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# The Safety of Nickel in Dental Alloys

*A continuing series of publications on environmental and human health issues related to nickel and its compounds.*

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## THE SAFETY OF NICKEL IN DENTAL ALLOYS

### 1. INTRODUCTION

#### 1.1. Preamble

Nickel has been successfully used in numerous alloys employed in the provision of dental care. Many of these alloys have applications in the construction of long-term restorations designed to remain in clinical service for many years, including crowns, fixed bridges and removable partial dentures, or may be used for shorter times, for example, in orthodontic appliances to move and straighten teeth over, typically, two or three years.

Dental crowns are restorations made to cover and protect the exposed portion of compromised teeth, thereby covering the 'clinical dental crown', and fixed in place for long term clinical service with dental cements. For damaged and unsightly front teeth, crowns may be made of tooth-colored materials such as ceramic or porcelain. These tooth colored materials may be used alone or veneered over a metal framework (metal-ceramic crowns). Crowns of metal alloys alone may be used for restoring back teeth. Bridges, or 'fixed partial dentures', are prosthetic restorations designed for long term service. They are securely retained by dental cements and replace the crowns of one or more missing teeth<sup>(1)</sup>. As with artificial crowns, fixed partial dentures are usually a structure of metal for strength that is veneered with tooth-colored porcelain for a natural esthetic appearance.

Removable partial dentures replace the crowns of one or more missing teeth and the associated soft tissues. They are retained by clasps that encircle the supporting teeth with flexible tips that engage below the contours of the teeth and include artificial teeth and typically plastic gumwork. They are able to be removed by the patient for cleaning, but are usually in place for most of the day. The framework of removable partial dentures needs to be made of strong materials that are rigid in thick section and flexible if in thin section. Overall, the requirements for the various materials used in dentistry are rigorous in respect of the physical

properties, including the ability to withstand the harsh oral environment that is moist, warm, corrosive and the place where food is chewed. In addition, the biological properties of dental materials are extremely important.

In 1985, an international symposium was held in Michigan on the biocompatibility, toxicity and hypersensitivity to alloy systems used in dentistry<sup>(2)</sup>. The workshop summary by Mjör<sup>(3)</sup> concluded that: "Despite the apparent lack of data on the biocompatibility of cast and wrought dental alloys, their clinical efficacy is established. Seemingly successful restorations and appliances made of fairly corrosion resistant alloys with a wide variety of clinical compositions are presently in use. This situation provides a unique opportunity to analyze possible clinical problems encountered, including failure rate, reasons for failure and biocompatibility of dental alloys." Some seventeen years after the Michigan Workshop, the safety of nickel in alloys used in dental care is still questioned, but their use in dental practice has continued.

Since the safety of nickel may still be a concern, and given the importance of nickel in the development of optimal qualities of alloys used in dentistry, it is considered important to provide periodically a contemporary, comprehensive, and as far as possible, evidence-based review of the existing knowledge and understanding of the biological reactions to, and the safety of nickel in dental alloys, with an emphasis on more recent publications in the field.

#### 1.2. Properties of Nickel

Nickel is a solid silver-white, hard, malleable transition metal with an atomic number of 28. It resists corrosion even at high temperatures, and it is present in alloys in widespread use including stainless steel. Nickel is also used in the production of coins, jewelry, nickel-cadmium batteries, and as a catalyst for the hydrogenation of liquid oils to solid fats such as oleomargarine and vegetable shortening. The worldwide annual production of nickel for year 2000 was reported to be 1080 kilotonnes<sup>(4)</sup>.

Nickel is essential for certain plants and animals. Nickel compounds are ubiquitous and are consumed as part of a normal diet from foods such as vegetables, with the daily intake estimated to be 100-600 µg/day<sup>(5,8)</sup>. Nickel is a component of certain enzyme systems in humans and is considered an essential "trace element" at least for some plants and animals. It is supplied in the amount of 5 µg per daily tablet in several multivitamins-and-minerals tablets (Boots Complete A-Z, Sanatogen, Centrum, Seven Seas).

### **1.3. Purpose**

The aim of the present work was to complete an up-to-date comprehensive review of the existing literature on the safety of nickel in dental alloys, with an emphasis on more recent publications in the field.

### **1.4. Scope**

To complete this review, the investigators undertook a comprehensive electronic and hand search of all relevant literature with particular emphasis on information sources created within the years since the 1985 International Workshop<sup>(2)</sup> held in Michigan, USA.

## **2. NICKEL AND NICKEL ALLOYS IN DENTISTRY**

### **2.1. Nickel and Nickel Alloys**

Many alloys containing nickel are used in dentistry including instruments such as dental syringes and hand instruments and other stainless steel equipment that may only briefly make contact with the patient's tissues. This paper will focus more on those items that are placed intra-orally for relatively short periods, for example, orthodontic appliances, and for longer times intra-orally as removable and fixed partial dentures and crowns, or placed into tissues as for implants.

Cost-effective and safe materials for dental reconstructions are continually being researched and developed. Gold alloys remained the most commonly used metal in fixed prosthodontics until the 1970s<sup>(6)</sup>. Since that time gold has

gradually been replaced by other metals largely as a consequence of its increasing price and through an increased knowledge and application of metallurgy. By 1980 more than half of fixed dental prostheses were made of non-precious alloys, with little, or no gold content<sup>(7)</sup>.

Common alloys in dental use are dental amalgam, nickel-chromium, cobalt-chromium, and stainless steel. Cobalt-chromium alloys usually contain chromium (Cr), cobalt (Co), nickel (Ni), molybdenum (Mo) and other trace materials. Nickel-chromium alloys contain nickel, chromium, molybdenum and traces of other elements. Dental stainless steel contains chromium, nickel, carbon (C), iron (Fe) and other trace materials. Stainless steel generally contains less than 15% nickel<sup>(8)</sup>.

Vilaplana *et al.*<sup>(6)</sup> summarized that stainless steel alloys (Cr 18%, Ni 8%, and Fe 73.5%) previously used widely have been replaced by alloys of the compositions such as Co 60%, Cr 30%, Mn 5%, Si 2% or Ni 70%, Cr 16%, Al 2%, Be 0.5%. Titanium and titanium alloys, including alloys with nickel, have also come into use in implantology, orthodontics and endodontics during the last 20 years.

### **2.2. The Use of Nickel-Containing Alloys in Dentistry**

Removable partial dentures (RPD's) of cobalt-chromium alloys have been in clinical service since 1929. Traditionally, cast metal prosthetic devices were made of gold alloys due to their ductility, low corrosion and durability in the oral environment. Before 1970, the non-gold alloys used were base metal alloys that contained cobalt, chromium and nickel. These alloys are still being used in the construction of removable partial dentures as an alternative to gold alloys for economical reasons and because of their low density compared to traditional gold alloys. Table 1 shows the elements and their weight percentage for some nickel and chromium containing base metal alloys.

High gold content alloys do not have as high strength and elastic modulus as base metal alloys, although the differences for these physical properties are not so great for base

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**Table 1: Examples of elemental composition (weight percent) of some base metal alloys**

Alloy	Elements										
	Cr	Co	Ni	Fe	Mo	W	Mn	Si	C	Be	Al
Co-Cr	30	62.5	-	1	5	-	0.5	0.5	0.3	-	-
Ni-Cr	17	-	67	-	5	-	5	0.5	Trace	-	-
Co-Cr-Ni	26	54	14	0.1	4	-	0.8	0.6	0.2	-	-
Fe-Cr	24	6	4	63	2.5	-	-	-	Trace	-	-

[from Morris, HF; Asgar K; Rowe AP<sup>(9)</sup>] Cr, chromium; Co, cobalt; Ni, nickel; Fe, iron; Mo, molybdenum; W, tungsten; Mn, manganese; Si, silicon; C, carbon; Be, beryllium; Al, aluminum

metal alloys over medium gold content alloys<sup>(10)</sup>.

**2.3. Use of Nickel-Containing Alloys in the Contemporary Clinical Practice of Dentistry**

Two major types of alloys have been used in removable prosthodontics. These are the hard gold alloys, and chromium alloys. The hard gold alloys usually contain 62 to 72 weight percent gold with additions of silver, copper, palladium and platinum. The cobalt-chromium (Co-Cr) alloys commonly contain about 60% cobalt and 25% chromium, with additions of molybdenum, iron, silicon, tungsten, nickel and carbon<sup>(11)</sup>.

Three general groups of alloys presently used with porcelain are the high noble, noble and predominantly base metal alloys. Palladium based alloys are commonly used with porcelain as they possess the characteristics of good castability, compatibility with porcelain, good

ability for porcelain bonding, and sag resistance during porcelain firing, but they tend to tarnish. As the palladium price is currently high, interest is returning to alloys such as high noble gold alloys and nickel-chromium alloys. Table 2 shows the elemental composition of several base metal nickel-chromium alloys for small dental castings.

Nickel and chromium alloys are used for a variety of applications including removable partial denture frameworks, components of appliances in orthodontics and pediatric dentistry and crowns and fixed bridges. Nickel-titanium (Ni-Ti) alloys are used in orthodontic applications since they have a lower modulus of elasticity than stainless steel, and super elasticity<sup>(14)</sup>. The composition of such alloys is generally 50% nickel and 50% titanium, but may be 55% nickel and 45% titanium<sup>(15)</sup>. Nickel increases the ductility of alloys<sup>(2)</sup>. However, Mohammed and Clark<sup>(16)</sup> reported that small amounts of titanium added to alloys decreases

**Table 2: Elemental composition (%) of some examples of base metal nickel-chromium alloys for small dental castings**

Element	Alloys									
	A	B	C	D	E	F	G	H	I	J
Nickel	80.75	79.67	78.51	68.96	80.86	68.75	63.36	67.21	71.20	77.36
Chromium	12.58	13.24	19.47	16.54	11.93	19.57	20.95	12.88	15.89	12.27
Iron	0.34	0.11	0.43	0.37	0.20	0.38	1.73	2.40	0.10	0.14
Aluminum	3.42	3.87	0.21	4.15	2.95	-	0.16	-	3.31	2.76
Molybdenum	1.53	1.52	-	5.10	1.87	4.22	8.40	6.80	4.50	4.84
Silicon	0.29	0.30	1.10	0.83	0.18	2.72	< 1	< 1	< 1	< 1
Beryllium	0.57	0.65	-	-	1.55	-	-	-	0.57	1.67
Copper	0.15	-	-	-	0.13	1.54	-	-	-	-
Manganese	0.13	0.12	-	3.05	0.14	1.24	< 1	< 1	4.28	-
Cobalt	-	-	-	0.42	-	-	-	< 1	-	< 1
Tin	-	-	-	-	-	1.25	-	-	-	-
Others							Nb 4.1, Ti < 1	Ga 7.0		Ti < 1

(Alloys A to F from<sup>(12)</sup>, Alloys G to J from<sup>(13)</sup>) Nb-niobium, Ti-titanium, Ga-gallium

ductility, but increases yield strength in cobalt-chromium-nickel-titanium systems.

Four common types of appliances are used in orthodontics: molar bands, brackets, arch wires and face bows. In corrosion tests, the least amount of nickel and chromium was released from arch wires. These arch wires were composed of an alloy containing 54% nickel and 46% titanium. Titanium is highly corrosion resistant and alloying with nickel results in a corrosion resistant alloy<sup>(17)</sup>.

Nickel and cobalt-based metal alloys, including those designed for use in association with porcelain have desirable relatively high fusion and casting temperatures. Minor composition changes to such base metal alloys can lead to significant beneficial changes in their ease of casting, bonding, hardness and strength properties. The sag of alloys at elevated temperatures can greatly affect the fit of castings. Lugassy and Kumamoto<sup>(18)</sup> found lower sag (high temperature creep) values for nickel-chromium (Ni-Cr) alloys than a gold alloy. Huget and co-workers<sup>(19)</sup> found high strength and rigidity for Ni-Cr alloys, but also reported problems with the fit and low bond strength to porcelain.

In recent years the use of nickel-titanium alloys has become widespread in endodontics for instrumentation of the root canals<sup>(14)</sup> and in orthodontics. Typical orthodontic "nitinol" shape memory alloys are approximately 50% nickel and 50% titanium. The localized potentiodynamic corrosion resistance of an alloy such as this in artificial saliva and saline has been shown to be slightly lower than that for 316 stainless steel<sup>(20)</sup>. Sarkar *et al.*<sup>(21)</sup> also showed that in corrosion tests in 1% sodium chloride (slightly higher than saliva) solution that the nickel component of the alloys may have a selectively higher dissolution rate from the corrosion pit.

### **3. ADVERSE EFFECTS OF MATERIALS USED IN DENTISTRY**

#### **3.1. Potential Adverse Effects**

Dental materials are a heterogeneous group of

materials. Distinctly different types of adverse effects may occur with dental materials: physical, related to improper design or placement of the appliance; and biological effects associated with agents leached from materials or released as a result of processes such as biodegradation and corrosion<sup>(22)</sup>. Some of the chemicals used in dental products have known toxic, carcinogenic and allergenic properties.

#### **3.2. Physical Effects**

Physical effects include local damage, such as a mucosal inflammatory reaction to an over-extended denture base or to a subgingival overhang on a restoration. Such effects are readily dealt with clinically and provided the necessary adjustments are made, no permanent damage occurs. These effects are independent of the type of material used. Furthermore, tissue reactions to uncorrected poor restoration form may also be misinterpreted to be a result of a toxic response to the restorative material.

#### **3.3. Potential Biological Effects**

Toxic reactions, including carcinogenic reactions, are dose dependent. The effects will primarily depend on the nature of the metal ions released from the dental material. Toxic effects may be initiated by a one time large dose above threshold or by repeated small doses, provided that the doses are cumulative to above threshold levels. Although the dose effect is indisputable in toxic reactions, it is important to point out that the thresholds for reactions vary from endpoint to endpoint and to some extent from individual to individual.

Since dental materials are largely insoluble, toxic reactions are unlikely as a result of a one time exposure as for dental instruments, simply because the release rates are generally slow, resulting in a dose below threshold. However, repeated small dose exposures, such as with orthodontic appliances, may potentially cause toxic reactions if above the threshold or if accumulated to above threshold. However, these again are unlikely to be associated with materials used in dentistry, and are extremely rare based on current literature<sup>(23)</sup>.

*Allergic responses* are mediated through the immune system. In a sensitized individual, they can be initiated by small amounts of the allergen. A number of allergens are found in dental materials, notably eugenol, mercury, nickel, chromium, cobalt, components of resin-based materials and a host of other chemical agents. Individuals are first sensitized by an allergen or allergens. The majority of dental allergies comprise hypersensitivity reactions, cell-mediated by the T-lymphocytes (Type IV), which is also true for dermal nickel exposure. The other common type of allergy is the "immediate hypersensitivity" (Type I), humorally mediated by IgE.

Although many common allergens are found in dental materials, few allergic reactions are associated with the use of dental materials. This may be because the mucous membranes are less reactive than skin in this context or that the material released may not be in a bioactive form (for example as metal ions), and in a concentration above the threshold level to elicit reaction (oral dose of 1.2-2.5 mg Ni/day)<sup>(24)</sup>. The intraoral use of materials that contain compounds to which the individual is sensitized, rarely causes allergic reactions. In fact, the use of intraoral appliances containing an allergen may be advantageous by inducing immunological tolerance<sup>(23, 25-28)</sup>.

Limited data appear to be available on the incidence of biological effects to patients from materials used in dentistry. Some estimates have been made based on limited studies in general dental practice. They indicated an overall frequency of adverse effects of 1:700 to 1:20,000<sup>(29, 30)</sup>. The incidence is highly dependent, however, on the type of practice and the materials employed<sup>(31, 32)</sup>. Hensten-Pettersen also noted that antigenic contacts to nickel and chromium may induce tolerance rather than sensitization<sup>(32)</sup>.

### **3.4. Risk Groups**

As happens in many other fields, it is difficult to evaluate the risks associated with low dose exposure to components in dental materials that are potentially toxic and carcinogenic. The low, and frequently miniscule, amounts of leachable components often lead to inconclusive findings.

Risk groups with higher exposures are, therefore, sought. The criterion for establishing such a group is that individuals can be identified that have been exposed to a higher dose than the general public, *e.g.*, by accidental exposure to the toxic agent in question or through occupational exposure. Adverse reactions in these individuals are then used as a basis for evaluation of possible signs and symptoms that might be present in those exposed to low doses of the toxic agent.

Dentists and dental assistants, and for certain materials also dental technicians<sup>(33, 34)</sup>, clearly can be identified as risk groups for occupational exposures. They work with various materials in their most volatile stage prior to setting, and after they are set, the materials are subjected to grinding, adjustments and polishing. Gloves may limit direct hand contact for dental personnel, although some inadvertent contacts may still occur.

In addition, dental personnel may receive another form of exposure during their own dental treatment, in common with most individuals. A number of studies in many countries have focused on disease patterns and cause of death of dentists and dental health personnel, especially related to the exposure to mercury. Adverse health effects are more likely to occur in situations of extremely poor mercury hygiene in the dental office. If the defined risk group exhibits no or minimal signs and symptoms of disease, it is unlikely that a low dose exposure as experienced by dental patients will result in adverse toxic effects. Exposures for a patient already sensitized to that ion might, however, be different.

Although there is potential to both dental personnel and patients for adverse biological reactions to the considerable range of materials used in dentistry (*e.g.*, mercury (Hg), nickel, cobalt, chromium and gold (Au)), the documented occupational cases are extremely few. For patients, toxic reactions are much less likely because of the low dose of leachable components from dental materials. Allergic reactions are also rare.

**3.5. Release of Nickel and Other Metallic Ions**

The ability of a metal to act as a potential allergen appears to be related to its pattern and mode of corrosion. It is the release of the constituent ions, and not necessarily the percent content of the metal, that determines the bioavailability and toxicity of an alloy. The tendency to corrode depends on factors such as the composition of the alloy, conditions during its production such as heat treatments, and its microstructure, as well as the conditions in the oral environment such as pH<sup>(35)</sup>. In general, element release from alloys is generally less for single-phase alloys, but element release data should be determined, as alloys of similar composition may have different corrosion behaviors<sup>(23)</sup>.

Metal ions also may be released by abrasion, as in chewing, and corrosion and dissolved in saliva. Increased pH and temperature results in an increased release of metal ions from stainless steel, as seen in studies *in vitro*, through chemical and electrolytic corrosion actions between dental prostheses<sup>(36)</sup>. The abrasion and corrosion rates of intraoral appliances are considered to be low during service<sup>(22)</sup>, resulting in low amounts of reactive metal ions to exert toxicity. *In vitro* corrosion studies that monitor the release rate for metal ions such as nickel are of greater value than those that measure loss of mass.

Barrett *et al.*, showed that nickel ion release from orthodontic appliances of both nickel titanium and stainless steel, stored *in vitro* in artificial saliva increases over the first week then diminishes with subsequent weeks<sup>(37)</sup>. Studies have showed that although orthodontic appliances corrode in the "as received" condition they release below the average dietary intake of nickel ions<sup>(38)</sup>, since the *in vivo* collected blood samples from 31 subjects under orthodontic treatment did not accumulate measurable concentrations of nickel in their blood during their initial course of orthodontic therapy when compared to their pre-orthodontic blood samples<sup>(39)</sup>.

There is evidence that metal ions are constantly being released from prostheses, albeit usually in

small amounts. It is important to determine the concentration of bio-active metal ions that could cause toxicity. With this important information the potential exposure may be determined to assess the potential risk which depends on dose-response and toxicity of the ion as well as the magnitude of the exposure.

The release of nickel ions has been investigated in various conditions. Park and Shearer measured the *in vitro* amounts of nickel and chromium released from simulated orthodontic appliances incubated in 0.05% sodium chloride solution. They found that the average daily release of nickel was 40 µg, which is less than the daily nickel intake consumed by Americans<sup>(38)</sup>. Gjerdet and Hero found that certain heat treatments of orthodontic arch-wires could markedly increase the *in vitro* release of metal ions 15 to 60 times over what was released from "as-received" wires<sup>(40)</sup>.

Kerosuo *et al.*<sup>(41)</sup> also applied dynamic test conditions to simulated metal appliances immersed in 0.9% sodium chloride solution *in vitro*. There was significantly higher cumulative release of nickel of 44 (s.d. 23) micrograms per appliance for the dynamic tested group compared to 17 (s.d. 3) micrograms per appliance for the static group.

Gjerdet *et al.*<sup>(42)</sup> conducted *in vivo* sampling of saliva from patients wearing fixed orthodontics appliances. For the initial samples, there was a significant increase in the concentration and mass of nickel detected as compared to the samples with no appliances present. After the first three weeks, however, there were no significant differences detected. It seems that there is an initial release of ions which diminishes after three weeks. Kerosuo *et al.*<sup>(43)</sup> also looked at saliva from patients with different types of appliances at four times over the first month after insertion. The results showed no significant difference in the concentration of nickel and chromium compared to the "no-appliance" group.

Newman *et al.*<sup>(44)</sup> evaluated the release of nickel from nickel-chromium alloys in autoclaved human saliva and found that the concentration of nickel rose from  $2 \times 10^{-7}$  M to  $2 \times 10^{-4}$  M over a seven-day period *in vitro*.

Wataha and Lockwood<sup>(45)</sup> measured the elemental release from dental casting alloys into cell culture medium over 10 months. The total mass released from the Ni-Cr alloy was among the lowest at about 6 µg/cm<sup>2</sup>. They attributed the lower release rate to be influenced by the pH 7.2 extraction medium. The total mass loss for pure nickel was 150 µg/cm<sup>2</sup>, as compared to a study by Geis-Gerstorfer and Passler<sup>(46)</sup> who found nickel release of 3300 µg/cm<sup>2</sup> over 35 days using extraction media with pH 2.3. This indicates that alloys can be very sensitive to routes of exposure in different environments, as with differing pH of the immersing extraction media. So differing corrosive influences of fluids bathing an implant and the clearance of corrosion products could have a different impact on an alloy compared to the same alloy composition being placed intra-orally, for example as a partial denture framework.

It should be noted that *in vivo* the nickel ions released from intra-oral dental materials and appliances generally will be swallowed and may not accumulate. Therefore, the concentration *in vivo* may be found to be low. Furthermore, the amount of nickel released is significantly less than that consumed orally *via* dietary intake<sup>(38)</sup>.

Mucosal allergy to metals may be rare for several reasons: a) saliva is constantly washing away potential allergens; b) the vascularity of the buccal mucosa allows for rapid dispersion of potential allergens; c) particulate metals may have a suppressive effect on chemotaxis, phagocytosis and immune response in some systems, and finally; d) the paucity of stratum corneum on mucous membranes may reduce the availability of carrier proteins to combine with metallic haptens to form complete antigens<sup>(36)</sup>. Nevertheless, biopsies of gingival tissues adjacent to metal dental restorations do show evidence in the tissues of at least one of the metal constituents of the alloy used for the restoration such as silver, gold, copper and palladium, compared to biopsies from control sites with no adjacent restoration<sup>(47)</sup>. Grimsdottir *et al.*<sup>(17)</sup> found that the release of nickel ions is not proportional to the nickel content of orthodontic wires, but seemed to be related to the total composition of the alloy and the method of construction of the appliance. The following factors would tend to decrease

the corrosion resistance of metallic materials in clinical handling: heating during soldering, welding, or extensive shaping and notching with pliers. Some mouthrinses may increase the deterioration of materials, especially for silver-soldered joints in orthodontic appliances<sup>(48)</sup>.

Sastri *et al.*<sup>(49)</sup> determined the corrosion rate of the two base metal alloys in chloride media. They found that Ni-Cr alloys have higher corrosion rates than Co-Cr alloys. Ewers and Thornber<sup>(50)</sup> showed that more than 20% of chromium content in Ni-Cr alloys decreased greatly the corrosion resistance of the alloys. Higher *in vitro* corrosion rates were found in Ni-Cr and Co-Cr alloys than in dental gold<sup>(51)</sup>.

### **3.6. The Nature, Occurrence and Importance of the Biological Effects**

Wataha and Hanks<sup>(52)</sup> stated that the route of exposure of metals to the body is important to their biological effects. The most damaging route of exposure for metal ions is intravenous exposure, as may occur during dialysis or as a contaminant in other administered drugs. The least toxic route of exposure is generally by oral ingestion; therefore the toxic concentration threshold of a metal can be several hundred times greater by an oral exposure than by an intravenous exposure. This concept is of fundamental importance to the knowledge and understanding of dental casting alloys since any dissolved metals are generally exposed to the body through the oral route. This is certainly true for nickel ions, and also gastrointestinal absorption rates for water soluble nickel compounds vary depending on the fasting state.

Skin exposure may occur in the handling of dental materials, however it seems that the skin exposure to the soluble metal salts leads to reactions somewhere between the extremes of intravenous and the oral route exposure. Schmalz<sup>(53)</sup> reported that although 20% of a group of patients reacted positive to soluble metal salts in patch testing, it was found that the metal corresponding to the metal salt tested was not a component of existing intraoral alloys for half of the patients.

**4. REACTIONS TO NICKEL-CONTAINING ALLOYS**

Nickel is one of the most common causes of allergic dermatitis, especially in women, and is higher among those with pierced skin<sup>(54-57)</sup>. For comparison, it should be noted that there is also an incidence of allergies and positive patch tests to compounds of other metals such as gold and palladium that may be used in dentistry. While allergic contact dermatitis to gold is rare considering the extensive use of this metal, studies have showed that gold allergy may be found to be significantly more common in individuals with dental gold<sup>(58, 59)</sup>. Also there has been an increase in the number of reports of palladium allergy, paralleling the increased use of this metal. In Austria, for palladium a sensitization rate of 8.3% has been found in unselected eczema patients<sup>(60)</sup>. There is a possible relationship between nickel, gold and palladium allergy since they frequently occur simultaneously in dental subjects<sup>(61)</sup>. Studies in the past investigated the symptoms of nickel hypersensitivity, finding higher nickel allergy in females and also in females suffering chronic fatigue syndrome<sup>(62)</sup>. It was also necessary to determine if a relationship exists between a patient with positive nickel sensitivity and the clinical response to dental alloys containing nickel. In a study using 10 nickel sensitive individuals, fixed dental prostheses containing 66% nickel were used. In follow-up examinations over 12 to 40 months, no adverse reactions were detected<sup>(7, 27)</sup>. While this is encouraging, it remains unclear if there is any correlation of oral exposure and nickel sensitivity.

To give an idea of regulatory guidelines set for levels of dermal nickel exposure, the European Council Directive 94/27/EC states that nickel and its compounds may not be used during epithelialization of the wound caused by piercing the ears if the nickel in the post exceeds 0.05% by mass. Furthermore, objects in direct and prolonged contact with the skin, such as necklaces, bracelets, rings, buttons etc., must release less than 0.5 µg Ni/cm<sup>2</sup>/week, as measured in synthetic sweat.

Dermatologists and allergists have carried out patch tests routinely to differentiate between

allergic and irritant contact dermatitis and identify the responsible allergens.

Patch testing may be carried out using a specimen of the metal(s) under test, or use a salt of that metal, for example nickel sulphate. The bioavailability of the ions from the metal compared to the salt are very different, and should be considered in the interpretation of the patch test results. Furthermore, patch testing in itself may induce sensitization.

There have been several studies on the population levels of sensitivity to nickel. Amongst them, was an unusually high result from Blanco-Dalmau *et al.*<sup>(62)</sup>, in a study carried out in Puerto Rico. They found that 29% of the population studied showed positive patch test reactions to nickel. There were striking differences found in hypersensitivity by gender: They found from the patch test results that 32% of women tested showed a positive reaction to nickel, compared to 21% of men tested. Schaffran *et al.*<sup>(63)</sup> patch-tested 136 asymptomatic individuals and found positive nickel reactions in 17% of those with no gold dental restorations, and 25% for those individuals with gold restorations.

Prystowsky *et al.*<sup>(64)</sup> found that 9% of females were nickel-sensitive relative to 0.9% of males. A significant correlation was found between females with pierced ears, earlobe rash and jewelry rash. Similarly, Peltonen *et al.* found an incidence of nickel sensitivity of 8% for females and 0.8% for males<sup>(65)</sup>.

Moffa *et al.*<sup>(66, 67)</sup> affixed for 96-hours a sample of a dental nickel-chromium alloy (Ultratek) to the forearm of 10 patients that were nickel sensitive. Erythema, papules or vesicles were seen for eight of the patients. This test was followed by placing, for 48-hours, a removable appliance holding discs of the nickel-chromium alloy and a control gold alloy (Jelenko O) into the mouths of these 10 patients and a control group of 10 non-nickel sensitive patients. Erythema and a burning sensation was experienced at the intra-oral contact site by one of the most sensitive patients, and three of the 10 nickel sensitive subjects showed exacerbations of the dermal reactions at their sites patch-tested three weeks earlier. There

were no reactions for the control subjects for either the nickel or gold alloys. To further determine if there was any correlation, Moffa *et al.*<sup>(68)</sup> conducted a retrospective epidemiological study involving 443 patients, about a third of whom possessed fixed prostheses of nickel-chromium. Testing showed that 90% of the nickel sensitive patients were female with pierced ears, and females aged 25-44 showed 4.8 times higher nickel sensitivity than all other age groups. When they examined the incidence of nickel sensitivity in patients with intra-oral exposure to dental alloys, 4% of female patients with a history of intra-oral exposure were also sensitive to nickel, compared to 6% of female patients with no oral exposure to nickel. Statistical analysis showed no significant difference between the test and control groups. Similar results were found with the male study participants. They could not find any correlation between the intraoral presence of nickel-containing dental alloys and increased nickel sensitivity. The slightly lower incidence in the oral exposed group even supports the possible induction of immunological tolerance to nickel and chromium<sup>(25)</sup>.

Another study by Kerosuo *et al.*<sup>(26)</sup> using 5% nickel sulphate found overall that 19% of subjects studied showed positive patch test reactions to nickel. The incidence of nickel allergy in girls (30%) was significantly more than in boys (3%), and also significantly different between subjects with pierced ears (31%) and those with no pierced ears (2%). They also found a significant relationship between a history of allergy to jewelry and nickel hypersensitivity. Their results showed that 81% of the subjects who had a history of allergy to jewelry were patch-test positive to nickel while the rest were not. Orthodontic treatment did not seem to adversely affect the prevalence of nickel sensitization. None of the girls who were treated with fixed orthodontic appliances before ear piercing showed hypersensitivity to nickel. However, 35% of the girls who had experienced ear piercing before the commencement of orthodontic treatment were sensitized to nickel. The results suggest that orthodontic treatment does not increase the risk of nickel hypersensitivity. Conversely, the data suggests that treatment with nickel-containing metallic orthodontic appliances before

sensitization to nickel (ear piercing) may have reduced the frequency of nickel hypersensitivity.

Indeed, a retrospective questionnaire survey<sup>(69)</sup> of 2176 patients attending nine patch test clinics in Europe revealed that ear piercing strongly favored allergic contact dermatitis, except that patients who had prior oral contacts with nickel-releasing appliances like dental braces, showed a reduced frequency of nickel hypersensitivity. The authors discussed animal studies whereby oral administration of T-dependent antigens before sensitization effectively induces systemic immune unresponsiveness. Such "oral tolerance" is persistent, dose-dependent, antigen-specific and presumably T suppressor cell-mediated.

Furthermore, a study using 39 subjects found that frequent sublingual applications of weak nickel sulfate solutions over periods of 16 months on average had hyposensitized patients with nickel allergy<sup>(70)</sup>.

Staerkjaer and Menne<sup>(71)</sup> consecutively collected questionnaires from 1085 girls in active orthodontic treatment or retention. They found no allergic reactions to nickel on the oral mucosa, and they concluded that their findings indicated that nickel sensitive persons are not at greater risk of developing discomfort in the oral cavity when wearing an intraoral orthodontic appliance.

Patients with allergic contact dermatitis to a range of dental alloys, not necessarily containing nickel, may complain or show signs of a metallic taste in the mouth, if not loss of taste, burning sensations, numbness, gingival tenderness, erythema, mucosal sloughing, facial swelling, hyper- or hyposialorrhea, cheilitis, erosions and glossitis. Itching is infrequent<sup>(36, 38, 72, 73)</sup>.

The development of dermal sensitization could be influenced by factors such as skin injury, increased environmental temperatures, mechanical irritation, duration of exposure and increased intensity, particularly for dermal exposures. Also, genetic factors may be found to play a role in the response of the immune system. It is unclear, however, how these factors may influence elicitation reactions from oral exposure to nickel-containing alloys in already sensitized individuals.

## 5. TOXIC REACTIONS TO NICKEL-CONTAINING DENTAL ALLOYS

Toxicology includes the study of physical and chemical factors involved in the material-tissue interactions and these responses<sup>(2)</sup>. In general, the toxicity of metal salts is related to their water solubility, but water solubility in itself does not imply toxicity. Lipid solubility, usually *via* an organic-metal complex, may allow a metal to gain access to cells through the lipid membrane and contribute to the toxic effects. For nickel accumulation it seems that calcium channel transport processes are involved for soluble nickel compounds<sup>(74)</sup>, while phagocytosis plays a role in cellular uptake of water-insoluble nickel compounds<sup>(88)</sup>.

To investigate the toxicity of a material, preliminary testing involves both *in vivo* and *in vitro* tests. Methodological problems occur when determining the profile of the toxicity of a material since alloys, unlike drugs, are intended to have a minimum solubility. Therefore, it is also important to understand the effect of different environments on the chemical and other characteristics of a material when determining its potential toxic properties<sup>(2)</sup>.

The cytotoxic effect could vary according to the toxicity of the primary irritant, concentration, exposure time, and route of exposure. When a primary irritant is present for sufficient time at an adequate concentration, a cytotoxic effect can occur<sup>(75)</sup>.

Woody *et al.*<sup>(76)</sup> investigated the cytotoxicity of dental casting alloys using a Fe-Cr alloy and three Ni-Cr alloys, comparing cast discs with the same alloys cast, then milled to powder, and pressed into tablets. They found that Ni-Cr tablet specimens showed cell alteration and manifest zones of cell lysis, whereas no cellular changes were found with Fe-Cr alloys. There were stronger cytotoxic effects with powders than bulk alloys. However, Kawata *et al.*<sup>(77)</sup> showed that additions of nickel and chromium to Pd-Co weakly cytotoxic alloys decreased the cytotoxicity.

Wataha *et al.*<sup>(78)</sup> stated that nickel ions in solution have caused the expression of inflammatory mediators from keratinocytes,

monocytes and endothelial cells. Their *in vitro* results, however, showed less harmful effects from pure nickel, titanium, and the biomedical alloys 18-8 stainless steel and Rexillium III, although a Ni-Ti alloy showed a potential risk of promoting inflammatory response in soft tissues by activating monocytes. Wataha *et al.*<sup>(79)</sup> also assessed the longer-term effects of ions of silver, copper, mercury, and nickel - four metal ions known to be released from dental alloys - on THP-1 human monocytes exposed to the metal ions for up to 4 weeks. Cu(2+) and Ni(2+) increased the nonviable component as a function of metal concentration. These effects were cumulative over the 4 weeks only for Ni(2+). All metal ions caused a significant reduction in cellular proliferation. The results of the current study indicate that metal ions released from metallic biomaterials may have adverse biological effects at concentrations lower than previously reported.

Hensten-Pettersen and Jacobsen<sup>(80)</sup> determined the effect on human epithelial cells of non-precious dental casting alloys containing up to 84% nickel. They found that the concentration of nickel liberated from the metals did not reach cytotoxic levels. Grimsdottir *et al.*<sup>(75)</sup> found from an investigation using mouse fibroblasts that nickel causes less toxic effect than copper. Orthodontic arch wires which contained 54% nickel caused no cytotoxic effect, and multi-component orthodontic devices had a very low cytotoxic effect possibly due to the small amount of silver and copper brazed solder. Similarly, Jia *et al.*<sup>(81)</sup> determined that the maximum amount of nickel released from orthodontic arch wires was 700 times lower than the amount necessary to elicit cytotoxic reaction in human peripheral blood mononuclear cell culture. Nickel is not very toxic when compared to other heavy metals<sup>(75)</sup>, and therefore requires more release of nickel ions to exert a toxic effect.

## 6. CARCINOGENIC REACTIONS TO NICKEL AND NICKEL-CONTAINING DENTAL ALLOYS

Nickel alloys are not currently classified as carcinogens in the European Union (EU), but will be considered under the EU Preparations

Directive. Elemental nickel and nickel metal are classified, however, as Category 3 carcinogens in the EU. Category 3 contains substances that potentially may cause carcinogenic effects but there is not sufficient information to make an assessment. Laboratory investigations into the carcinogenicity of dental and orthopedic alloys were undertaken decades ago, when it was noticed that workers in nickel and chromate refining had higher risks of nasal and lung tumors<sup>(82)</sup>. This suggests that there may be risks to industrial and laboratory personnel exposed to forms of nickel in dust or vapors during refining or casting and grinding procedures<sup>(83)</sup>. Nickel metal and nickel alloy powders are not used, however, for dental casting and the amounts of dental nickel alloy ingots that are melted are much less. Furthermore, the grinding to shape and polishing of castings in the dental laboratory should be accomplished using ducted air evacuation at the workbench so exposure to nickel-containing dusts should be minimal.

Epidemiological studies of the mortality experience of nickel refinery workers have been conducted<sup>(84, 85)</sup>. Cause and effect conclusions in these studies are complex since workers in these industries are exposed to many different substances in addition to nickel, some of which may have evidence of carcinogenicity. Workers in this field have not been able to show an association between working at those particular sites and increased incidence of respiratory cancer<sup>(84, 85)</sup>. The only route of exposure consistently associated with increased risk of cancer- respiratory tumors (nasal and pulmonary), has been with inhalation of high amounts of certain nickel compounds. However, Lewis and Sunderland note that there have not been many reports in humans of the development of tumors close to orthopedic stainless steel or superalloy implants, despite the very corrosive location of the implants<sup>(86)</sup>.

### **6.1. Mechanistic Data for Nickel Compounds**

The mechanism by which certain nickel compounds may induce respiratory tumors is not yet well understood. Nickel compounds, while otherwise only weakly mutagenic, have been shown *in vitro* to increase ultra violet (UV)-induced cytotoxicity and mutagenicity and

disrupt DNA-protein interactions involved in DNA damage recognition probably by displacement of metal ions<sup>(87)</sup>, thus interfering with repair of UV-induced DNA lesions<sup>(88)</sup>. Nickel is thought to interfere with the binding of a protein to UV-damaged DNA, and the repair of DNA is involved in prevention of carcinogenesis<sup>(89)</sup>.

Using human kidney epithelial cells *in vitro*, Mollerup *et al.*<sup>(90)</sup> suggested that nickel carcinogenesis may involve changes in sets of genes important in normal growth regulation. Costa writes that in tissue culture studies carcinogenic, water-insoluble particulate nickel compounds are phagocytized by cells; and the particles undergo dissolution inside the cell, releasing nickel ions that may damage chromatin<sup>(91)</sup>. Werfel *et al.*, observed DNA damage such as single strand breakage in lymphocytes of (human) welders occupationally exposed to chromium and nickel<sup>(92)</sup>.

The promotion of oxidative damage seems to take the leading role in explaining mechanisms of carcinogenicity and acute toxicity of metals like nickel, and chromium and their compounds as observed *in vitro* and in metal-induced tumors<sup>(93)</sup>. It has been suggested that the carcinogenesis of nickel (II) is mainly due to the effect of free radicals<sup>(94)</sup>, binding of Ni(II) to nuclear proteins<sup>(95)</sup>, and that any toxic reactions are not simply aroused by nickel itself but by induced reactive oxygen species in intact mammalian cells<sup>(96)</sup> at different sites specific to DNA damage<sup>(97)</sup>. Martin Mateo *et al.*, using erythrocytes *in vitro*, suggested that soluble nickel salts, by generating highly reactive oxygenated species, is seen to alter and inhibit catalase activity in colon cancer<sup>(98)</sup>. In contrast, soluble nickel salts did not induce tumor in rats' testes and was also a weaker inhibitor of 8-oxo-dGTPase than Cd II in both cell free systems and cultured cells<sup>(99)</sup>.

The various nickel compounds exert differing toxicities (including carcinogenicity) depending on their different physical and chemical properties. For this reason it is not possible to directly apply findings of a particular study to other nickel compounds or to nickel itself. While the ultimate mechanism is still unknown, it has been shown in animals that the respiratory carcinogenic potential of nickel compounds can

vary depending on solubility, cellular uptake, and clearance<sup>(100)</sup>. These factors ultimately determine the nickel ion bio-availability at target nuclear sites needed to induce tumors. Certain types of nickel compounds tend to be carcinogenic depending on whether the nickel compound is water-soluble or not. *In vivo* investigations show that water-insoluble nickel compounds can enter cells through phagocytosis and are then more likely to be carcinogenic<sup>(101, 102)</sup>. The highly water-soluble salts of nickel including nickel chloride will not easily enter cells and may not be carcinogenic<sup>(101)</sup>. It has been suggested from *in vivo* investigation that magnesium is able to protect against nickel-induced cytotoxicity and genotoxicity by reducing either intracellular nickel concentration or reactive oxygen formation<sup>(103, 104)</sup>.

Dunnick *et al.*<sup>(100)</sup> subjected rats and mice to inhale different nickel compounds for 6 hour/day, 5 days/week for 2-years. Results showed that nickel subsulfide and nickel oxide caused an increase in the incidence of alveolar/bronchiolar lung tumors and adrenal medulla neoplasms in rats. Nickel sulfate hexahydrate had none of the above effects.

### **6.2. Mechanistic Data for Nickel Alloys**

Nickel-titanium shape memory alloys (NiTiSMA) (approximately 50% titanium/50% nickel) have been shown to have good biocompatibility, no obvious tissue reaction, carcinogenicity or erosion of implants, either experimentally or clinically<sup>(105, 106)</sup>. This is evidence of the release of nickel ion being more important than the content of nickel in the alloy. However, a cell-culture study suggested that NiTiSMA may be able to induce transformation of hamster kidney cells, while NiTiSMA particles encapsulated by titanium oxide did not<sup>(107)</sup>. Transformation of cells is a negative finding in cell culture studies, but it may not necessarily indicate carcinogenicity.

Reports related to nickel carcinogenesis have been mainly concerned with inhalation exposure to certain nickel compounds present in particular refining operations and the incidence of lung and nasal cancer was also related to cigarette smoking. In contrast, no reports were found concerning nickel carcinogenesis associated with

exposure (inhalation or dermal) to metallic nickel or nickel-containing alloys. Similarly, there have been no reports of carcinogenicity associated with the intra-oral use of dental alloys, which suggests that the corrosion of nickel-containing alloys in oral conditions may not fulfill the conditions for nickel ions, let alone other metal ions (*i.e.*, chromium) to exhibit any carcinogenic effects. Furthermore, it has not been yet been fully determined what is the particular form in which the metals are present in the mouth or may be formed *in vivo* from the alloys present (*e.g.*, either massive alloys, wear particle alloy, or soluble ions).

### **7. THE RISK OF USING NICKEL-CONTAINING ALLOYS IN DENTISTRY**

*In vivo* investigations of prosthodontic alloys show the presence of an acquired pellicle or layer of bacterial accumulation that may modify corrosion behavior. Siegrist *et al.*<sup>(108)</sup> showed that the amount of early bacterial deposits on different metal alloys used in fixed bridges (with a removable facing to study the quality and quantity of build-up) seem to be related to their surface roughness, rather than the alloy composition. Smooth surfaces were noted to have sparser deposits relative to rough surfaces. Using transmission electron microscopy, Hannig<sup>(109)</sup> found that the built-up deposits were qualitatively similar on different alloys. Salivary glycoprotein films develop on exposed oral surfaces<sup>(110)</sup>, which apparently masks any difference among materials, with regard to surface properties and biocompatibility. However, there was a difference in the thickness of the pellicle built-up based on location, for example with buccal surfaces collecting thicker layers than lingual surfaces<sup>(111)</sup>, which may influence bacterial plaque formation and removal, and, in turn, any plaque induced inflammation in the adjacent soft tissues.

While there is a relatively high frequency of cutaneous nickel allergy, there are few documented case reports of oral allergic reactions in the dental literature, probably because it has been found that five to 12 times higher concentrations of the allergen were needed to elicit reactions in the oral mucosa than in the skin<sup>(112)</sup>. So, a person with a positive

skin test to nickel and whom experiences allergic skin reactions to nickel may be able to tolerate nickel-containing dental materials and prostheses<sup>(113)</sup>. Also, Spiechowicz *et al.*<sup>(27)</sup> followed 16 patients with long standing histories of skin reactions to nickel. Observations at intervals over 15-years, by the examining dentists found that none of these patients showed any mucosal or systemic reactions, or any exacerbation of the skin reactions. Furthermore, after 8-15 years of exposure to their fixed dental restorations with 66% nickel, skin lesions that were previously evident disappeared for over 80% of these individuals. It seems that in spite of some metal corrosion in nickel-based alloys, a higher concentration of nickel may be needed to cause oral allergies.

Furthermore, in a review of 915 fixed and 87 removable prostheses with up to 31 years of service in 335 patients, no gingival tissue reactions or, at most, minor gingival tissue reactions were noted<sup>(114)</sup>. Almost half of the prostheses were made from base metal alloys, mainly nickel-chromium alloys for the fixed prostheses. The mucosal reactions were less prevalent for prostheses made from base metal alloys than gold alloys. Reactions to silver palladium alloys were less frequent than to other dental casting alloys, but the differences were small and considered to be due to factors other than the metal components<sup>(114)</sup>.

Kerosuo *et al.*<sup>(26)</sup> found from investigations involving 700 Finnish adolescents that orthodontic treatment did not seem to affect the prevalence of nickel sensitization. None of the girls surveyed who were treated with fixed orthodontic appliances before ear piercing showed hypersensitivity to nickel, whereas 35% of the girls who had experienced ear piercing before the onset of orthodontic treatment were sensitized to nickel. The findings suggest that orthodontic treatment with nickel-containing appliances may have reduced the frequency of nickel hypersensitivity in non-sensitized individuals. Studies using oral administration of nickel to animals have also demonstrated immune tolerance to nickel<sup>(25)</sup>.

Overall, there is currently no significant evidence of widespread systemic disease or adverse

patient reactions to nickel-containing dental alloys<sup>(23, 32)</sup>.

## 8. CONCLUSIONS

Nickel is found in many alloys used in dental treatment. These alloys have a long-standing history of successful use in dentistry with no significant reports of biological effects. Nickel is known to be a potential allergen, as detected by patch testing for contact allergies, but there is no evidence that individual patients are at a significant risk of developing sensitivity solely due to contact with nickel-containing dental appliances and restorations. Hypersensitivity reactions are more likely to occur with prior sensitization from non-dental contacts.

Conversely, it seems that earlier dental and non-dental oral contacts with the metal or metal compounds may even induce tolerance and result in a lower prevalence of nickel sensitivity in non-sensitized individuals.

Some nickel compounds, but not nickel metal nor nickel alloys, have been implicated as potential carcinogens in some human and animal studies by inhalation in industrial settings and where exposures were much higher than those usually present in dentistry-related operations. Nickel compounds, metals, or alloys have not been associated with increased cancer risk by oral or dermal routes of exposure. Nickel is not judged to pose a risk for dental patients or members of the dental team, especially in view of the low abrasion and corrosion rates of intraoral appliances during service. **There is currently no significant evidence of widespread systemic disease or reactions to nickel-containing dental alloys.**

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