 reported two controlled studies in males (Lauwerys et al 1985; Alcser et al 1989) of occupational exposure to mercury vapour. For the former group average concentrations were 14.6 μg/l for blood mercury level and 52.4 μg/g creatinine for urine. No statistical difference was found between the numbers of children born to this group and a control group. In Alcser et al's study associations also were not demonstrated between mercury exposure and decreased fertility, increased rates of major malformations or serious childhood disease.

When considering possible low level mercury exposure and effects on reproduction in females, the WHO 1991 report refers to four reports which did not find any link between occupational mercury exposure and the effects on reproduction in female dental staff. One study from Poland purporting to demonstrate such a link was referred to relatively extensively, where the high prevalence of working procedures not equivalent to modern dental clinic mercury hygiene regimes was pointed out. A Swedish study of 8,157 children born to dental staff was also mentioned in detail in the same context. This study did not confirm the findings of the Polish study. Larsson (1995) expressed major reservations about the Polish study (see chapter 7). The 1991 WHO report drew no specific conclusions concerning mercury exposure and effects on reproduction in females.

The 1992 Swedish report concluded that 'adverse effects on reproduction have not been conclusively linked to mercury vapour exposure in industry or dental offices, nor in dental patients following low-dosage mercury exposure from dental amalgam therapy during pregnancy'.

In 1994 Rowland et al reported a questionnaire survey of 418 dental assistants, who had become pregnant in the previous four years, from an overall sample of 7,000. Detailed information was collected on mercury handling practices and the number of menstrual cycles without contraception it had taken to become pregnant. Women with high occupational exposure were less fertile than unexposed controls. Women with low exposure were more fertile than unexposed controls.

Sundby and Dahl (1994) compared the time to pregnancy among Norwegian female dentists and teachers. The female dentists were not found to be less fertile or

to report increased pregnancy disorders despite the possible occupational exposure to mercury vapour.

Hanf et al (1996) correlated the number of dental amalgam fillings with mercury concentrations in morning urine and ejaculate from 80 husbands of women presenting for infertility treatment. No positive correlation could be established between subject mercury concentrations in urine and ejaculate and the quality of their semen, expressed as a fertility index. Equally, no such correlation could be established between the fertility index and the number of their dental amalgam fillings. The authors concluded that no evidence could be derived for the alleged relation between the mercury burden from dental amalgam fillings and male fertility disorders.

5.3.6 Antibiotic cross resistance

Summers and co-workers (1993) suggested, based on animal studies, that mercury released from dental amalgam could promote and maintain antibiotic resistance in association with mercury resistance in the normal human gastrointestinal microflora.

Edlund et al (1996) and Österblad and co-workers (1995) studied human patients with dental amalgam restorations, those who had previously had dental amalgam restorations removed and those who had never had dental amalgam restorations. Significant differences were not found in either mercury resistance or antibiotic resistance in the faecal anaerobic and aerobic gram-negative flora. The faecal mercury concentration, however, was 13-fold higher in those with dental amalgam restorations than the other groups.

5.3.7 Local reactions and dental amalgam

Our consideration of local reactions to dental amalgam was confined to tissue responses of the dental pulp, gingivae and oral mucosa. The point was made that because of its extensive use there is more information about local reactions and the biocompatibility of dental amalgam than about any other dental restorative material.

The NIH technology assessment conference on dental restorative materials (1992) stated that 'local side-effects are due to inflammatory changes or associated with hypersensitivity to specific materials. The incidence of allergic reactions appears to be small and idiosyncratic'. Also that 'very few patients appear to be at risk of developing a local toxic or allergic reaction in response to the placement of restorations. Even when such reactions occur, they may not cause a significant clinical effect'.

5.3.7.1 Lichenoid reactions

The Swedish 1992 report agreed with the above conclusions and pointed out that when lichenoid oral mucosa lesions occur in contact with dental amalgam fillings and skin testing of these patients with various antigens is undertaken, 'hyperactivity' to mercury compounds has been shown in some cases. However the report also states, 'studies of lichenoid lesions or normal mucosa in contact with dental amalgam fillings have revealed no differences in lymphocyte reactivity or in the availability of specific markers in lymphocytes. When such lichenoid reactions occur, they can be eliminated by the removal of the restoration.'

In reviewing the most recent research, the report of the 1994 Swedish expert group concluded that mercury from dental amalgam had not been shown to have an adverse effect on health with the exception of isolated cases of allergic reactions.

More recent research brought to the group's attention found no distinct differences between areas of mucosa exposed to mercury in patients with and without oral lichenoid lesions (Warfvinge et al 1994). Warfvinge and Åkesson (1994) however have called into question the relevance of patch testing on skin and suggested that direct intra-oral mucosa tests may be more relevant.

Ostman et al (1994) found that of 51 consecutive patients diagnosed with oral lichenoid reactions, 33 % were allergic to mercury. Smart et al (1995) observed both an improvement and resolution of symptoms to oral lichenoid reactions following the removal of dental amalgam restorations in 12 out 13 of cases who had patch tested positive to ammoniated mercuric chloride. These authors recommended that removal of all dental amalgam fillings in such cases need not be necessary.

Larsson and Warfvinge (1995) investigated 479 biopsies from lichenoid reactions and concluded that dental amalgam-associated lichenoid lesions present a wide spectrum of histopathologic patterns resembling similar patterns in dermatopathology but with no evidence of association with specific disease. Also that mercury accumulation may play a role in maintaining the chronicity of such oral lichenoid lesions.

Lichenoid reactions have also been reported in direct contact with other dental materials (Lind 1988; Hensten-Pettersen 1992; Larsson and Warfvinge 1995).

5.3.7.2 Local effects on the dental pulp and the gingivae

Local toxic effects of dental amalgam on the surrounding tissues have been investigated *in vitro* and *in vivo*. Most *in vitro* studies show that freshly mixed dental amalgam is cytotoxic but less so when the amalgam specimens are aged before testing (Kawahara et al 1975; Nakamura and Kawahara 1979: Milleding et al 1985; Kaga et al 1990; Schedle et al 1993). Persistent *in vitro* toxicity of dental amalgam has also been reported by Nakamura and Kawahara (1979). Zinc containing dental amalgam has been shown to be more cytotoxic than zinc free dental amalgam (Schmalz 1981b; Schmalz and Schmalz 1981: Nakamura and Kawahara 1979). When composite materials and dental amalgam fillings have been tested for *in vitro* toxicity with the same test, both materials show similar reactions.

Local toxic effects of dental amalgam in direct contact with tissue have also been investigated intensively in implantation studies. Freshly mixed material caused an inflammatory reaction whilst seven day old mixed material was considered inert (Schmalz and Schmalz 1981).

Several *in vivo* studies on the effects of dental amalgam on dental pulp tissues have been carried out. Investigations by Langeland (1959) did not show any acute or chronic pulp irritation caused by unlined dental amalgam fillings. In contrast, some authors (Swerdlow and Stanley 1962; Granath and Möller 1969; Schmalz 1981a) describe an initial pulp reaction, which diminishes four weeks after the placement of the unlined dental amalgam fillings. The pulps then showed no sign of inflammation, however increased deposition of dentine at the end of the dentinal tubules contacting the pulp indicated initial pulp damage caused by the effect of

cavity preparation and placement of the filling. Irritation of the dental pulp however can also be observed with other direct filling materials (USPHS 1993).

The 1993 US report also concluded that there are few documented adverse effects and no adverse pulpal responses from mercury. That whilst corrosion may limit marginal leakage, this may in the long-term lead to breakdown of marginal integrity, especially with the lower copper containing dental amalgam fillings. Information on the mucosal diffusion of corrosion products of dental alloys was scarce. Also that dental amalgam fillings are considered to be innocuous to gingival tissues, but are capable of conducting heat to the dental pulp when unlined.

Dental amalgam fillings are also considered to be inert to gingival tissues but may, to a limited extent, like most dental materials, accumulate plaque on their surfaces. This accumulation may be the reason for localized gingivitis, especially if the cavity margin is located below the margin of the gingivae. The potential for plaque to form, though, is less than for composite resins (Hammer and Hotz 1979).

Localised black pigmentation of the gingivae may be caused by the incorporation of dental amalgam particles. These 'amalgam tattoos' are clinically asymptomatic and non-irritating (Langford and Ruf 1990; Tolsdorff and Schützenberger 1991; Owens et al 1992; Ashinoff and Tanenbaum 1994) and are due to silver or sulphur deposits in the connective tissue and the base membrane (Hartman et al 1986). Initial mercury release from dental amalgam particles decreased with time to an unmeasurable level (Eley 1990). Implanted dental amalgam does not produce an acute tissue response and does not need to be removed except for diagnostic reasons where nevi or malignant melanoma are suspected (Holmstrup 1991).

5.3.8 Symptoms attributed to dental amalgam and general health

A wide variety of symptoms has been attributed to the presence of dental amalgam fillings (**Table 3**).

Table 3

Frequencies (%) of oral, somatic and psychologic symptoms among 218 patients with self-diagnosed oral galvanism (Herrström and Högstedt 1993)

	%
Oral symptoms	
Burning sensations	19
Metal taste	16
Toothache	10
Dry mouth	8
Painful chewing muscles	4
Somatic symptoms	
Muscle pain	37
Headache	27
Neurological symptoms (e.g. impaired memory and concentration, restless legs and symptoms related to stroke and Multiple Sclerosis)	25
Painful joints	24
Dizziness	20
Abdominal distress	17
Impaired vision	15
Allergy (nose, eyes)	14
Skin problems	13
Coughing, shortness of breath	12
Chest pains	11
Heart palpitations	11
Lower back pain	11
Genital symptoms	7
Hearing loss, tinnitus	7
Diarrhoea	6
Sweating	6
Constipation	5
Loss of hair	5
Psychologic symptoms	
Lack of energy to cope with daily work or household duties	51
Impaired quality of life	47
Tiredness	35
Anxiety	31
Depression	28
Inability to relax	18
Sleeping disorder	15
Easily annoyed	12

5.3.8.1 Oral galvanism

Patients whose teeth have been restored with metallic materials (including dental amalgam) occasionally complain of electric currents, a metallic taste, pain, tingling associations and a wide variety of other symptoms inside or even far from the oral cavity. Physical damage in such cases has never been demonstrated (Schuurs and Boere 1994).

Where symptoms are considered to be due to electrochemical dissolution in saliva the condition is often referred to as 'oral galvanism'. In some European countries however, for example in Scandinavia, this term has been used more broadly to describe any symptoms attributed to the presence of dental amalgam. As the dissolution rate differs among the restorative metals used in the oral cavity, differences in electromotive force between the metallic restorations occur which generate currents and corrosive effects. There is considerable doubt, however, whether it is possible to measure accurately electric currents in the mouth (Schuurs and Boere 1994). Whilst Bergman et al (1978) suggested that for 90 % of patients such currents do not exceed 36 μA (microampères) other measurements have varied between 4 and 50 μA; occasionally currents of up to 160 μA have been reported (Axell et al 1983).

Epidemiological studies (Nilner and Nilsson 1982; Bergman et al 1982; Johansson et al 1984; Anusavice et al 1993) have shown that those suffering from oral symptoms allegedly caused by oral galvanism do not always have higher electro-chemical currents in their mouth than those without such symptoms. A correlation has been found between the quality of restorations placed and such oral symptoms (Nilner et al 1982). Measurements of electrical taste thresholds have been observed to be lower in patients presenting with symptoms of oral galvanism (Nilner and Nilsson 1982; Axell et al 1983). Haraldson (1985) revealed that about half of 62 patients claiming symptoms of electric currents were found to suffer from symptoms of mandibular dysfunction. Hugoson (1986) investigated and treated 100 patients with complaints related to oral galvanism and found in most cases several oral, dental and medical explanations for the symptoms. With adequate dental or medical treatment or both, the symptoms regressed in most patients. Only in very few patients could the symptoms and the clinical diagnosis be attributed to dental restorative materials.

Since the late 1980s, the reported frequency of the phenomenon oral galvanism has declined. This may be due to a change in attitude of this patient group as evidence is presented to challenge their beliefs (Anusavice et al 1993).

Recently Herrström and Högstedt (1993) followed a group of 218 patients with self-diagnosed oral galvanism and reported that in every case it was considered possible to identify one or several diagnoses (among these two cases of cancer). The authors found 23 cases of previously undiagnosed conditions and called attention to the fact that there is a need for thorough medical investigation of this group of patients.

5.3.8.2 Other general health complaints attributed to dental amalgam

A number of authors have found a psychogenic component behind such complaints (Jontell et al 1985; Hugoson 1986; Hampf et al 1987; Ekholm et al 1987; Agerberg 1987; Hammaren and Hugoson 1989; Herrström and Högstedt 1993; Lindberg et al 1994).

The 1991 WHO report mentioned that 'there are many people with sometimes clearly incapacitating complaints who believe that these are caused by dental amalgam. Reports describing different types of symptoms or other effects ... do not allow any conclusions to be reached concerning their cause. ... The symptomatic picture is highly diverse and characterized by a variety of different symptoms. Some studies reported that patients improved after their dental amalgam fillings were replaced by another dental filling material. However, these reports have not been controlled for potential placebo effects.'

According to the US NIH-report (1992) 'There are numerous anecdotal reports of the association of a variety of neurologic, neuropsychiatric and allergic diseases with the presence of dental amalgam, with palliation following removal being reported in some but not all cases'. '... "improvement" after removal of dental amalgam may be coincidental, especially when the complete exposure situation has not been determined.' In the conclusions it was stated that 'available data do not justify discontinuing the use of any currently available dental restorative materials or recommending their replacement.'

The 1992 Swedish report concluded that 'Published reports of systemic toxic effects documented to have been caused by mercury from dental amalgam, are not

available in the scientific literature'. It was further stated that 'available scientific evidence does not justify the discontinuation of the use of dental amalgam, nor does it endorse a clinical concept that recommends the removal and replacement of satisfactory dental amalgam fillings with other materials'.

The US PHS report (1993) concluded, 'At present, there is scant evidence that the health of the vast majority of people with dental amalgam is compromised, nor that removing dental amalgam has a beneficial effect on health. ... Likewise, there is no evidence that removing amalgam has a beneficial effect on health, despite anecdotal reports of 'improvement' after amalgam removal in patients with certain chronic illnesses'.

The 1994 Swedish report reviewed data obtained from 7 Swedish dental treatment centers for referred patients with symptoms allegedly caused by dental amalgam. In the summary of the report it was stated that 'follow-up studies of large patient material show that many patients, in some cases the majority of the subjects, have persistent symptoms and discomfort even after removal of amalgam fillings. It has been shown that the patients' so-called illness quotient (number of days on sick-leave or invalid pension) does not decrease after removal of amalgam fillings. The patients' problems have generally been attributable to diagnoses other than mercury poisoning. The expert group considers that these presentations and follow-up studies further support the view that there is no causal relationship between dental amalgam fillings and general health'. 'Scrutiny of the results from recent research, including material presented to the expert group by the Swedish Association of Dental Patients, has not shown that mercury from dental amalgam has an adverse effect on health with the exception of isolated cases of allergic reactions.'

Lindforss et al (1994) reported on 700 patients who had their dental amalgam fillings removed and found by personal interviews that more than 50 % of the patients felt well or better. By detailed interviews it was demonstrated that pain symptoms and complaints of a metallic taste had decreased whereas other symptoms (anxiety, sleep disturbances, tiredness etc.) had increased by 10-20 %. The authors concluded that their results were ambiguous; 64 % of the patients said they felt better but at the same time reported more symptoms than before dental amalgam removal.

Lindberg et al (1994) investigated the significance of psychogenic factors in illness considered by the subjects to be caused by dental amalgam and concluded that the

symptoms of the patients could be explained by psychotraumatic life events. Tanchyk (1994) reviewed the literature on dental amalgam removal as a remedy for rheumatoid arthritis and concluded that dental amalgam removal can be classified as a harmful, unproven remedy and that quackery is involved because the claim that dental amalgam removal would cure or improve arthritis is false.

Ahlqwist et al (1995) made a follow up study on 1462 Swedish women previously examined in 1968/69. The results from a number of biochemical analyses of blood, serum and urine were analyzed for a possible statistical relationship to the number of dental amalgam fillings. Specifically, dental amalgam fillings were found not to be associated with impairment of kidney function or with immunological status. When potential confounders were taken into consideration, no significant correlations of clinical importance remained.

Berglund and Molin (1996) investigated mercury vapour release from dental amalgam in patients with symptoms allegedly caused by dental amalgam fillings. The symptom group had neither a higher estimated daily uptake of inhaled mercury vapour, nor a higher mercury concentration in blood and urine than the control group. The authors concluded that the study provided no scientific support for the belief that the symptoms of the patients examined originated from an enhanced mercury release from their dental amalgam restorations.

5.3.9 The effect of dental amalgam on the immune system

The possible influence of dental amalgam on the immune system has attracted increasing interest in the past few years. Different experimental approaches have been used, including cell culture studies, animal experiments and clinical trials. Most of these experiments have been designed to test the constituents, usually mercury, of dental amalgam rather than the mixed material.

In the WHO report (1991) it was stated that 'A special problem in the risk assessment of mercury is the fact that mercury can give rise to allergic and immunotoxic reactions, which are partly genetically regulated. There may well be a small fraction of the population that is particularly sensitive, as has been observed in animal studies. A consequence of an immunological etiology is that it is not scientifically possible to set a level for mercury, e.g. in blood or urine, below which

mercury-related symptoms will not occur in individual cases, since dose response studies for groups of immunologically sensitive individuals are not yet available.'

The 1992 NIH report concluded that systemic hypersensitivity reactions to mercury remain unproven. If they do exist, they are extremely rare, and the antigenic load responsible for these reactions could be from sources of mercury other than dental amalgam.

The Swedish Medical Research Council (1992) concluded, "In summary, there are no data to support the idea that the mercury from amalgam fillings is responsible for autoimmune disease or kidney lesions in man, or that mercury from amalgam fillings negatively affects the immune system."

In the Swedish Report (1994) it was stated that 'The expert group has found no support for the claim that mercury released from dental amalgam causes immunological disease or general immunological symptoms in humans, although in rare cases mercury can cause localized allergic reactions.'

5.3.9.1 Hypersensitivity to mercury and other components of dental amalgam

It is agreed by most authors that mercury can lead to hypersensitivity reactions. Sensitization through mucous membranes, however, is less likely than through skin and it is questionable whether mercury released from dental amalgam restorations is able to sensitize a patient (Holmstrup 1992; Warfvinge and Åkesson 1994). If immunologic hypersensitivity to mercury released from dental amalgam occurs, it is likely to be a delayed hypersensitivity reaction (Type IV). A few cases of generalized symptoms caused by type IV mercury hypersensitivity have been reported (Holmstrup 1992).

Using a standard screening technique for contact allergy, 955 patients with a tentative diagnosis of contact allergy to dental materials were tested at 16 dermatological clinics. The incidence of allergic reactions to components of dental amalgam other than mercury appeared to be low (Björkner 1990). Evidence from

case studies has indicated that allergic reactions may occur with metals, including silver, copper and tin (NIH 1992 report).

In animal experiments mercury compounds, silver, tin and copper have been found to have effects on different parts of the immune system. The significance of these data for humans, however, remains to be elucidated. Based on studies in genetically susceptible strings of animals Eneström and Hultman (1995) suggest that further studies are needed to ascertain, whether the combined exposure to the metals in dental amalgam may lower the threshold for adverse immunological reactions.

5.3.9.2 Hypersensitivity to dental amalgam and other interactions with the immune system

Eggleston (1984) found that the levels of T lymphocytes appeared to increase when all dental amalgam restorations were removed. He concluded that dental amalgam can adversely affect the quantity of T-lymphocytes.

Mackert et al (1991) compared lymphocyte subsets for subjects with and without dental amalgam restorations. The results showed no indication that dental amalgam restorations affect the human immune system.

Wilhelm et al (1992) failed to detect any effect of the dental amalgam restorations on the immune system in the peripheral blood lymphocyte populations investigated.

Nordlind and Lidén (1993) reported that mercuric chloride produced a significantly higher level of IFN-γ (interferon gamma) in the lymphocyte cultures of the patient group, with oral mucosal changes adjacent to dental amalgam restorations compared with the control group.

Cascorbi et al (1994) examined immunological parameters in 78 patients who attributed a variety of symptoms to dental amalgam fillings. Significant differences between these patients and a control group of healthy individuals with no dental amalgam fillings were not found. The authors suggested that the immunological functions of the patient group were within normal ranges.

A small proportion of mercury-sensitized individuals respond adversely to the placement of dental amalgam restorations. Adverse allergic reactions to dental

amalgam which involve skin reactions, such as rashes and eczematous lesions, sometimes occur as reactions remote from the initiating site. Gingivitis and stomatitis may also occur. (Nakayama et al 1983; Feuerman 1975).

A few cases of immediate, anaphylactic responses after placement of dental amalgam restorations have been interpreted as being caused by mercury (Dupas 1973; Duxbury et al 1982; Bolewska 1986). Verification is often based only on the remission of the lesions following removal of dental amalgam. A few cases of type III hypersensitivity (immune complex mediated) have also been reported.

Vernon and coworkers (1986) reviewed 41 published cases of allergy to dental amalgam. The reactions occurred 2 to 24 hours after dental amalgam was placed. Some of these cases went into remission even though the patient was not treated, but most cleared up after the dental amalgam was removed.

It is believed that dental amalgam whilst eliciting reactions in sensitised individuals, does not generally induce sensitisation (also see 'casting alloys' section 6.3). However, there are only a few studies that address this directly (Götz and Fortman 1959; Djerassi and Berova 1969).

Herrström and Högstedt (1994) in studying 349 Swedish pupils found no evidence to support an association between the allergic diseases, eczema, allergic rhinoconjunctivitis and asthma and the dental restorative materials, amalgam, composite resin and glass ionomer cement.

6. Biocompatibility of Alternatives to Dental Amalgam

A balanced discussion on the biocompatibility of dental amalgam requires consideration of the materials that could potentially serve as alternatives to it.

To carry this out it was recognised that from a physical, biological and economic point of view the ideal dental restorative material does not exist. Consequently there is a wide variety of restorative materials used in dentistry, each with different properties, which has proved useful in different clinical situations. Dental amalgam has broad clinical indications and is comparatively insensitive to variations in placement technique. The group wished to stress that the materials mentioned below are at present considered not to be a complete replacement for dental amalgam. Ideally, the choice of material used is based on the clinical situation, the clinician's knowledge and abilities and the properties of the material together with the informed consent of the patient. This chapter deals mainly with the hazards associated with alternative materials to dental amalgam i.e. composite resins, glass ionomer cements, casting alloys, ceramics and gallium based alloys.

It must be emphasised that time constraints dictated that the group was only able to consider these materials in the context of alternatives to dental amalgam and not to the same depth as that material. Our remarks are based mostly on the findings of the 1992 NIH and the 1993 USPHS reports and more recent material. Estimates of risks for potential hazards to these materials and dental amalgam are discussed in chapter 7.

It is clear that problems both reported in the literature and scrutinised by NIOM, (Scandinavian Institute of Dental Materials) which has collected this type of information for the last twenty years, relate mostly to local reactions. NIOM's information involves the range of materials used in dentistry to provide restorative treatment and covers materials used for temporary restorations, impression taking and delivery systems as well as the permanent materials considered in this and the previous chapter.

The greatest exposure to dental restorative materials and the variety of hazards associated with them occurs in the occupational setting. Since toxic effects are dose dependent, it was recognised that the higher exposure of these people meant they were more likely than the general population to experience adverse effects to dental restorative materials.

A variety of reactions has been described which are generally mild in nature. More recently more severe reactions have been reported in the literature (Hallström 1993; Grex et al 1995; Hutchinson 1994; Rix and Anderson 1995; Petersen 1996). Lichenoid reactions have also been observed for the most commonly used materials. The presence of components regarded as allergens in these materials does not necessarily mean they are the cause of a reaction seen in a patient. This requires confirmation by an acknowledged specialist in the field of allergy testing. As seen at section 5.3.7.1 some doubt has been cast recently on the reliability of cutaneous patch testing for detecting allergic responses to dental materials. It is emphasised, however, that the diagnosis of an allergy must be based on scientifically recognised methods.

Virtually all materials used for tooth restorations contain constituents that could contribute to local reactions. The alternatives to dental amalgam include a large number of organic materials, particularly monomers which are irritant above a 1-2 % concentration and which can result in painful mucosae or paraesthesia (Fischer 1982; Seppäläinen and Rajaniemi 1984).

6.1 Composite resins

Composite resins can be used as direct or indirect filling materials (composite resin inlays). There is more information available on the former.

The substances that combine to form a composite resin fall broadly into three categories. Those substances that:

- form the polymer network - the main component of the matrix,
- control the reaction process by which the composite sets,
- comprise or affect the filler particles.

Compared with dental amalgam the chemistry of these tooth coloured resins is complicated. There are at least 40 substances known which could be used. These are mostly organic chemicals and include liquid dimethacrylate monomers, initiators, accelerators, inhibitors, ultra violet absorbers, diluents, inorganic fillers and coupling agents. Any composite resin product comprises a variety of substances from these different categories.

These materials are increasingly being used in conjunction with agents to improve bonding to dentine which include methacrylates, dimethacrylates, phosphonated penta-acrylate esters, aldehydes and organic acids (Van Meerbeek et al 1992).

The potential for side effects is present not only with these materials per se, but also with the impurities they may contain together with incomplete curing and degradation mechanisms which can be hydrolytic, mechanical or enzymatic. The degradation products include dimethacrylates (including comonomers such as TEGDMA), filler components, impurities and aldehydes (including formaldehyde formed as a result of the setting reaction and which enhances tissue reactions to methylmethacrylate monomers (Öysäd et al 1988; Hanks et al 1991; Bayne 1992; Wataha et al 1994b; Ferracane 1994). The hazards and risks need to be evaluated on a case by case basis since components may vary between each composition and manufactured batch. Detailed consideration therefore of these hazards and risks was precluded for the purposes of this report.

Many authors have reported that freshly made composite resins are cytotoxic *in vitro* (Sayegh and Reed 1969; Schmalz 1985; Hanks et al 1988; Geurtsen 1988; Hetem et al 1989; Kaga et al 1990; Bruce et al 1993). Comparative studies have shown that both composite resin and dental amalgam, aged under standardised conditions, are cytotoxic to a similar degree initially and this effect disappears for both materials at seven days (Schedle et al 1994). Other comparative studies resulted in similar findings (Schmalz 1981b; Kaga et al 1990).

With unlined fillings the potential exists for the leaching of monomers into the dental pulp. Pulp reactions towards composite resins have frequently been described. However the toxicity of released substances as well as bacteria at the cavity floor have been recorded as causing these reactions. Shrinkage of the composite material, a significant feature of their setting reaction leads to marginal gaps at the cavity wall as a result of contraction and this facilitates bacterial invasion. Bacterial growth is enhanced by composite resins (Friedl et al 1992).

The potential for local inflammation of the gingivae and oral mucosa in the vicinity of composite resins is mainly due to the retention of bacterial plaque on the composite surface.

Large restorations particularly when placed with the use of an etching technique on tooth tissue and between cusps, increase the potential for causing cracks or fractures in hard tooth tissue due to the polymerisation shrinkage mentioned earlier.

Composite resin components and formaldehyde are common sensitisers and may cause Type IV allergic reactions; there are a number of clinical reports of contact eczema both for dental personnel and for patients. Allergic reactions are also being increasingly reported amongst dental personnel (Kanerva et al 1991a, 1991b, 1994a and 1994b; Munksgaard et al 1996).

Data on recent dentine adhesives are mixed. They have been shown to be cytotoxic (Arenholt-Bindslev et al 1994). On the other hand, they improve the marginal seal between the composite resin and the dentine, although not totally preventing gap formation, so reducing bacterial invasion to the cavity floor. There exists indeed some evidence from experimental studies with healthy pulps that, if bacterial leakage can be prevented, pulp alterations do not occur after application of dentine adhesives on intact dentine (Torstenson 1995). However, it has been claimed that pulp damage may occur, if dentine adhesives are used in deep cavities (al-Darwood and Wennberg 1993) and where the pulp is already impaired. The use of dentine adhesives as direct pulp capping material is strongly debated; there are, however, no clinical long-term studies available with these substances. Furthermore, some components of dentine adhesives are mutagenic *in vitro* with bacterial and mammalian cells (Li et al 1990; Schweikl et al 1994).

Anaphylactoid reactions following the placement of fissure sealants (which use the same organic constituents as composite resins) have also been reported (Hallström 1993; Grex 1995; Rix and Andersen 1995).

There are few data and little research on systemic reactions to composite resins, however these are usually toxicological data on the chemical components used in dental restorative materials. These data can be used to identify possible hazards such as the mutagenic potential of some components or methylmethacrylate neurotoxicity. In assessing the associated risks the route of administration and species specificity need to be considered.

Bisphenol A is part of certain composite resin molecules and was shown to evoke oestrogen-like reactions on relevant cells. Bisphenol A was identified in saliva samples ranging from 90 to 931 µg/ml collected during one hour after placement of one fissure sealant (Olea et al 1996). Corresponding saliva samples were oestrogenic *in vitro*. For composite resins the authors reported the presence of Bisphenol A only after heat treatment at pH 1 and 12. The clinical relevance of these short term *in vitro* experiments is unclear and require more critical analysis as well as further research.

6.2 Glass ionomer cements and related materials

Glass ionomer cements are mainly tooth-coloured and basically a mixture of an aqueous solution of polyacrylic acid and different silica glass powders (containing 5 - 10 % aluminium).

When glass ionomer cements were first formulated about twenty years ago they were regarded as part of the group of water-based cements which also includes zinc phosphate, silicate and silicophosphate cements. They have poor wear resistance and that deficiency makes these materials unsuitable as a complete alternative to dental amalgam. Their strength, especially their flexural strength, is too low for large restorations involving occlusal surfaces. (Prosser et al 1986).

Hybrid compounds of glass ionomer and composite resins (also known as light cured glass ionomer cements and compomers) have more recently been released onto the market. These materials encompass a variety of products with widely varying compositions. Some of the products are strongly glass ionomeric in character, whilst others are essentially modified composite resins and are known as 'compomers'. Degradation products may include substances eluted from the composite resin component, uncured monomers and formaldehyde. (Ruyter 1995).

Glass ionomers and resin-modified glass ionomers were found by Braem et al (1995) to be similar in fatigue behaviour to the microfilled composites; the latter are known from clinical experience to cause fatigue in stress-bearing areas (Lambrechts et al 1987).

To improve the mechanical properties of the earlier glass ionomer formulations some products also contain materials such as silanated, sintered, high purity silver particles or dental amalgam powder (Levartovsky et al 1994).

The current standard for glass ionomer and other water-based cements (EN 29917: 1994) specifies upper limits for heavy metal contaminants (acid soluble contents, Pb (Lead): 100 mg/kg, and As (Arsenic): 2 mg/kg). Degradation is from the surface or by diffusion through cracks and the bulk of the material and is mostly of fluoride and a small amount of aluminium. There are no studies available on the systemic effect of the elution of silver from silver-containing glass ionomers.

In vitro glass ionomers are initially cytotoxic. No pulp reactions were observed, when these materials were placed in shallow or medium deep cavities, if bacterial contamination of the cavity floor was prevented. However, severe pulp inflammation occurred when glass ionomer cement was placed in direct contact with the pulp tissue (Schmalz et al 1994b).

Resin-modified glass ionomers show a very heterogenous reaction pattern. Some of them are only initially cytotoxic, others are cytotoxic over a longer period (Schmalz et al 1994a). However there are some indications that damage to the dental pulp may not occur (Deux et al 1990; Dogon et al 1992), however data are sparse. One preparation showed *in vitro* and *in vivo* genotoxicity (Heil et al 1996).

There are no data or complaints of systemic reactions, apart from one case of general urticaria (Mjör 1992).

6.3 Casting alloys and other solid metallic materials

There are over one thousand dental casting alloy products currently on the market, drawn from a range of more than 36 elements. These alloys are mainly based on gold, palladium, cobalt-chrome, silver, nickel or titanium. Most of these alloys are intended for the manufacture of fixed or removable partial prostheses (i.e. bridges or dentures) and not for dental filling materials. They are usually based on higher amounts of base metals compared with alloys for lower stress bearing structures such as inlays, onlays or crowns.

Several *in vitro* studies have shown that metal cations may be released by dental casting alloys (Wataha et al 1991a; Geis-Gerstorfer et al 1991). The cytotoxic potential of these metal ions has been demonstrated by various investigators (Wataha et al 1991b; Wataha et al 1992; Schedle et al 1995). Under certain circumstances metal cations may be released from dental alloys *in vivo* and the release of such elements may be associated with local inflammation or other adverse reactions (Wirz and Schmidli 1987a and 1987b; Wirz 1993; Reuling et al 1990). Respective mechanisms have been analysed by various investigators. Bergenholtz et al (1965) reported on the transport of metal ions from gold inlays into environmental tissues.

The processing of these alloys in the laboratory influences any subsequent corrosion in the mouth. Degradation in the mouth is also dependent on the alloy's composition as well as the local surface and environmental conditions.

Copper-based alloys (bronzes) and certain palladium-based alloys have caused stomatitis. There is one case report of a palladium-based alloy causing a lichenoid reaction (Downey 1989). Wirz and Schmidli (1988) and Wirz (1993) have reported gingival reactions with low-gold and gold-free alloys.

Nickel is not intended to be present in present-day dental amalgam or the non-metallic dental restorative materials. At the Commission's request we devoted part of our time to a specific consideration of nickel allergies because it may be present in metallic alternative materials (see **Annex 2**).

At least ten elements used for dental casting alloys are known to be allergens. These include gold, platinum, palladium, nickel, copper, cobalt and chromium. Thus casting alloys have the potential to cause allergy. It is believed that dental casting alloys, whilst eliciting reactions in sensitised individuals, do not generally induce sensitisation. Allergic reactions to metal alloys, however, are rarely reported. Titanium has been considered not to cause allergic reactions, however recent evidence brings this into doubt (Lalor et al 1991).

Information is sparse for systemic reactions. A carcinoma of the tongue in direct contact with a corroding palladium gold crown was claimed (Kinnebrew et al 1984). Chromium and nickel are potential carcinogens and occupationally, dental technicians are likely to be at some risk since they inhale dust and fumes. However clinical reports are not very well documented.

It should be remembered that these restorations can be cemented with a variety of cements, which are usually water-based and this therefore adds another set of materials which could be responsible for any adverse reactions.

6.4 Ceramics

These tooth coloured materials are based on silica, aluminia and other oxides, and are fired, cast, pressed or machined outside the mouth.

Degradation takes place, but at a very slow rate. They are considered to be the most inert of dental restorative materials, however they have been associated in the past with low rates of radioactivity present naturally and which are allowed for in current standards[1]. Ceramic fillings require cementation and it is understood that this is usually carried out with resin based materials; this may need to be borne in mind when attributing any adverse effects to such restorations.

6.5 Gallium alloys

Gallium is a liquid at room temperature and suitably alloyed has been proposed as an alternative to dental mercury. It has a high boiling point. Whilst values given in the literature vary from 1980° C to 2400° C our group considered that there should be no concern regarding the production of gallium vapour by the body.

Some increase in research activity has been noted in recent years, mainly on *in vitro* cytotoxicity and physical properties such as corrosion, oxidation, microleakage, electrochemical and thermal behaviour. The sparse information on cytotoxic aspects appears to be equivocal. For example, Chandler et al (1994) suggested that gallium is less toxic than mercury, whilst gallium based dental alloys have been shown by Wataha et al (1994a) and by Bumgardner and Johansson (1996) to be more cytotoxic than conventional alloys. Psarras et al (1992), however, did not find any difference.

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[1] E.G. ISO 6872: 1995 – Dental Ceramic.

A clinical trial of 30 gallium alloy restorations by Navarro et al (1996) was discontinued after 8 months following relatively high rates of post-operative sensitivity and other effects including intense tarnish and corrosion.

There are at present two gallium-based dental alloys commercially available. One of them has been given the right to affix the CE-mark, with an indication for its use as a filling material for the restoration of small cavities. The certificate is valid for 2 years.

Our group recognised there was limited published information on gallium alloys and from the published information available to the group there appeared to be doubt about their clinical acceptability.

7. Risk Assessment

7.1 Introduction

Conclusions and opinions expressed in this section are taken from a wide range of reports and experiences based upon the literature cited in chapters 5 and 6 (See also review list in chapter 14). For this reason it is not feasible to indicate all reference sources. Where, however, there is a specific reference included then the source of this is indicated.

The exposure of patients and health care workers to dental materials is widespread and involves over half the population of western societies. The 1992 US National Institute of Health (NIH) report noted that all **materials** introduced into the oral cavity may present some risk to the general population and that some individuals and groups may experience greater risks because of heredity or unusual clinical characteristics. The materials used as dental restorative materials, generally, are increasing in number and complexity. There was agreement in the group that absolute safety (i.e. a total lack of risk) cannot be guaranteed to the patient, users and others. Indeed the concept of absolute safety is of itself flawed. Furthermore risks should be balanced against benefits arising from the procedures in question and it follows from this that risks may be justified in the light of clearly evident benefits. It is reasonable to expect however that legislation affords a suitable level of protection from unjustifiable health risks. It was recognised that analyses of risk and assessments of safety are related and that risk analysis and risk management are separate and consecutive processes.

The Medical Devices Directive (MDD) recognises that, whilst a device used in its intended manner should not compromise the health and safety of patients, users and others, the acceptability of risks is related to the benefits to the patient of the device. This risk-benefit concept is the basis of the Essential Requirements contained in Annex 1 of the MDD and is stressed particularly at sections 1 and 6 of that annex.

The benefits of dental amalgam are addressed to some extent later in this chapter.

A standard (EN 1441) entitled 'Medical Devices: Risk Analysis' has been drafted by a CEN/BTS3 working group, under a mandate from the Commission to provide a framework for risk analysis of medical devices in line with the MDD. The standard takes into account the risk to the health of both the patient and users of the device.

The definition of risk (see **Annex 5**) in the EN 1441 standard is a link to the MDD which requires that account has to be taken of the benefit of the device and the state of the art in analysing risks. The scope of the standard is restricted to risk analysis and it neither considers nor gives detailed guidance on risk management. It is not intended to cover decisions regarding the indications and contra-indications for the use of a particular device since these are risk management tools derived using the risk analysis. Importantly an acceptable level of safety cannot be defined in the standard nor in the MDD and given the diversity of devices needs to be established on a case by case basis.

The heart of EN 1441 is a flow chart showing successive steps to follow in order to:

- identify characteristics which could affect safety
- identify hazards associated with the use of the device
- estimate the risk for each identified hazard
- reduce each risk to an acceptable level (if possible)
- avoid generating new hazards when modifying the device to reduce an already-estimated risk
- report the results of the analysis to enable a decision on device safety to be made
- periodically update analyses in the light of additional knowledge.

All these steps require a thorough knowledge of the device. Where it appears that there is insufficient information available, either to identify a hazard or to estimate the associated risk, the standard requires that appropriate data are collected. This may require that complementary tests or clinical investigations are performed.

There is also a requirement for the manufacturer to provide documentation on how the risk analysis has been performed, step by step, and how all the risks identified have been shown to be at an acceptable level. A number of the hazards identified are likely to represent possible consequences for which the actual risk is theoretical rather than actual, however these considerations should still be documented. Also, the MDD implies that risk analysis is an on-going procedure for any device placed on the market with regular updating in light of experience and additional knowledge to reflect the state of the art and this is addressed in EN 1441. The principles

behind risk analyses in more specialised areas are described in other standards such as EN 30993-1[2] and ISO CD 14538[3].

It was recognised that risk analyses for devices such as dental amalgam placed on the market under previous legislation, in contrast to new devices being brought to the market for the first time, are likely to rely extensively on historical data. Although these historical data may be less than ideal, it would be neither ethical nor feasible to repeat the pre-clinical studies necessary for a new device when clinical data on safety and efficacy exist, albeit often in an unstructured form.

To facilitate our risk analysis we applied criteria set out in an annex of document IEC 601-1-4 (1996)[4]. This categorises risk into three regions after taking account of the likelihood of a hazardous event and the severity of the consequence of the hazardous event:

The regions in descending order of severity and likelihood are:

1. Intolerable

2. As low as reasonably practicable (ALARP)

3. Broadly acceptable.

In our analysis risks were identified in the two lower categories. Any risk should be reduced to a level which is 'as low as reasonably practicable'. When however the severity or the probability, or both, of a hazard is so low that the risk is negligible compared with the risk of other hazards which are accepted, risk reduction need not be actively pursued; such risks are judged to be in the 'broadly acceptable' region. (**Annex 3**).

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[2] EN 30993-1 1994, ISO 10993-1: Biological evaluation of medical devices. Part 1: Guidance on selection of tests.
ISO 10993-1 1992: Biological evaluation of medical devices. Part 1: Evaluation and testing. (Revision, awaiting publication).
[3]ISO CD 14538 (1995): Method for the establishment of allowable limits for residues in medical devices using health based risk assessment.
[4]IEC 601-1-4 (1996): Medical electrical equipment Part 1: General requirements for safety - 4. Collateral standard: Programmable electrical medical systems.

7.2 Establishment of a cause and effect relationship

The establishment of a cause and effect relationship centres upon the examination of two principal concepts, namely association and causation. The former uses a number of techniques to establish whether the incidence of the coexistence of the suggested cause and the effect is higher than would be expected by chance. The latter involves the elucidation of the mechanism by which the proposed cause exerts its effect.

The plausibility of hypotheses constructed for this can be examined empirically.

While it is unusual for causation to be investigated in the absence of any evidence for association, it must be acknowledged that it is possible for a cause to operate even though the effect cannot be detected in the exposed population.

Cause and effect studies, however, should be properly designed and performed using appropriate controls. A disturbing tendency has been noted when considering dental amalgam, to seize upon experimental findings as proof, irrespective of the conclusiveness or quality of the data. While it is entirely legitimate to report case histories or to carry out studies to investigate effects in selected populations, findings from such studies are relevant only to the subjects studied and cannot be applied to the general population or considered conclusive with regard to causality. Several authors have pointed to cases where an improvement in clinical condition has followed dental amalgam removal, suggesting that this is confirmation of cause and effect. Other reports are conflicting and it is difficult to avoid the possibility that psychological effects may have some influence. Where neither association nor causation provide a valid argument for the existence of a link between an effect and a supposed cause, it is reasonable, provided sufficient evidence has been gathered, to reject that link.

7.3 Dental amalgam

An initial observation of the group was that there was a limited amount of reported clinical material identified in chapter 5, in relation to toxicity due to dental amalgam fillings in the general population, even though dental amalgam has been placed in billions of teeth. However it was acknowledged that whilst this did not

indicate safety or a lack of risk, it may provide an estimate of the magnitude of the risks posed by dental amalgam since, given the extent of the exposure in the population, significant risks should have been observable.

Our risk analysis of dental amalgam, in identifying characteristics which could affect safety, primarily considers the presence of mercury and its availability. There are other aspects, however, which cannot be ignored. The hazards arising from dental amalgam can be considered in three groups: mechanical properties affecting performance, the dental amalgam restoration *per se* and its chemical components.

The majority of the concern has focussed on the release of mercury vapour but it must be noted that other sources, such as diet, ambient air, water, cosmetics and drug therapy, contribute to the total mercury exposure. The group noted the statement made in the 1992 NIH report that neither all the sources of mercury that contribute to the total body burden nor their duration of exposure are identified routinely.

7.3.1 Mechanical properties

The hazards arising from the mechanical properties are mainly dimensional change of the restoration and stress within the restoration which may lead to breakage and release of dental amalgam particles. These mechanical properties are dependent upon the composition of the mixed dental amalgam but may also be influenced by the user's technique. Dental amalgam formulations can be very different. The recent development of dental amalgam (for example non-gamma 2 amalgam) has concentrated on producing a material whose mechanical and physical properties are more reliable and predictable and thus show improved clinical properties.

The way the materials are presented to the user and the manufacturer's instructions for use are designed to ensure that dental amalgam restorations are correctly produced to exhibit specified mechanical properties in the clinical situation. Thus those risks which are independent of clinical technique are generally low and residual risks are controlled in the labelling (instructions for use). Those risks dependent on clinical technique are addressed by the professional training of the user and this should limit any residual risk. However these are outside the control of the manufacturer and of the scope of the MDD.

7.3.2 Dental amalgam ingestion and local effects

The potential hazards associated with the restorations themselves could be considered to arise from the release of particulates, the dental amalgam phases, corrosion with concomitant release of corrosion products, local adverse effects and possibly hypersensitivity. However, as it is not possible to ascertain whether the last of these is due to dental amalgam itself or to one or more of its chemical components discussion will be included with the chemical components.

The release of particulates may be due to stress fractures, as discussed above, or wear. It is probable that small particles will be swallowed, although larger particles may be spat out. The fate of dental amalgam particles in the gastrointestinal tract is unclear. They may pass through as particles and be eliminated in faeces or the metallic constituents may be ionised in the gastrointestinal contents. In the case of particles, current knowledge from extensive studies of gastrointestinal physiology and drug delivery suggests the total gastrointestinal transit time is likely to be under 24 hours. As described in chapter 5 freshly mixed dental amalgam has been shown to exert cytotoxic effects *in vitro*, which decrease as dental amalgam ages. The *in vivo* significance of this cytotoxicity is unclear and it appears to be a transient property of dental amalgam which does not cause long term adverse effects in local tissues. The gastrointestinal epithelium and the gastrointestinal microflora may be exposed to the particles during the gastrointestinal transit period. However given the tissue tolerance of dental amalgam this is unlikely to be a significant risk.

The ionisation of particles is most likely to occur in the acidic environment of the stomach and the products are likely to be similar to those produced by the *in situ* corrosion of dental amalgam. The products of both these processes are likely to be ionic forms of the component chemicals although the possibility of more complex ions being formed from the dental amalgam phases cannot be excluded. Since the toxicological hazards of these ions are inherent in their chemical nature these will be outlined below. The intestinal transit time will be similar to that for particles, however a small proportion may be absorbed or subject to metabolism by the gastrointestinal microflora.

7.3.3 Chemical constituents

The chemical components of dental amalgam are primarily mercury, silver, tin and copper although small amounts of other metals such as palladium may also be incorporated. Quantitatively mercury is the largest component and is admixed with dental amalgam alloy prior to use. The dental amalgam sets with the formation of a variety of intermetallic phases and alloy particles.

The inherent toxicological hazards of all the principal components are briefly stated below (for mercury this is a brief summary of the information in chapter 5). The body is potentially exposed to five major sources of exposure; ions of silver, tin, copper and mercury derived from corrosion of the dental amalgam or ingestion of particulates plus mercury vapour released from the surface of the restoration. There may also be exposure to ions of minor components of dental amalgam but the levels of these are probably insignificant.

The systemic exposure to the four ions is dependent on the rates of corrosion, particle shedding and absorption of the ions from the gastrointestinal tract. It should be noted that absorption in the gastrointestinal tract is primarily of uncharged compounds and that the uptake of charged molecules relies on either temporary formation of an uncharged species in the local environment or the operation of specialised transport mechanisms. The latter primarily transport essential ions into the internal milieu, however many of these special systems are capable of transporting other ions but at reduced efficiencies. Thus although ions may be absorbed to a limited extent by these two mechanisms, the total exposure is assumed to be low.

The systemic exposure to mercury vapour is dependent on the release rate from the restoration surface which in turn may be related to its size, migration rates of mercury within the restoration to replace the denuded surface mercury con-- centration, respiratory rate and ratio of oral to nasal breathing and the extent of pulmonary absorption. It is possible that some mercury vapour could dissolve in saliva, be ionised and swallowed. Thus the estimates of exposure can be influenced by these parameters and it is essential that realistic assumptions are utilised. Since mercury is considered the most significant potential hazard the risks associated with it will be discussed in far greater detail than those posed by the other components.

7.3.3.1 Tin

Tin is not an essential element. Tin will not evaporate at body temperatures and thus inhalation exposure can be discounted.

Occupational exposure in tin mining and smelting has been associated with pneumoconiosis. This is due to inhalation of tin particles or fumes. In the United Kingdom the Occupational Exposure Standard (OES, see **Annex 5**) for this is 2 mg/m^3, thus it is of little relevance to the mode of exposure from dental amalgam which does not pose such a risk. The low solubility of tin and tin oxide means that their absorption from the intestine is very poor. Tin does not pose a risk of systemic toxicity at these exposures. Local gastrointestinal effects have not been reported at the levels of tin available from dental amalgam. A Provisional Tolerable Weekly Intake (PTWI) of 14 mg/kg has been set by a Joint FAO/WHO Expert Committee on Food Additives (JECFA) and as the exposure from dental amalgam will be in the microgram range, tin can be discounted as a significant risk.

The organotin compounds are associated in a dose dependent manner with cerebral oedema and ototoxicity. Dental amalgam does not contain organotin compounds so that there is no direct risk of these effects. However the possibility that the gastrointestinal microflora may methylate tin ions cannot be completely excluded. Microfloral methylation and demethylation have both been demonstrated *in vitro*, however the balance of these reactions *in vivo* has not been established nor has the fate of such microbial metabolites. There are no data on the *in vitro* or *in vivo* methylation of tin but data on methylation of other metals suggest this is likely to be under 1 %. The main site of such transformations is the large intestine, the absorptive capacity of the large intestine is generally low and the transit time is limited. It is unlikely therefore that a significant amount of the tin would be methylated and absorbed by such a route and thus the systemic exposure would be far lower than that needed to result in profound toxicity. Thus although a theoretical possibility of organotin exposure exists, this does not appear to be significant probability in practice.

The risk of toxicity caused by the tin component of dental amalgam is therefore low and judged to be in the lowest category of risk of 'broadly acceptable' according to the concepts described in **Annex 3** of this report.

7.3.3.2 Copper

Copper is an essential element for utilisation of iron and the activity of several enzymes. There are a variety of sources of copper exposure but humans appear resistant to copper toxicity provided dietary iron, zinc, molybdenum and sulphate are adequate. The safe and adequate daily intake of copper is around 1.2 - 3 mg/day in adults. Toxicity has been observed after ingestion of greater than 15-75 mg of copper salts. Copper will not evaporate at body temperatures and thus inhalation exposure can be discounted (OES = 1 mg/m^3). Since copper is present at less than 15 % in dental amalgam restorations when it conforms with the current European standard (EN 21559: 1991, see section 8.8), the total amount of copper if released would not significantly add to the body burden. Since toxicity is not associated with such body burdens of copper there is no significant toxic risk to the general population from the copper component of dental amalgam.

The possibility of copper allergy cannot be excluded as it has been reported following skin contact with copper dust and salts or exposure to copper containing intrauterine devices. However there are no reports attributing copper allergy to dental amalgam and the risk of allergy induction is probably very low and 'broadly acceptable' (**Annex 3**). However it may be prudent to avoid exposure to copper sensitive individuals.

7.3.3.3 Silver

Silver is not an essential element in the body's biochemistry. Exposure can occur from occupational sources, jewellery and therapeutic use of silver compounds. It has also been used as a colouring in confectionery. The most recognised toxic effect is of a patchy discolouration of the skin. Silver compounds can be absorbed by inhalation, but the extent of this has not been quantified in man. Silver will not evaporate at body temperatures and thus for dental amalgam, inhalation exposure can be discounted (OES = 0.1 mg/m^3).

The absorption of silver salts from the gastrointestinal tract is 10-20 %. The possibility of immune effects cannot be discounted, however there are no data to suggest there is a significant degree of silver sensitivity in man.

Drasch et al (1995) measured silver concentrations in the liver, kidney cortex and 5 brain regions of 173 deceased persons and compared these with the number of dental amalgam fillings and previously determined inorganic mercury concentrations in the same tissues. In a sub-group of 93 males aged 11 - 50 years, the number of teeth with dental amalgam correlated with the silver concentrations in liver and cerebral cortex but not for the kidney, whilst silver and mercury concentrations only correlated in the liver. A marked sex difference in silver distribution was observed with mean liver and brain silver concentrations being double in females compared with males. Samples from one subject with possible occupational exposure were excluded as outliers (all values were >3 SD) but there were neither neurological symptoms nor argyrosis in this subject. The lack of toxicity even in this occupational case indicates a lack of significant silver toxicity from dental amalgam, but there are several unexplained findings and extrapolations of the significance of these results seem unsustainable from the published data.

The level of risk of toxicity for silver was considered to be 'broadly acceptable' according to the concepts described in **Annex 3** of this report.

7.3.3.4 Zinc and other components

The composition requirements within the dental amalgam product standards allow the incorporation of up to 2 % zinc and other metals within the alloy. The other metals are generally present at very low to trace concentrations in both the alloy and the dental amalgam. The potential dose is therefore small and it is considered that there are no significant toxicological risks from these materials. Zinc is an essential element with a total intake of 12-15 mg/day.

There are no reports of zinc toxicity from these intakes, although chronic and acute ingestion of significantly greater quantities result in a variety of toxic effects. The maximum potential contribution of dental amalgam to this would be at the microgram level and it can thus be discounted as a significant contribution to daily zinc intakes.

Zinc will not evaporate at body temperatures and thus inhalation exposure can be discounted.

It was considered that for zinc and for these other metals the level of toxicology was in the lowest category of risk of 'broadly acceptable' according to the concepts described in **Annex 3** of this report.

7.4 Mercury

As has been stated at chapter 5, information on overt mercury toxicity can be taken from available animal or human data in the literature. A number of adverse effects are attributable to mercury exposure including neurotoxicity, nephrotoxicity, reproductive toxicity, immunological effects, skin reactions, hypersensitivity and local effects. The classical signs of elemental and organic mercury toxicity are neurotoxic effects. This has been seen in dental personnel when mercury has been repeatedly mishandled resulting in high exposure to mercury vapour. In contrast, the principal toxic effects of inorganic mercury are due to kidney damage.

The risk analyses involving mercury exposure from dental amalgam are not related to overt toxicity at high mercury exposures, but to low dose levels over a long period. As acknowledged in chapter 5 on biocompatibility, dental amalgam can be a source of mercury found in tissues, blood, urine and saliva. The question which then arises is whether the levels of the constituents of dental amalgam and mercury in particular, are of any clinical significance to human health. It was pointed out in the 1994 Swedish report that whilst many studies have investigated the possible association between the number of tooth surfaces restored with amalgam and various systemic symptoms, no such association had been shown. It was also pointed out that the presence of mercury in tissues does not necessarily mean it is the cause of the signs or symptoms reported. There were no good data to establish if these represented a cause and effect relationship rather than mere coincidence.

7.4.1 Inorganic mercury neurotoxicity

The critical toxic effects seen with elemental mercury are neurotoxic in origin. The available dose effect data from occupational exposure can be compared with the best estimates of mercury exposure from dental amalgam to estimate the probable margin of safety below which an acceptable risk could be assured. The data suggest

that overt mercury toxicity is seen at occupational exposures above 100 $\mu g/m^3$ but there are reports of subclinical effects at lower occupational exposures.

Whilst the significance of these subclinical effects remains the subject of some debate, they were prudently considered to represent a human effect level.

There are a few reports of subclinical effects at doses below 50 $\mu g/m^3$ but the estimates of mercury concentration in these studies appear flawed and are not a sound basis for comparison. It appears therefore that, whilst the precise dose response curve cannot be described, subclinical effects have only been reliably observed at occupational exposures above 50 $\mu g/m^3$.

7.4.2 Exposure

A number of estimates of mercury exposure from dental amalgam have been published; most reviewers quote a wide range of about 1 - 27 μg per day without qualification. This, however, gives a false impression of these data since this range derives from a highly skewed rather than a normal distribution. The majority of the estimates are in the 1 - 5 μg per day range with two results in the 15 - 20 μg per day range. In addition, at least one of these estimates has been revised downwards by its authors to 10 μg per day and most critiques of these data suggest this correction should be even greater (16 fold lower) (**Tables 1 and 2**). The Swedish 1992 report stated that 'Considering all known forms of mercury uptake and routes of absorption a patient with an average number of dental amalgam surfaces (20 - 30) will have a daily uptake of no more than 10 μg mercury from these dental amalgam fillings.' The international reviews and recent papers indicate that despite the apparent skewed distribution the majority of dental amalgam bearers are exposed in total to less than 5 μg mercury/day.

7.4.3 Comparison of occupational and dental amalgam intakes

The mercury dose associated with subclinical neurotoxic effects can be estimated from human occupational exposure data. The US NIH report suggested a value of 50 $\mu g/m^3$ as the cut-off for subclinical effects but the 1991 WHO report includes

some studies which report subclinical effects at estimated occupational exposures between 30 and 50 $\mu g/m^3$.

Those studies considered in detail (for example Fawer et al. 1983) suggest these lower exposure estimates are unreliable (i.e. using a single measurement taken under the controls existing at the time of testing as the basis for historical exposure). For the purposes of this comparison, however, it was felt that the WHO range would provide a conservative estimate of the range of occupational exposures associated with subclinical effects (i.e. 30 to 50 $\mu g/m^3$).

Because of differences in the exposure pattern (for example duration and frequency), a direct comparison between occupational exposure and the mercury dose derived from dental amalgam is not possible. In order to allow a meaningful comparison with exposure from dental amalgam, the subclinical effect level seen in occupational studies first needs to be adjusted to take account of these differences.

Unfortunately, there are a number of uncertainties which prevent the establishment of an agreed physiologically based toxicokinetic model for mercury in man (for example toxicokinetics at low doses, mercury partition parameters, rate of oxidation to mercuric ions by catalase and other enzymes, discontinuous exposure, dynamic and static tissue levels). It is therefore not possible to produce an accurate detailed comparison of occupational exposure with that from dental amalgam. However, a number of assumptions allow an estimate to be made of the weekly absorbed dose associated with occupational exposures. These represent simplifications of the industrial exposure schedule and of physiological parameters. A number of these assumptions form the basis for extrapolation routinely used to set occupational exposure limits. These are that the occupational exposure takes place over five standard 8 hour days per standard 40 hour working week, the air intake for 8 hours is 10 cubic meters and the absorption of mercury vapour across the lung is 80 %.

Using the range of occupational exposures (30 to 50 $\mu g/m^3$) identified as the subclinical effect level and the assumptions detailed above, the minimum range of the weekly absorbed dose from occupational exposure associated with subclinical effects can be calculated as 1200 to 2000 μg.

A number of estimates for mercury exposure from dental amalgam exist; these form a highly skewed distribution with the majority of the estimates in the range of 1 to 5 μg per day (**Tables 1 and 2**). Using this range the estimated actual weekly dose of mercury is 7 to 35 μg.

A simple comparison of the absorbed dose of elemental mercury with the extrapolated subclinical effect level provides a ranking of these two disparate exposure levels and a crude comparison of their relative risks. This suggests that actual exposure to mercury from dental amalgam is 35 to 285 times lower than the subclinical effect level.

In view of the conservatism associated with many of the assumptions above this could be regarded as the minimum range. This could be considered a sufficient margin of safety even in the absence of any benefits, however dental amalgam also has a number of advantages (section 7.6). It was concluded that the toxicological risk was 'broadly acceptable', that is in the lowest category of risk according to the concepts outlined in **Annex 3** of this report.

7.4.4. Risks to the users of dental amalgam

Users are potentially exposed to greater mercury exposure than patients since they may prepare and place dental amalgam fillings daily. This possibility has been recognised and led to the production of professional guidelines on the use of dental amalgam. Risks to users are manageable and can be controlled provided the guidance given in the labelling and agreed codes of practice on handling mercury and dental amalgam are followed in line with national legislation establishing acceptable exposure standards.

7.4.5 Inorganic mercury nephrotoxicity

Inorganic mercury absorption from the gastrointestinal tract is 5 - 10 % and absorbed inorganic mercury is evenly distributed between the plasma and red blood cells. The critical target organ for inorganic mercury toxicity is the kidney since ionic forms of mercury cannot cross the blood brain barrier. The estimated dose of mercury ions from dental amalgam via the gastrointestinal route is around 1 μg/day based on an estimate that total gastrointestinal mercury burden from dental amalgam is less than 10 μg/day. This does not add significantly to the risks associated with the elemental mercury vapour dose.

There are data on effect levels and the dose response relationship from studies using inorganic mercury to induce nephrotoxicity in experimental animals. The levels of mercury utilised in the animal model studies are much higher than the potential exposure to mercury ions from dental amalgam. In the occupational setting nephrotoxicity is not seen at exposures below 100 $\mu g/m^3$, a level associated with marked neurotoxicity. It is apparent that exposures to mercury vapour which do not cause significant neurotoxicity would carry little or no risk of nephrotoxicity. Both this and the animal models suggest the risk of nephrotoxicity from dental amalgam is minimal.

Attempts to assess directly the risk of nephrotoxicity from dental amalgam have used sensitive urinary markers of renal damage. The group's attention was drawn to three recent papers on this, neither of which detected significant renal damage. Eti et al (1995) examined the urinary mercury concentration and N-acetyl-ß-glucosamidase (NAG) excretion in 100 volunteers (18-44 years old) divided into those, with (n=66) or without (n=34) dental amalgam fillings. NAG is a renal tubular lysosomal enzyme whose excretion is an extremely sensitive test for nephrotoxicity. The authors concluded that, although there was a very small difference in urinary NAG which probably indicates an apparent renal effect from metal absorbed from dental amalgam fillings this is insufficient to be a public health hazard for renal injury.

A similar study by Herrström et al (1995) used several proteins including NAG as markers of renal damage in 48 Swedish volunteers. These findings were also confirmed by Sandborgh-Englund et al (1996).

These three studies failed to detect any significant indication of renal dysfunction or damage from the release of mercury from dental amalgam. In combination with the information from both animal studies and occupational exposure they form a persuasive argument that for healthy individuals the risk of direct mercury nephrotoxicity from dental amalgam is low. According to the concepts in **Annex 3** this risk was considered 'broadly acceptable'. For those individuals with kidney disease there are no data.

A second mechanism for renal damage, an immunologically mediated glomerulonephritis.has been reported in some occupationally exposed workers and in certain susceptible animal strains. The mechanism by which this occurs is unclear and may differ between species but there does appear to be a genetic component. The group's attention was drawn to the WHO 1991 statement that 'a consequence of an

immunological aetiology is that it is not scientifically possible to set a level for mercury, e.g. in blood or urine, below which mercury-related symptoms will not occur in individual cases, since dose-response studies for groups of immunologically sensitive individuals are not yet available'. The human occupational form of the disease follows chronic high dose exposure and appears to have an aetiology which involves at least two stages, the first of which is reversible. This implies that a threshold for these effects may exist in man. The risk of an immunologically mediated glomerulonephritis at the exposure levels likely from dental amalgam is low but, as a threshold either cannot be established or does not exist, this risk cannot entirely be discounted and therefore was considered 'as low as reasonably practicable', according to the concepts described in **Annex 3**.

7.4.6 Reproductive toxicity and fetotoxicity

There is no evidence of adverse effects on fetal development or infant health at the levels of exposure estimated from dental amalgam restorations. In animal studies a NOAEL of at least 100 $\mu g/m^3$ has been identified for embryotoxic and teratogenic effects, since this is higher than the effect level for other end-points in man it is reasonable to assume that embryotoxic and teratogenic effects will not occur when a tolerable limit is based on these end-points in man. Although Drasch and co-workers (1994) have reported that mercury levels in some fetal and infant tissues related to the number of maternal dental amalgam fillings, there were neither pathological findings nor indications of the biological significance of this mercury burden. There has been considerable technical criticism of both the methodology and results of this paper, the incomplete information and its significance is unclear. These data do not appear to provide a basis for conclusions on this hazard.

Although one study (Sikorski et al 1987) suggested that the fertility of female dental workers might be affected by occupational exposure to mercury vapour, this was not supported by subsequent work. It has subsequently emerged that the underlying data in this study may not have been correctly interpreted and the conclusions were thus flawed (Larsson 1995).

The risk of reproductive toxicity and fetotoxicity was judged to be 'broadly acceptable' using the concepts described in **Annex 3**.

7.4.7 Hypersensitivity to dental amalgam

A number of dental amalgam components (copper, silver, mercury) are known to be capable of causing hypersensitivity. It is uncertain whether the levels of those associated with dental amalgam restorations are sufficient to induce hypersensitivity. It is apparent however that these levels are sufficient to cause allergic reactions such as oral lichenoid lesions in some sensitised individuals. The risk of this occurring in an individual cannot be estimated, but the available data indicate that the effects can be alleviated by removal of the filling. It may be prudent to avoid additional exposure to dental amalgam and its constituents in already sensitised individuals. Since the sensitisation can occur from a variety of external sources which are beyond the control of manufacturers or clinicians it is not possible to decrease the risk by the design of the product. Other risk control measures therefore, such as labelling, need to be considered.

Our group judged this risk to be 'as low as reasonably practicable', according to the concepts described in **Annex 3**.

7.4.8 Local reactions other than hypersensitivity

Local reactions towards dental amalgam fillings may occur at tissues which are in direct contact with the filling material; for example the dental pulp, the gingivae and the oral mucosa. Local reactions of the oral mucosa are mainly lichenoid in type and have therefore been considered elsewhere (section 5.3.7).

Dental amalgam has been shown to be initially (i.e. immediately after mixing) cytotoxic and irritating if implanted into muscular and other connective tissues (non-specific local toxicity). Thus dental amalgam might have the potential to harm both the pulp and the gingivae. However, after the material has set, cytotoxicity and non-specific local toxicity decline considerably and in some studies toxic effects have not been observed. This process takes from hours to a few days, depending upon the formulation of the alloy.

Likewise, clinical and histological pulp reactions, if observed at all, occur immediately, or within a few days after placement of the filling. The reaction of the dental pulp seems to be more pronounced in deep cavities thus being inversely related to remaining thickness of dentine. Whilst diffusion of dental amalgam cor-

rosion products through the dentine has been demonstrated, the effective concentration of the metal ions was too small to cause any long term inflammatory reaction of the dental pulp. By the application of adequate bases, liners, varnishes or other suitable substances before the insertion of the filling material, the temporary irritation of the pulp described above can be avoided.

As stated in chapter 5 implanted dental amalgam does not produce an acute tissue response and does not need to be removed except for diagnostic reasons where nevi or malignant melanoma are suspected.

Slight gingivitis in the vicinity of dental amalgam has been observed but seems mainly related to plaque accumulation on the filling material surface or its margins. Similar or even more pronounced reactions of the gingivae have been observed in direct contact with composite resin fillings. Plaque related gingivitis can almost completely be prevented by standard oral hygiene measures.

The risk of dental amalgam causing adverse local reactions other than hypersensitivity is therefore considered to be 'broadly acceptable' using the concepts described in **Annex 3**.

7.5 Alternatives to dental amalgam

The alternative restorative materials to dental amalgam can be broken down into several groups: composite resins, glass ionomers, metal, mostly alloys, and ceramics.

The risks associated with alternative restorative materials can be described in four categories; mechanical properties, effects of the finished material, effects and by-products caused by the *in situ* reaction to produce the material and the chemical components of the material.

It was stressed in chapter 6 that it was not possible to consider alternatives with the same rigour as dental amalgam, nor given the vast variety of constituents, could all hazards be identified except on a case by case basis.

The risk analysis of alternatives must similarly be limited to a few general points and the observation that detailed risk analyses need to be performed not only on the generic materials but on each individual formulation.

A number of alternative restorative materials are based on the *in situ* reaction of complex mixtures of organic chemicals selected from up to 40 individual constituents. It is self-evident that in order to produce a working reactive system the constituents must include reactive chemical groups which may pose a marked risk as a function of their reactivity. A number of the principal monomers used to make polymeric restorative materials are well established sensitisers and the risks for these should be established. Similarly a number of the constituents contain chemical groups which would necessitate detailed evaluation of their mutagenic potential. It is known that there is incomplete setting of many materials and the unincorporated constituents could leach from the material and be ingested. Again the risks cannot be estimated without data on the identity, toxicity and leaching of each individual constituent. The degradation of the filling material may also release the precursors themselves or their modified degradation products. These would need to be identified and evaluated for a full risk assessment.

Components of alternative dental restorative materials to dental amalgam particularly composite resins and related materials have been shown to have mutagenic potential *in vitro* and *in vivo*. The identification of a mutagenic hazard is based on a battery of *in vitro* tests examining different mutagenic end points, but evaluation of mutagenic risk requires confirmation that this is expressed *in vivo*. The *in vitro* data does not provide information on the *in vivo* dose response. There are few data on exposure of patients to potential mutagenic hazards in the alternative dental restorative materials to dental amalgam. The frequency and extent of exposure to mutagenic hazards is probably higher for dental personnel. It is not possible to estimate accurately either the local or systemic mutagenic risks arising from the use of these chemicals in dental restorative materials. Additional data on their availability from dental restorative materials in use, *in vivo* fate and further characterisation of their mutagenc potential *in vitro* and *in vivo* are desirable and this should be considered within the research priorities.

The mechanical properties of alternative restorative materials vary and none has the same properties and uses as dental amalgam. Thus the risks are not directly comparable but vary with the site and use of each particular material. The alternative restorative materials are also felt to be more technique dependent and whilst training may diminish these risks they would appear to be greater than for dental amalgam.

The only area where a direct comparison of risks appears possible is in terms of hypersensitivity. As was noted above many of the components of alternative restorative materials are sensitisers. These include nickel in alloys (see **Annex 2**) and methacrylates in polymeric restorative materials. Although the data are limited there appears to be a greater incidence of hypersensitivity to resin based restorative materials in comparison with dental amalgam. This is seen most markedly amongst users of these materials. Users are exposed to the same chemical hazards from dental materials used as alternatives to dental amalgam as are patients. The risks to users may differ from those to patients as they have potential for more frequent contact with the unset material. There is legislation on controlling risks from occupational exposure to chemicals. The labelling should contain instructions to allow compliance with such legislation and permit users to manage and control the associated risks.

7.6 The benefits of dental amalgam

As pointed out in the introduction to this chapter, as far as the MDD is concerned, considerations of risk of a medical device when used as the manufacturer intends, must be judged against a level of acceptability relating to the benefit of the device to patients which is compatible with a high level of protection of health and safety for patients, users and others.

The reason for using any dental restorative material is the replacement of lost or deficient natural tooth tissue, with the secondary intention of bringing the tooth back into function. The principal benefit therefore of any dental restorative material is the retention of the tooth. Potentially the loss of a tooth from an otherwise intact dentition can have many and various consequences. It is generally recognised that since all dental restorative materials to date have disadvantages of one sort or another, there is no ideal substitute for natural tooth tissue.

The 1992 US NIH report suggested that the major benefits of restorative dentistry are to arrest disease, relieve pain and discomfort, retain teeth, enhance speech and articulation, enhance mastication and its effects on nutrition, improve facial aesthetics and improve quality of life. It is clear that these benefits accrue irrespective of the restorative material used, however each restorative material will

have a range of specific properties which results in different assessments of risk-benefit and cost-benefit.

The benefits suggested by the 1992 US NIH report apply to dental amalgam restorations generally and a number of specific benefits of dental amalgam were recognised both in that report and the 1993 USPHS review.

Our group considered the following benefits to be the most pertinent in this context:

1. The use of dental amalgam, following changes in treatment philosophy by dentists in recent years, together with the increasing use of modern retention devices dispenses with the need for the extensive removal of sound tooth tissue during cavity preparation.

2. When considering the placement and finishing of a dental amalgam restoration, the material is considered to be the least technique sensitive of the permanent restorative materials. This results in restorations with satisfactory mechanical properties provided under a wide range of operating conditions and variation in the skill levels of clinicians. This contrasts with the increasingly complex placement of plastic tooth coloured restorations requiring the use of layering techniques and intermediary materials to condition, prime and bond the restorations to tooth substance; these being used to overcome discrepancies in physical properties with tooth tissue.

3. Generally the equipment needed to provide dental amalgam restorations is relatively inexpensive and straightforward mechanically and therefore easy to maintain. The materials require, at the most, mechanical mixing followed by the use usually of simple hand instruments to place in cavities. This contrasts with the use of curing lights for the command setting of tooth coloured restorations and the expense of using laboratories or specialised machinery or both, to provide cast metal and ceramic restorations.

4. Dental amalgam restorations have a proven history of durability. The 1992 NIH report took a variety of data over the previous twenty years and compared the use of dental amalgam with composite resin, compacted gold and gold inlays. It was recognised that caution should be exercised in interpreting such information

since data published from well-controlled studies in dental school environments are different from those from general practices. It was also pointed out that more recently some materials have improved more than others and that some are still being improved. Consequently more recent data may affect ranking in the long-term. Nevertheless with these reservations in mind, median longevity was estimated at between eight to ten years for dental amalgam. In comparison that for composite resin was estimated as four to seven years, compacted gold (single surface) 22 years and inlaid gold (three surfaces) 14 years. Also, more recent studies indicate that the longevity of dental amalgam is clearly superior to that of composite resins (Jokstad et al 1994; van Dijken and Qvist 1997). - The above data refers to the restoration of permanent teeth. Information on deciduous teeth is sparse. Work by Qvist et al (1990a and b) indicated that the median longevity of dental amalgam restorations was double that of composite resin restorations, irrespective of the number of surfaces restored by the filling.

5. Dental amalgam can be used for a broad range of restorations in both deciduous and permanent dentitions. They are considered by most authorities to be appropriate for use in all ages. In contrast to composite resin or glass ionomer restorations, dental amalgam fillings are currently the only plastic permanent restorative material considered to be strong enough to withstand extensive occlusal forces on posterior teeth in extensive cavities. When correctly placed in cavities of appropriate size dental amalgam fillings are resistant to fracture.

6. Dental amalgam has wear characteristics similar to those of natural teeth. This is an important benefit particularly when considering the longevity of some restorations. As a result tooth substance and dental amalgam will tend to wear at the same relatively slow rate. When ceramic restorative materials oppose and contact natural tooth surfaces or each other accelerated wear may result. Glass ionomer restorations when subject to forces of abrasion or attrition do not have the same degree of resistance as dental amalgam. Long term clinical studies in this respect with composite resins were not available.

7. Dental amalgam is a plastic material. It is mixed as a paste and inserted into a prepared cavity. Unlike cast gold or most ceramic restorations, laboratory procedures are not required. Dental amalgam restorations can be placed in one visit at the chairside demonstrating the ease of use and the convenience of the material both for the patient and the clinician.

8. Overall dental amalgam is the least expensive of the permanent restorative materials in terms of direct cost, frequency of replacement and requirement of professional time.

8. Standards and Dental Amalgam

8.1 Introduction

The draft mandate required us to examine standardisation activities at national, European and international levels and to explore whether and to what extent these may need to be enlarged. In relating these activities to the Medical Devices Directive (MDD), the role of standards accepted by the European Committee for Standardisation (CEN) is particularly important. National standardisation activities in this area with respect to the EEA countries are being superceded by those of the European and international standards bodies.

In other chapters of this document reference is made to particular standards. This chapter concentrates on those standards which are of direct relevance to dental amalgam products. Information, including labelling, supplied by the manufacturer is discussed in detail in chapter 9.

Article 5 of the MDD states that compliance with harmonised standards is a means to fulfil the essential requirements of the Directive. Also under Article 6 of the Directive a mechanism exists to address those harmonised standards that are considered not to meet entirely the essential requirements of the Directive.

The first standard specification for dental amalgam was actively pursued in the USA from 1919 to 1926 and resulted in the development by the National Bureau of Standards of American Dental Association Specification No 1: Alloys for dental amalgam. The first international standard on alloys for dental amalgam was Specification No 1, published by the Fédération Dentaire Internationale (FDI) in 1926.

In 1970 the International Organisation for Standardisation (ISO) technical committee on dentistry, (TC 106) adopted the FDI Specification No 1 as ISO Recommendation 1559. This was revised and issued in 1978 as ISO 1559, 'alloys for dental amalgam', the first ISO standard for this material. Planned programmes of revision resulted in further editions being issued in 1986 and 1995.

In 1988 the CEN technical committee on dentistry (TC 55) resolved to adopt standards developed by ISO TC 106 as European reference documents with a view, wherever possible, to their acceptance without change as European standards. In

line with this CEN published EN 21559 in 1991 which is identical with the 1986 edition of ISO 1559.

In 1980 a technical report on the biological testing of dental materials (ISO TR 7405) was published as a first attempt to standardise biological testing methods. In recent years, this technical report has been thoroughly revised. It is currently in the process of being published as an EN-standard and as an ISO-standard.

Concerning methods and the philosophy of testing for medical devices in general, a technical committee (TC 194) was established at ISO level in 1989. Since then a series of standards has been produced by this technical committee, with some of them produced in parallel at ISO and CEN levels. These series of standards are ISO 10993 and EN 30993 for ISO and CEN levels respectively.

In the course of the implementation of the MDD, harmonization of all the existing dental standards was not regarded as possible because of their large number. Therefore, CEN TC 55 (Dentistry) resolved in 1996 to link existing standards with one of four group standards at level 2 (see below). One of these (EN 1641) covers dental restorative materials, including dental amalgam.

Other relevant standards cover mercury used for dental amalgam (EN 21560, ISO 1560) or are related to devices used in the processing of dental amalgam; for example mixing devices (EN ISO 7488: Dental Amalgamators; EN ISO 8282: Dental equipment - Mercury and alloy mixers and dispensers). Currently, within an ISO TC-106 working group a document is being prepared on dental amalgam capsules. This applies to both predispensed and reusable capsules. All the requirements for capsules within ISO 1559 and ISO 7488 are to be included in this proposed standard.

Within ISO TC 106 a document is being drafted to specify a standard for equipment which separates dental amalgam from other clinical waste. Currently a level of 95 % separation of an appropriate range of clinically relevant particle size is specified in the document.

8.2 Standards' levels

As with all other medical devices used in dentistry, European standards which relate to dental amalgam are divided into three levels. These levels are:

- Level 1: ('horizontal standards'). These deal with general requirements, test methods or other aspects that are common for many medical devices. They are often European harmonised standards and those relevant to dental amalgam include EN 1441 on risk analysis, EN 540 on clinical investigation and parts of the EN 30993 series on the biological evaluation of medical devices.

- Level 2: ('semi-horizontal or group standards'). These contain test methods and requirements for families of medical devices, for example those used in dentistry and they link Level 1 standards to those standards of Level 3. Relevant standards for dental amalgam are EN 1641 and EN ISO 7405.

- Level 3 ('vertical or product standards'). These comprise specific tests and requirements for types of medical devices, for example dental amalgam. Relevant standards include EN 21559: 1991 and ISO 1559: 1995.

8.3 EN 1441: Medical devices - Risk analysis

This standard specifies a procedure to predict, using available information, the safety of a medical device, by identifying hazards and estimating the risks associated with the device. This standard does not stipulate levels of acceptability. Furthermore, it is not intended to give detailed guidance on the management of risks. However, this standard describes procedures for risk analysis, based on probability, for the possible consequences of a postulated event relating to the application of a medical device. The risk analysis process is the initial step in the overall process referred to as risk management.

8.4 ISO 10993/EN 30993: Biological evaluation of medical devices

Both standards comprise a series of parts, covering different aspects of the biological evaluation of Medical Devices; for example part 1: Guidance on selection of tests, part 3 with tests for genotoxicity, carcinogenicity and reproductive toxicity, part 5 also with tests for cytotoxicity: *in vitro* methods, part 6 for local effects after implantation and part 10 covers tests for irritation and sensitization.

8.5 EN ISO 7405: Dentistry - Preclinical evaluation of biocompatibility of medical devices used in dentistry - Test methods for dental materials

This standard specifies methods for the evaluation of biological effects of dental materials. Many test methods previously included in ISO TR 7405: 1984 are now included in ISO 10993/EN 30993 series of standards and details have therefore been excluded from this standard but corresponding references are made to the relevant parts of ISO 10993/EN 30993. It is intended when testing for risks that this standard should complement those in ISO 10993/EN 30993. Furthermore, specific cell culture tests have been included, which have special relevance for the testing of dental materials.

8.6 EN 1641: Dentistry - Medical devices for dentistry - Materials

This European harmonised standard specifies general requirements for materials which are medical devices used in the practice of dentistry for the restoration of the form and function of the dentition. According to this specification, dental amalgam would fall under the requirements of this standard. The standard includes requirements for intended performance, design attributes, components, sterilization, packaging, marking, labelling, and information supplied by the manufacturer. It is mainly a compilation of existing international standards for the different dental

materials which fall under its scope. The compilation has been set out in a structured way in order to assist the fulfilment of the essential requirements of the MDD.

8.7 EN 21560:1991: Dentistry - Dental mercury

This standard specifies requirements and test methods for mercury suitable for the preparation of dental amalgam. There are requirements for packaging and marking; in particular that containers shall be airtight and sufficiently strong to contain and protect the mercury under normal conditions of transport and handling. Each container has to be marked to enable reference to the supplier's batch or lot records. The container also has to be labelled with a specified hazard warning or its equivalent, although this is not intended to replace any national or regional requirements which may be more demanding.

8.8 ISO 1559: 1995/EN 21559: 1991: Dental materials - Alloys for dental amalgam

These standards specifically address the chemical composition of alloys used for making dental amalgam and requirements of physical and other properties of the final product.

8.8.1 Chemical composition

The compositional requirements are based on extensive clinical experience. The group noted that making a dental amalgam requires the admixture of mercury to an alloy powder and it is dealt with in this way in the alloy standards. The requirements for mercury are specified in EN 21560: 1991 which is identical with ISO 1560: 1985. There are, however, some compositional differences between EN 21559: 1991 and ISO 1559: 1995 as set out in the table below.

Compositions within the limits of EN 21559:1991, together with the physical and mechanical requirements in this and other related standards are supposed to fulfil the essential requirements at Annex I of the MDD.

Some deviations from the composition limits in the table above are allowed in the standards, if the manufacturer provides evidence of biological and clinical safety in the mouth (EN 21559:1991) or if approved by regulatory authorities (ISO 1559:1995) (See section 8.8.2.4).

Table 4

The requirements for the chemical composition of alloy powder

(content % m/m)

	EN 21559: 1991	ISO 1559: 1995
Silver	40 min	40 min
Tin	32 max	32 max
Copper	30 max	30 max
Indium		5 max
Palladium		1 max
Platinum		1 max
Zinc	2 max	2 max
Mercury	3 max	3 max

8.8.2 Physical/mechanical properties

The functional behaviour and related properties of a dental amalgam are determined greatly by the composition of the mixed alloy powder and mercury. The requirements of the properties given in the alloy standards restrict the range of suitable chemical compositions.

Physical and mechanical properties particularly addressed in these standards are creep, dimensional change and compressive strength.

8.8.2.1 Creep

Creep is a slow, permanent plastic deformation that takes place under mechanical pressure lower than the flow stress. It has been shown clinically to have a highly significant relationship to the marginal breakdown of a dental amalgam filling. Creep must be less than 3 % when tested according to the current ISO and EN standards. In recent years copper has been found to reduce creep significantly, therefore the maximum limit for copper was raised to 30 % in the 1986 edition of the ISO standard. An important consequence of increasing the copper content was to reduce considerably the most corrodible phase within dental amalgam (the tin-mercury or gamma 2 phase).

8.8.2.2 Dimensional change

After placement into the prepared tooth cavity the dental amalgam filling may undergo either an expansion or contraction due to its setting reaction. This is undesirable if either of these changes are excessive.

Requirements for acceptable dimensional change measured under specified conditions are included in the standards.

8.8.2.3 Compressive strength

The dental amalgam filling should be strong enough to resist breaking following normal biting forces after placement in a cavity. For this reason the standards contain minimum compressive strength requirements after both one and 24 hours following amalgamation.

8.8.2.4 Other requirements

The current EN (1991) and ISO (1995) standards on alloys for dental amalgam have requirements for loss of mercury in capsules during mixing and on marking, labelling, packaging and the need for manufacturer's instructions to accompany

each container. This is considered in more detail in chapter 9. The ISO standard also contains a requirement for the maximum allowable amount of foreign material and, when comparing with EN 21559: 1991 alone, is more detailed in listing the information to be supplied by the manufacturer. The level 2 standard EN 1641 however, to which EN 21559 is cross referenced, requires more extensive information to be supplied by the manufacturer in support of Directive 93/42/EEC.

One other important difference between these particular EN and ISO standards is the lack in the current ISO standard of specific references to biocompatibility testing. This is an apparent drawback of this standard which, with the lack of a requirement and test method for corrosion resistance, has raised an objection from CEN/TC 55 to the transposition of ISO 1559: 1995 as EN ISO 1559.

The current EN standard permits deviations in chemical composition to replace parts of tin and copper provided that the manufacturer presents evidence in accordance with ISO TR 7405 to show that the alloy is safe to use in the mouth (Also see section 8.8.1). ISO TR 7405 has though been superseded by the ISO 10993 series of standards on biological evluation of medical devices and an updated ISO 7405 standard dealing with specific test methods for the preclinical evaluation of biocompatibility of dental materials. EN 1641, nevertheless, cross references all (dental) restorative materials and requires they be assessed for biocompatibility under various parts of the EN 30993 series and dual numbered EN ISO 10993 series as well as the EN ISO 7405 standard.

8.9 EN ISO 7488: 1995 - Dental amalgamators

EN ISO 7488: 1995 is essentially concerned with the mixing of dental amalgam alloy and mercury for dental amalgam to ensure reproducibility of amalgamation. Instructions for use are to accompany the equipment and has to include the recommended filling and, if applicable, cleaning procedures including the procedure for recovery of spilled mercury. The manufacturer's recommended time and speed requirements for identified alloys and capsules must also be stated.

8.10 EN ISO 8282: 1997: Dental equipment - Mercury and alloy mixers and dispensers

EN ISO 8282: 1997 contains a requirement and visual test for mercury leakage and manufacturer's instructions for use, which are to be included, must contain precautinary notes necessary to avoiding spilling mercury whilst filling and also a caution statement to exercise care to prevent mercury spills and leakage and to keep the equipment and mercury at less than 25° C. Marking of the dispenser is also required with the following statement, 'Caution: Operate with care to contain any mercury leakage.'

8.11 Future work in standardisation

In ISO/TC 106 work on a corrosion test for dental amalgam is being taken forward. This work addresses the amount of ions leaching out, the amount of mercury vapour liberated and the deterioration of mechanical properties with time. Some interlaboratory testing is being carried out. Progress, however, is slow because ISO lacks financial resources for development work.

CEN/TC 55 resolved in 1995 that the following be communicated to CEN Central Secretariat for onward transmission to the European Commission: 'CEN/TC 55 has reviewed the standardization related health and safety aspects of dental alloys and has found no documented scientific evidence of any problems. However, the Technical Committee notes the lack of knowledge on correlation between biological testing, clinical findings and physical chemical properties of alloys and would wish to stress the importance of the development of corrosion test methods. The Technical Committee recommends to the Commission that priority should be given to funding such work. CEN/TC 55 supports the development together with CEN/TC 206 of test methods incorporating risk benefit methods. There is uncertainty about the frequency of the reporting of adverse events. The Technical Committee hopes that the establishment of a uniform post-marketing surveillance system for medical devices used in dentistry, as required by the Directive will improve matters.'

It was further resolved to request BTS 3 to approve a new work item for a European standard on corrosion test methods applicable to dental alloys and to transfer that work to ISO/TC 106 under the Vienna Agreement. CEN/TC 55 further resolved and requested that an International Standard on corrosion test methods be worked out by ISO/TC 106. A Committee Draft (CD) of December 1996 has been circulated to member bodies of ISO/TC 106 SC2 for voting. This CD, however, does not specify test methods applicable for dental amalgam.

Our consideration of research needs in chapter 10 identified the development of more sensitive test methods for evaluating the degradation of dental materials in the oral environment as a priority area. We considered that biological testing within Standards represents a solid base of knowledge and should be expanded according to the state of the art.

8.12 Conclusions

8.12.1 Dental amalgam

It is envisaged that EN 1641 will be adequate for the purpose of showing compliance with the essential requirements of the MDD. There are, however, deficiencies in the product standard EN 21559 due to lack of scientific knowledge. Therefore, research needs to be intensified, particularly with respect to corrosion testing and measurement of mercury release.

8.12.2 Alternative materials

EN 1641 specifically lists all the product standards available at present. There are, however, many alternative dental restorative materials on the market which have not been the subject of standardisation work but which should be subject to further CEN/TC 55 activities.

EN 1641 will need to be updated when new product standards are published.

9. Information supplied by the Manufacturer

9.1 Requirements in the Medical Devices Directive and in the relevant standards

According to the Medical Devices Directive each device must be accompanied by the information needed to use it safely, taking account of the training and knowledge of the potential users, and to identify the manufacturer. This information comprises the details on the label and the data in the instructions for use and can be linked to the general essential requirement of the Directive at Annex 1, paragraph 1.2 that the solutions adopted by the manufacturer (in the design and construction of the devices) must conform to safety principles amongst which is a need to 'inform users of the residual risks due to any shortcomings of the protection measures adopted'.

As far as practicable and appropriate, the information needed to use the device safely must be set out on the device itself or on the packaging for each unit, or both, or where appropriate, on the sales packaging. If individual packaging of each unit is not practicable, the information must be set out in the leaflet supplied with one or more devices.

Instructions for use must be included in the packaging for every device. By way of exception, no such instructions for use are needed for devices in Class 1 or IIa if they can be used safely without any such instructions. Dental filling materials currently fall under class IIa, however we return to this later.

Where appropriate, this information should take the form of symbols. Any symbol or identification colour used must conform to the harmonized standards. In areas for which no standards exist, the symbols and colours must be described in the documentation supplied with the device.

In line with the essential requirements at Annex 1 of the MDD are the European standards EN 980 (graphical symbols for use in the labelling of medical devices) and prEN 1041 (information supplied by the manufacturer with medical devices).

The label shall bear the following minimum information, which is derived from the Directive, and further developed in prEN 1041 and specified for dentistry in EN 1641:

a. the name or registered trade mark and address of the manufacturer. In the case of imported restorative materials the name and address and the authorised representative of the manufacturer in the community or the importer;

b. a description of the contents, including name, quantity, form (for example powder, liquid, paste) shade where appropriate, and the principal chemical constituents in order to identify the type of material;

c. the batch code, preceded by the word 'LOT' or the symbol LOT related to the records of raw materials, manufacture and packaging;

d. where appropriate, the expiry date expressed in accordance with the relevant standard;

e. if the device is intended for clinical investigations, the words, 'exclusively for clinical investigations';

f. any special storage and/or handling conditions;

g. any warnings and/or precautions to take.

According to the MDD, prEN 1041 and EN 1641 the **instruction leaflet** shall contain the following minimum information:

a. all data required for the labelling with the exception of points c) and d) above;

b. the intended purpose of the restorative material and any undesirable side effects;

c. if the restorative material is intended to be used in combination with other restorative materials or devices for its intended purpose, sufficient details of its characteristics to identify the correct equipment and procedures to be used in order to obtain a safe combination;

d. where appropriate, information to avoid risks in connection with the use of the restorative material;

e. details of any further treatment or handling needed for the proper use of the restorative material. These should include, where applicable, details of application, method of preparation, proportioning, mixing or trituration, working time, setting time, recommended fusion, casting or curing procedures and method of finishing;

f. information on the environmental conditions which may adversely effect the materials, such as temperature, humidity or ambient light, and the disposal of waste, if precautions are necessary;

g. the instruction leaflet, if applicable, shall also include details allowing the dental personnel to brief the patient on the contra-indications and the precautions to be taken. These details shall cover in particular:

- precautions to be taken in the event of changes in the performance of the dental material;
- information on the risks to the patient that may arise after placement;
- adequate information if the material contains a medicinal product;
- adequate information, where appropriate, for the care of finished restorations.

9.1.1 Information to the patient and the user

The group considered that the information supplied by the manufacturer about dental amalgam should be made in the context of considerations concerning information supplied on all materials substituting lost tooth substance. As the dental professional is responsible for providing the patient with the relevant information, he or she must have sufficient information from the manufacturer to be able to discuss the choice of material and choose the optimum material for the individual patient at each occasion of treatment. For example there must be information about the inclusion of substances that may cause an allergic reaction.

Besides the information supplied by the manufacturer the material of choice should be based upon the knowledge, expertise and experience of the dental professional and the information given on health status by the patient (or their carer). Treatment decisions should be made with the informed consent of the patient.

Therefore, in this context and irrespective of the classification within the MDD, our group considered that all dental restorative materials should be accompanied by instructions for use.

9.2 Additional information

Formal and technical details will to some extent be particular for each material. In the context of biocompatibility and safety some information is general for all dental amalgam products. To encourage uniformity the group suggested that the following is reflected in the instruction leaflet:

- In the course of risk management comprehensive information of the components of the filling material is highly desirable. As an example we would point out that a list of elements present in the alloy in concentrations greater than 0.1 % m/m has to be marked on the container to conform with standard EN 21559.

- In individual cases, local mucosal reactions (lichenoid) have been observed. Such local reactions may be of an irritative (mechanical, chemical, electrochemical) or allergic nature. In the case of allergy to components of dental amalgam the use of suitable alternative materials must be considered.

- After placement or removal of dental amalgam restorations increased mercury concentration in blood and urine has been observed. According to available scientific knowledge this increase has not been associated with any adverse health effects.

- If placed in close contact with other metal restorations galvanic effects may occur. In most cases they will be of short lasting duration. If the effect persists the user should consider replacement of the dental amalgam filling with another material.

- There are no proven adverse effects on the fetus associated with the placement or presence of dental amalgam fillings in the mother. It is sensible however, where clinically feasible, to minimise health interventions during pregnancy and avoid any unnecessary chemical exposure of the fetus. This precaution should be observed with the use of all dental materials.

- Unnecesary exposure to mercury vapour or dental amalgam particles during handling, placement or removal of dental amalgam should be avoided. Placement and removal of dental amalgam fillings should be performed with appropriate water spray and vacuum suction.

- Instructions and regulations for storage and disposal of dental amalgam waste must be observed.

10. Research Needs

10.1 General remarks

Our mandate required us to analyse available results of research relating to the safety of dental amalgam and to consider relevant research topics which may be required to support further decision making. To some extent chapters 5, 6 and 7 have addressed the available results of research. This chapter therefore concentrates on the research needs identified by our group to support further decision making and is based on the scientific literature previously considered. As a result of our consideration set out in chapter 6 we judged it important to set relevant research needs in the context not only of dental amalgam but also materials which are likely to be considered as alternatives to it. In addition, selected points have been considered to be topics of present administrative and regulatory concern.

When considering adverse health effects and dental materials we felt there were some special points that needed to be borne in mind. These were:

- Dental restorative materials are mainly designed for long term use.

- There is perceived to be an increase in public concern on possible adverse effects of dental restorative materials.

- The prevalence of adverse effects related to dental restorative materials and patients is generally low. Although available data are sparse, literature overviews and research articles indicate this to be less than 0.1 % of the general population.

- A broad majority of the general population in the western world is exposed to dental materials, for example in Germany it is estimated that 80 million fillings are placed each year. Special risk groups, therefore, may be affected which will not be detected in conventional prospective clinical studies.

- Following debate on the use of dental amalgam in some countries, a variety of new non-amalgam dental filling materials, of which there is only limited clinical experience, has been introduced onto the market.

- There are indications from those handling the materials and patients' histories that non-amalgam dental filling materials are associated with similar adverse effects to those ascribed to dental amalgam.

As a result of our consideration of these points it would appear that:

- The scientific basis for the evaluation of adverse effects of dental restorative materials needs to be enlarged. In particular that research should not be solely limited to dental amalgam but should include alternative dental restorative materials.

- Special methods and structured approaches which take into account the specific points listed above need to be developed further.

- Encouragement should be given to increased co-operation between various research centres.

10.2 Research areas identified

In considering research needs related to dental amalgam and its alternatives we felt that future research topics could be divided into three main categories. These were related to:

DEGRADATION (including corrosion)

BIOKINETICS

BIOLOGICAL EFFECTS

10.2.1 Degradation

Although the primary aim of any dental restorative material is to replace damaged dental tissue it should also be relatively inert. It is well established that almost all dental materials release substances as a result of degradation and the biocompatibility of dental materials is strongly influenced by factors affecting this

process *in situ* in the oral cavity. These include chemical, physical, bacterial and enzymatic interactions between the materials and the oral environment. At present more is known about the degradation behaviour of dental amalgam and factors influencing it than about the degradation processes and products released from some materials used as alternatives. Composite resin systems, a common alternative, may be of some concern since substances released from them may elicit, for example, allergic reactions.

The underlying mechanisms for the release of bioactive substances and their effects on the oral environment are not fully understood. Therefore studies on the degradation of dental restorative materials are considered to be required for more accurate risk analysis as well as for the identification of mechanisms associated with adverse reactions observed clinically.

10.2.1.1 Priority areas of research into degradation

Generally we considered priority areas should cover:

- The development of more sensitive analytical methods for identifying substances released into body fluids or tissues from dental materials.
- The development of more sensitive test methods for evaluating the degradation (including corrosion) of dental materials in the oral environment.

Topics for research where we felt we could be more specific included the following:

- The characterisation of appropriate elution procedures and substances simulating that found in the oral environment, for use with dental filling materials and standards for medical devices.
- The identification of the normal ranges of exposure to mercury and other substances released from dental materials, the diet and the environment for various age groups in Europe.

- The characterisation of substances released from resin materials into saliva or taken up by oral tissues using appropriate analytical techniques.

10.2.2 Biokinetics

Substances released from dental filling materials may interact not only with the local tissues but may also be taken up by the systemic circulation and reach 'critical' target organs or cell systems. We noted that public concern tends to be directed towards putative systemic effects rather than local effects, although the latter are likely to be more prevalent.

Following exposure to dental materials and any subsequent degradation the released substances may be inhaled and absorbed, distributed via the blood system, metabolised and then eliminated. Each of these processes will determine the fate of such substances in the body. Consequently the extent and duration of any effects is also determined by the kinetic properties of the substance. For example, it is well established that mercury is released from dental amalgam to a varying degree but the biokinetics of inorganic mercury in humans is not fully elucidated. Such information is fundamental in order to understand any toxicological effects as well as any risks associated with the use of dental amalgam. Information in this area, however, is especially sparse for the non-amalgam restorative materials.

10.2.2.1 Priority areas of research into biokinetics

We considered the following areas to have priority:

- Studies on the biokinetics of inorganic mercury derived from dental amalgam. Its absorption, distribution, metabolism and elimination both in children and adults.

- Studies of accumulation and effects on critical organs i.e. kidney, CNS, following exposure to inorganic mercury in children and adults.

- Information on the degree of uptake by inhalation or absorption of substances released from non-amalgam restorative materials and their metabolic transformation.

- *In vivo* and *in vitro* studies into the mechanisms by which inorganic mercury and other substances released from dental materials are taken up by damaged or intact mucosa, including that of the respiratory and gastrointestinal tracts and the oral mucosa.

Topics for research where we felt we could be more specific included the following:

- The extent to which inorganic mercury or other degradation products from dental materials is absorbed from the gastrointestinal tract and whether there is a difference in absorption between children and adults.

- The extent to which infants are exposed to inorganic mercury or other degradation products from dental materials via breast milk.

- The extent to which inorganic mercury, or other degradation products from dental materials is bound to plasma proteins or metabolised; the half life of inorganic mercury in the growing individual and the rate of renal clearance.

- The degree to which inorganic mercury or other degradation products from dental materials interacts with the microflora in the gastrointestinal tract; the influence of physiological barriers on this process and to gain more information, if this causes antibiotic resistance.

- The balance of the opposing actions *in vivo* of bacterial conversion of mercuric ions to methylmercury and vice versa.

The group discussed specifically the need for further research into the distribution of mercury occurring by diffusion into the mucosa from dental amalgam restorations and concluded that this need not necessarily be a priority on the grounds that the circumstantial evidence suggests that these amounts are likely to be minimal.

10.2.3 Biological effects

Knowledge on degradation and biokinetics forms the basis for the study of biological effects of substances released from dental materials and for the interpre-

tation of data gained from clinical investigations. Whilst clinical investigations of side effects are of importance, animal, as well as *in vitro* methods are also needed as adjunctive tools for understanding the mechanisms responsible for the observed clinical side effects. Research therefore should be directed towards both animal and *in vitro* studies as well as human studies.

As was mentioned at the start of this chapter, the number of clinically observed adverse effects for dental materials is relatively low. In order to have a meaningful number of cases at hand for analysis, reports from different clinical centres must be combined and in a consistent format. This can only be done if harmonisation of data collection, on the nature and extent of the adverse reactions to dental restorative materials in patients and dental personnel, is developed further. In this context particular attention should be paid to the extent of occupational exposure of groups or individuals to dental materials as well as taking note of the likely influence of exposure from the environment, food and an individual's dental restorations. This more detailed approach is supported by the increasing frequency of reported side effects ascribed to composite resins among dental personnel handling these materials on a daily basis.

10.2.3.1 Priority areas of research into biological effects

These were judged to include:

- The development of basic biocompatibility models for dental materials examining all major interaction mechanisms between materials components and humans.

- Studies on any adverse effects of substances released from dental materials, including mercury from dental amalgam fillings, on the immune system and in particular the role of autoimmune responses and identification of special groups who may be considered at higher risk.

- The identification of any low level exposure effects exerted by mercury and other substances released from dental materials in relation to placement and removal of dental fillings. This to include those persons occupationally exposed and those with severe renal disease.

- The harmonisation of data collection and follow-up studies on the nature and extent of adverse reactions to dental restorative materials in both patients and dental personnel.

Topics for research where we felt we could be more specific included the following:

- The establishment of diagnostic procedures for evaluating patients with mucosal symptoms allegedly related to substances released from dental materials. This could include studies on cytotoxicity and histology using skin equivalent organ cultures and the investigation of special effects on a cellular basis, using specific test systems for example that of oestrogenicity on special target cells.

- Long term *in vitro* studies of substances released from dental materials on primary target cells such as those in the kidney, oral mucosa and the dental pulp.

- Development of specific tests for the evaluation of local toxicity, immunotoxicity and neurotoxicity of dental materials with relevance for their risk assessment and the establishment of a database for biological effects.

- The development of routine procedures for the evaluation and diagnosis of respiratory symptoms related to the occupational handling of dental materials, particularly composite and other resins.

- The development of more sensitive routine methods for evaluating and controlling the efficacy of preventive measures, in particular the penetration of dental resins through protective gloves.

- To carry out a controlled clinical study on the effects in humans following the placement and replacement of dental restorations.

- The harmonisation of data collection on biological and adverse reactions to restorative materials both in patients and dental personnel, with a view for use as a basis for co-operation on an international level.

- Improved methods to make dental material information available, to include use of the internet.

10.3 Conclusions

In order to support further decision making in the area of research we concluded that there was a need:

- to develop more sensitive test methods for the evaluation of degradation products of dental materials, including dental amalgam, together with relevant biological evaluation of any effects,
- to develop criteria to establish whether a subpopulation is potentially at greater risk from dental materials and to identify such patients,
- for studies on the biokinetics of inorganic mercury derived from dental amalgam; its absorption, distribution, metabolism and elimination both in children and adults.

11. Conclusions

This report attempts to set up-to-date information on safety aspects of dental amalgam within the risk-benefit context of the Medical Devices Directive and the regulatory framework of Member States of the EEA. The conclusions set out below have been drawn with this in mind.

1. All dental restorative materials including dental amalgam as well as its alternatives have the potential for causing some adverse reactions and most contain components which are toxic, usually at much higher doses than from this intended use.

2. In recent years toxicological and biocompatibility aspects of dental amalgam have been reviewed extensively both nationally and internationally and risk analyses carried out. Currently available date indicate that mercury from dental amalgams will not cause an unacceptable health risk to the general population. There is little evidence that an unacceptable health risk is associated with occupational exposure of dental personnel providing due care is used in the preparation and handling of dental amalgam.

3. Mercury vapour and inorganic mercury are released from dental amalgam fillings. Studies demonstrating a correlation between dental amalgam fillings *in vivo* and uptake of mercury species in tissues, blood and excretion by urine have been published. Whilst the significance of these is not completely clear, the levels of mercury found in tissues, blood and urine and associated with dental amalgam fillings are considerably below the levels at which systemic dose-dependent toxic effects have been shown to occur.

4. No systemic dose-dependent toxic effects have been shown to be related to the release of mercury from dental amalgam fillings. In particular, evaluation of the literature indicates that no systemic dose-dependent toxic effects would be expected to arise from exposure to mercury at levels associated with the presence of dental amalgam fillings. The hypothesis that there is a significant toxicological risk from dental amalgam fillings cannot be substantiated by the available evidence.

5. Local reactions to dental amalgam fillings and other dental restorative materials do occur but are relatively rare. They are generally allergic or irritative in type and usually resolve following the removal of the material. There is some evidence that a greater and increasing incidence of sensitisation is associated with occupational exposure of dental personnel to some dental restorative materials used as alternatives to dental amalgam. Systemic allergic reactions to dental amalgam have been reported, but are extremely rare. Recently reports have also indicated cases of such reactions to materials used as alternatives to dental amalgam.

6. There is no scientific evidence that the use of dental amalgam is related to adverse effects on pre- and post-natal health or fertility. It is sensible however, where clinically feasible, to minimise health interventions during pregnancy and avoid any unnecessary chemical exposure of the fetus. This precaution should be observed with the use of all dental materials.

7. There are data to estimate the risks associated with dental amalgam in line with the requirements of the Medical Devices Directive. As with any risk assessment additional research could improve the precision of these estimates. Whilst meriting further consideration any additional research needs to be prioritised not only within this field but also in relation to other device issues. Taking the evidence that our group has reviewed, the benefits of restoring teeth with dental amalgam outweigh significantly the documented risks. This risk-benefit ratio corresponds to the currently acknowledged and accepted state of the art.

8. There is no indication that clinically satisfactory dental amalgam fillings should be removed except in cases of a confirmed diagnosis of allergy to this material.

9. An appropriate framework for European standards for dental restorative materials, including dental amalgam is in place. It was recognised that these standards represented the current state of the art but would continue to develop as scientific knowledge in this area evolves. Individual product standards, including those for dental amalgam alloys and other dental restorative materials, should be updated as this occurs. The lack of a suitable corrosion or degradation test in the standards for dental restorative materials was recognised and it was agreed that the development and validation of corrosion and degradation tests should be given priority.

10. Labelling and instructions for use for any dental restorative material must be based on the regulatory requirements as indicated in the Medical Devices Directive 93/42/EEC. Emphasis is placed on the need for warnings, on the labelling and the instructions for use of the particular risk associated with hypersensitivity.

11. Research needs have been identified taking into consideration that less information is currently available on the toxicity of alternative dental filling materials than on dental amalgam.

12. Recommendations

We recommend that

1. Taking particular account of conclusion II in chapter 11, further research should include:

   1.I. the development of more sensitive test methods for the evaluation of degradation products of dental materials with respect to their use in the oral environment,

   1.II. the development of criteria for the identification of groups of patients potentially at risk from the use of dental materials.

2. Administrative structures for co-operation in research should be established between clinical centres which diagnose and treat patients with side-effects considered to be related to dental materials.

3. The product standard EN 21559:1991 'Dental Materials - Alloys for dental amalgam' should include a requirement for a corrosion test.

4. The Commission together with the Member States should formulate guidelines on how the instructions for use and the labelling of dental materials could be constructed and what they in principle should contain, derived from the essential requirements.

5. In respect of user protection instructions for use should include that drilling, polishing and grinding dental amalgam fillings, should always be combined with water-cooling and suction under a vacuum.

6. The experiences of the notified bodies should be utilized systematically to determine how the requirements of the Medical Devices Directive 93/42/EEC concerning instructions for use and labelling, for instance on the aspect of biocompatibility, are being met by the manufacturers.

7. Consideration should be given to mechanisms for the exchange of information on adverse reactions to dental materials between the EEA and other countries in

the World since this would improve the power of the reports to facilitate earlier detection of potential problems.

8. Dental filling materials used or proposed as alternatives to dental amalgam should be evaluated to the same extent as for dental amalgam.

9. Decision making processes in the risk assessment and management of dental filling materials need to be developed further.

13. Annexes

Annex 1: Questionnaire on national regulations and policies relating to the use of dental filling materials, particularly dental amalgam

Country .....

Name of respondent .....

Organisation .....

1. What are the requirements[5] in your country which affect directly the placing on the market and the use of dental filling materials in humans ?

2. Describe those aspects of the requirements which are legally binding in your country and specify those aspects which implement Directive 93/42.

3. List the requirements of your country, which restrict the placing on the market of dental amalgam or its use in humans, or both, and which are legally binding.

4. List the requirements of your country, which restrict the placing on the market of dental amalgam or its use in humans, or both, and which are **not** legally binding.

5. Describe any plans for implementing further requirements in your country, before June 1998, which affect directly the placing on the market of dental amalgam or its use in humans. - Will these plans be legally binding ?

6. Describe any further information which your Government considers relevant to the placing on the market of dental filling materials or their use in humans.

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[5] These could include the law or regulations in your country; policies, guidance, rules of recommendations of your Government or national Dental Association.

Annex 2: Nickel

In dentistry nickel is primarily used as part of prefabricated alloy materials for orthodontic treatment, preformed crowns for use in children and as part of casting alloys for extracoronal restorations and partial dentures.

The main biological problem with the presence of nickel relates to its allergenicity, although Wirz et al (1993) have attributed gingivitis and periodontal disease in the neighbourhood of nickel containing alloys to the toxicity of released nickel.

Nickel is a relatively common allergen; this is well known from the use of nickel as buttons for clothing or in jewellery. Patch testing of patients referred for allergy testing for nickel hypersensitivity has shown positive response rates from 9.4 to 39 % in women and from 3.5 to 7.9 % in men (Council of dental materials, instruments and equipment 1985; Hensten-Pettersen 1984; Massone et al 1991).

Cross reactions have been observed between nickel and palladium. Augthun et al (1990) found 39.1 % of those sensitive to nickel also had a palladium allergy. Todd and Burrows (1992) investigated 536 patients for suspected contact dermatitis and diagnosed a frequent and simultaneous occurrence of palladium and nickel allergy.

Good contact, moisture, friction and time are required to develop an allergy to nickel. In dentistry this is sometimes seen following skin contact with nickel-containing headgear and fixed bands used for orthodontic treatment. There may be enhanced tolerance to nickel following orthodontic treatment with nickel-containing wire (Kerosuo et al 1996). These studies, however, are few and need to be confirmed since it was also noted that there are a few reports in the literature of nickel alloys used in orthodontic appliances and dental prostheses resulting in a nickel allergy (Dunlap et al 1989; Veien et al 1994; al-Waheidi 1995).

Annex 3: Risk concepts (IEC 601-1-4 1996)

RISK

The concept of RISK has two elements:

- likelihood of a hazardous event;
- SEVERITY of the consequence of the hazardous event.

RISKS can be categorized into three regions:

- intolerable region;
- ALARP (As Low As Reasonably Practicable) region;
- broadly acceptable region.

Intolerable region

The RISK of some HAZARDS is so severe that a system in which they exist would not be tolerated. A RISK in this region will be reduced by reducing the SEVERITY and/or the likelihood of the HAZARD.

ALARP region

The region between the intolerable and the broadly acceptable regions is called the ALARP region. In the ALARP region RISKS are reduced to the lowest level practicable, bearing in mind the benefits of accepting the RISK and the cost of further reduction. Any RISK should be reduced to a level which is 'as low as reasonably practicable' (ALARP). Near the limit of intolerable RISK, RISKS would normally be reduced even at considerable cost.

Broadly acceptable region

In some cases, either the SEVERITY and/or the probability of a HAZARD is so low that the RISK is negligible compared with the RISK of other HAZARDS which are accepted. For these HAZARDS, RISK reduction need not be pursued.

SEVERITY levels

SEVERITY is one component of RISK. The following four levels are a qualitative measure of the possible consequences of a HAZARD:

- catastrophic: potential of multiple deaths or serious injuries;
- critical: potential of death or serious injury;
- marginal: potential injury;
- negligible: little or no potential of injury.

Annex 4: Documents considered by the Dental Amalgam Ad Hoc Working Group on 15/16 October 1998

1. Letter of Mr. P. Møller to Mr. N. Anselmann regarding paper by Weiss, B. and Simon, W. of March 3, 1998.

2. Letter of the European Society of the National Associations for Dental Patients (ESNADP) to Mr. N. Anselmann of March 15, 1998 (with enclosures).

3. Centre for Metal Biology in co-operation with the ESNADP. Mercury and Dental Amalgams II. A selection of scientific abstracts published in 1997 collected to the meetings with the EU-commission and WHO, Uppsala Sweden, 1998.

4. Letter of Mr. I. Cooper to Ms. S. Starzmann of November 24, 1997.

5. Letter of Ms. M. Saeter, Den Norske Tannlegeforening, to Mr. I. Cooper of November 10, 1997 (with enclosures).

6. Letter of Mr. I. Cooper to Dr. P.A. Christoffersen of November 3. 1997 (with enclosures).

7. Letter of Mr. I. Cooper to Ms. S. Starzmann of November 3, 1997.

8. Letter of Mr. W.H. Koch, Internationale Gesellschaft für Ganzheitliche Zahn-Medizin e.V. to the European Commission of October 20. 1997 (with enclosures).

9. Letter of Mr. B. Gran. IAOMT-Sweden to Mr. N. Anselmann of October 25.1997 (with enclosures).

10. Amalgam Frågan from the Swedish Council for Planning and Coordination of Research.

11. NIMB Beam Interactions with Material & Atoms. U. Lindh et al: Nuclear microscopy in biomedical analysis with special emphasis on clinical metal biology.

12. D. Echeverria et al: Neurobehavioral Effects from Exposure to Dental Amalgam Hg^{o}: New Distinctions Between Recent Exposure and Hg Body Burden.

13. Centre for Metal Biology, Uppsala, Sweden. Mercury and Dental Amalgams. A specific selection of scientific abstracts published 1994-1997 for the WHO Consultation on assessing the risks and benefits to health, oral care and the environment using dental amalgam and its replacement. March 3-7, 1997.

14. Letter from Dr. Schorn to the EU-Commission regarding the position of the Draft of June 1997 of the Dental Amalgam Ad Hoc Working Group. December 16, 1997.

15. Letter from Dr. Schorn to the members of the Medical Devices Expert Group regarding restorative materials in dentistry including dental amalgam. May 6, 1998.

16. Letter from Mr. P. Møller to Mr. N. Anselmann regarding Draft of June 1997 of April 26, 1998.

17. Letter from Mr. P. Møller to Mr. N. Anselmann regarding Draft of June 1997 of April 26, 1998.

18. Letter/fax from Mr. I. Cooper regarding a statement of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (UK) of April 29, 1998.

19. Letter of Dr. S.-O. Grönqvist to Mr. N. Anselmann regarding ESNADP comments of May 10, 1998.

20. Letter of Dr. S.-O. Grönqvist to Mr. N. Anselmann regarding conclusions and ESNADP recommendations of May 16, 1998.

21. Conseil Supérieur d'Hygiène Publique de France – Avis Relatif a l'Amalgame Dentaire of May 19, 1998.

22. Letter from Mr. R. Voelksen to Mr. N. Anselmann regarding the WHO Dental Amalgam and Alternative Direct Restorative Materials, Editors I.A. Mjör & G.N.P. Pakhomov, of May 18, 1998.

23. Letter from Dr. A. Schedle to Mr. I. Cooper of October 14, 1998.

24. Submission from Ms. H. Harnack of August 15, 1998.

25. Report of the Conseil Supérieur d'Hygiène Publique de France, entitled l'amalgame dentaire et ses alternatives: evaluation et gestion du risque.

26. Statements to the National Agency for Medicine, Helsinki, Finland, from: National Research and Development Centre of Welfare and Health, Finnish Dental Society, University of Oulu, Dept. of Dentistry, University of Helsinki, Dept. of Dentistry, Finnish Institute of Occupational Health.

27. Letter from Dr. Schorn regarding a paper by K.E. von Mühlendahl of May 20, 1998.

Annex 5: Definitions

In this report the terms below have been used with the following meanings:

Allergic reaction.	All those symptoms or reactions that occur when a sensitised subject comes into contact with the relevant antigen.
Allergy:	Altered reactivity on second contact with an antigen.
Hazard:	A potential source of harm (as defined in the European Standard EN 1441).
Hypersensitivity:	An adaptive response occurring in an exaggerated or inappropriate form causing tissue damage.
OES:	The Occupational Exposure Standard, the concentration in the atmosphere posing minimal risk over a working day. Data from Document EH 40/93. Occupational Exposure Limits. Health and Safety Executive.
Risk:	The probable rate of occurrence of a hazard causing harm and the degree of severity of the harm.
Sensitisation:	All those processes that lead to the altered reactivity stated above in the term 'allergy'.

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