Anders Tillberg

A multidisciplinary risk assessment of dental restorative materials

Dissertation No. 1196, 2008
Department of Odontology
Umeå University, Sweden
A multidisciplinary risk assessment of dental restorative materials

Anders Tillberg
Cover Photo:
Anders Tillberg
Life is not an evidence-based experience.
And if it was, I would be bored to death.

LT Lindh
from “The Kitchen Philosopher”
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Abstract

Amalgam has been used as a dental restorative material for centuries, but its potential health effects and biopersistance has lead to a decreased use, especially in the Nordic countries. New materials have been introduced, partly to replace the mercury containing amalgam and partly because of estethical reasons. The possible health effects of amalgam have been studied extensively and the material has been replaced with other less well-examined materials during the last few decades. The prevalence of side effects of dental materials is considered to be low in relation to the vast number of dental treatments undertaken. With the introduction of new and more complex materials, side effects related to dental treatment may increase. Epidemiological data suggest that the side effects of dental resins that have almost completely replaced amalgam fillings in Scandinavia, possess a risk for adverse reactions; however, the causal relation has not been fully established. Therefore, the type and extent of side effects caused by resin-based dental materials are of interest.

The aims of the present study were:

– to describe the change in health over time for patients with problems related to their dental materials. The hypothesis was that the patients could be divided into subgroups based on their symptoms and that the ability to recover differs between these groups [Paper I]. Furthermore, to determine whether factors such as the replacement of dental restorative materials and follow-up time had any impact on the perceived health.

– to assess the long-term development of symptoms and their social consequences among patients referred for diagnosis and treatment of symptoms related to dental materials [Paper II]

– to investigate the possible risks with dental restorative materials other than amalgam [Paper III]

– to describe side effects assessed to be caused by resin-based materials that occurred in a group of patients as well as treatment and long-term consequences of the reactions [Paper IV]

Material and methods: A questionnaire was sent to 614 patients [Paper I and II] that had been referred to the School of Dentistry, Umeå, Sweden, with symptoms allegedly caused by dental materials. The questionnaire contained questions on, among others; civil status, present health, medical and dental treatment and other measures and precautions taken because of and psychosocial problems related to current employment situation, feelings, self-image and coping behavior. Moreover, information was collected [Paper III] from the Swedish Dental Materials Register 2003 (DentMr), a compilation of MSDS for 487 products, and information from the user guide of the materials. The Material Safety Data Sheets (MSDS) included in the DentMR were examined regarding the given composition of the products, the occurrence of CAS-numbers and the risk- and safety phrases of the substances. Information was collected [Paper IV] on 36 patients with reactions to resin-based restorative materials from the Swedish National Register of Side-Effects of Dental Materials.

Results: Patients with complex symptoms had a more unfavorable long-term prognosis concerning persistent complaints than those with local symptoms only. Furthermore, the results indicate that the patients might experience health improvements after removal of their dental restorative materials. However, the reason for this improvement was unclear. Replacement of dental restorative materials had no significant impact on the ability to recover completely. Our results also indicate a relationship between patients’ self-related health and social consequences in daily life. Those with remaining complex symptoms had more often stopped working or had decreased their work hours because of their symptoms. The information about hazards with dental materials seems insufficiently described in MSDS and there might be materials with side effects unknown to both
patients and dental personnel. A literature search indicated that some of the listed substances had possible hazards, e.g. substances with embryotoxic and neurotoxic potential.

Conclusions: The patients were very heterogeneous; a few with only local symptom free reactions while other had more complex symptoms. The latter group would gain from a multidisciplinary approach, i.e. dental, medical, as well as social and probably psychological factors have to be considered when developing care management programs for this group of patients. Furthermore, there is a need for stronger regulations of dental materials such as those applied to pharmaceutical drugs. Finally, it was found that the majority of symptoms suspected to be caused by resin-based materials were local or a combination of local and extra oral symptoms that appeared within the first 24 hours after treatment. The most frequent adverse effect reported was skin problems/dermatitis. It appears as though immediate reactions to resin based materials are not uncommon and more prevalent than allergic reactions. Still, we have had difficulties in verifying associations between the dental restorative materials and adverse reactions and also to identify the offending component.

Keywords: Dental materials, adverse reactions, follow-up study, subgroups, long term prognosis, perceived health, social factors, self-reported health, material safety data sheet, resin-based dental materials, allergy.

Papers in this thesis

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:


IV. Tillberg A, Stenberg B, Berglund A. Side-effects related to resin-based dental materials - data reported to the Swedish National Register. Submitted.
Introduction

Dental restorative materials, principally amalgam, have been controversial ever since it was introduced more than 170 years ago. This debate has intensified in Scandinavia during the last few decades (Koppang et al. 1985). In Sweden, as well as in other Scandinavian countries, this debate was focused on dental amalgam. In the early 1980’s the electrochemical corrosion occurring within and between alloys in the oral cavity was discussed as a source of cause for side effects (Nilner 1981; Hugosson 1986; Johansson 1986; Yontchev 1986). Since then, interest has shifted from electrochemical corrosion to the release of mercury vapor from amalgam restorations and its’ possible adverse side effects on general health. Today, the number of amalgam fillings placed has decreased dramatically and alternatives such as resin-based materials have replaced amalgam as the most used dental restorative material in Scandinavia.

The anxiety for adverse reactions from substances that are present in our surroundings has increased over the years. Different environmental related syndromes have engaged the general public, the care sector, researchers and mass media. Some specific environmental factors such as inadequate air quality (Stenberg 1994; Eriksson 1996), electromagnetic radiation, e.g. electrical devices and display units (Stenberg et al. 2002; Bergdahl et al. 2004), “multiple chemical sensitivity” (Das Munshi et al. 2007) and dental restorative materials, in particular dental amalgam have been in focus.

Dental Restorative Materials

Nowadays, dentistry involves a wide range of materials. The number of specialized and complex dental restorative materials introduced on the market is continuously growing (Bergman 1990; Kanerva et al. 1999; Bergman 2000; Rubel et al. 2000). An increasing demand for safety evaluation and control of dental materials has been seen during the last few decades, most likely due to the fact that dental restorative materials is being incorporated in the human body for decades. Dental materials are regulated according to the European guideline for Medical Devices (European guidelines 93/42/EEG).

It is important to emphasize that the results of cytotoxicity tests for certain products reported in scientific publications might not necessarily be representative for similar products. Different analyses and different nomenclatures for chemical substances might have been used, which in turn make it difficult to compare different products. The content of a product can also change over time. Moreover, cytotoxicity tests can be limited with regard to their applicability to clinical situations.

Amalgam

Due to its’ favorable durability and mechanical properties dental amalgam has been used as restorative material for over 170 years. Dental amalgam is a combination of alloy powder and mercury. Silver, tin and copper are the main content of the alloy powder but also smaller amounts of indium, palladium, platinum and zinc can be part of the powder. A mixture of about 50% liquid mercury and 50 % powder is common. The toxicity of mercury has been extensively investigated, and many studies have been published regarding whether mercury in amalgam can cause disease but no clear conclusion can be drawn.

In meetings between national and international expert groups (The Swedish Medical Research Council 1992; The Swedish National Board of Health and Welfare 1994; WHO 1997) it has been stated that there is no scientific evidence that mercury released from dental amalgam presents a significant health hazard to the general population, although a small number of patients might experience allergic responses to components released from amalgam. However, there are scientists who have come to different conclusions (Richardsson 1995; Berlin 1999).
Silver, tin, copper and zinc are other elements in dental amalgam. These elements can cause allergic reactions as individual elements, however, used in dental amalgam they are not considered to be a source for adverse side effects in dental personnel or/and patients (SCENIHR 2008).

Amalgams’ potential health effects and biopersistance has lead to a decreased use especially in Scandinavia (Mackert & Berglund 1997; Brownell et al. 2005; Magos & Clarkson 2007). The discussion about the risks of mercury in dental amalgam has concerned rather rare side effects at low doses. It is reasonable that alternative, less investigated dental restorative materials should be considered from similar aspects.

Alternative direct restorative filling materials

When introduced in the 1950s, resin composite was seen as a replacement to silicate cement, which had dominated as the esthetic alternative to amalgam during the first half of 20th century. The physical properties of resin composite, such as polymerization shrinkage, leakage and discoloration were deemed unsatisfactory and recurrent caries and pulp inflammation were not uncommon. The resin-based materials have been continuously improved and today it is the most commonly used filling material in Sweden.

Resins composite contain a polymerizable organic matrix, inorganic reinforcing fillers and a silane-coupling agent, which bridges the organic and inorganic components (Ferracane 1995). The organic matrix consists of several (co)monomers and various additives which function as (co)initiators, stabilizers or inhibitors (Table 1).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Some allergens in resin based alternatives to dental amalgam: (primers, bonding agents, composites, glass ionomers, resin modified glass-ionomers, composites, etc.).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methacrylate monomers</strong></td>
<td>2-hydroxy ethyl methacrylate (HEMA) &lt;br&gt; Triethylene glycol dimethacrylate (TEGDMA) &lt;br&gt; Pyromelilitic acid dimethylmethacrylate &lt;br&gt; Bisphenol-A glycidyl methacrylate (Bis-GMA) &lt;br&gt; Urethane dimethacrylate (UDMA) &lt;br&gt; Bis-phenol-A polyethylene glycol diether dimethacrylate &lt;br&gt; Ethylene glycol dimethacrylate (EGMDA)</td>
</tr>
<tr>
<td><strong>Other substances</strong></td>
<td>Benzoyl peroxide, camphoroquinone (initiators) &lt;br&gt; Tertiary aromatic amine (activator) &lt;br&gt; Methylhydroquinone (inhibitor) &lt;br&gt; 2-hydroxy-4-methoxy benzophenones, (UV absorber) &lt;br&gt; 2-(2-hydroxy-5 methylphenyl) benzotriazole (Tinuvin P)</td>
</tr>
</tbody>
</table>

Various factors determine the biocompatibility of resin-based materials, particularly the amount and nature of leachable components (Geurtsen 2000). All organic ingredients of a resin composite are extractable by organic solvents after polymerization (Lygre et al. 1999; Michelsen et al. 2003). It has been shown that TEGDMA-based resins may release considerable amounts of monomers into water (Moharamzadeh et al. 2007). Several resin composites were also found to liberate formaldehyde into water in amounts sufficient to cause local allergic reactions (Koch & Staehle 1997). It has been reported that methylmethacrylate (MMA) may be teratogenic and can cause adverse cardiovascular effects in animals (Karlsson et al. 1995).

Epidemiological data suggest that the majority of adverse reactions of dental resins are allergic contact dermatitis (Kanerva et al. 2000). Among dental personnel, allergic contact dermatitis has been studied in a number of papers (Örtengren 2000; Wallenhammar et al. 2000; Wrangsjö et al. 2001). However, published information on contact allergy in patients has mainly been based on case reports (Carmichael et al. 1997; Kanerva & Alenko 1998; Koch 2003; Connolly et al. 2006).
During the last 3 decades glass ionomer has developed and become an alternative to resin composites. It is a water-based material and contains components such as silica, calcium fluoride and alumina. This material is considered to be better than silicate cements, but the mechanical properties are poorer than those of resin-based materials. Glass ionomer cements are considered as having good clinical biocompatibility even if tissue reactions in rats have been reported (de Oliveira Mussel et al. 2007).

A variety of hybrid structures, resin modified glass ionomer (RMGI) cement and polyacid-modified resin composites, (PMRC) have been introduced to the market in order to combine the good properties from resin-based materials and glass ionomer cements. Both have been found to release HEMA and TEGDMA (Lygre et al. 1999; Michelsen et al. 2003).

**Indirect Restorations**

Noble metals, gold in particular, have been used since the 1850s. In the beginning gold foil was used for smaller fillings, but nowadays gold is used as a dental casting alloy for different prosthetic reconstructions. The content of gold in different alloys differs and also contains other metals such as platinum, palladium, silver and copper. Allergic contact reactions to gold have been reported in several studies (Hensten-Pettersen 1992; Räsinnen et al. 1996; Vammes et al. 2000; Ahlgren et al. 2002; Tschernitschek et al. 2005). In crowns and Fixed Partial Dentures (FPD), alloys with different palladium content have replaced conventional gold alloys. Oral lichen has been reported in connection to reconstructions containing palladium (Hensten-Pettersen 1992) and in patients with a nickel allergy, palladium is considered as a potential risk for contact allergy (Kielhorn et al. 2002).

Low ductility, high compressive strength but low tensile and flexural strength, resistant to wear, excellent esthetics and high biocompatibility are characteristics associated with dental ceramics. New ceramics are now available and the majority of them are reinforced with a variety of inorganic materials, which consist of non-metallic and metallic chemically bonded elements.

Aluminum, sodium, potassium, magnesium, calcium, silicon, boron oxide and metal oxides are the constituents of ceramic materials. The main components in the reinforced core material are alumina and zirconium. The use of the latter has increased and is now an adequate alternative for crowns. Toxicity has been reported on cell function (Hensten-Pettersen et al. 2000) but ceramics are regarded as safe in a clinical setting since the systemic toxic effects are evaluated as negligible.

**Titanium** has increasingly been used for implants and indirect restorations (crown and bridges) over the last few decades. The advantage of titanium compared to noble metals is its biocompatibility, high resistance to corrosion and low cost. Moreover, reports have questioned whether metal sensitivity may arise from exposure to titanium (Lalor et al. 1991; Tschernitschek et al. 2005). Possible allergic contact dermatitis from titanium has been reported (Bircher and Stert 2001). However, in a literature review the author concluded (Ohkubo et al. 2008) that titanium could be recommended as an alternative for patients with metal allergies.

Non-noble alloys based on nickel are not commonly used in Sweden. The content of these alloys is mainly nickel but other metals like chromium and molybdenum is present. In a recently published Swedish study (Fors et al. 2008), patch testing showed nickel sensitization in 11.8% of girls and 1.6% of boys. In comparison to previous data the prevalence of nickel sensitization was higher for girls and slightly lower for boys.

**Endodontic materials**

Endodontic materials are either placed directly onto living tissues or may leach through dentine, therefore the biocompatibility is important. In vitro and in vivo tests can be performed to evaluate the
biocompatibility of different materials (Wennberg 1980).

Gutta-percha is the most commonly root filling material used. Zinc oxide is the main component (60-70%) of the points. Gutta-percha is considered to have an acceptable biocompatibility with a low degree of toxicity (Wolfson & Seltzer 1975). However, gutta-percha cones have been shown to be cytotoxic in *in vitro* tests (Spångberg 1969; Pascon & Spångberg 1990) probably due to the high content of zinc oxide. Contrary to this belief, results from a study (Sunzel et al. 1997) showed that the addition of zinc reduced the toxicity and appeared to be cytoprotective.

Zinc oxide-eugenol sealers. These sealers are zinc oxide-eugenol (ZnOE) cements modified for endodontic use. Cytotoxicity has been reported (Guigand 1999), and also activation of the complement system (Serene et al. 1988).

Calcium hydroxide sealers (Geurtsen et al. 1998; Huang et al. 2002) and Glass ionomer cements (Buck 2002) are generally considered as having good cytocompatibility.

Formaldehyde-containing sealers contain paraformaldehyde. Of these, N2 has been the most frequently studied. As far as toxicity is concerned N2 is not much different from other paraformaldehyde containing sealers. Root-canal sealers based on formaldehyde is no longer in use because they been found to be both cytotoxic and genotoxic (Tai et al. 2002; Huang et al. 2005).

Chloroform-based sealers have been commonly used. They consist of white gutta-percha and chloroform and derive their toxicity from the chloroform component, which has been shown to cause irritation (Sjögren et al. 1995). The use of chloroform has been reduced in recent years due to concerns about its toxicity. Polymers contain epoxy resin sealers, methacrylate-based sealers, polyvinyl-based sealers and polydimethylsiloxane and are reported to be genotoxic (Schweikl et al. 1995; Huang et al. 2002). The release of formaldehyde from these sealers is lower than the long-term release from formaldehyde-containing sealers such as N2 (Leonardo et al. 1999).

**Materials for removable dentures**

Polymethyl methacrylate is the most common denture base material in use today. Orthodontics, crowns and bridges are areas within dentistry where polymethyl methacrylate is frequently utilized. There are several methods of polymerization, auto, heat- and microwave polymerization.

There are findings that indicate that auto-polymerized resins are more cytotoxic than the heat-polymerized denture base resins, which in turn are more cytotoxic than the microwave-polymerized resins (Sheridan et al. 1997). In a number of Norwegian studies (Lygre et al. 1994; Lygre et al. 1995; Lygre 2002) leachable components from the polymer were discovered.

Resin used for denture bases, display allergic reactions in vivo, probably caused by unreacted components remaining after the polymerization process (Koutis & Freeman 2001; Tanoue et al. 2005).

Chromium-Cobalt alloys are still the most common metal for frameworks to partial removable dentures. These alloys can also contain smaller amounts of nickel and molybdenum. All these metals can cause an allergic reaction (Lygre 2002; Ditrichova et al. 2007; Fors et al. 2008).

**Legal aspects of dental materials**

Dental materials are regulated according to European guidelines for Medical Devices (European guidelines 93/42/EEG). Usually they are classified as Class IIa, in which the producer asks a certifying body to certify that the material is in accordance with the regulations. Moreover, the certifying body monitors the quality system of the producer usually based on data given by the producer. There are around 800 technical control authorities for the guidelines. Of these 60 are accredited as notified bodies to perform evaluations of Medical Devices.
Before a product can be released into the European market, classification, risk assessment and technical documentation must be available together with proof of conformity to the Medical Directive. For products where clinical documentation is missing, clinical evaluation to obtain a CE certificate is needed. This can be via a clinical investigation or as a critical evaluation of available scientific literature. In Sweden, permission to perform a clinical investigation has to be obtained from the Medical Products Agency, which is also the supervisory unit for the Medical Devices in Sweden (SOSFS 2001; LVFS 2001).

The REACH regulation took effect on 1st June 2007 - Regulation (EC) No. 1907/2006 of the European Parliament and of the Council (REACH 2006). Various parts will be implemented gradually but the provision on safety data sheets applies from 1st June 2007. Suppliers of certain substances or preparations must provide the user with a safety data sheet in Swedish for products that are placed on the Swedish market (KI 3031).

REACH is a European Community regulation and applies directly in Sweden. It replaces a great number of other EC rules, which mainly had the form of directives and since been implemented into Swedish legislation. These rules will be changed or abrogated concurrently with the gradually implementation of the various parts of REACH (KI 4763).

The International Organization for Standardization (ISO) issues standards for dental materials. The central secretariat in Geneva, Switzerland coordinates the network of the national standard institute consisting of 146 countries. Development of standards for medical and dental materials and devices is done by subgroups of the network. Both government institutes and the industry are represented in the network. Different groups of materials are specified regarding the composition of the material and some materials might also be highlighted regarding the content of possible potential harmful constituents.

Swedish National Board of Health and Welfares

In 1988 the Swedish National Board of Health and Welfare published general guidelines (SOSFS 1988;9) aimed for both dental and medical personnel regarding the recommendation of care management programs for patients with subjective symptoms related to their dental restorative materials, particularly dental amalgam.

It was also concluded that there was no scientific evidence supporting the idea that dental amalgam could cause adverse reactions, a conclusion supported in later publications by the Swedish National Board of Health and Welfare and WHO (SOSFS 1991:6, SoS-rapport 1994:21, WHO 1997).

"Västerbottensmodellen"

In 1991, a care management program (Västerbottens Läns Landsting 1991; Bergdahl et al. 1996) for patients with subjective symptoms related to their dental materials was established in Umeå, Sweden. It was a collaboration between representatives from the Dental School in Umeå, Primary Health Care, the local Social Insurance Board and the regional office of the Swedish National Board of Health and Welfare. The collaboration was based on the general advice from 1991 (SOSFS 1991:6) where the Swedish National Board of Health and Welfare emphasized that these patients should be examined by both a physician and a dentist.

The care management program “Västerbottensmodellen” emphasized that the patient should be taken care of locally assuming collaboration between the patients’ dentist and physician. Patients can also be referred to a special unit at the Department of Oral Diagnosis, School of Dentistry, when an extensive examination of the patients is carried out. The program, used since 1991, has been successful. This was verified in questionnaires to both patients (Carlén Mårell et al. 1998) physicians and dentists (Bäckman et al. 1999).
Patients examined at the clinic were predominantly women, only one-third of the patients were men (Verksamhetsrapport 2000). Symptoms from joints, muscles and stomach were most frequently reported and no distinct difference between men and women was found.

The Swedish National Register Of Side Effects Of Dental Materials

The Swedish National Board of Health and Welfare’s Register of Side Effects of Dental Materials was established in Sweden in 1996 to monitor and evaluate adverse reactions from dental materials. This register was set up in collaboration with the Medical-Odontological faculty of the University of Umeå, Sweden. A similar reporting procedure had been in existence since 1993 at the University of Bergen, Norway (Gjerdet 1997; Gjerdet & Askevold 1998) and a national reporting system was also established in the United Kingdom in 1999 (van Noort et al. 2004).

Clinical experience from units which worked with the patients referred to the Department of Oral Diagnosis, School of Dentistry, Umeå, Sweden, as well as findings from the national reporting system (The Swedish National Board of Health and Welfare 2001), were that patients with many symptoms were less likely to recover than patients with few and localized symptoms. This was also found through research regarding complaints similar in nature; a study on perceived hypersensitivity to electricity and skin symptoms related to the use of visual display terminals (Stenberg et al. 2002).

Material Safety Data Sheets

MSDS (Material Safety Data Sheet) is widely used for cataloging information on chemicals, chemical compounds and chemical mixtures. A MSDS shall provide sixteen mandatory standard headings (EG no. 1907/2006, Reach (REACH 2006) (Table 2). All information about properties dangerous to human health and environment, information of importance for increased safety at the workplace and protection of the environment is to be provided. Labels include hazard symbols such as the Saint Andrew’s Cross, a black diagonal cross on an orange background which is used in the European Union to denote a harmful or irritant substance.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Sixteen mandatory standard headings of a MSDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Product and company identification</td>
</tr>
<tr>
<td>2.</td>
<td>Hazard identification</td>
</tr>
<tr>
<td>3.</td>
<td>Composition/information on ingredients</td>
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<tr>
<td>4.</td>
<td>First-aid measures</td>
</tr>
<tr>
<td>5.</td>
<td>Fire-fighting measures</td>
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<tr>
<td>6.</td>
<td>Accidental release measures</td>
</tr>
<tr>
<td>7.</td>
<td>Handling and storage</td>
</tr>
<tr>
<td>8.</td>
<td>Exposure controls/personal protection</td>
</tr>
<tr>
<td>9.</td>
<td>Physical and chemical properties</td>
</tr>
<tr>
<td>10.</td>
<td>Stability and reactivity</td>
</tr>
<tr>
<td>11.</td>
<td>Toxicological information</td>
</tr>
<tr>
<td>12.</td>
<td>Ecological information</td>
</tr>
<tr>
<td>13.</td>
<td>Disposal considerations</td>
</tr>
<tr>
<td>14.</td>
<td>Transport information</td>
</tr>
<tr>
<td>15.</td>
<td>Regulatory information</td>
</tr>
<tr>
<td>16.</td>
<td>Other information</td>
</tr>
</tbody>
</table>

CAS registry number

CAS registry numbers are unique numerical identifiers for chemical compounds, polymers, biological sequences, mixtures and alloys. They are also referred to as CAS numbers, CAS RNs or CAS #s. Chemical Abstract Services (CAS), Columbus, Ohio, assigns the substance a registry number.

Risk and Safety Statements

Risk and Safety Statements, also known as R/S statements, R/S numbers, R/S phrases, and R/S sentences, is a system of hazard codes and phrases for labeling dangerous chemicals and compounds. The R/S statement of a compound consists of a risk part (R) and a safety part (S), each followed by a combination of numbers. Each number corresponds to a phrase. The phrase corresponding to the letter/number combination has the same meaning in different languages. The European Union (EU) requires that Risk and Safety Statements (R- and S-phrases) and a symbol is present on each label and safety data sheet for hazardous chemicals (Fact Box No. 1).
List of R-phrases

R-phrases are in European Union Directive 67/548/EEC defined as: *Nature of special risks attributed to dangerous substances and preparations*. The list was consolidated and republished in the Directive 2001/59/EC.

List of S-phrases

S-phrases are in European Union Directive 67/548/EEC defined as: *Safety advice concerning dangerous substances and preparations*. The list was consolidated and republished in the Directive 2001/59/EC.

These risk and safety phrases are used internationally not just in Europe and there is an ongoing effort towards a complete international harmonization.

Hazard symbols

Examples of hazard symbols can be seen in Fact Box No. 1.

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**Fact Box No. 1 - Example of risk- and safety phrases and hazard symbols**

<table>
<thead>
<tr>
<th>Risk phrases - <em>Italic indicates flammable and explosive properties</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>R 1 Explosive when dry</td>
</tr>
<tr>
<td>R 2 Risk of explosion by shock, friction, fire or other sources of ignition</td>
</tr>
<tr>
<td>R 3 Extreme risk of explosion by shock, friction, fire or other sources of ignition</td>
</tr>
<tr>
<td>R 4 Forms very sensitive explosive metallic compounds</td>
</tr>
<tr>
<td>R 5 Heating may cause an explosion</td>
</tr>
<tr>
<td>R 6 Explosive with and without contact with air</td>
</tr>
<tr>
<td>R 7 May cause fire</td>
</tr>
<tr>
<td>R 8 Contact with combustible material may cause fire</td>
</tr>
<tr>
<td>R 14/15 Reacts violently with water, liberating extremely flammable gases</td>
</tr>
<tr>
<td>R 15/29 Contact with water liberates toxic, extremely flammable gas</td>
</tr>
<tr>
<td>R 20/21 Harmful by inhalation and in contact with skin</td>
</tr>
<tr>
<td>R 20/22 Harmful by inhalation and if swallowed</td>
</tr>
<tr>
<td>R 20/21/22 Harmful by inhalation, in contact with skin and if swallowed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety Phrases - <em>Italic indicates flammable and explosive properties</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>S 1 Keep locked up</td>
</tr>
<tr>
<td>S 2 Keep out of the reach of children</td>
</tr>
<tr>
<td>S 3 Keep in a cool place</td>
</tr>
<tr>
<td>S 4 Keep away from living quarters</td>
</tr>
<tr>
<td>S 5 Keep contents under ... <em>(appropriate liquid to be specified by the manufacturer)</em></td>
</tr>
<tr>
<td>S 6 Keep under ... <em>(inert gas to be specified by the manufacturer)</em></td>
</tr>
<tr>
<td>S 7 Keep container tightly closed</td>
</tr>
<tr>
<td>S 8 Keep container dry</td>
</tr>
<tr>
<td>S 1/2 Keep locked up and out of the reach of children</td>
</tr>
<tr>
<td>S 3/7 Keep container tightly closed in a cool place</td>
</tr>
<tr>
<td>S 3/9/14 Keep in a cool, well-ventilated place away from... <em>(incompatible materials to be indicated by the manufacturer)</em></td>
</tr>
<tr>
<td>S 3/9/14/49 Keep only in the original container in a cool, well ventilated place away from... <em>(in compatible materials to be indicated by the manufacturer)</em></td>
</tr>
<tr>
<td>S 3/9/49 Keep only in the original container in a cool, well-ventilated place</td>
</tr>
</tbody>
</table>

**Hazard symbols**

- Irritant (Xi) or Harmful (Xn)
- Toxic (T or T+), Flammable (F or F+)
- Environmental Hazard (N)
- Oxidizing (O)
- Corrosive (C)

**Hypersensitivity reactions**

When substances are released from dental materials different types of allergies may occur. Since there is a possibility that the reaction can be toxic (non-allergic), it is important to separate these two concepts (Figure 1). Unlike toxic reactions, allergic reactions are not dose-dependent. The latter could occur with low-concentration exposures of substances released from dental materials.

Antigens that provoke an allergic reaction are called allergens. Typical allergens are pollen, drugs, bacteria, food or chemicals. The immune system contains several mechanisms that normally protect the body against antigens. Prominent among these are the lymphocytes, cells that are specialized to react to specific antigens. There are two kinds of lymphocytes, B-cells and T-cells. B-cells produce antibodies, which are proteins that bind to and destroy or neutralize antigens. T-cells do not produce antibodies; instead, they bind directly to an antigen and stimulate an attack on it. Allergic reactions can have immediate or delayed effects, depending on whether the antigen triggers a response by B- or T-cells. Allergic reactions with immediate effects can be divided into three basic types (I, II and III) and one type with delayed effects (Fact Box No. 2).

![Potential adverse reactions to dental materials](https://example.com/figure1.png)

*Source: Lygre H. 2002.*
Fact box No. 2 - Allergic reactions and examples of dermatological definitions

**Occurrence of side effects**

The patient's exposure to dental materials is often ongoing during several decades. The frequency of adverse reactions to dental materials is considered to be low in relation to the number of dental treatments undertaken and varies with the type of treatment. Reported side effects vary from objective reactions to more unspecific, general reactions (Hensten-Pettersen & Jacobsen 1990; Hensten-Pettersen 1998; Mjör 1999). It has been suggested that some sort of adverse reaction may occur with an incidence of between 1:2600 and 1:700 dental procedures (Jacobsen & Hensten-Pettersen 1989; Jacobsen & Hensten-Pettersen 1989; Kallus & Mjör 1991; Jacobsen & Aasenden et al. 1991; Garhammer et al. 2001). Allergic contact dermatitis (Kanerva et al. 2000) seems to be the most common side effect of resin-based materials (Fact Box No. 2). Most studies have been conducted among dental personnel (Rustemayer & Frosch 1996; Carmichael et al. 1997; Wal-

**Type I reactions (Anaphylactic reactions, antibody-mediated)**

A systemic IgE reaction located over the entire body. Histamine is responsible for the visible symptoms of an allergic attack, such as running nose, wheezing, and tissue swelling. A severe, often fatal, type I allergic reaction, with an obstruction of the respiratory system and cardiovascular collapse, is known as anaphylaxis.

**Type II reactions (Cytolytic or cytotoxic reactions)**

When antibodies (IgM or IgG) react with antigens that are found on the surface of certain cells. The antigen-antibody complex activates the complement system, a protein system with series of potent enzymes that destroy the target cell.

**Type III reactions (Immune complex reaction)**

In a type III reaction, the antigen (IgM and IgG)-antibody complex accumulates on the walls of the small blood vessels. The complex then triggers the complement system, which produces inflammation and vascular damage.

Type II and type III reactions are, unlike type I, not dependent on a genetic predisposition.

**Type IV reactions (Delayed-type hypersensitivity reaction)**

In contrast to the systemic nature of type I allergy reactions the type IV or delayed allergic reactions depends on a complex interaction of T cells, which take longer to accumulate at the site where the antigen is present compared to B-cell antibodies. The allergic responses appear 12 to 24 hours or more after exposure and reactions are limited to the areas contacted by allergens, which usually are chemicals and proteins. A common delayed allergic reaction is contact dermatitis, a skin disorder.

**Dermatitis**

is literally meaning "inflammation of the skin".

**Contact dermatitis (Contact exzema)**

is of two types: allergic (delayed reaction, cell mediated), and non-allergic (direct reaction). The latter is more common. The allergic type is caused by an allergen, e.g. nickel, unlike non-allergic, which is a result of an irritants, e.g. solvents and detergents.

**Atopy**

is an allergic hypersensitivity affecting parts of the body not in direct contact with the allergen. It may involve dry itching eczema (atopic dermatitis), hay fever and asthma. It is related to IgE. There appears to be a strong hereditary component.

**Atopic eczema (atopic dermatitis)**

is believed to have a hereditary component, and often runs in families whose members also have hay fever and asthma. Itchy rash is also particularly noticeable inside of elbows and behind knees. Atopic dermatitis in older children and adults can be confused with psoriasis.

**Asthma**

is a chronic condition involving the respiratory system in which the airways occasionally constricts, becomes inflamed. This airway narrowing causes symptoms such as wheezing, shortness of breath, chest tightness, and coughing.

**Hay fever (Allergic rhinitis)**

is caused by pollens of specific seasonal plants, airborne chemicals and dust particles in people who are allergic to these substances. Sneezing, runny nose and itching eyes characterize it.
lenhammar et al. 2000; Wrangsjö et al. 2001; Geukens & Goossens 2001) while contact allergy in patients has mainly been reported as case reports (Kanerva et al. 1999; Geukens & Goossens 2001; Koutis & Freeman 2001; Koch 2003; Tanoue et al. 2005; Connolly et al. 2006).

Several authors (Axell et al. 1983; Bjerner & Hjelm 1991; Herrström & Högstedt 1993; Bratel et al. 1997; Vamnes et al. 2004) have in the scientific literature described the group of patients with symptoms allegedly caused by dental materials. These patients have often reported various both local and general symptoms. The oral symptoms reported are a burning mouth, gustatory disturbance, dry mouth and temporomandibular joint problems. Common general problems are muscular-skeletal pain, sleeping problems, nausea along with cognitive disturbances such as concentration difficulties and memory problems.

Burning mouth syndrome (BMS) is a condition that is characterized by burning, smarting or painful symptoms affecting a normal oral mucosa. The most frequent location is the tongue with lip and cheek area also commonly affected (Lamey & Lamb 1988; Bergdahl & Bergdahl 1999). BMS is relatively common (0.7%-4.6%), but occurs more frequently among women and increases with age (Bergdahl & Bergdahl 1999; Scalla et al. 2003). BMS has been described as a subjective, painful condition with a multifactorial etiology and can be present among patients with an anxiety to side effects related to dental materials (Bergdahl & Bergdahl 2001), and can also be associated with different states of ill health, drugs (Bergdahl & Bergdahl 1999) and depression (Bergdahl & Anneroth 1993; Bergdahl et al. 1995; Bergdahl & Bergdahl 1999). Taste disturbance is associated with local factors such as low saliva secretion (Fox et al. 1985), presence of amalgam fillings (Thorstensson & Hugosson 1996) and BMS (Grushka & Sessle 1991) and has been reported to vary from 0.6% to over 20% (Hoffman et al. 1998; Bergdahl & Bergdahl 2002)

Oral lichen planus (OLP) is a chronic inflammatory condition in the oral mucosa caused by an immunological mechanism (Porter et al. 1997; Scully et al. 1998). The prevalence has been found to be between 0.9%-2.2% and is more common among women and is related to increasing age (Mollaoglu 2000; Al-Hashimi et al. 2007). The etiology behind OLP is considered to be multifactorial, but reactions to dental materials and candida infection are common (Blomgren et al. 1996; Dunsche et al. 2003). The importance of psychological factors is disputed. Some mean that psychobiological and psycho-immunological mechanism might initiate autoimmune reactions, which are important for the pathogenesis of OLP (Prolo et al. 2002). Others are of the opinion that there are no etiological factors of psychological nature, but stress, anxiety and depression symptoms are seen along with OLP as a secondary reaction to the condition itself (Scully et al. 1998; Rödström et al. 2001).

Studies have been performed on patients who related their subjective symptoms to their dental amalgam. In a few Swedish studies it was found that patients who related their symptoms to dental materials, were not exposed to mercury in a higher degree than persons in a symptom free control group (Aronsson et al 1989; Kallus & Mjör 1991; Berglund & Molin 1996).

In a study on reported side effects it was found that around 30 % of the patients reported that they reacted to amalgam and 16 % to composite, while over 50 % of the dental personnel reacted to composite and 25 % reacted to gloves (The Swedish National Board of Health and Welfares 2001). The differences can probably be explained by the fact that the materials are in their most reactive phase when the dental staff are handling them, while the patients often are exposed to set materials.

**Self-reported health**

Over the last two decades the influence of working conditions on health has been studied extensively (Karasek et al. 1981;
Cheng Y et al. 2001). Job demand, job control and social support at work are the most studied characteristics of the working conditions in relation to health (Bourbonnais et al. 1999). Poor working conditions may be an important precursor of stress and may, therefore, contribute to the development of depression or anxiety (Plaisier et al. 2007). There are findings that indicate that higher social support increases the self-reported quality of life of workers (Rusli et al. 2008).

A multidisciplinary approach is most likely to be beneficial for the patients since mental, psychosocial as well as social problems are more pronounced in patterns of illness. Self-rated health could contribute to a more complete view of a patient’s situation. Furthermore, each individual’s perspective should be considered on its own (Undén & Elofsson 2006). There is a lack of relevant data regarding sociological factors influence on self-reported health in patients that relate their symptoms to their dental restorative material. However, research regarding complaints of a similar nature (Eriksson et al. 1997) has shown that social factors can be of importance for reporting of symptoms.

Aims of the study

Paper I and II
– to investigate if a group of patients with symptoms self-related to their dental restorative materials could be divided into subgroups based on their symptoms regarding their ability to recover (Paper I). Patients with local symptoms only are believed to have a better chance to recover than those with a wide variety of general symptoms.
– to examine the long-term development of symptoms and their social consequences in a group of patients with symptoms self-related to their dental restorative materials (Paper II). The hypothesis was that patients with more complex symptoms had a worse medical (more remaining symptoms at follow-up) as well as social prognosis compared with patients with local symptoms only.

Paper III
– to investigate which prognostic factors (gender, age, follow-up time and replacement of dental restorative materials, medical, social) had an impact on the perceived health and reported symptoms at follow-up.

Paper IV
– to determine which types of adverse reactions occurred, the duration of the reactions, and which treatment that was carried out in a group of patients with adverse reactions assessed to be caused by resin-based materials.
**Design and summary of results - Paper I and II**

**Study population**

The study group comprised of consecutive patients (n=751) seen at the Department of Oral Diagnosis, School of Dentistry, Umeå, Sweden, from 1991 to 1998 for an examination of symptoms allegedly caused by dental materials (Figure 2). A total of 137 patients did not participate. The reasons were various; missing or incomplete dental records (n=86), a medical diagnosis that explained the symptoms (n=11), death of patient (n=3) and refusal to participate (n=37).

**Reference population**

Our results were compared to a reference population sample taken from the general population in Sweden (Eriksson & Stenberg 2006). The distribution and collection of the questionnaires were conducted by Statistics Sweden (SCB). The sample was randomly selected and consisted of 3000 men and women with an age between 18-64 years. The study consisted of a self-administered questionnaire assessing symptoms and potential risk-indicators.

**Questionnaire**

The questionnaire, identical to the one used at the baseline investigation, was based on a questionnaire previously used in the Office Illness Project in Northern Sweden (Stenberg 1994; Eriksson 1996), and in a project on health effects of Electricity and Visual Display Units (Stenberg et al. 2002; Bergdahl et al. 2004). At follow-up, a questionnaire was mailed to 614 patients. The data collection lasted from June to October 2000 (Appendix I & Fact Box No. 3).

The questionnaire contained questions on, among others, civil status, present health, medical and dental treatment and other measures and precautions taken owing to the problems referred for, social consequences of the problems, current employment situation, feelings, self-image and coping behavior. Consequences for daily life was evaluated as well as the sociological issues that included questions regarding influence on daily life and consideration and understanding from relatives, friends and work colleagues. Psychological issues were evaluated with SASB (Structure Analysis of Social Behavior), CRI (Coping Resources Inventory) and SCL-90 (Symptom Check List 90). The evaluation of the psychological issues, e.g., personality type and traits, is not a part of this dissertation and will be published in future papers.

Forty-five patients returned more or less incomplete questionnaires together with a personal letter.
Fact box No. 3 - The content of the questionnaire

**Background variables**
- Sex, age, marital status, no. of children, education, type of work, working hours, work task

**Symptoms**
- Intra oral symptoms: e.g., burning mouth, dry mouth, increased salivation, taste disorder, TMJ pain, stiffness/numbness
- General symptoms: e.g., fatigue, headache, nausea, anxiety, depression, sleeping problems, vertigo, eye symptoms, skin symptoms, circulatory symptoms, muscular and joint problems

**Aggravating factors**
- Dental treatment, other

**General well-being and general health**
- VAS scale (Visual Analog Scale)

**Replacement of dental restorative materials**
- Total, partial or no replacement

**Reactions in connection with replacement of dental restorative materials**
- Type of reaction

**Remaining problems (symptoms) at follow-up**
- Symptoms remain unchanged, almost unchanged, remained to a limited extent, symptoms disappeared

**Examined by**
- Dentists, physicians (general practitioners or specialist), complimentary care

**Diseases prior to baseline examination**
- Diseases of importance for the patients’ symptoms: asthma, hay fever, eczema, atopy

**Consequences for work related issues**
- Stop working, change of work place, change of work task, working capacity (work hours, sick-leave, disability pension, early retirement pension), changes in electrical environment

**Social factors**
- Consequences for daily life, consideration and understanding at home and at work, possibility to relieve the symptoms

**Work conditions**
- Current employment situation, work demands, relation to colleagues at work, comfort and well-being at work

**Social Analysis of Social Behavior (SASB)**
- Feelings and self-image

**Coping Resources Inventory (CRI)**
- Coping behavior

**SL-90**
- Symptom Check-list

**Baseline investigation**
The distribution according to gender was similar for both the non-responders and the responders. The mean age among non-responders was 4 yrs lower than that of the responders. General and local symptoms were equally distributed, except for vertigo, which was overrepresented among the non-responders, 20.7% compared with 13.7% for the responders. Lichenoid reactions among the responders were significantly more common compared to the non-responders, 15.6% and 8.6%, respectively.

**Drop out analysis - telephone interview**
A total of 280 persons (45%) did not return a complete questionnaire. Of these, 45 patients returned a more or less incomplete questionnaire together with a personal letter.

The dropout group was subdivided into four subgroups, “oral lesions only”, “local symptoms only”, “local and general symptoms” and “general symptoms only”. These groups were further divided regarding gender and time for follow-up (“early visits”, i.e. before 1995 and “late visits” from 1995). From the sixteen sub-groups formed, every sixth patient was contacted for a telephone interview. A total of 46 patients were interviewed and the most common reason for not responding was dissatisfaction with the questionnaire, especially with the psychological questions.
Statistical methods

Chi-square or Fischer’s test were used to test differences in proportions. Test for trends was done by means of a Mantel-Haensel extension test [Paper I]. When analyzing the social factors correlation analysis (Pearson’s correlation coefficient) and reliability test (Cronbach Alpha) were used in order to find out if construction of indices was feasible. The Kruskal-Wallis test was used to test differences across subgroups followed by paired comparisons using the Mann-Whitney test [Paper II].

To reveal a possible association between multiple independent variables and the outcome variable, odds ratio and 95% confidence interval (CI) were calculated using univariate and multivariate logistic regression model [Paper I and II]. The statistical package for the Social Science (SPPS) was used for statistical calculations. Because of multiple comparisons, the significance level was set to 0.01 when comparing symptoms between baseline and follow-up. In all other comparisons, a p-value of less or equal to 0.05 was considered as statistically significant.

Summary of results - Paper I

A partial or total replacement of the dental restorative materials had been carried out by 75% of the patients. Total replacement of dental restorative materials had no significant impact on the ability to recover completely. However, the patients that had replaced their restorations completely perceived a significantly (p>0.01) larger alleviation of their symptoms compared to the others. It was mainly oral symptoms that had decreased significantly between baseline and follow-up. On the other hand the majority of the self-reported general symptoms had increased between baseline and follow-up for both men and women. Fatigue, difficulties in concentrating, eye irritation, dry eyes nasal symptoms, cough, hoarseness, and a lump in the throat sensation increased significantly (p<0.01) among women. Regarding skin problems, dry facial skin, facial erythema, facial sensory symptoms and body itchiness had increased significantly (p<0.01) for women. However, joint pain was the only general symptom that decreased significantly (p<0.01) for men between baseline and follow-up, and it was reduced by almost half.

The risk of having any remaining complaints was significantly higher for patients with complex symptoms (p<0.05) and it was more frequent among men. The prevalence of symptoms, both oral and general, at follow-up were significantly (p<0.01) higher in comparison with our adult reference population (Figure 3).
Summary of results - Paper II

Even though dental treatment was the most common action taken for both men and women, they had been subjected to many different “interventions” due to the complaints (Figure 4).
Among patients with complex symptoms the replacement of dental restorations was significantly (p<0.05) more common compared to those with local symptoms only. “Stopped working” showed a positive correlation with reported complex symptoms and it was significantly (p<0.05) more common among women with complex symptoms compared to men with similar symptoms. Change of work tasks was significantly (p<0.05) more common among both men and women with complex symptoms compared to those with local symptoms only.

Table 3. Logistic regression analyses of factors associated with unchanged or almost unchanged symptoms at follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>1. Crude OR (95% CI)</th>
<th>2. Multivariate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual factors</td>
<td>Women</td>
<td>1.0</td>
<td>1.86 (1.10-3.13)</td>
</tr>
<tr>
<td>Age &lt;56 yr</td>
<td>Men</td>
<td>1.0</td>
<td>0.96 (0.61-1.50)</td>
</tr>
<tr>
<td>Follow-up time</td>
<td>Age &gt;56 yr</td>
<td>1.0</td>
<td>0.96 (0.61-1.50)</td>
</tr>
<tr>
<td>“Illness” Symptom group</td>
<td>Local only</td>
<td>1.0</td>
<td>1.80 (1.05-3.07)</td>
</tr>
<tr>
<td></td>
<td>Local + general</td>
<td>1.22 (0.54-2.76)</td>
<td>1.12 (0.56-2.25)</td>
</tr>
<tr>
<td></td>
<td>General only</td>
<td>0.72 (0.33-1.60)</td>
<td>0.72 (0.33-1.60)</td>
</tr>
<tr>
<td>Changes Replacement of dental restorations</td>
<td>Total exchange</td>
<td>1.0</td>
<td>2.45 (1.39-4.30)</td>
</tr>
<tr>
<td></td>
<td>Partial exchange</td>
<td>2.36 (1.26-4.43)</td>
<td>2.36 (1.26-4.43)</td>
</tr>
<tr>
<td></td>
<td>No exchange</td>
<td>1.0</td>
<td>2.23 (1.14-4.36)</td>
</tr>
<tr>
<td></td>
<td>Stopped working*</td>
<td>No</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>0.68 (0.27-1.70)</td>
</tr>
<tr>
<td></td>
<td>Change of work place*</td>
<td>No</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>1.08 (0.55-2.13)</td>
</tr>
<tr>
<td></td>
<td>Change of work task*</td>
<td>No</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>1.08 (0.55-2.13)</td>
</tr>
<tr>
<td></td>
<td>Decreased work hours*</td>
<td>No</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Changes in electrical environment</td>
<td>Yes</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Because a part of the patients had oral lesions only without symptoms (n=33), they were excluded from the analysis at follow-up.

* Patients excluded at follow-up due to retirement (65+).
Regarding the social factor influence on daily life, patients with complex symptoms reported a significantly (p<0.05) higher influence than those with local symptoms only. Family and friends/relatives have shown more understanding and consideration of the patient’s complaints compared to workmates and colleagues, especially for those with complex symptoms. Women received more consideration than men (p<0.05), whereas no gender difference was found regarding understanding.

**Design and summary of results – Paper III**

Information was collected from the Swedish Dental Materials Register 2003 (DentMr 2003). DentMr was a register with information on almost 500 dental materials. The information contained among others indications, content of the materials and Material Safety Data Sheet (MSDS). The MSDS included in the DentMr was examined regarding the given composition of the products, the occurrence of CAS-numbers and risk- and safety phrases of the substances.

Furthermore, complementary information about risk- and safety phrases for substances with missing information in the MSDS was collected by using two easily available databases on the Internet, the Swedish Chemicals Inspectorate Classification Register and the Sigma-Aldrich® product register.

**Summary of results - Paper III**

An examination of the information on the 482 dental products showed that 377 different substances could be identified in the MSDS. “Different substances” meant that they were not spelled exactly as other substances and that it was not possible with 100% certainty to say that the substances was exactly the same as other substances given. A deeper examination showed that among these 377, 120 were synonyms and 38 were undefined substances, e.g. inert filler, glass powder, etc. (Figure 5). Only 23% of the remaining 219 substances had information about both CAS-numbers and risk- and safety phrases. For a fourth of the substances, merely CAS-numbers were given, while 3% had information only about risk- and safety phrases (Figure 5). No information was found in (49%) of the substances (n=106).

Via two data registers (Internet) the number of substances in DentMR 2003 with both CAS-numbers and risk- and safety phrases could be tripled.
The Swedish National Board of Health and Welfare Register of Side Effects of Dental Materials was established in Sweden in 1996 to monitor and evaluate adverse reactions from dental materials. The study group consisted of patients with symptoms related to treatment with resin-based materials that were reported to the Register from 1996 to 1999.

The reporting system was based on voluntary reporting of symptoms suspected to be caused by dental materials. Dentists, dental hygienists, and physicians were allowed to report. A special reporting form was used (Appendix II).

**Telephone interview**

The patients identified as fulfilling the inclusion criteria were telephone interviewed using a questionnaire with pre-determined questions developed in collaboration with the Side-Effect Registers Expert group (Appendix III).

The inclusion criteria were that the patients should have:

- reactions suspected to be caused by resin-based materials for direct dental restorations
- reactions that the Side-Effects Registers Expert group had assessed to be “Probable” or “Possible”
- reactions occurring during the years 1996-1999
Summary of results - Paper IV

The majority of patients (n=30) had symptoms that appeared within the first 24 h after treatment (Figure 6) of which 19 patients reacted already during the dental treatment. The most common type of resin material suspected to cause reaction was primer and bonding, 80% of the patients showed reaction to some of these materials. Out of the 19 that had reactions during the dental treatment 15 showed reaction to primer and bonding.

The symptoms were local or a combination of local and extra-oral symptoms. Skin problems, oral ulcers and a burning mouth were the most common adverse effects reported (Table 4).

![Figure 6. Distribution of the patients stratified by location of symptoms and delay between dental treatment and reaction.](image)

Table 4. Type of symptoms and signs

<table>
<thead>
<tr>
<th>Symptom</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra oral symptoms</td>
<td>7</td>
</tr>
<tr>
<td>Intra oral sore</td>
<td>7</td>
</tr>
<tr>
<td>Burning mouth</td>
<td>7</td>
</tr>
<tr>
<td>Symptom free necrosis of the oral mucosa</td>
<td>5</td>
</tr>
<tr>
<td>Swollen lips, intra oral &amp; throat</td>
<td>4</td>
</tr>
<tr>
<td>Extra oral symptoms</td>
<td>4</td>
</tr>
<tr>
<td>Skin problem (rash, itching)</td>
<td>10</td>
</tr>
<tr>
<td>Swollen face</td>
<td>7</td>
</tr>
<tr>
<td>Extra oral symptoms, not mentioned above*</td>
<td>5</td>
</tr>
<tr>
<td>Asthmatic reactions</td>
<td>2</td>
</tr>
<tr>
<td>Extra oral sore</td>
<td>2</td>
</tr>
</tbody>
</table>

* headache, anxiety, difficulties in concentrating, vertigo, fatigue, palpitation, pain from muscles and joints

No action was taken in 50% (n=19) of the patients (Table 5). In 15 of these patients the reactions disappeared within less than a week. Four of the patients that removed the resin-based material that they reacted to, experienced relief of the symptoms within a week after removal.
Table 5. Action taken due to symptoms

<table>
<thead>
<tr>
<th>Action taken</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>19</td>
</tr>
<tr>
<td>Removal of dental materials</td>
<td>8</td>
</tr>
<tr>
<td>Corticosteroid treatment (1 topical and 3 systemic)</td>
<td>4</td>
</tr>
<tr>
<td>Antihistamine tabs.</td>
<td>2</td>
</tr>
<tr>
<td>Chlorhexidine (mouth rinse)</td>
<td>1</td>
</tr>
<tr>
<td>Stopped working (dental nurse)</td>
<td>1</td>
</tr>
<tr>
<td>Attended hospital</td>
<td>1</td>
</tr>
</tbody>
</table>

Regarding the consequences of the reactions, 12 patients reported that they did not experience any consequences, while 12 patients had avoided restoring their teeth again with the same material. Furthermore, six patients had the material removed while four of the patients had not dared to go to the dentist at all after the reaction. One patient had visited the dentist but denied the dentist to restore her teeth because she was afraid of new reactions.

Thirty of the patients were never on any sick leave because of the problems. Three patients were on sick leave for two weeks or less and three for 9-28 months. These three patients had had problems with dental materials of many years' duration. At the time for the interview one of the patients had problems to eat and swallow after 28 months and where still on sick leave due to these problems.

Ethics

The studies (paper I, II and IV) were approved by The Committee for Medical Research Ethics in Umeå, Sweden.

Discussion

Study population [Paper I and II]

The study population [Paper I and II] consisted of consecutive patients referred by dentists/physicians to the Department of Oral Diagnosis at the School of Dentistry in Umeå, during 1991 to 1998 for an examination of symptoms allegedly related to their dental materials. The exclusion of some patients was due to reasons such as missing dental records, no dental examination, confirmed medical diagnosis that explained the symptoms and patients that had passed away between the first examination (baseline) and the follow-up. A methodological problem is the relatively low response rate (61%, personal letters included).

The clinical baseline data for all patients was available and no considerable differences between the group of responders and non-responders at baseline were observed. Furthermore, a drop out analysis (telephone interview) was done and the differences that were found between responders and non-responders at follow-up indicated a risk of underestimation of the complaints at follow-up. Furthermore, studies have indicated that individuals with most health problems may not respond to health-related surveys (Macera et al. 1990), which increases the risk of an underestimation of remaining complaints at follow-up for the entire study population.

Reference population [Paper I and II]

Since it was of great interest to determine whether our patients had significantly more symptoms than the general population, an adult control population consisting of 2,154 individuals was used, selected in 1998 by the public authority Statistics Sweden, Stockholm, Sweden, on commission of the authors (Eriksson & Stenberg 2006). The reference population was sampled from the general population in Sweden. In May 1998, 3000 randomly selected men and women, between 18-64 years, were surveyed. The study consisted
of a self-administered questionnaire assessing symptoms and potential risk-indicators. The distribution and collection of the questionnaires were conducted by Statistics Sweden (SCB).

The response rate was 70% (2154 cases). Of the 2154 respondents, 67.2% (1447 individuals) were working at the time for the survey. The data was collected in order to be used as a reference for studies on the environmental syndromes: “Sick-building syndromes” (Stenberg 1994; Eriksson 1996), “Hypersensitivity to electricity and visual display units” (Stenberg et al. 2002; Bergdahl et al. 2004) and the present study. In the result section, mainly weighted data was presented. Bias due to selection and drop-outs was taken into consideration in the weight-procedure and the calibrations were performed by Statistics Sweden (SCB), to the estimated population of 18-64 years in May 1998.

The response rate of the reference group was higher compared to the response rate of the present study group at the time for the follow-up. However, lower response rates than those regarded as acceptable do not necessarily compromise the results of epidemiological studies (Locker 1993).

Drop-out analysis [Paper I and II]
The telephone interviewed drop-outs perceived worse health status and well-being in comparison with the response group. Their complaints, causing the baseline investigation, were still present to a higher degree, whereas sick leave and retirement due to medical reasons were less common in this group than among the responders. Of the patients interviewed, 30.1% experienced no change regarding reported problems compared to 19.1% in the response group. The drop out analysis indicates that the result from the follow-up study might be an underestimation of the extent of remaining complaints and therefore not fully reflects the situation in the entire study population. Non-responders can be overrepresented among individuals with multiple health problems (Macera et al. 1990), and this increases the risk of underestimation. Even so, it was found that the respondents in the present study had a larger number of reported symptoms compared to a reference population (Eriksson & Stenberg 2006).

Telephone interviews with non-respondents (drop-out analyses) are a valuable instrument to increase not only the response rate, but are also a way to produce less biased samples than mail-only protocols (Fowler et al. 2002). However, some have suggested that, in most cases, the nature of the response differs little between face-to-face, telephone and postal administration of questionnaires (Marcus & Crane 1986).

Methodological reflections
The study population [Paper I and II] consisted of consecutive patients referred by dentists/physicians to the Department of Oral Diagnosis for examination of symptoms suspected to be caused by dental materials. Since the study population was not randomly selected within the general population, it can be discussed if the study population represents the underlying population and to which extent this affects the validity. Instead the patients in the present follow-up studies [Paper I and II] were consecutive patients conveniently available at the Department as referrals that fulfilled the inclusion criteria for the study. An adult Swedish control population was used to determine whether our patients had significantly more symptoms than the general population, which increased the external validity of our results.

A retrospective data collection was facilitated since the examination at baseline was performed using structured interviews and clinical protocols. However, data in the records might be incomplete in some cases due to the fact that the patients were recorded for routine treatment, not for research purposes. The study population was divided into subgroups based by on symptoms and some patients may have been misclassified, a misclassification considered to be non-differential, which in turn
might have diluted the differences between the subgroups.

The information of the baseline investigation was collected over a period of eight years. Minor variation in diagnostic routines over the years and the composition of personnel could have influenced the result of the clinical examination. Furthermore, patients might have moved between the subgroups since the pattern of the patient’s symptoms might have changed over time.

The questionnaire (Fact Box No. 3) at follow-up was identical to the one used at baseline. The questionnaire consisted of a protocol with pre-determined questions and it was based on a questionnaire previously used in a research project regarding complaints of a similar nature (Stenberg 1994; Eriksson 1996; Stenberg et al. 2002; Bergdahl et al. 2004), which allowed comparison and hence increased the external validity. However, this does not concern the social issues evaluated because they were recorded only in the follow-up study. Even if the questionnaires at baseline and follow-up were identical one has to consider that there is a time difference of 2-9 years between these two occasions. The patients have become older and normally more symptoms will appear and surely affect the pattern of reporting. The questionnaires at baseline and follow-up were also answered in different settings (in the clinic and “at home”). The milieu at home was probably less stressful compared to the surroundings at the clinic, which might have affected the answers and therefore introduced bias to the results. The variable “cold hands and feet” was reported in 1% of the study population at baseline compared to 24% at follow-up. Replacement of dental restorative materials (mainly amalgam) was the most common action between baseline and follow up, and the interpretation could be that the frequency of the variable “cold hands and feet” increased after the replacements, which probably is not the case. This could be a result of what is discussed above regarding age and settings.

Ahead of the construction of indices [Paper II], the internal consistency of the scales for the social factors influence on daily life, understanding and consideration were evaluated using correlation analysis (Pearson’s correlation coefficient) and reliability test (Cronbach’s Alpha). For both tests a multi-item scale of 0.70 or higher is considered to indicate sufficient internal consistency. All subscales presented acceptable consistency (>0.70) and therefore construction of indices was feasible.

It is assumed that there was examiner variability between the different dentists, dental hygienist and physicians who reported [Paper IV] the suspected adverse reaction to the Swedish National Register of Side-Effects. It has been suggested (Lygre 2005, Dissertation, p.48) that the reporting form should have included more detailed guidance regarding intraoral signs that the informants should have taken into consideration in order to lower the inter examiners variability. Therefore, more accurate information regarding “objective” intraoral findings could have been gathered.

Although Evidence-Based Medicine/Dentistry (EBM/D) is regarded as the "golden standard" for clinical practice and treatment guidelines, in some cases, such as in the present study, conducting randomized, placebo-controlled trials could be considered as “unethical”. From our clinical experience of this patient group, it would be difficult to randomize them by treatment (replacement of dental restoration or not). The patients are convinced that their problems are related to their dental restorations and they would probably not give informed consent to be involved in a clinical survey based on randomizing. Critics of EBM/D say that the more the data is pooled and aggregated, the more difficult is it to compare the patients in the studies with the patient in front of the doctor/dentist - that is, EBM/D applies to populations, not necessarily to individuals. It has been argued (Tonelli 2006) that spokesmen of evidence-based medicine/dentistry discredit the value of clinical experience.
Since EBM/D is difficult to apply on the present study population, it is necessary to evaluate the patients from an individual and multidisciplinary point of view, which means that we are highly dependent upon our clinical experience.

**Replacements of dental restorative materials [Paper I and II]**

Extensive discussions regarding health problems related to dental restorative material, especially amalgam, has taken place over the last few decades. Patients with anxiety for side effects that they relate to dental materials are often dissatisfied, suspicious and critical since they believe that their complaints are caused by incorrect treatment with health-impairing dental restorative materials. The patients also claim that the dental/health personnel do not take their problems seriously, which leads to that the patients look for complimentary care where they might get their "self diagnosis" confirmed. There is no clear and distinct scientific proof showing that dental restorative materials could cause poisoning or general ill health, even if allergy or other hypersensitivity reactions to different constituents are reported (WHO 1997; Kanerva et al. 2000; Örtengren 2000; Lygre et al. 2005).

Patients that associate their adverse reactions to their dental restorative materials have reported a various number of both local and general symptoms (Axell et al. 1983; Bjerner & Hjelm 1991; Herrström & Högestedt 1993; Bratel et al. 1997; Malt et al. 1997; Vamnes et al. 2004). In Scandinavia, studies have been published (Lindfors et al. 1994; Strömberg & Langworth 1998; Langworth et al. 2002; Lindh et al. 2002; Nerdrum et al. 2004; Lygre et al. 2005) regarding the effect of the removal of amalgam restorations on general health and the results have been inconclusive and disputed. Moreover, these studies can be difficult to compare since the methodology of evaluation varied.

In general, these patients related their symptoms to dental restorative materials, mainly amalgam, and improvements of the symptoms were reported after removal of their dental fillings but the symptoms were not reduced to the level of a general population (Nerdrum et al. 2004). This is in accordance with our findings in Paper I. However, many patients reported that their health had improved over time after the replacement of their dental restorations, but significantly for oral symptoms only, which was in accordance with a Norwegian study (Lygre et al. 2005). Still, the symptoms were more frequent in comparison to a reference group (Eriksson & Stenberg 2006). No improvement was found among patients with complex general symptoms, on the contrary these symptoms had increased.

At baseline oral lichenoid reactions were verified in 15.3% of the patients. This is higher than the estimated 1-2% reported earlier in a general population (Axell & Rundquist 1987; Pindborg et al. 1997; Mollaoglu 2000; Miller et al. 2001; Al-Hashimi et al. 2007). The prevalence differences can be explained by the fact that the present study population were consecutive patients referred to the Unit and therefore did not reflect the underlying population. This group of patients is subjected to further studies, and the results from a clinical follow-up investigation will be reported in a future paper.

Despite the lack of scientific evidence of a connection between dental materials and general health, a considerable number of patients still claim that dental restorative materials are causing their diseases and/or symptoms. Some of these patients also claim that exposure to electricity; visual display units and bad indoor air quality affects their problems (Stenberg 1994; Eriksson 1996; Bergdahl et al. 1998; Hansson-Mild et al. 1998), which increases the diagnostic complexity even further.

The replacement of amalgam fillings and its effect on sick leave has been studied by the Social Insurance Office in Stockholm, Sweden (Eliasch C et al. 1994). The results showed that after the amalgam replacement, the share of patients that had
increased their number of sick-leave days was as large as the share that had decreased their number of sick-leave days. Because the regulation and guidelines regarding reasons for sick leave has been changed, an analysis of sick-leave pattern is associated with difficulties.

Psychologically, these patients have been reported to differ from a reference population (Bergdahl et al. 1994; Bergdahl et al. 1995; Bergdahl, Östman et al. 1995). Psychological conditions such as stress, anxiety and depression have been commonly reported but even specific personality types and traits have been emphasized (Bratel et al. 1997; Bergdahl & Bergdahl 2001; Dalen et al 2003; Bergdahl et al. 2005). In the present study population results from personality assessments will be reported and discussed in a future paper.

Even though the patients after replacement of their dental restorative materials claim that the alleviation of their symptoms is an effect of decreased exposure to the materials suspected, there might be other explanations for the patients’ improved health. The alleviation of symptoms might also be an effect of patients’ expectations, spontaneous recovery, changes of attitudes and changes in psychosocial situation.

**Social factors and self-reported health**

(Paper II)

Initially this group of patients was referred to the special unit because they claimed that their symptoms were caused by their dental restorations (mainly amalgam). The patients had been subjected to many different treatments, even though dental treatment was the most common action/intervention taken for both genders. The patients themselves did not see any connection between their symptoms and work related issues. Despite this, we could see that “stopped working” showed a correlation with reported symptoms as well as replacement of dental fillings. The social factors seemed to be more important for patients that reported problems with complex symptoms and consequently also with the degree of replacement of their dental restorations.

“Interventions” is, as we see it, more of an active action from the patients’ point of view (replacement of dental restorations) with the “expectation” to get a positive outcome, while a “change at work site” is less active and not directly oriented against what the patient believes is causing the problems. But, as such actions were correlated with health, it indicates that social factors might have had an impact and, therefore, have to be considered in future research. Furthermore, research regarding complaints of a similar nature (Eriksson et al. 1997) has shown that social factors can be of importance for reporting of symptoms.

The strongest evidence for therapeutic interventions is supposed to be provided by systematic review of randomized, double blind, placebo controlled trials involving a homogeneous patient population. In contrast, patient testimonials and case reports have little value as proof because of the placebo effect and the biases inherent in observation and reporting of cases (Elstein 2004). Accordingly, our outcome regarding self-reported health is considered to have little value as proof if one totally accepts the concept of evidence based knowledge solely. As pointed out earlier, the spokesmen of EBM/D (evidence-based medicine/dentistry) have been criticized (Tonelli 2006) for discrediting the value of clinical experience. Since EBM/D is difficult to apply to the present study population it is necessary to consider the patients as individuals, which means that we are highly dependent upon our clinical experience. The quality of evidence to support a clinical decision could be a combination of the quality of research data and the clinical ‘directness’ of the data (Atkins 2004).

Self-rated health has been reported as a good predictor of future morbidity and mortality in several studies (Idler & Benyamini 1998; Burström & Fredlund 2001; Benjamins et al. 2004). Recently published studies (Undén & Elofsson 2006; Molorius
et al. 2007; Fischer & Sousa-Poza 2008; Lau and Knardahl 2008) supports the notion that both social and material conditions as well as lifestyle factors are related to poor self-rated health and, therefore, social factors have to be considered in future research.

We have not been able to analyze how the causal order and to which extent different factors influences the outcome. Even if the patients claimed that the replacement of dental restorative materials contributed to the alleviation of symptoms, only one sixth of the patients in our study reported a total relief of complaints at follow-up after replacement of their dental restorative material. Furthermore, in a recently published study on patients with symptoms self-related to their amalgam fillings (Melchart et al. 2008), it was found that there was no significant difference in alleviation of symptoms between the patients that had their amalgams replaced, the patients who had replaced their amalgam in combination with “detoxification treatment”, and those who had participated in a health promotion program only.

In addition, many of our patients sought complimentary care, which is an indication that traditional dental and medical care has, to some extent, failed in caring for these patients. The interest for complementary care can also be a result of the bio-medical models’ shortcoming in the management of these patients. Therefore, this group of patients should be looked upon from a more holistic and individual point of view.

Material Safety Data Sheet [Paper III]

The present study shows that health risks of dental materials often are unknown or insufficiently described in MSDS to the patients and dental personnel. This lack of accurate information emphasizes the need for improvement of the MSDS. Mainly less well-examined resin composite materials have replaced amalgam, which has been studied extensively as a direct restorative material. It has been noticed in earlier studies (Henriks-Eckerman & Kanerva 1997; Kanerva et al. 1997; Henriks-Eckerman et al. 2004) that the information in the MSDS is insufficient regarding CAS-numbers and risk- and safety phrases both for resin-based materials and other materials as well. The full chemical specification of these alternative restorative materials is not always given and it may be difficult to obtain information of what they contain. Therefore, the information available is often insufficient concerning exposure and toxicity. All these materials should be considered as possible hazards and caution should be taken before new (alternative) materials are introduced into the market.

Several studies (Kolp et al. 1995; Frazier et al. 2001; Keegel et al. 2007) outside the dental field have also assessed the health information given in MSDS. Kolp et al. assessed 150 MSDS and only 37% were found to have accurate health effects data. Frazier et al. assessed the quality of health information regarding asthma on a random sample of MSDS for toluene diisocyanate (TDI) from 30 manufacturers. Only 50% of the manufactures had listed asthma as a potential health effect. Finally, Keegel et al. reported that only 58% of the MSDS audited in their study complied with the level of hazardous substances. This represents a poor level of accuracy from the manufacturers responsible for the preparation of MSDS. The lack of risk and safety phrases of substances in the MSDS might also indicate insufficient toxicological competence among the manufacturers.

MSDS’s are an essential part of making a safer environment. Earlier guidelines of preparing these documents gave the manufacturers the right to exclude key information about non-hazardous components, proprietary contents, substances with sensitization potential and possible consequences of diseases. The REACH Regulation (REACH 2006), which took effect on June 1st 2007, gives greater responsibility to industry to manage the risks from chemicals and to provide safety information on the substances. Manufacturers and importers will be required to gather information on the properties of their
chemical substances, which will facilitate a safer handling.

Even though it is reasonable to put the burden of evaluation on the manufacturers, it has been suggested (Bernstein 2002) that the health care professionals have an obligation to better educate themselves regarding the interpretation of MSDS’s and also recognize that MSDS’s often provide incomplete data.

The hazard communication system is highly dependent upon the quality of the information available regarding hazardous substances and the effectiveness of communicating this information to health care providers and patients. Furthermore, an examination of the accuracy of health information on MSDS’s should be required regularly in order to assure that provided information is adequate and reliable.

Reactions to resin-based materials [Paper IV]
The patients in the study group were reported to the Swedish National Register of Side-Effects because of adverse effects related to resin-based dental materials. The mechanism of adverse effects could be either toxic or allergic. Objective findings can be found that confirm the patients complaint but subjective complaints/symptoms without objective findings are also common. Toxic reactions are, unlike allergic reactions, dose-dependent. Substances from different dental materials are released and may cause toxic side effect (Spångberg 1969; Pascon & Spångberg 1990; Koch & Staehle 1997; Guigand 1999; Geurtsen 2000; Tai et al. 2002; Huang et al. 2005; de Oliveria Mussel et al. 2007). In general, the release of substances from dental restorative materials is low and the knowledge of which exposure level that is needed to cause health effects is not well known.

Allergic reactions are not dose-dependent and also low-concentration exposures from dental restorative materials can cause reactions. Both resin-based materials and metals can cause allergic reactions (Hensten-Pettersen 1992; Räsänen et al. 1996; Vannes et al. 2000; Örtengren 2000; Wallenhammar et al. 2000; Wrangsjö et al. 2001; Ahlgen et al. 2002; Tvinne-Reim et al. 2003). Allergic reactions can be acute or chronic. Acute conditions are rare but can be life threatening, e.g., latex allergy. In order to be able to give correct information to the patient it is necessary to have knowledge of the underlying causes to different reactions that may appear.

Skin problems and contact dermatitis were the most common adverse effects reported in the present study, which is in line with earlier findings (Kanerva et al. 2000). Intra oral ulcers, swollen lips and respiratory reactions such as swollen throat and asthma were the most frequent oral manifestations, of which the latter also has been reported to be common among dental personnel (Pirilä et al. 2002).

Almost 90% of the patients with reactions to resin based materials in the present study, reported that most reactions occurred during or close after insertion of the dental restorative material, which is in line with earlier case reports (Carmichael et al. 1997; Kanerva et al. 1999; Koutis and Freeman 2001; Koch 2003; Martin et al. 2003; Tanoue et al. 2005; Connolly et al. 2006). Immediate reactions to resin based materials were more prevalent than delayed allergic reactions and is usually a type I (IgE sensitization) reaction, if the reaction is confirmed as allergic (Fact Box No. 2). This type of reaction affects above all atopic patients and the allergen is usually a protein/polypeptide, which for example is a part of the content in latex. Only three of the patients were through a patch test, confirmed to be allergic to resin-based dental materials, in other words they had a delayed hypersensitive reaction.

It is known that proteins are not a part of the content in resin-based dental restorative materials (composites) and in the present study group atopy was not more common among those patients with immediate reaction, which indicates that the mechanism of the adverse reaction was most probably non-allergic/toxic. However, from occupa-
tional settings where isocyanate is involved, IgE sensitization has been reported (Jones et al. 2006; Wisnewski 2007). Therefore, dentists have to be observant and also have the knowledge to be able to evaluate if the complaint is of an allergic nature or if there are other reasons, e.g., non-allergic/toxic reactions, causing the patients’ problem. Hence, in order to improve the handling of the patients it is very important to develop provocation tests that can establish the relationship between the materials and the adverse reactions when it is of non-allergic/toxic nature.

Bio-psycho-social ill health model

Although the awareness of the relationship between body and soul has been known for thousands of years there has still not been a breakthrough within medicine. The reason for this is that it is likely that the biomedical paradigm is predominating the health- and dental care. The biomedical approach emanates on the belief that diseases only can be defined by measurable biological variables and therefore no space is provided for social, psychological or behavioral dimensions of ill health (Engel 1977). It has been reported (Molin 1999) that despite the success within the biomedical research there is a growing dissatisfaction with the lack of attention and with the diagnostics and treatment within the health care system because the psychological and social aspects have been neglected.

The influx of patients with psychosomatic problems has increased markedly. A considerable share of patients (30 % in primary health care and 15 % in district dental clinics) have reported complex psychosomatic problems which means that general practitioners (physicians/dentists) meet these patients on a regularly basis (Wikman 1998). The quality of life, i.e., our subjective experience of our health and life situation is considered to be a very important etiological factor for psychosomatic condition (Testa & Simonson 1996). Education level, living conditions, income and social network such as family, close friends and colleagues at work are important psychosocial factors for the quality of life. The quality of life also depends on events a person is exposed to. Stress is of great importance for the development of different medical conditions (Miller 2002). However, traumatic life events are not the only source for stress but also subtle and prolonged strain can be a determining factor for health (Öhman 2007).

It is reasonable that a modern dental school should include education about psychosomatics, psychology and sociology (Piko and Kopp 2004). Furthermore, cognitive techniques for clinical attitude, diagnostic and intervention should also be included in the dental education, which will enable the dentist to apply a bio-psychosocial approach. Therefore we have to question and challenge the prevailing bio-medical paradigm and replace it with a bio-psychosocial approach that give us possibilities to consider all aspect of ill health and disease (Dworkin 2001).

General conclusion

In the present study group, patients with complex symptoms had a more unfavorable long-term prognosis concerning remaining complaints than those with local symptoms only. Therefore, the hypothesis that patients could be divided into subgroups based on their symptoms and that the ability to recover differs between the groups, was supported.

Unchanged complaints at follow-up were higher among men with complex symptoms than in women. Patients might experience health improvements after replacement of their dental restorations, especially for oral symptoms. Furthermore, the prevalence of symptoms, both local and general, was higher than in a control population.

The findings indicate a relationship between patients with complex symptoms and social consequences in daily life. The patients with complex symptoms had, to a higher degree, stopped working compared to patients with local symptoms only. This
study indicates that social factors can be of importance for self-reported health. Therefore, social as well as dental, medical and most likely psychological factors have to be considered when examining patients with symptoms related to dental materials.

The information about the hazards of dental materials seems insufficiently described in MSDS and there might be materials with side effects unknown to both patients and dental personnel. Therefore, stronger regulations of dental materials are desirable. For some dental restorative materials, e.g., those incorporated for decades, regulations similar to those for pharmaceutical drugs seem reasonable. Since the number and complexity of dental materials increases, there is a need for a material register regarding the content of the materials as well as a reporting system for adverse reaction.

There is no clear and distinct scientific proof showing that dental restorative materials cause poisoning or general ill health, even if contact allergy or other local hypersensitivity reactions to different constituents are reported. It seems as if non-allergic immediate reactions to resin based materials are common and much more prevalent than allergic reactions. Still we have had great difficulties in verifying the association between the reaction and the material and also to identify the offending component.

It seems reasonable to challenge the prevailing biomedical paradigm and replace it with a bio-psychosocial approach that gives us the possibilities to consider all aspects of ill health and disease when patients with symptoms related to dental materials are investigated.

**Future studies**

Even though the psychological issues have not been evaluated in the present study group, but will be in a future paper, it seems obvious that these patients must be investigated from a bio-psycho-social point of view in order to enable analyze not only on biological factors but also social and psychological factors as well. Future research on similar patient groups should include all these factors with potential importance for evaluation of adverse health effects.

Since our interdisciplinary research group has been working with different environmentally related factors (inadequate air quality, electromagnetic radiation, e.g., electrical devices and display units and dental materials) and their impact on health, a comparison between these patient groups would be of interest.

The number of dental materials will be increasing and it is important to evaluate possible reactions to the new and sometimes rather complex materials. The evaluation is highly dependent on the available information given for each material, i.e., the MSDS provided by the producer should contain accurate information regarding hazardous constituents. Therefore, an investigation into the accuracy of health information in MSDSs should be required, as a suggestion, every 2 or 3 years in order to assure that the provided information is adequate and reliable.

Immediate reactions to resin based materials were more prevalent than delayed allergic reactions and the mechanism of the immediate reactions is probably non-allergic in most cases. Due to the lack of relevant provocation tests for immediate reactions we have had difficulties to verify the association between a reaction and the offending component. It is an important research issue for the future to develop provocation test for this type of reaction.
Acknowledgements

I wish to express my gratitude to all those who made this study possible and particularly to:

**Anders Berglund**, head supervisor, co-author and friend. I am grateful for your professional guidance and invaluable support during these years.

**Professor Bengt Järvholm**, second supervisor and co-author on paper III, for your excellent guidance.

**Nils Eriksson**, second supervisor and co-author on paper II, for introducing me to the world of Sociology and for your competent and effective supervision. You have really broadened my “intellectual” horizon.

**Lars Widman**, second supervisor and co-author on paper I, for your persistency, without it this project would not have materialized.

**Berndt Stenberg**, co-author on paper IV, for providing skillful and prompt response during the writing process.

**Lena Mårell** (“Mamma Lena”), co-author, for all the hearty laughs over the years.

**Professor Jan Bergdahl**, co-author, for not only scientific guidance but also for being my personal adviser concerning life in general. Your and your wife Maud’s support is most appreciated.

**Gerd Lindén**, for her superb administrative support and assistance with the patients’ records.

**Hans Stenlund**, for invaluable statistical guidance.

**Ewa Gruffman**, for being the positive and helpful person you are. It is a privilege to know a person that possesses these inestimable qualities.

**Tomas Lindh**, for numerous things, but above all for being a good friend. All the hilarious puns and punch-lines you have ….Gosh!

The Lindh/Lundqvist family, **Tomas, Carina, Lovisa** and **Johan**. You all made my summer unforgettable pleasant. Thank you very much for your hospitality and support.

**Johan Lindh**, you have ensured my future career as an agent for professional football players. There is only one option: “The Gunners”. Snyggt, Va?

The staff at the Dental Technician School in Umeå, **Ewa Sundgren**, **Inger Idenäs Reinholdson**, **Anna-Karin Hulterström**, **Monica Norlund**, **Eva Berglund**, **Dodd Johansson**, **Staffan Wede**, and **Dirk Prüss**. I have enjoyed your company during the countless and prolonged coffee breaks.

**Professor Harald Eriksen**, Institute of Clinical Dentistry, Faculty of Medicine, University of Tromsø, Norway, for letting me spend the summer of 2008 in front of my computer. “Harald: tu eres un hombre muy simpatico”.

**Glen McGrath**, for his swift and skillful revision of the English.

Last but not least, myself for not giving up prematurely. Writing a thesis is not all beer and skittles. Thank God it’s over!
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