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Risk of sensitisation of humans to nickel by piercing post assemblies

Final Report

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RISK OF SENSITISATION OF HUMANS TO NICKEL BY PIERCING POST ASSEMBLIES

Executive Summary

In reviewing the literature and papers, there is insufficient information on the levels of nickel release from different grades of stainless steels used in piercing to undertake a complete risk assessment. There have been a limited number of studies on the potential for stainless steel to cause primary sensitisation, but only estimates could be made on the level of nickel release that would cause nickel sensitisation. In many cases, these studies have been incomplete in evaluating the extent of existing sensitisation or have an insufficiently large sample population to confidently extrapolate findings into the general population.

Where studies report on the release of nickel from different grades of stainless steels, many of these have been undertaken under non-standardised conditions prior to introduction of the European Standardised method, EN 1811. This study has measured nickel release from a number of different stainless steels but with differing compositions using three fluids (artificial sweat, blood plasma and urine) likely to be in contact with the post assemblies during the period of epithilization. The results have shown that stainless steel of similar composition will release nickel at different rates dependent on their surface finish. For finished stainless steel wires and commercial stainless steel piercing post assemblies the release of nickel cannot be measured, as any value for nickel release is below the limit of detection of the instrumentation (0.01 µg/cm²/week). For stainless steels where nickel release can be measured, it can be shown that twice as much nickel will be released into urine and blood plasma as compared with artificial sweat.

In the absence of conclusive data on levels of nickel that will induce sensitisation that the existing nickel release requirement of 0.5 µg/cm²/week for articles in prolonged contact with the skin should form the basis of a nickel release requirement for post assemblies. Given the existing methodology EN 1811 uses artificial sweat, an adjustment in the limit should be made to account for increased rate of nickel release into blood plasma and the limit should be reduced accordingly. Therefore it has been

recommended that the existing requirement in the Nickel Directive for a maximum nickel content of 0.05% m/m in post assemblies as described is replaced by a nickel migration limit for all post assemblies of 0.2 µg/cm^2/week using the methodology specified in EN 1811.

1. Introduction

Nickel has long been recognised as an element that can, when in direct contact with the skin, cause a variety of allergic reactions ranging from mild irritation to severe eczema. Medical studies have shown that at least 10 per cent of European women and 1 per cent of men suffer from nickel allergy from items, particularly jewellery, worn next to the skin. These studies also indicate that the majority of those sensitised to nickel became sensitised after ear piercing. Once sensitised, subsequent direct and prolonged contact with items that release nickel can elicit an allergic reaction.

This report has been compiled to evaluate the extent of scientific knowledge in the literature on stainless steels used in body piercing with respect to nickel release and the ability of such steels to cause allergic contact dermatitis to nickel.

2. European Directive 94/27/EC - 'The Nickel Directive'

The European 'Nickel' Directive, 94/27/EC, adopted in 1994, seeks to prevent nickel sensitisation by restricting the use of nickel and its compounds in products that come into close and prolonged contact with the skin. It addresses three main groups of products that might lead to sensitisation by stating that nickel and its compounds may not be used:

1. in post assemblies which are inserted into pierced ears and other pierced parts of the human body during epithelization of the wound caused by piercing, whether subsequently removed or not, unless such post assemblies are homogeneous and the concentration of nickel – expressed as mass of nickel to total mass – is less than 0.05%;

2. in products intended to come into direct and prolonged contact with the skin such as:

   - earrings,
   - necklaces, bracelets and chains, anklets, finger rings,
   - wrist-watch cases, watch straps and tighteners,
   - rivet buttons, tighteners, zippers and metal marks, when these are used in garments

   if the rate of nickel release from the parts of these products coming into direct and prolonged contact with the skin is greater than 0.5 µg/cm²/week;

3. in products listed in point 2 above, where these have a non-nickel coating unless such a coating is sufficient to ensure that the rate of nickel release from those parts of such products coming into direct and prolonged contact with the skin will not exceed 0.5 µg/cm²/week for a period of at least two years of normal use of the product.

Such products may not be placed on the market unless they conform to the requirements set out above.

These requirements appear to recognise that it is the rate of nickel ion release from products in direct and prolonged contact with skin that can give rise to sensitisation, rather than the nickel content. In the case of body piercing, extra consumer safety is provided during the period of epithelisation by specifying the use of post assemblies with an essentially zero nickel content and, hence, a zero nickel release.

In order to confirm that products comply with the Directive, the European Standardisation body, CEN, has produced test methods for determining nickel content and nickel release into artificial sweat, viz:

- EN 1810:1998, *'Body-Piercing Post Assemblies - Reference Test Method for Determination of Nickel Content by Flame Atomic Absorption Spectrometry'*. This European Standard specifies a method for the determination of nickel in aluminium, titanium, copper, silver, gold and their alloys and in steels by flame atomic absorption spectrophotometry. The method is primarily suitable when the nickel content of a sample lies between 0.03% and 0.07% (m/m).

- EN 1811:1999, *'Reference Test Method for Release of Nickel from Products Intended to come into Direct and Prolonged Contact with the Skin'*. This European Standard specifies a method for simulating the release of nickel from consumer items in direct and prolonged contact with the skin in order to determine whether such items release nickel at a rate greater than 0.5 µg/cm²/week. The item to be tested for nickel release is placed in an artificial sweat test solution for 1 week. The concentration of dissolved nickel in the solution is determined by atomic absorption spectrometry or other appropriate analytical methodology. The nickel release is expressed in micrograms per square centimetre per week (µg/cm²/week).

The Directive has implications for the body-piercing industry because of the use of some grades of austenitic stainless steel (e.g. AISI 316 and 316L) in body piercing. However, the high nickel content of these grades prohibits their use in post assemblies in body piercing during the period of epithelisation. Even high-grade austenitic stainless steel specified for surgical implants and intended to remain in the human

body for long periods is prohibited for use in body piercing during the healing period of the wound.

It is claimed by the body-piercing industry that the nickel release rate for certain grades of austenitic stainless steel is much less than 0.5 μg/cm²/week and that they should be permitted for use in body piercing. The martensitic and ferritic grades of stainless steel possess no significant nickel content (less than 0.5%) but are not very suitable for use in post assemblies because most grades are insufficiently resistant to corrosion under physiological conditions. This has effectively limited material selection for body piercing to the more expensive metals such as gold, silver, platinum, titanium etc.

3. Stainless Steels

Stainless steels are defined in European Standard EN 10088 as iron-based alloys containing at least 10.5% chromium and a maximum of 1.2% carbon. One of the most important properties of stainless steel is resistance to corrosion. This is provided by the chromium in the steel which has a great affinity for oxygen and forms a continuous surface layer of chromium oxide that is passive, tenacious and self-renewing. The greater the chromium content above the minimum of 10.5%, the greater the stability of the surface layer. The addition of elements such as nickel and molybdenum contribute to corrosion resistance.

There are different systems currently in existence for designating stainless steels. Common designations include the AISI (American Iron & Steel Industries) system used in the USA, and the European Standard adopted for use in the European Union. Under the USA system, austenitic steels are in the 300 series; martensitic and ferritic grades are in the 400 series.
A designated grade can possess slight variations in elemental composition and physical and mechanical properties depending on the manufactured form and end use.

It should be noted that for some AISI designated steels there exists more than one European (EN) classification. This occurs due to the more restrictive and precise compositional descriptions specified in EN 10088-1.

Examples of stainless steel grades with corresponding AISI and European Standard designations are presented in the following table:

Stainless steel structure	AISI designation	European Standard designation	
		Name	Number
Austenitic	301	X10 CrNi 18-8	1.4310
	301L	X2 CrNiN 18-7	1.4318
	304	X5 CrNi 18-10	1.4301
	304L	X2 CrNi 18-9	1.4307
	305	X4 CrNi 18-12	1.4303
	316	X5 CrNiMo 17-12-2	1.4401
	316L	X2 CrNiMo 17-12-2	1.4404
	316L	X2 CrNiMo 18-14-3	1.4435
	321	X6 CrNiTi 18-10	1.4541

Stainless steel structure	AISI designation	European Standard designation	
		Name	Number
Martensitic	410	X12 Cr 13	1.4006
	420	X30 Cr 13	1.4028
Ferritic	430	X6 Cr 17	1.4016
	409	X2 CrTi 12	1.4512
	434	X6 CrMo 17-1	1.4113
	436	X6 CrMoNb 17-1	1.4526
	441	X2 CrTiNb 18	1.4509

Stainless steels are subdivided into a series of categories according to their metallurgical structure and chemical composition, i.e.

- Ferritic
- Martensitic
- Austenitic
- Austenic-ferritic (Duplex)
- Precipitation-hardening steels

3.1 Ferritic steels

Ferritic stainless steels are plain ferromagnetic chromium steels (typically 12.5% or 17% chromium) with low carbon content (< 0.08%) and no significant nickel content (residual 0.1% - 0.5% unless very carefully refined). As a group, they are more corrosive resistant than the martensitic grades, but generally inferior to the austenitic grades. Such steels are therefore most suitable for general and high-temperature corrosion applications rather than severe corrosion applications requiring high strength. These steels are magnetic but cannot be hardened or strengthened by heat treatment. They can be cold-worked and softened by annealing.

Ferritic grades (AISI):

Type 430 – The basic ferritic grade, with a little less corrosion resistance than Type 304. Type 430 combines high resistance to such corrosives as nitric acid, sulphur gases, and many organic and food acids.

Type 405 – Type 405 has lower chromium and added aluminium to prevent hardening when cooled from high temperatures.

Type 409 – Type 409 contains the lowest chromium content of all stainless steels and is also the least expensive.

Type 434 – Type 434 has molybdenum added for improved corrosion resistance.

Type 436 - Type 436 has niobium added for corrosion and heat resistance.

Type 442 – Type 442 has increased chromium to improve scaling resistance.

Type 446 – Type 446 contains even more chromium added to further improve corrosion and scaling resistance at high temperatures. Especially good for oxidation resistance in sulphuric atmospheres.

3.2 Martensitic steels

Martensitic grades were developed in order to provide a group of stainless alloys that would be corrosion resistant and hardenable by heat-treating. The martensitic grades are straight chromium steels usually containing no significant nickel. They are magnetic and can be hardened by heat-treating. The martensitic grades are mainly used where hardness, strength, and wear resistance are required.

Martensitic grades (AISI):

Type 410 – Type 410 is the basic martensitic grade, containing the lowest alloy content of the three basic stainless steels (304, 430, and 410). A low cost, general purpose, heat treatable stainless steel that is used widely where corrosion is not severe (air, water, some chemicals, and food acids.

Type 414 – Type 414 steels have nickel added (2%) for improved corrosion resistance.

Type 416 – Type 416 steels contain added phosphorus and sulphur for improved machinability.

Type 420 – Type 420 steels contain increased carbon to improve mechanical properties.

Type 431 – Type 431 steels contain increased chromium for greater corrosion resistance and good mechanical properties.

Type 440 – The chromium and carbon content of Type 440 steels is further increased to improve hardness and corrosion resistance.

3.3 Austenitic steels

Austenitic stainless steels are a class of alloys with a face-centred-cubic lattice structure of austenite over the whole temperature range from room temperature (and below) to the melting point. When 18% chromium and 8% nickel are added, the crystal structure of austenite remains stable over all temperatures.

Austenitic stainless steels, widely known as the (AISI) 300 series, offer a greater resistance to corrosion due to the substantial nickel content and higher levels of chromium that they contain. Such steels are not magnetic and are hardened and strengthened through cold working (changing the structure and shape of steel by applying stress at low temperature). Ductility (ability to change shape without fracture) is exceptional. Excellent weldability and superior performance in very low temperature services are additional features of such steels.

L Grades - The “L” grades are used to provide extra corrosion resistance after welding. The letter “L” after a stainless steel type indicates low carbon (as in 304L). The carbon is kept low to avoid carbide precipitation. Carbon in steel when heated will precipitate out to combine with the chromium and gather on the grain boundaries. This deprives the steel of the chromium in solution and promotes corrosion adjacent to the grain boundaries. By controlling the amount of carbon, this is minimised.

H Grades - The “H” grades contain a minimum of 0.04% carbon and a maximum of 1.0% carbon and are designated by the letter “H” after the alloy. These can be used at extreme temperatures as the higher carbon helps the material retain strength. Carbides which may precipitate or moved to the grain boundaries are put back into solution (dispersed) into the matrix of the metal by the annealing.

Austenitic grades (AISI):

Type 304 – Type 304 is the most common austenitic grade of steel, containing approximately 18% chromium and 8% nickel.

Type 316 – Type 316 steels contain 16% to 18% chromium and 11% to 14% nickel. They differ from 304 steels by the addition of molybdenum to control pit corrosion.

Type 317 – Type 317 steels contain a higher percentage of molybdenum than 316 for highly corrosive environments.

Type 317L – The maximum carbon and silicon content of Type 317L steels is restricted for extra corrosion resistance.

Type 317LM – Type 317LM steels require a molybdenum content of 4.00% minimum.

Type 317LMN – Type 317LMN steels require a minimum molybdenum content of 4.00% and a minimum nitrogen content of 0.15%.

Type 321 and Type 347 – These types were developed for intergranular corrosive resistance for repeated intermittent exposure to high temperature. Type 321 is made by the addition of titanium and Type 347 is made by the addition of tantalum/niobium.

3.4 Other types of stainless steels

Duplex grades are the newest types of the stainless steels. These steels have a mixture of austenitic and ferritic material in their structure. Nitrogen is added to provide higher strength and superior resistance to stress corrosion cracking. These steels find use in machinery, petrochemical equipment and pipework applications.

Precipitation-hardening grades, as a class, offer the designer a unique combination of fabricability, strength, ease of heat treatment, and corrosion resistance not found in any other class of material. The austenitic precipitation-hardenable alloys have, to a large extent, been replaced by the more sophisticated and higher strength superalloys. The martensitic precipitation-hardenable stainless steels are really the workhorse of the family. While designed primarily as a material to be used for bar, rods, wire, forgings, etc., martensitic precipitation-hardenable alloys are beginning to find more

use in the flat rolled form. While the semi-austenitic precipitation-hardenable stainless steels were primarily designed as a sheet and strip product, they have found many applications in other product forms. Developed primarily as aerospace materials, many of these steels are gaining commercial acceptance as truly cost-effective materials in many applications.

The austenitic grades account for about 75% of stainless steel production and the ferritic grades account for much of the remaining 25% of stainless steel production. EN 10088-1 provides a list of stainless steels.

3.5 Stainless Steel for Medical Implants

ISO 5832-1 specifies the characteristics of wrought stainless steel for use in the manufacture of surgical implants; and ISO 5832-9 specifies the characteristics for wrought stainless steel containing 0.25% to 0.5% nitrogen for use in the manufacture of surgical implants for which high levels of strength and corrosion resistance are required. These steels must have a structure free from delta ferrite. The elemental compositions of these 'surgical' steels are as follows:

	Compositional Limits (% m/m)		
	ISO 5832-1		**ISO 5832-9**
Element	**Composition D**	**Composition E**	**High Nitrogen Content**
Carbon	0.03 max	0.030 max	0.08 max
Silicon	1.0 max	1.0 max	0.75 max
Manganese	2.0 max	2.0 max	2 to 4.26
Phosphorous	0.025 max	0.025 max	0.025 max
Sulphur	0.010 max	0.010 max	0.01 max
Nitrogen	0.10 max	0.10 to 0.20	0.25 to 0.5
Chromium	17.0 to 19.0	17.0 to 19.0	19.5 to 22
Molybdenum	2.25 to 3.5	2.35 to 4.2	2 to 3
Nickel	13.0 to 15.0	14.0 to 16.0	9 to 11
Copper	0.50 max	0.50 max	0.25 max
Iron	Balance	Balance	Balance

AISI 316L steel is also used for surgical implants and its suitability for such purpose is recognised by USA Federal Food and Drug Administration. However, it should be noted that, although similar, the specification for ISO 5832 steel is relatively superior to AISI 316L stainless steel due to its increased resistance to corrosion.

Although certain AISI 316L steels are able to meet the compositional requirements of the ISO specification, there are significant metallurgical differences between AISI 316L and ISO 5832 steels.

The percentage elemental differences between 316L and ISO 5832-1 stainless steels are given in the following table:

Elemental differences (% m/m) between AISI 316L and ISO 5832-1 stainless steel

Grade	Chromium	Molybdenum	Nickel	Sulphur	Phosphorus	Nitrogen
ISO 5832-1 Type D	17.0 to 19.0	2.25 to 3.5	13.0 to 15.0	0.010 max	0.025 max	0.10 max
ISO 5832-1 Type E	17.0 to 19.0	2.35 to 4.2	14.0 to 16.0	0.010 max	0.025 max	0.10 to 0.20
AISI 316L	16 to 18	2.0 to 3.0	10 to 14	0.03 max	0.045 max	0.10 max

The higher values for chromium, nickel, molybdenum and nitrogen, and the lower values for sulfur and phosphorus in the ISO standard, provide increased corrosion resistance. The higher values for nitrogen and nickel ensure a fully austenitic (face-centred cubic) structure. Some forms of AISI 316L steel contain small amounts of delta ferrite (body-centred cubic structure) which is generally considered to reduce corrosion performance.

4. Metabolism And Toxicology of Nickel

Nickel is a transitional element as are the other common metal allergens, cobalt and chromium. Nickel salts are recognized to be induce acute toxic effects when administered to animals by the oral or parenteral routes (Sunderman & Brown, 1985). Nickel is an essential nutritional element for animals. Rats deficient in nickel show retarded growth and a reduction in haemoglobin due to impaired intestinal absorption of iron (Schnegg & Kirchgessner, 1976). Nickel and cobalt are actively absorbed from the intestinal mucosa, probably by the transfer system for iron. In human serum, nickel binds to albumin and to a specific 9.5S alpha-glycoprotein (Sunderman, 1977) and is also found in the form of nickel-L-histidine (Sarkar, 1984).

Nickel is present in the normal diet but estimates of the normal daily intake vary. Schroeder and colleagues (1962) calculated the daily intake to be between 300 and 600ug but this is probably an overestimate. Using better analytical methods, Myron et al (1978) assessed the daily dietary intake of elemental nickel to be 165 µg (range 107 to 221 µg). Foods high in nickel include baking powder, cocoa, chocolate, tea, coffee, oyster, kippers, gelatin, rye, maize, oats, red kidney beans, peas and soya (Schroeder et al, 1962). Cooking using stainless steel utensils can increase the nickel content if the foods contain natural acids, e.g. rhubarb, apples, tomatoes, citrus fruits and some berries (Brun, 1979). Canned food can have a higher nickel content than its fresh equivalent (Brun, 1979). The amount of nickel in tap water varies but is usually below 1.0 µg/L (Gammelgaard & Andersen, 1985).

Most ingested nickel is excreted in the faeces without being absorbed into the body. Faecal excretion of nickel varies considerably: 10 subjects on a normal diet showed values between 80 and 540 µg/day with a mean of 258 (Horak and Sunderman, 1973). The same authors found urinary levels of 0.7 to 5.2 µg/day (mean 2.6). Serum levels of nickel in normal individuals are <1.0 µg/l (Gawkrodger et al, 1986). Acute nickel intoxication with elevation of the serum nickel was been described in an incident where dialysis patients suffered acute nausea, vomiting, headache and palpitations when their dialysis fluid was contaminated by a water heater (Webster et al, 1980).

The contribution of dietary nickel to dermatitis is unclear (Gawkrodger et al, 1986). Orally administered nickel can cause a dermatitis in nickel-sensitive individuals but only at high doses which are unlikely to be encountered in the normal diet, and in quantities over ten times the usual daily intake (Gawkrodger et al, 1986). The value of a low nickel diet is questioned but, in one study, a reduction in the dietary intake of nickel produced a reduction in the activity of dermatitis in 58 of 90 nickel-allergic subjects (Veien et al, 1993).

Occupational exposure to nickel can cause industrial disease particularly in the nickel refining, smelting and plating industries. The biggest problem is acute inhalation of the gas nickel carbonyl causing acute poisoning. Long-term inhalation can lead to tumours of the nasal cavities and lungs. Chronic rhinitis and asthma can follow aerosol exposure. Contact dermatitis usually of the hands or arms is found from skin contact. Urinary levels are used to monitor exposure in individuals employed in nickel refinery plants.

When the cell viability of cultured human keratinocytes is assessed *in vitro* on exposure to nickel (Ni II) chloride ($NiCl_2$), the IC_{50} value is about 1000 umol/L (Little et al, 1996). The exposure *in vitro* of proliferating cultured keratinocytes to Ni (II) salts can induce up-regulation of the expression of intercellular adhesion molecule-1, an important signal in cell-cell mediated immune mechanisms (Little et al, 1998). This indicates a possible 'pre-immune' effect for nickel that may enhance the likelihood of the subsequent induction of contact sensitisation.

5. Demography of Nickel Dermatitis

Nickel dermatitis was first described in nickel-platers in the late 19th century. In current times, nickel sensitivity is common and affects 10% of women and 1% of men in western countries, as judged by patch testing (Peltonen, 1979). It is the most frequent contact allergen in women and the eighth most prevalent in men. Immunological contact urticaria to nickel can occur (Estlander et al, 1993) but the most usual manifestation of nickel allergy is contact dermatitis. Mostly, nickel sensitivity is a nuisance phenomenon related to jewellery dermatitis but it has a role as an occupational allergen (Shah et al, 1998).

Nickel allergy is demonstrated by patch testing during which small quantities of pre-prepared nickel sulphate ($NiSO_4.6H_2O$; 5% in petrolatum gel) are applied under occlusion using 8mm aluminium discs on adhesive tape to the upper back for 2 days, removed and read, and then read again after a further 2 days. A small patch of dermatitis at the site of the patch signifies a positive result. Of subjects allergic to nickel, approximately 34% are also allergic to cobalt and 18% to palladium (Gawkrodger et al, 2000).

Patterns of nickel dermatitis have changed over the years. In the 1950s, nickel-containing suspenders sensitised women in their third and fourth decades but since then, the age of onset has fallen and, in the early 21st century, most women are sensitised in their teenage years (Schubert & Berova, 1987). Nickel allergy can occur at any age and can even affect children who usually have had their ears pierced (Shah et al, 1997). The frequency of nickel sensitivity, ascertained by patch testing, is significantly increased in women who have had their ears pierced compared to those with unpierced ears (McDonagh et al, 1993). Ear piercing and the use of metallic earrings, ear studs, ear clasps and ear clips by young girls seem to explain the earlier age of nickel sensitisation (Schubert & Berova, 1987). Other items of jewellery such as necklaces, wrist watches, bracelets and rings can also sensitise, as can spectacle frames, jeans studs, brassiere hooks, zips and fasteners (Schubert & Berova, 1987). There is evidence from Scandinavian countries were control of nickel in jewellery

was introduced some years ago, that the rates of sensitisation to nickel are less (Jensen et al, 2002).

There may be a genetic predisposition to the development of nickel sensitivity as there is a higher concordance for monozygotic compared to dizygotic twins for both jewellery dermatitis and for positive patch tests to nickel, 0.32 compared to 0.14 and 0.29 compared to 0.08 respectively (Menne et al, 1983). However, environmental factors play a predominant part. The risk ratio for the development of nickel dermatitis for a first-degree relative of an individual with allergic contact dermatitis to nickel is 2.83 (Fleming et al, 1999).

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6. Nickel Sensitisation and Release from Stainless Steel

6.1 Literature Search

Cross *et al.* (1999) have carried out the most recent review of nickel sensitisation and the release of nickel from stainless steel. They report that in many of the studies of nickel release from stainless steel into artificial sweat and other biological fluids, such as blood, plasma and saliva, the stainless steel is poorly characterised in terms of grade, elemental composition, size or surface area. Therefore, although nickel release has been demonstrated under various experimental conditions, the results are difficult to interpret. The most reliable data on the release of nickel from stainless steel comes from the following studies where the stainless steels are fairly well defined:

Haudrechy *et al*. (1994) showed that particular examples (all containing equal to or less than 0.007% sulfur) of stainless steel grades AISI 304, 316L and 430 released less than 0.03 µg/cm^2/week of nickel into artificial sweat at pH 4.5. These samples elicited no skin reactions in patients already sensitised to nickel. In contrast, nickel-plated samples released around 100 µg/cm^2/week of nickel and samples of resulfurised stainless steel (AISI 303), containing approximately 0.3% sulfur, released about 1 µg/cm^2/week of nickel under the same conditions. These samples also elicited positive reactions (96% and 14%, respectively) in clinical patch tests on patients already sensitised to nickel. The elemental composition (% *m/m*) of the stainless steels was as follows:

Grade	Cr	Ni	Mo	C	S	Mn	Si	Ti	Nb	P
AISI 303	17.25	8.45	0.26	0.06	0.28	1.79	0.54	0.002	0.012	0.03
AISI 304	18.18	8.65	0.26	0.04	0.007	0.81	0.49	0.002	0.004	0.02
AISI 316L	17.87	11.29	2.15	0.02	0.002	1.67	0.61	0.004	<0.002	0.02
AISI 430	16.59	0.11	0.11	0.04	0.001	0.43	0.33	0.007	<0.002	0.02

The main conclusion of this study was that low-sulfur stainless steels like AISI 304, 316L and 430 showed no evidence of the potential to elicit nickel contact dermatitis in nickel-sensitised individuals, and, therefore, can be used without any problem in prolonged contact with skin.

The relatively poor resistance of AISI 303 steel to pitting corrosion is a consequence of its sulfur content, which, in combination with manganese, initiates pitting corrosion sites. This pitting corrosion accounts for the elevated levels of nickel release relative to the other steels tested. Therefore, the use of high-sulfur stainless steel (e.g. AISI 303) should be avoided where prolonged skin contact might occur.

Haudrechy *et al*. (1997) followed up their earlier work with a study of stainless steels with an intermediate sulphur content of approximately 0.03%. Three stainless steels complying with the specifications for AISI 304L, AISI 304L + Ca, and AISI 304L + Cu were tested. A low-sulphur AISI 304 and a high-sulphur AISI 303 were used as a reference. The elemental composition (% *m/m*) of the stainless steel samples used in this study was as follows:

Grade	Cr	Ni	Mo	C	S	Mn	Si	Ca
AISI 304	18.2	8.65	0.26	0.036	0.007	0.82	0.49	
AISI 304L	18.0	9.28	0.35	0.018	0.024	1.09	0.46	
AISI 304L + Ca	18.3	9.14	0.25	0.021	0.026	1.13	0.61	0.004
AISI 304L Cu	17.2	9.12	0.34	0.012	0.026	0.84	0.36	0.006
AISI 303	17.3	8.45	0.26	0.064	0.275	1.79	0.54	0.006

Nickel release tests showed that the three intermediate-sulfur grades released less than 0.3 µg/cm^2/week in artificial sweat at pH 4.5, and less than the detection limit (0.09 µg/cm^2/week) at pH 6.6. The high-sulphur AISI 303 released 1.4 µg/cm^2/week nickel at pH 4.5 and 0.3 µg/cm^2/week at pH 6.6. Clinical patch tests again showed that some (4%) of nickel-sensitised patients reacted to AISI 303, while none reacted to the other grades. Thus, this study confirms that low- and intermediate-sulfur stainless steels (S ≤ 0.03%) like AISI 304 and 304L should not elicit contact dermatitis in people already sensitised to nickel, while the high-sulfur grades (S > 0.1%) should be avoided.

In another (unpublished) study by Haudrechy and Pedarre in 1997, the nickel release of a more extensive range of stainless steels was investigated using the then latest version of prEN 1811. The pH of the synthetic sweat was 6.5, the value in the current

standard. Elemental composition of the stainless steels tested and their corresponding nickel release rates (uncorrected) are presented in the following table:

Grade	Elemental composition (% *m/m*)				Nickel release (µg/cm^2/week)
	Cr	Ni	Mo	S	
AISI 303	17.2	8.61	0.30	0.31	3.27
AISI 304	18.5	8.71	0.19	0.0045	0.005
AISI 304L	18.3	9.05	0.24	0.025	0.01
AISI 316	17.1	10.5	2.20	0.0011	0.01
AISI 316L	16.8	11.0	2.02	0.026	0.015
AISI 310S	24.7	19.5	0.06	0.0007	0.015
AISI 430	16.4	0.16	0.03	0.0015	0.012

These results demonstrate that, under the conditions specified in EN 1811, the nickel release rates of these steels, with the exception of AISI 303, are negligible. Prolonged skin contact with these particular grades of stainless steel (excluding AISI 303) is unlikely to result in skin reactions in nickel-sensitised subjects.

In a short study in 2001 (unpublished), **Sheffield Analytical Services** were commissioned to carry out the European Standard nickel content and nickel release test methods on twenty samples of AISI 316L stainless steel and twenty samples of gold-plated AISI 316L stainless steel ear piercing post assemblies. The elemental composition of the AISI 316L stainless steel post assemblies was claimed to be as follows:

Cr (% *m/m*)	**Ni** (% *m/m*)	**Mo** (% *m/m*)	**C** (% *m/m*)	**S** (% *m/m*)	**Mn** (% *m/m*)	**Si** (% *m/m*)	**Cu** (% *m/m*)	**N** (% *m/m*)	**P** (% *m/m*)
16.99	10.22	2.06	0.02	0.025	1.53	0.61	0.41	0.05	0.027

Following the method described in EN 1811, the mean nickel release rate (uncorrected) into artificial sweat was 0.12 µg/cm^2/week for both the gold-plated and non-coated 316L stainless steel post assemblies. The mean nickel content of the gold-plated and non-coated post assemblies was found to be 10.1% and 9.9%, respectively.

Samitz and Katz (1975) examined nickel release from stainless steel prostheses and other surgical accessories into various biological fluids. The objects were immersed in physiological saline, sweat, whole blood or plasma for one week at room temperature. The lowest concentrations of nickel were measured in plasma, which gave a range of results from 'not detected' (n.d.) to 1.0 ppm, and the highest concentrations in sweat (range n.d. – 99 ppm). Nickel levels in saline ranged from 'not detected' to 9.8 ppm; and in whole blood 'not detected' to 17.4 ppm. The detection limit was 1.0 µg (which we estimate corresponds to a release rate of about 0.5 µg/cm^2/week). With some items tested, the type of steel was reported (AISI 302, 303 or 316L). The study shows that, under the conditions of this experiment, detectable amounts of nickel are released into biological fluids from stainless steel. However, there was insufficient information to allow the variation between different biological fluids to be explored.

Menné *et al.* (1987) tested subjects previously sensitised to nickel in a patch-testing study using discs of stainless steel containing 18% chromium, 9% nickel and 70% iron. Nickel release from these discs into artificial sweat was approximately 0.04 µg/cm^2/week. The subjects were exposed to the discs for 48 hours and the response assessed after 48 and/or 72 hours. Two out of 66 subjects gave a positive response to the stainless steel. The results from this study indicate that the stainless steel tested elicits a weak response from people with prior sensitisation to nickel. Nickel release and patch test results from other nickel alloys, including stainless steel, tested in this study showed the following trend:

- Alloys with a nickel release >1.0 µg/cm^2/week elicit a positive skin reaction in >50% of subjects with prior sensitisation;
- Alloys with a nickel release <0.5 µg/cm^2/week elicit a positive skin reaction in <30% of subjects with prior sensitisation.

Lidén *et al.* (1996) carried out a series of patch-testing experiments using a range of nickel-containing alloys including stainless steel. The study involved 100 nickel-sensitised subjects and 20 non-nickel-sensitised subjects acting as controls. The latter subjects were confirmed to be non-sensitive to nickel by patch testing. Three stainless steels were tested: surgical grade (ISO 5832) 13-15% nickel AISI 317; 18/8 grade

ISO 683 XIII 6.5-9.5% nickel AISI 304; and stainless steel SS 142382, <0.5% nickel (probably a martensitic or ferritic stainless steel). A gold-plated version of the 18/8 stainless steel was also tested. Samples were applied to the upper back of each subject for 48 hours and the skin response was assessed after the third day. The three stainless steels were negative in all nickel-sensitised and non-nickel-sensitive subjects. The gold-plated stainless steel gave 4 positive responses out of 100 but was not statistically significant. The three stainless steels were then tested in 20 of the nickel-sensitive subjects by using the ear lobe as the exposure site over a 7-day period. No positive responses occurred with any of these stainless steels.

This study also investigated the types of objects that had caused dermatitis, as reported by nickel-positive subjects. Eighty-eight per cent had had their ears pierced, but only 23% of these suspected that they had been sensitised to nickel in the same year as their ears were pierced. Sixty-one per cent suspected sensitisation one or more years after ear piercing, and 12% one or more years before. Four per cent were uncertain when sensitisation occurred.

Räsänen *et al.* (1993) investigated nickel sensitivity in a group of nine volunteers who had had their ears pierced using 'stainless steel' ear piercing kits. The subjects, all females, had no reported history of nickel sensitivity, although this was not confirmed by patch testing before ear piercing. The subjects were monitored for symptoms of sensitisation after ear piercing and were patch tested. Six of the females exhibited symptoms of itching, swelling or discharge within one to three weeks of piercing and gave positive responses to nickel in patch tests. The nine ear-piercing kits were tested for nickel release in plasma and distilled water. The highest nickel release occurred in plasma, although displaying wide variability, i.e. 0.03 – 104 $\mu g/cm^2$/week. The maximum nickel release in distilled water was 1.39 $\mu g/cm^2$/week. In a subsequent communication (**Fisher 1994**), it was reported that although the ear-piercing kits were all made of stainless steel, four of these were plated with gold with a layer of nickel underneath the gold. Three of the females using the gold-plated ear-piercing kits showed local symptoms and patch tested positive to nickel. Because the subjects were not checked to confirm non-sensitivity to nickel before the start of the study, and because the chemical composition of the kits is not clear, this study does

not allow any conclusions to be drawn regarding the potential of stainless steel to induce sensitisation.

Cross *et al*. (1999) also reviewed a number of case-reports which have reported health effects in individuals who have received surgical or dental prosthetic devices made of stainless steel. Overall, it was considered these studies provide no reliable information on which to assess the potential of stainless steel to elicit allergic responses or induce sensitisation. However, given the large number of people who are exposed to stainless steel by way of surgical implants, it is notable that so few case-reports of suspected sensitisation are available.

Ingber *et al*. (paper submitted for publication) have recently carried out a study to investigate whether stainless steel ear-piercing post assemblies elicit an allergic response in nickel sensitive subjects. Twenty-three female and two male subjects, known to be nickel-sensitive by patch testing, had their ears pierced using AISI 316L stainless steel ear piercing post assemblies.

The subjects were examined on day 7, 14, 30 and 42, and none showed any evidence of contact dermatitis during the six weeks of the study. Seven of the post assemblies were selected at random and tested for nickel content and nickel release into artificial sweat. The nickel content of the post assemblies ranged from 11.5% to 12.9% and the nickel release was below the detection limit [assumed to be 0.05 µg/cm^2/week (uncorrected)].

6.2 Discussion

There are currently no peer-reviewed papers that directly address the extent to which stainless steel body-piercing post assemblies will cause allergic reactions in nickel sensitive subjects. There are indications in the literature that certain types of austenitic stainless steels (in particular those containing less than 0.03% sulfur) **that come into prolonged and close contact with the skin** are unlikely to elicit an allergic response for the majority of people previously sensitised to nickel, for items

There is evidence to demonstrate that some grades of stainless steel will release nickel into artificial sweat at a rate considerably less than the 0.5 µg/cm^2/week limit specified in the Directive when tested in accordance with EN 1811.

There is no data on the use of high-grade stainless steel meeting the requirements of ISO 5823 (surgical implants) for body piercing. Although, research on nickel sensitisation from surgical steels present in the body has been investigated, there is a difference in the risk of primary sensitisation and elicitation from stainless steel in prolonged contact with the skin and stainless steel implanted in the human body.

At this stage, the lack of conclusive data would make it difficult to identify with confidence a specific grade(s) of stainless steel to specify for use in body piercing. Also in detailing specific grade(s) or type of stainless steel there would be an impact on regulatory authorities to undertake expensive elemental compositional analysis in order to assess compliance with a specified grade. Furthermore, apart from limiting the choice of materials available to industry and stifling innovation, such a requirement would not be based on sound science (as physical parameters like crystal structure and surface finish are equally as important as chemical composition).

An alternative approach would be to set an appropriate nickel release rate for all stainless steel ear and body posts, whether or not used during the period of epithelisation using test procedure EN 1811. Test procedure EN 1811 has been correlated with the nickel release rate of 0.5 µg/cm^2/week specified in the Directive for products (other than piercing post assemblies) for direct and prolonged contact with the (unbroken) skin. However, there is little or no data on nickel release

correlating the release of nickel ions into blood, sweat and (possibly) urine where body piercing takes place.

6.3 Conclusion

Studies that have investigated the potential for stainless steels to produce an allergic skin response in people have been published in the scientific literature. These studies generally address one or both of the following issues:

- the potential of stainless steel to *elicit* skin responses in people previously sensitised to nickel; and/or
- the potential of stainless steel to *induce* sensitisation to nickel in non-sensitised people.

There is evidence in the studies by Haudrechy to show that certain austenitic grades of stainless steel (in particular those containing less than 0.03% sulfur) are unlikely to elicit an allergic response in the majority of people previously sensitised to nickel, when used in items that come into prolonged and close contact with the skin.

Menné in 1987 stated that certain grades of stainless steel are unlikely to induce sensitisation in non-sensitised people. This is because a substantial nickel release rate is usually required to induce primary sensitisation, and this is unlikely to occur with these stainless steels in prolonged and close contact with the skin. However, this opinion relates only to nickel release from stainless steel in prolonged and close contact with *intact* skin and sweat – it is not intended to apply to stainless steel used in ear or body piercing posts when in contact with broken skin, blood and sweat, i.e. during the period of epithelisation.

There is very little data in the literature about the potential for stainless steel to induce primary sensitisation to nickel in confirmed non-sensitised people. Lidén *et al.* (1996) showed that a control group of 20 confirmed non-sensitised people were not sensitised to nickel when in contact with three stainless steel grades. Again however, this study does not address the use of stainless steel in ear or body piercing when in contact with broken skin, blood and sweat. The study by Räsänen et al. (1993) does investigate the potential for non-sensitised people to become sensitised to nickel from stainless steel

after ear piercing. However, the results are inconclusive because: non-sensitisation was not confirmed by patch testing prior to ear piercing; the elemental composition of the ear piercing kits was unclear (some of the kits were plated with gold over a nickel interliner – a procedure that is known to release significant amounts of nickel); and, unsurprisingly, there was wide variation in the results for nickel release into blood plasma.

It might appear there is an anomaly in the Directive in that high-grade stainless steel meeting the requirements of ISO 5823 is allowed inside the human body as a surgical implant, but prohibited for use in body piercing. However, there is a difference in the risk of primary sensitisation and elicitation from stainless steel in prolonged contact with the skin, and stainless steel implanted in the human body with no prolonged skin contact.

Nevertheless, the risk of sensitisation to nickel during the period of epithelisation should not be overstated. Although ear-piercing and the associated wearing of ear-rings is a major cause of allergic contact dermatitis to nickel, the study by Lidén *et al*. found the majority of those with pierced ears who have developed nickel allergy, thought that their sensitisation occurred one or more years after having their ears pierced. As the wound caused by ear piercing generally heals within about six weeks, these findings indicate that the wearing of nickel-releasing ear-rings following the period of epithelisation may be of more significance than the piercing/healing process itself. Furthermore, there has been some discussion on the meaning of *"the period of epithelisation"*. As Point 1 of the Annex to the Nickel Directive applies *"during epithelisation of the wound caused by piercing"*, the general view is that the nickel content requirement applies only during the healing period immediately following a piercing. However, it is not uncommon for a subsequent wound to occur, particularly if posts are inserted into ears after a period of non-use. Therefore, consideration should be given to extending any new requirement for piercing posts to all posts, whether or not they are used during the initial period of epithelisation.

Many of the studies quoted in the literature search have attempted to measure the nickel release from the materials being evaluated. However, until the publication of EN 1811: 1999, *'Reference Test Method for Release of Nickel from Products Intended*

to come into Direct and Prolonged Contact with the Skin', there has been no standardisation of the methodology used for this analysis. Since the nickel release obtained during testing depends on many factors, including the temperature and composition of the simulant, it has often been impossible to compare the results obtained by different workers. Another difficulty is the paucity of information in many papers on the precise composition of the materials studied. Despite these drawbacks, there is evidence to show that certain grades of stainless steel will release nickel into artificial sweat at a rate considerably less than the 0.5 $\mu g/cm^2$/week limit specified in the Directive, when tested in accordance with EN 1811.

Although dated, the study reported by Samitz and Katz in 1975 indicated that the release of nickel from stainless steel prostheses into blood or plasma is likely to be less than the nickel release from these items into sweat. This conclusion, however, needs confirming using well-defined materials and modern sophisticated analytical techniques. A weakness in the study was the relatively high detection limit for nickel compared with current attainable detection limits.

Theoretically, ferritic stainless steels containing less than 0.05% nickel can be used to manufacture posts for use during the period of epithelisation. However, ferritic steels typically contain between 0.1% and 0.5% nickel, with some types containing up to 1.6% nickel. To obtain any steel with a nickel content of less than 0.05%, as required by the Nickel Directive, needs special manufacturing conditions. Such steels can corrode more readily than austenitic steels and they have not found favour with the ear and body piercing manufacturers. For reference, a Type 430 stainless steel containing 0.11% nickel releases about as much, or rather as little, nickel (0.01 $\mu g/cm^2$/week) as a Type 316 stainless steel containing 10.5% nickel.

An issue not discussed in the literature is the effect of surface finishing on the stainless steel piercing post. From a metallurgical point of view, whether a steel is electropolished, rolled or machined is pertinent to its resistance to corrosion and hence to its nickel release. Although it is accepted that only a smooth finish on piercing post assemblies is likely to be acceptable to the consumer, the effect of surface finish would need to be considered should the approach of allowing particular stainless steels be adopted. In this case, minimum requirements for surface finish

may need to be specified. However, if a regulatory approach for piercing post assemblies were to be established by the specification of a maximum nickel release value, the issue of composition, metallurgical structure and surface finish would become essentially irrelevant.

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7. Evaluation of High Grade Stainless Steels

The Nickel' Directive, 94/27/EC states that nickel and its compounds may not be used in post assemblies which are inserted into pierced ears and other pierced parts of the human body during epithelization of the wound caused by piercing, whether subsequently removed or not, unless such post assemblies are homogeneous and the concentration of nickel – expressed as mass of nickel to total mass – is less than 0.05%. This requirement effectively prohibits most types of stainless steel, as a high nickel content is necessary to improve the corrosion characteristics of steel. However, the use of 'surgical steel' for piercing posts has been suggested as a suitable material based on its use in medical implants. 'Surgical steel' contains between 13-16% m/m of nickel but there is little or no data on the release of nickel from 'surgical steel' used in prostheses. The question of corrosivity from contact with blood and the release of nickel ions into blood has been raised but not documented nor measured, although there are suggestions it is detectable at microgram levels.

Where experiments have measured nickel release from stainless steel (other than 'surgical steel') the results have pre-dated the current standardised procedure EN 1811. This has lead to uncertainty in the comparing different data sets where nickel release from different types of stainless steels has been measured. Especially as the nickel measurements have used different techniques with varying sensitivities.

The data produced by researchers on stainless steel have provided valuable information within the context of each experiment but has made comparison of data between experiments difficult to evaluate as the experimental conditions have varied. A number of factors have been suggested as having an effect on the release on nickel ions from stainless steel. These can be summarised as:

- Sulfur content
- Contact fluid i.e. sweat or blood plasma
- Surface finish and
- Nickel content
- Corrosivity

Corrositivity appears to be the major influence on nickel release from stainless steels and the interactions between different types of fluids, pH of fluid, oxygenation and composition and finish of the stainless.

In constructing an experimental plan to determine the effects of the different factors the primary consideration was to measure nickel release from stainless steels that either corresponded to the 'surgical steel' specification ISO 5832-1 or the nearest equivalent grade. The jewellery industry outside of the European Union use AISI 316L steel for stainless steel piercing posts. The compositional differences between the specifications for ISO 5832-1 and AISI 316L steel are higher values for chromium, nickel, molybdenum and nitrogen in ISO 5832-1, and the lower values for sulfur and phosphorus. These differences are minimal and in certain cases an AISI 316L steel will meet the specification for stainless steels. The steel industry[12] was contacted and asked to provide stainless steel samples of known composition that closest matched the specification for 'surgical steels'. The jewellery industry[3] agreed to provide commercial stainless steel piercing posts with known compositional details and surface finishes. Each sample came with a certificate of composition and therefore it was not considered necessary to confirm composition.

A major factor identified, as having a possible effect on nickel release was the type of fluid in which the stainless steel post would be in contact. The current Standard EN 1811 specifies artificial sweat of known salt composition and pH adjustment as the simulant solution to measure the nickel release from metallic articles. From the literature it appeared that there had been no research to measure nickel release into biological fluids i.e. blood plasma neither during piercing nor during the period of epithalization. Therefore it was decided that experiments using blood plasma or the equivalent should be undertaken using the conditions described in EN1811 to enable a comparative assessment of nickel release from the same stainless steel as sweat. Another biological fluid that was considered as presenting a foreseeable risk was urine. It is well known that piercings take place in the genital area and that urine could present conditions not otherwise found with blood plasma. As the use of biological fluids in a laboratory is subject to (COSHH) controls requiring experiments to be

[1] Stainless steel Plates provided by AvestaPolarit Ltd
[2] Stainless Steel Wires provided by Winterbottom Wire (UK) & Metinox Steels Ltd (UK)

undertaken in controlled environments. Efforts were made to find viable alternative simulants for both blood plasma and urine but evaluation of the literature did not identify suitable alternatives. Therefore human blood plasma was obtained from a local hospital[4] and freeze-dried human urine was obtained from a commercial company[5]. Unfortunately, availability and quantity of fresh human blood plasma from a single person limited the number of experiments that could be undertaken to ensure consistency between results.

In the literature review, it was highlighted that the surface finish could have an impact on nickel release but there was little or no data comparing surface finishes of stainless steels with nickel release. It had been suggested that certain stainless steels would not release nickel due to their composition and therefore in any future legislation a particular grade of steel could be permitted. However, it was suspected that surface finish could have an effect and this could be investigated and correlated with nickel release values from artificial sweat, blood plasma and urine.

7.1 Methodology

The nickel release from stainless was to be measured according to EN 1811 where the item to be tested for nickel release is placed in an artificial sweat test solution for 1 week. The concentration of dissolved nickel in the solution is determined by atomic absorption spectrometry, inductively-coupled plasma spectrometry or other appropriate analytical method. The nickel release is expressed in micrograms per square centimetre per week (µg/cm^2/week). Deviations from the method included the use of blood plasma and urine as the test solution and the use of High Resolution-Inductively Coupled Plasma-Mass Spectrometry (HR-ICP-MS). The use of HR-ICP-MS enabled a much lower detection limit for nickel to be achieved compared to atomic absorption spectrometry and inductively-coupled plasma spectrometry and is permitted within the scope of the method. The use of blood plasma and urine are not described in EN 1811 but where the test solution is specified these solutions were used in the same proportions as the artificial sweat. The pH of the blood plasma and urine were not adjusted.

[3] Piercing Posts & Burterfly clips provided by Studex UK Ltd & Carpenters Ltd
[4] Kingston Hospital (UK).
[5] Sigma Chemicals,

7.2 Samples

The following stainless steel samples were received and have been presented in three tables in order of processing. The steel plates shown in Table 1 and Photographs 1 & 2, demonstrates the differences in finishing that are possible and ranges from a dull matt finish to a mirrored finish. The SEM examination shown in photographs 4-7 shows the surface effects at the micron level for the plates.

The steel wires shown in Table 2 are not in the form that would be used for piercing but give an indication of a semi-processed material that could be further worked.

Commercial stainless steel piercing posts and butterflies are shown in Table 3. & Photograph 3.

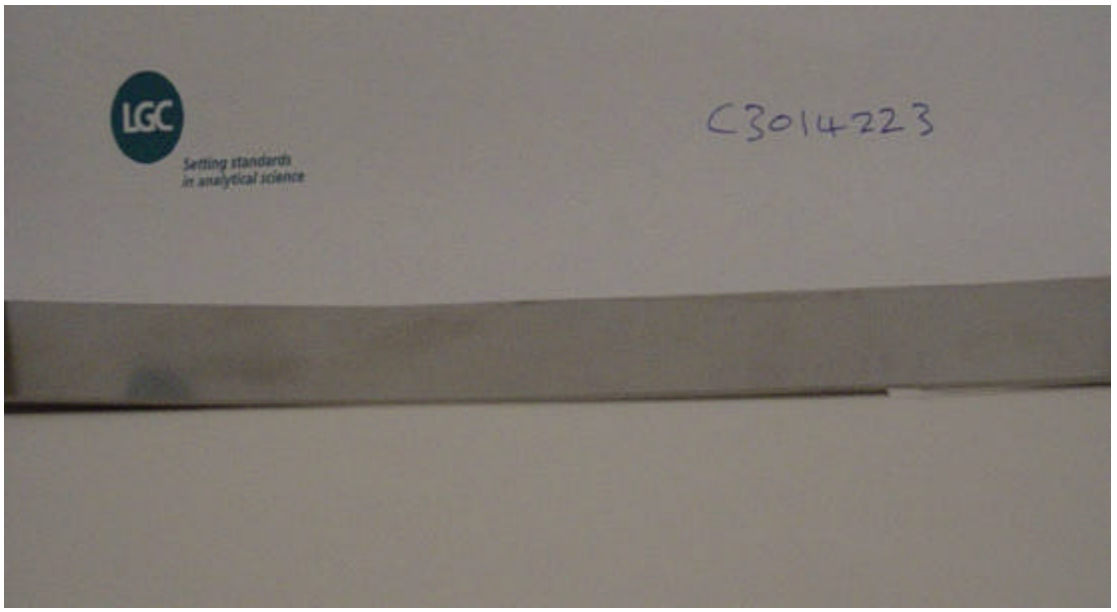
Table 1. 316L Stainless Steel Plates

Sample No	Item	**Description**	**Composition % m/m**	
C3012226	Sandvik Bioline 316LVM material, Stainless steel bright cold rolled strip (cast 829938)	Plate with matt finish	**C** (Carbon) **Si** (Silicon) **Mn** (Manganese) **P** (Phosporous) **Cr** (Chromium) **Mo** (Molybdium) **Ni** (Nickel) **N** (Nitrogen) **S** (Sulfur) **Cu** (Copper)	0.019 0.52 1.81 0.017 17.53 2.75 13.79 0.072 0.001 0.063
C3012227	Sandvik Bioline 316LVM material, Stainless steel bright cold rolled strip (cast 855642)	Plate with matt finish	**C** (Carbon) **Si** (Silicon) **Mn** (Manganese) **P** (Phosporous) **Cr** (Chromium) **Mo** (Molybdium) **Ni** (Nickel) **N** (Nitrogen) **S** (Sulfur) **Cu** (Copper)	0.016 0.53 1.58 0.017 17.44 2.80 13.79 0.069 0.001 0.064

Table 1. (cont'd) 316L Stainless Steel Plates

Sample No	Item	Description	Composition % m/m	
C3012228	316L(melt code 316XW), Coil: KO306, Cast: L4964	Polished surface with dull finish	**C** (Carbon) **Si** (Silicon) **Mn** (Manganese) **P** (Phosporous) **Cr** (Chromium) **Mo** (Molybdium) **Ni** (Nickel) **N** (Nitrogen) **S** (Sulfur) **Cu** (Copper)	0.022 0.42 1.29 0.029 17.12 2.23 11.7 0.033 0.002 0.3
C3012229	316L (melt code 316ZA), Coil: K9400/1, Cast: 20327, Finish: BA	Plate with mirrored finish	**C** (Carbon) **Si** (Silicon) **Mn** (Manganese) **P** (Phosporous) **Cr** (Chromium) **Mo** (Molybdium) **Ni** (Nickel) **N** (Nitrogen) **S** (Sulfur) **Cu** (Copper)	0.021 0.41 1.27 0.023 16.65 2.07 10.04 0.029 0.001 0.34
C3012230	316L (melt code 316ZA), Coil: K8295, Cast: L7106, Finish: 2B	Plate with mirrored finish	**C** (Carbon) **Si** (Silicon) **Mn** (Manganese) **P** (Phosporous) **Cr** (Chromium) **Mo** (Molybdium) **Ni** (Nickel) **N** (Nitrogen) **S** (Sulfur) **Cu** (Copper)	0.021 0.41 1.29 0.026 16.69 2.05 10.06 0.035 0.001 0.34
C3014223	1.4435, 316S13 *(316VO)*, Cast: L6231	Plate with matt finish	**C** (Carbon) **Si** (Silicon) **Mn** (Manganese) **P** (Phosporous) **Cr** (Chromium) **Mo** (Molybdium) **Ni** (Nickel) **N** (Nitrogen) **S** (Sulfur) **Cu** (Copper)	0.01 0.3 1.5 0 17 2.5 12.5 0.04 0 0.05

Photograph 1



Photograph 2

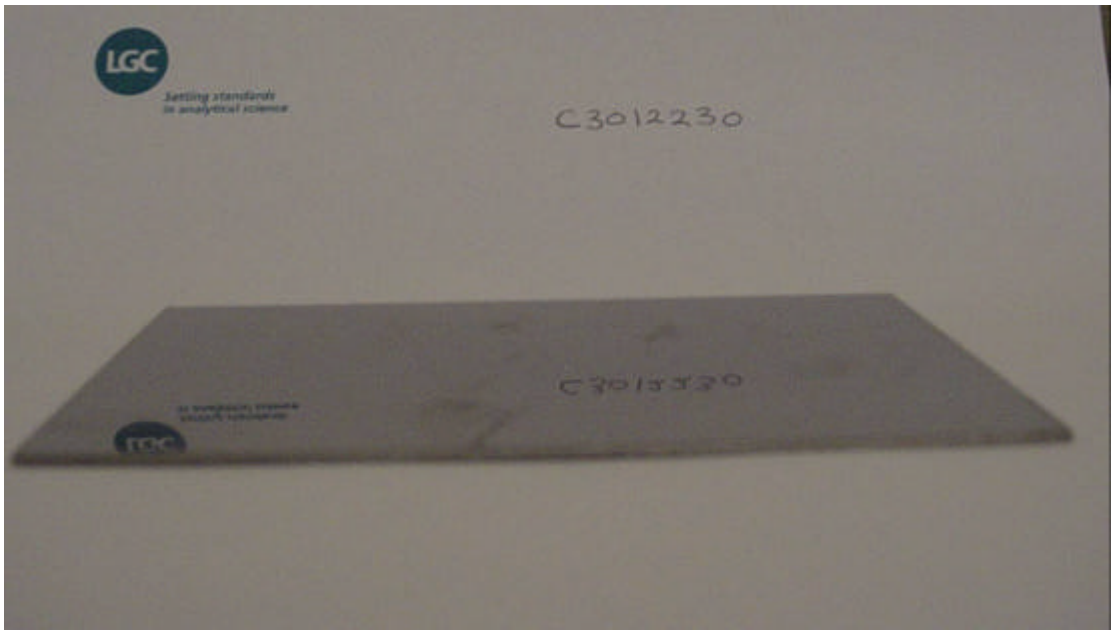


Table 2. Stainless Steel Wires

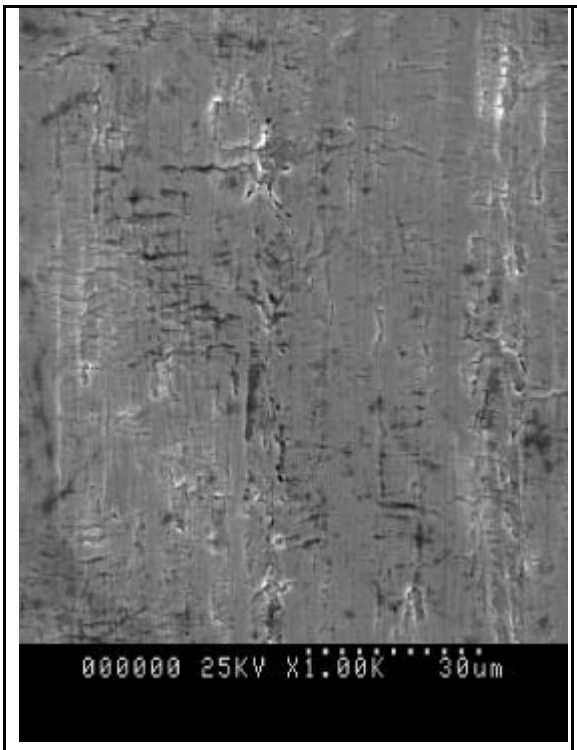
Sample No	Item	Description	Composition % m/m	
D3000053	1.4404 Stainless steel wire, 1.6mm Diameter	Wire with silver mirrored finish	**C** (Carbon) **Si** (Silicon) **Mn** (Manganese) **P** (Phosporous) **Cr** (Chromium) **Mo** (Molybdium) **Ni** (Nickel) **N** (Nitrogen) **S** (Sulfur) **Cu** (Copper)	0.017 0.50 0.64 0.024 16.66 2.02 11.06 - 0.0007 0.08
D3000054	Sandvik Bioline 316LVM Stainless steel ground and polished bar, 2.0 mm Diameter (cast 823009)	Wire with silver mirrored finish	**C** (Carbon) **Si** (Silicon) **Mn** (Manganese) **P** (Phosporous) **Cr** (Chromium) **Mo** (Molybdium) **Ni** (Nickel) **N** (Nitrogen) **S** (Sulfur) **Cu** (Copper)	0.017 0.53 1.71 0.021 17.86 2.74 14.24 0.059 0.001 --

Table 3. Stainless Steel Piercing Post Assemblies

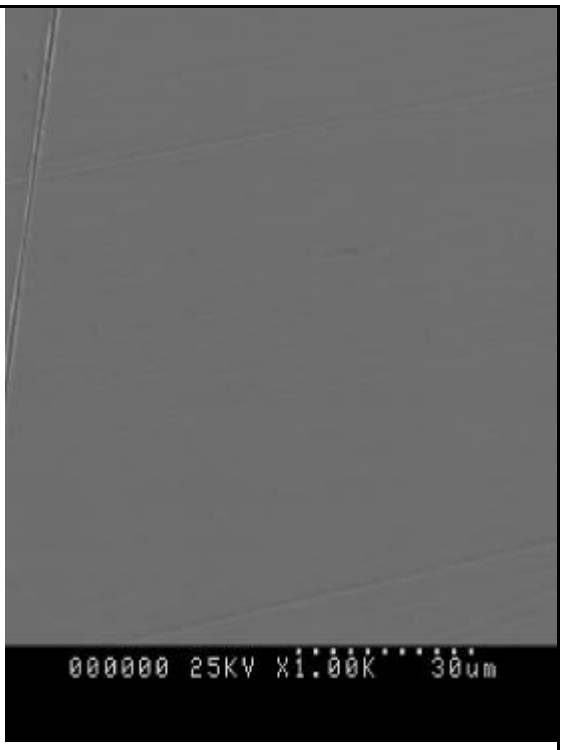
Sample No	Item	Description	Composition % m/m	
C3012231	316L Project 70 stainless ear studs Annealed cold drawn (Heat No: 724345)	Post with silver mirrored finish	**C** (Carbon) **Si** (Silicon) **Mn** (Manganese) **P** (Phosporous) **Cr** (Chromium) **Mo** (Molybdium) **Ni** (Nickel) **N** (Nitrogen) **S** (Sulfur) **Cu** (Copper)	0.02 0.61 1.53 0.027 16.99 2.06 10.22 0.05 0.025 0.41
C3012232	316L Project 70 Gold plated stainless ear studs Annealed cold drawn (Heat No: 724345)	Post with gold mirrored finish	**C** (Carbon) **Si** (Silicon) **Mn** (Manganese) **P** (Phosporous) **Cr** (Chromium) **Mo** (Molybdium) **Ni** (Nickel) **N** (Nitrogen) **S** (Sulfur) **Cu** (Copper)	0.02 0.61 1.53 0.027 16.99 2.06 10.22 0.05 0.025 0.41
C3014220	30200 AISI Butterflies (Heat 3471)	Butterfly with silver mirrored finish	**C** (Carbon) **Si** (Silicon) **Mn** (Manganese) **P** (Phosporous) **Cr** (Chromium) **Mo** (Molybdium) **Ni** (Nickel) **N** (Nitrogen) **S** (Sulfur) **Cu** (Copper)	0.06 0.52 1.69 0.026 18.23 0.37 8.62 0.02 0.001 0.28

Photograph 3

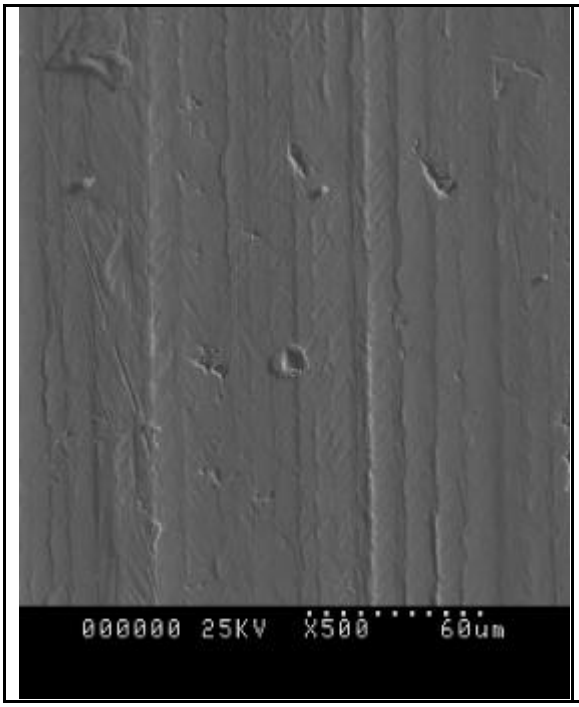
Photograph 4
Sample No. C301226 (Before Polishing)



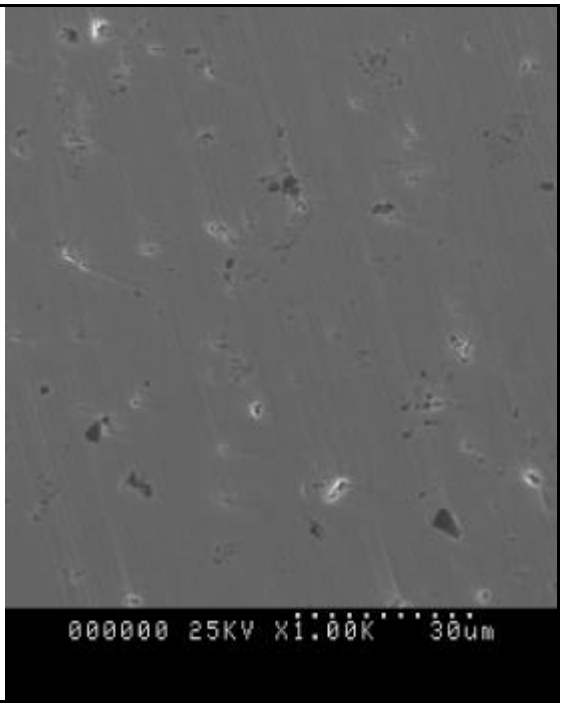
Photograph 5
Sample No. C301226 (After Polishing)



Photograph 6
Sample No. C301227 (Before Polishing)



Photograph 7
Sample No. C301227 (After Polishing)



7.3 Results

Table 4. Nickel Release from Stainless Steel Plates in Different Simulants

C3012226 Sandvik Bioline 316LVM material, Stainless steel bright cold rolled strip (cast 829938)

A. Test soln: **Sweat**		B. Test soln: **Urine**		C. Test soln: **Plasma**	
0.349		0.874		0.543	
0.359		1.225		1.057	
0.479		0.774		0.556	
0.458		1.078		0.642	
0.562	**Mean = 0.45 µg/cm^2/week**	1.347	**Mean = 1.06 µg/cm^2/week**	0.439	**Mean = 0.62 µg/cm^2/week**
0.475	SD = ± 0.08	1.071	SD= ± 0.21	0.502	SD = ± 0.22

A. Retested Test soln: **Sweat**		D. Test soln: **Sweat**		E. Polished Plate Test soln**: Urine**	
0.262		0.489		0.647	
0.544		0.737		0.681	
0.299		0.547		0.662	
0.544		0.527		0.906	
0.504		0.559		0.795	
0.529	**Mean = 0.45 µg/cm^2/week**	0.529	**Mean = 0.57 µg/cm^2/week**	0.471	**Mean = 0.69 µg/cm^2/week**
	SD = ± 0.13		SD= ± 0.09		SD = ± 0.15

All results are calculated as µg/cm^2/week and have been blank corrected

Table 4. (Cont'd) Nickel Release from Stainless Steel Plates in Different Simulants Using EN 1811

C3012227 Sandvik Bioline 316LVM material, Stainless steel bright cold rolled strip (cast 855642)

A. Test soln: **Sweat**		B. Test soln: **Urine**		C. Test soln: **Plasma**	
0.448		1.763		0.511	
0.408		0.572		0.522	
0.365		1.275		0.481	
0.452		1.536		1.463	
0.281	**Mean = 0.43 µg/cm^2/week**	0.439	**Mean = 1.15 µg/cm^2/week**	1.816	**Mean = 1.05 µg/cm^2/week**
0.595	SD = ± 0.11	1.320	SD= ± 0.53	1.507	SD = ± 0.61

A. Retested Test soln: **Sweat**		D. Test soln: **Sweat**		E. Polished Plate Test soln: **Urine**	
0.524		0.511		0.980	
0.354		0.501		0.839	
0.734		0.399		0.517	
0.291		0.437		0.498	
0.472	**Mean = 0.47 µg/cm^2/week**	0.347	**Mean = 0.42 µg/cm^2/week**	0.449	**Mean = 0.64 µg/cm^2/week**
0.425	SD = ± 0.16	0.319	SD= ± 0.08	0.537	SD = ± 0.22

C3012228 316L (melt code 316XW), Coil: KO306, Cast: L4964,

A. Test soln: **Sweat**		B. Test soln: **Urine**		C. Test soln: **Plasma**	
0.219		7.229		4.607	
0.218		6.464		4.426	
0.159		6.251		2.941	
0.232		5.577		4.832	
0.213	**Mean = 0.2 µg/cm^2/week**	6.065	**Mean = 6.5 µg/cm^2/week**	5.429	**Mean = 4.6 µg/cm^2/week**
0.218	SD = ± 0.3	7.226	SD= ± 0.66	5.220	SD =± 0.88

All results are calculated as µg/cm^2/week and have been blank corrected

Table 4. (Cont'd) Nickel Release from Stainless Steel Plates in Different Simulants Using EN 1811

C3012229 316L (melt code 316ZA), Coil: K9400/1, Cast: 20327, Finish: Plate with BA

A. Test soln: **Sweat**		B. Test soln: **Urine**		C. Test soln: **Plasma**	
0.505		0.363		0.201	
0.539		0.458		0.298	
0.547		0.371		0.621	
0.351		0.544		0.499	
0.658	**Mean = 0.52 µg/cm^2/week**	0.630	**Mean = 0.50 µg/cm^2/week**	0.589	**Mean = 0.40 µg/cm^2/week**
0.520	SD = ± 0.10 µg/cm^2/week	0.638	SD= ± 0.12 µg/cm^2/week	0.186	SD = ± 0.20 µg/cm^2/week

C3012230 316L (melt code 316ZA), Coil: K8295, Cast: L7106

A. Test soln: **Sweat**		B. Test soln: **Urine**		C. Test soln: **Plasma**	
0.022		0.022		0.063	
0.021		0.044		0.078	
0.015		0.034		0.038	
0.005		0.027		0.046	
0.038	**Mean = 0.02 µg/cm^2/week**	0.029	**Mean = 0.04 µg/cm^2/week**	0.046	**Mean = 0.05 µg/cm^2/week**
0.019	SD = ± 0.01 µg/cm^2/week	0.052	SD= ± 0.01 µg/cm^2/week	0.033	SD = ± 0.02 µg/cm^2/week

C3014223 EN 1.4435, 316S13 *(316VO*), Cast L6231

A. Test soln: **Sweat**		B. Test soln: **Urine**		C. Test soln: **Plasma**	
0.577		0.907		1.205	
0.643		0.967		0.964	
0.592		0.924		1.662	
0.305		0.961		1.133	
0.391	**Mean = 0.53 µg/cm^2/week**	0.838	**Mean = 1.1 µg/cm^2/week**	0.400	**Mean = 1.03 µg/cm^2/week**
0.664	SD = ± 0.15 µg/cm^2/week	2.094	SD= ± 0.48 µg/cm^2/week	0.824	SD = ± 0.42 µg/cm^2/week

All results are calculated as µg/cm^2/week and have been blank corrected

Table 5 Nickel Release from Stainless Steel Wire in Different Simulants Using EN 1811

D3000053 EN 1.4404 Stainless steel wire, 1.6mm Diameter

A. Test soln: **Sweat**		B. Test soln: **Urine**		C. Test soln: **Plasma**	
0.029		0.100		0.152	
0.016		0.097		0.054	
0.021		0.105		0.053	
0.019		0.100		0.047	
0.018		0.095		0.045	
0.016	**Mean = 0.02 µg/cm^2/week** SD = ± 0.01 µg/cm^2/week	0.087	**Mean = 0.1 µg/cm^2/week** SD= ± 0.01 µg/cm^2/week	0.051	**Mean = 0.07 µg/cm^2/week** SD = ± 0.04 µg/cm^2/week

D3000054 Sandvik Bioline 316LVM Stainless steel ground and polished bar, 2.0 mm Diameter (cast 823009)

A. Test soln: **Sweat**		B. Test soln: **Urine**		C. Test soln: **Plasma**	
0.021		0.157		0.058	
0.019		0.099		0.056	
0.022		0.092		0.070	
0.028		0.103		0.070	
0.016	**Mean = 0.02 µg/cm^2/week** SD = ± 0.005 µg/cm^2/week	0.082	**Mean = 0.11 µg/cm^2/week** SD= ± 0.03 µg/cm^2/week	0.044	**Mean = 0.06 µg/cm^2/week** SD = ± 0.01 µg/cm^2/week
0.016		0.128		0.051	

All results are calculated as µg/cm^2/week and have been blank corrected

Table 6 Nickel Release from Finished Articles in Different Simulants Using EN 1811

C3012231 316L Project 70 stainless ear studs Annealed cold drawn (Heat No: 724345)

A. Test soln: **Sweat**		B. Test soln: **Urine**		C. Test soln: **Plasma**	
<0.01		<0.01		0.032	
<0.01		<0.01		0.033	
<0.01		<0.01		<0.01	
<0.01		<0.01		0.031	
<0.01		<0.01		0.031	**Mean = 0.03 µg/cm^2/week**
<0.01	**Mean = <0.01 µg/cm^2/week**	<0.01	**Mean = <0.01 µg/cm^2/week**	<0.01	SD = ± 0.001 µg/cm^2/week

C. Test soln: **Sweat**		D. Test soln: **Urine**		E. Test soln: **Plasma**	
0.013		0.030		0.011	
0.011		0.028		0.011	
0.010		0.025		<0.01	
0.011		0.017		<0.01	
0.011	**Mean = 0.01 µg/cm^2/week**	0.018	**Mean = 0.02 µg/cm^2/week**	<0.01	**Mean = 0.01 µg/cm^2/week**
0.011	SD = ± 0.001 µg/cm^2/week	0.020	SD= ± 0.005 µg/cm^2/week	<0.01	SD = ± 0.001 µg/cm^2/week

All results are calculated as µg/cm^2/week and have been blank corrected

Table 6 (Cont'd) Nickel Release from Finished Articles in Different Simulants Using EN 1811

C3012232 316L Project 70 Gold plated stainless ear studs Annealed cold drawn (Heat No: 724345)

A. Test soln: **Sweat**		B. Test soln: **Urine**		C. Test soln: **Plasma**	
<0.01		<0.01		<0.01	
<0.01		<0.01		<0.01	
<0.01		<0.01		<0.01	
<0.01		<0.01		<0.01	
<0.01		<0.01		<0.01	
<0.01	**Mean = <0.01 µg/cm^2/week**	<0.01	**Mean = <0.01 µg/cm^2/week**	<0.01	**Mean = <0.01 µg/cm^2/week**

C. Test soln: **Sweat**		D. Test soln: **Urine**	
0.094		0.026	
0.029		0.026	
0.014		0.043	
0.037		0.021	
0.052	**Mean = 0.04 µg/cm^2/week**	0.020	**Mean = 0.03 µg/cm^2/week**
0.004	SD = ± 0.03 µg/cm^2/week	0.031	SD = ± 0.01 µg/cm^2/week

C3014220 30200 AISI Butterflies (Heat 3471), polished finish

A. Test soln: **Sweat**		B. Test soln: **Urine**		C. Test soln: **Plasma**	
<0.01		<0.01		<0.01	
<0.01		<0.01		<0.01	
<0.01		<0.01		<0.01	
<0.01		<0.01		<0.01	
<0.01		<0.01		0.012	**Mean = 0.01 µg/cm^2/week**
<0.01	**Mean <0.01 µg/cm^2/week**	<0.01	**Mean = <0.01 µg/cm^2/week**	<0.01	SD = ± 0.001 **µg/cm^2/week**

All results are calculated as µg/cm^2/week and have been blank corrected

Table 7. Nickel Release from Stainless Steel Wire Using EN 1811 by Birmingham Assay Office UK.

D3000053 EN 1.4404 Stainless steel wire, 1.6mm Diameter

Test soln: **Sweat**	
<0.1 <0.1	**Mean = <0.1µg/cm^2/week**

D3000054 EN 1.4404 Stainless steel wire, 1.6mm Diameter

Test soln: **Sweat**	
<0.1 <0.1	**Mean = <0.1µg/cm^2/week**

Detection limit <0.025 µg/cm^2/week

Table 8. Nickel Release from Stainless Steel Wire Using EN 1811 by Sheffield Assay Office UK.

D3000053 EN 1.4404 Stainless steel wire, 1.6mm Diameter

Test soln: **Sweat**	
<0.1 <0.1	**Mean = <0.1µg/cm^2/week**

D3000054 EN 1.4404 Stainless steel wire, 1.6mm Diameter

Test soln: **Sweat**	
<0.1 <0.1	**Mean = <0.1µg/cm^2/week**

Detection limit <0.02 µg/cm^2/week

7.4 Experimental Assessment

The experimental assessment on the stainless steel samples and finished articles has provided a number of observations that are relevant to the factors that determine nickel release from stainless steel. The initial view was that 316L stainless steel or equivalent 'surgical steel' would not release significant amounts of nickel due to the composition of steel. From the results obtained in Tables 4-6, the compositions of the steels have remained fairly consistent with the key analytes for sulfur and nickel broadly similar. The comparison between artificial sweat, urine and plasma has shown significant differences where nickel release from the stainless steel sample has been relatively substantial. The results indicate that the biological fluids urine and plasma release twice as much nickel in comparison as the artificial sweat. The reasons for this are not entirely clear; it was thought that the acidity/alkalinity of the different fluids had a contribution. To clarify the situation the pH was measured for each fluid and gave the following values; artificial sweat pH 6.5, urine pH 6 and blood plasma pH 7. The narrow range of pH of the solutions does not suggest that acidity/alkalinity is a significant factor but is more a relationship of the biological complexing of the metal ion and the organic component.

More significantly was the surface finish of the materials and the subsequent release of nickel ions. Analysis showed where the metal surface is more polished or worked the release of nickel decreases. To show the effect of polishing a number of plates (Table 4.) that gave significant values for nickel release for urine were further polished[6] and retested in accordance with EN1811 using urine, the nickel release decreased by half. Combined with the low release values obtained from the commercial piercing posts and stainless steel wires it is apparent that the surface finish is a significant factor for the release of nickel ions irrespective of composition.

Results for polished articles and wires (Tables 5 & 6) showed the nickel release to be predominately below the detection limit of $<0.01\ \mu g/cm^2$/week or to a maximum release value of $0.03\ \mu g/cm^2$/week for all test solutions using HR-ICP-MS. Confirmation of nickel release values for the stainless wires (D3000053 & D3000054) were sought from two commercial

laboratories in the UK (Tables 7 & 8), who confirmed the nickel release values were <0.1 µg/cm^2/week.

[6] Polishing undertaken by the National Physical Laboratory (UK)

8. Nickel Hypersensitivity and Allergic Contact Dermatitis: Considerations for Risk Assessment

Nickel toxicity and the risks to human health following occupational and non-occupational exposures to nickel have been reviewed and reported in a number of comprehensive articles (ATSDR, 1997; Coogan *et al*., 1989; Fairhurst and Illing, 1987; USEPA, 1996, 1991, 2001; WHO, 1991). Despite the extensive evidence base available for nickel, few studies have been reported which relate to nickel released from stainless steel and hypersensitivity and allergic contact dermatitis (ACD) in humans.

The allergenic potential of nickel in humans is a complex issue which has been linked to a number of factors including nickel bioavailability, dermal penetration of nickel; exposure level and duration; whether the skin is irritated and damaged; age; gender, race and genetic predisposition (Maibach and Menne, 1989; Hostynek and Maibach, 2001 and NiPERA, 1998). The relationship between these factors and nickel hypersensitivity and ACD observed in the general population has not been well characterised.

The risk of sensitisation to nickel and the development of ACD in humans from piercing post assemblies, can essentially be expressed as a function of nickel exposure, quantified by the amount of nickel released from stainless steel per cm^2 of skin in a given time period, and the effect level for each respective endpoint. There is currently insufficient experimental evidence from which thresholds for the induction of nickel sensitivity and elicitation of ACD can be determined. Furthermore, there is insufficient epidemiological evidence from which the prevalence and characteristics of hypersensitivity induced specifically by nickel released from stainless steel used in ear and body piercing or critical exposure factors can be fully assessment. A robust risk assessment can not therefore be carried out at present. In this section, relevant literature and its utility and limitations has been highlighted and discussed.

8.1 Nickel hypersensitivity and allergic contact dermatitis

Elemental nickel and its water soluble salts are potent skin sensitisers in humans, which cause allergic contact dermatitis (ACD). During prolonged and intimate contact with skin, nickel can solubilise to form ions at a rate which depends on the substance and the physiological environment of the skin surface. Nickel ions which are able to pass through the skin barrier, bind to carrier proteins to form the allergen which induces Type IV hypersensitivity mediated by reagins and allergen-specific T lymphocytes. Allergic reactions can manifest in a range of cutaneous eruptions following dermal or systemic exposure (Hostynek and Maibach, 2002). Although ACD and immunological contact urticaria are the primary manifestations of nickel hypersensitivity which can occur in areas of contact as well as distant sites, ACD is more common ((Estlander et al., 1993; Shah et al, 1998).

Two steps are associated with the pathogenesis of nickel ACD. In the first step an individual becomes immunologically sensitised to nickel. This is termed the induction or sensitisation phase and can result from between 1 to 3 weeks of intimate skin contact with a form of nickel that can provide sufficient soluble nickel ions to the skin via sweat. If the skin is already damaged, sensitisation can be induced more quickly and by lower amounts of the solubilised nickel. Temperature, the presence of other allergic conditions, race, gender and age may also be determining factors in the susceptibility for, and the speed, of sensitisation to nickel. Induction of ACD is more common if exposure is combined with skin irritants and/or moist skin. When a sensitised individual is dermally re-exposed to nickel ions on the skin in sufficient amounts, they may experience an allergic response within a few hours. This is termed the elicitation phase which often occurs at a much lower concentration of nickel than required for inducing sensitisation. The elicitation of nickel ACD can occur in skin remote from the site of nickel contact (Zenz and Mosky, 1994).

8.2 Nickel bioavailability

The sensitising potential of nickel released from stainless steel depends on the extent to which nickel ions are able to pass into and across the skin. There is also some evidence that

nickel ACD may be elicited in dermally sensitised individuals following oral, inhalation and intravenous as well as dermal exposure.

Human and animal studies on dermal absorption have been reviewed extensively by Hostynek *et al* (2002) but few robust experimental data were found from which percutaneous nickel absorption could be fully characterised. The penetration pathway is essentially unknown and results from quantification studies vary. Dermal animal and excised human skin studies have reported that nickel compounds were poorly absorbed (i.e. <1%) into the bloodstream, with most of the applied dose remaining on the skin surface. Some studies have discussed the possible biochemical basis for the poor dermal absorption of nickel. Nickel has an affinity for keratin in stratum corneum cells which has a retarding effect on skin penetration rates. Absorption through the appendages (i.e. sweat ducts, follicles and sebaceous glands) appears to proceed at a faster rate than transcellularly. When applied to skin, certain nickel salts were found to require a long induction (lag) period, in the order of 24 to 90 hours before, measurable penetration could be observed due to binding to cellular and intracellular components. Nickel bound to epidermal and dermal tissue was found to form ‘depots’ of the metal in the epidermis which functions as a local reservoir for xenobiotics. Part of the applied dose received by tissues in the skin is therefore likely to be lost by exfoliation. In some studies nickel which had penetrated through the appendages appeared to be sequestered by chelation, primarily by uroanic acid and histidine occuring in human sweat. This process was proposed to prevent nickel absorption.

The potential for stainless steel to release nickel ions on contact with skin has been discussed by Hostynek and Maibach (Hostynek and Maibach, 2002). When tested in artificial sweat using the CEN EN 1811:1998 procedure, most stainless steels show no measurable release of nickel. Stainless steels in a full passive condition (i.e. covered in an intact surface film) have not been found to elicit ACD. If the passive oxide film becomes unstable in a corrosive environment, the stainless steel will become active and may undergo a high rate of corrosion. Release of metal ions could reach significant levels but wide variations are associated with different grades of steel. Favourable exposure conditions for

the loss of passivity include acidity and presence of chloride ions. The severity of the conditions necessary to cause loss of passivity is a function of the grade of stainless steel.

When stainless steel articles form a crevice, for example by tight contact with the skin, the solution within the crevice loses oxygen and acidity can develop by hydrolysis. The fall in pH is dependent on the dimensions of the crevice, the composition of the sweat and the steel and the time taken to reach equilibrium. A patch test conducted on a specimen tightly bound to the skin without movement for 48 hours is proposed to provide a severe corrosive environment for stainless steel. Several studies have been reported where close contact of stainless steel articles with the skin has apparently caused dermatitis.

It has been reported that about 20-35% of nickel is absorbed following inhalation exposure. Most nickel in food remains unabsorbed from the gastrointestinal tract. Human studies have reported that 27% and 0.7% of nickel sulphate in drinking water and food respectively is systemically absorbed.

8.2 Dose-response relationship for induction of sensitisation and elicitation of allergic contact dermatitis

Most experimental protocols employed to investigate nickel hypersensitivity have used patch testing with aqueous solutions of nickel. Few studies have examined the potential for stainless steel to induce sensitisation or considered critical nickel release rates.
Nickel has not been found to be a potent sensitiser in experimental animals. More than twenty- five methods employing combinations of epicuteneous, intradermal and intramuscular administration of nickel sulphate have been used in attempts to induce contact sensitivity in experimental animals and sensitisation rates have varied greatly (Maibach and Menne, 1989). The apparent lack of correlation between the poor allergenic potential of nickel in experimental animals and the high prevalence of hypersensitivity in humans suggest that animals may not be good surrogates for studying nickel immunotoxicity in humans.

The dose-response relationship for the development of nickel sensitivity has been examined in mice (Siller and Suymour, 1994). The sensitisation procedure involved placing an occluded 6 mm pad containing 45 µL of a 0%, 1%, 5%, 10%, or 20% nickel sulphate solution on the shaved abdominal skin of mice for 7 days. The lowest-observed-adverse-effect-level (LOAEL) for sensitisation in mice was reported as 1% aqueous nickel sulphate.

The dose-response relationship for the development of nickel hypersensitivity in humans has not been established and sensitisation studies cannot now be carried out due to the risk of inducing clinical disease. Furthermore, there is some concern that the skin patch test used routinely to diagnose nickel sensitivity can give false results because unsensitised people can become sensitised by the test method.

Although, the robustness and validity many early human sensitisation studies has been questioned, two relevant studies have provided an insight into nickel hypersensitivity in man (Maibach and Menne, 1989). In 1963, Vanderberg and Epstein reported a 9% nickel experimental sensitising rate in a study of 172 subjects exposed to a 48-hour occlusive dermal patch containing a Lintine disc saturated with 25% nickel chloride in a 0.1% sodium lauryl sulphate solution. (Vandenberg and Epstein, 1963). The procedure was repeated three times at 5 day intervals. Ten days after the third exposure, subjects were challenged with 5% and 10% aqueous solutions of nickel chloride. After four months, twenty subjects which had given a negative nickel sensitivity test where re-exposed using the same dosing regime. One of the twenty subjects had developed nickel sensitivity in the interim and 5/19 (26%) subjects developed sensitivity following the second period of exposure. It was reported that prolonged exposure increased the frequency of nickel sensitisation. Furthermore, no experimentally sensitised subjects demonstrated clinical sensitivity to nickel on daily contact which suggested that individuals sensitised using the patch-test method may be able to tolerate daily nickel exposures. In the 1966 Kingman study, the highest induction rate of 12/25 (48%) subjects was obtained with a 10% nickel solution when carried out under optimised conditions (i.e in irritated skin), and a 2.5% nickel solution was found to be the threshold concentration for eliciting contact dermatitis, (Kingman, 1966).

Few studies have been carried out to determine the sensitisation potential of nickel alloys and nickel in stainless steel. Several studies have shown an association between ear-piercing with high nickel content alloy earrings and their subsequent wear and nickel sensitivity (McDonagh et al., 1992; Larsson-Stymne et al., 1985).

Various elicitation studies have been carried out using patch test methods and aqueous solutions of nickel. Patch test studies in sensitive individuals have shown a dose-response relationship between the amount of nickel and the severity of the test response (Emmett et al., 1988; Eun and Marks, 1990). The LOAEL concentration in aqueous solution was 0.0316% (316 ppm).

Athough most patch testing is carried out using nickel sulphate because it is less irritating than nickel chloride, exposure of the skin to nickel alloys results in the release of nickel chloride due to the physiological composition of human sweat. Nickel chloride is the more relevant nickel salt for examining threshold concentrations (Menne, 1994). Meene and Calvin (1993) reported an 8% response rate in sensitised subjects exposed to 0.1% nickel chloride solution.

At the 1997 Dermal Nickel Sensitisation Workshop, the Nickel Producers Environmental Research Association (NiPERA) reported that the percent of sensitised individuals that react to nickel alloys and coatings varies with the rate if nickel released (NIPERA, 1998). It was proposed that percentage reactivity in sensitised individuals increases proportionally with the nickel release rate in µg/cm^2/week. It was suggested that 10% of sensitised individuals are likely to experience allergic contact dermatitis when the release rate is 0.5 µg/cm^2/week (Liden *et al*., 1996). Other studies suggest that up to 30% of the sensitised population may react to a release rate of 0.5 µg/cm^2/week. Studies have reported that some sensitised individuals may react to levels of about 0.05 µg/cm^2/week (Menne et al, 1987; Fischer et al., 1984; Gawkrodger, 1996).

8.4 Immunotolerance

Some studies have reported that non-dermal exposure to nickel can induce immunotolerance in certain individuals which can prevent hypersensitivity occurring after a potentially sensitising exposure. Contrary to expectations, occupational studies of nickel-producing and nickel-using industries have rarely reported workers presenting with symptoms of nickel ACD. The apparent lack of hypersensitivity in occupationally exposed groups may be associated with immunotolerance. Several studies have reported a possible relationship between oral nickel intake the potential for sensitisation to take place. A study of 2159 subjects examining the relationship between ear piercing and orthodontic treatment found that nickel sensitivity was reduced when orthodontic treatment preceded ear piercing (23% versus 38.1% , p,0.005) (van Hoogstraten *et al.,* 1994). The investigators hypothesised that subjects who had been orally exposed to nickel during orthodontic treatment may have become immunotolerant to nickel which helped prevent the sensitisation that occurred following ear piercing with earrings containing nickel. Orthodontic treatment after ear piercing was not found to affect the risk of sensitisation. These findings were supported by an animal study which reported that nickel sensitivity in mice could only be induced consistently when metal frames used to cover cages and water nipples that released nickel were replaced with glass covers and nipples free of nickel (van Hoogstraten et al., 1994). Oral treatment of guinea pigs with nickel sulphate (30 mg/week for 6 weeks) has also been shown to prevent dermal sensitisation (van Hoogstraten et al., 1994). Dermal exposure of guinea pigs to non-sensitising levels of nickel before oral exposure has also been shown to interfere with oral tolerance induction. Immunotolerance has also been demonstrated in mice following either intravenous or oral nickel exposure. Furthermore, T-lymphocytes from nickel tolerant mice could be successfully transferred to other mice to protect them from developing nickel hypersensitivity.

8.5 Non-dermal nickel exposure and elicitation of allergic contact dermatitis

Although systemic elicitation of ACD in sensitised individuals by direct skin contact has been well documented, some controversy exists about the ability of nickel to elicit a

systemic allergic response when ingested, inhaled or received intravenously (Menne et al, 1994).

A number of studies have reported that the ingestion of nickel salts can induce dermatitis in individuals who have a propensity to develop allergic dermatitis from dermal contact with nickel (ATSDR, 1997; USEPA, 2001; WHO, 1991). These studies have reported that a large number of adult dermatitis patients with patch test sensitivity to nickel suffer an exacerbation of their skin conditions when given nickel at doses in the range 0.5-2.5 mg /day (7-35 µg/kg bodyweight/day). These studies were, however generally difficult to interpret with confidence because only small numbers of patients were tested; observed effects could not exclusively be associated with nickel and placebo-treated controls where not studied. A few studies have shown that nickel-sensitive individuals orally given 0.5 mg/day nickel (as $NiSO_4$) as a single dose had a dermal allergic response.

The contribution of dietary nickel to dermatitis is unclear (Gawkrodger et al, 1986). Although orally administered nickel has been shown to elicit dermatitis in nickel-sensitive individuals, this is likely to be associated with high doses which are unlikely to be encountered in the normal diet (Gawkrodger et al, 1986). Given that the average daily dietary intakes of nickel range from 140-150 µg/day for UK adults and 14-250ug for UK children and around 1 –10% of the ingested dose is likely to be absorbed, (EGVM, 2002) dietary exposure to nickel is unlikely to present a significant risk of eliciting ACD in nickel sensitive individuals. Some researchers suggest that dietary control of nickel intake may help in the ongoing treatment of nickel ACD caused by other sources.

Studies have reported that intravenous administration of 1-3 mg of nickel can elicit severe ACD in sensitised patients.

The potential aggregate and cumulative risks of developing ACD following combined dermal and non-dermal exposures to nickel, including possible effects of non-dermal exposures on dermal elicitation thresholds is not known.

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9. Discussion

In the interim report it was recommended that the following points should be addressed:

- To determine the nickel release rate into artificial sweat, blood, plasma and urine of two well-characterised AISI 316L stainless steels.
- To complete the risk assessment into the potential of stainless steels to induce sensitisation to nickel after ear or body piercing.
- To consider the issue of homogeneity.
- Applicability of the current nickel-release test method, EN 1811, to ear and body piercing post assemblies; particularly in terms of the simulant employed.
- To make recommendations on how the Nickel Directive could be amended to achieve a sensible and practicable requirement and a high degree of safety, for the marketing and use of piercing post assemblies.

The measurement of nickel release into artificial sweat blood, plasma and urine from a number of different AISI 316L stainless steel plates, wires and articles have shown that the surface finish is a factor as well as the composition. This has shown that designating a particular grade of steel (i.e. surgical steel') only by its composition as being acceptable for use as piercing posts is incorrect. More importantly, is whether the stainless steel has been polished or finished. This is not to say that AISI 316L or 'surgical steel' should not be used but unless a minimum quality of finishing can be specified or designated it cannot be assumed that no measurable nickel will be released. The results also show that where nickel is released from stainless steel the rate of release is approximately double for blood plasma and urine compared to artificial sweat. The reasons for increased nickel release using the biological fluids are not clear although nickel ions may be preferentially complexed with the components in the blood or urine (it is known that ammonia ions will complex nickel). Whatever the reasons for increased rate of nickel release into blood plasma and urine, it is worth reiterating that for finished/polished stainless steels plates and post assemblies the levels of nickel release were around the detection limit <0.01 $\mu g/cm^2$/week using the more

sensitive analytical detection technique (ICP-MS). Other laboratories that tested the same samples using a more widely available technique (ICP-OES) had detection limits of 0.02-0.025 µg/cm^2/week. Normally, for trace analysis work the limit of detection would not provide the certainty of a positive result and a quantitation limit (LOQ) is specified as the lowest level uncertainty is acceptable. This is usually a matter of judgement but for this type of work but usually the detection limit is multiplied by a factor of ten. From the analytical perspective a limit of quantification (LOQ) would be <0.1 µg/cm^2/week for ICP-MS and <0.2-0.25 µg/cm^2/week for ICP-OES can be attained. Therefore it is possible for most laboratories to measure a LOQ value of <0.2 µg/cm^2/week.

In compiling a risk assessment it become apparent that there is no conclusive data that enables a value for nickel release from stainless steel piercing posts that will induce sensitisation in humans to be determined. It is also unlikely that such a value will be able to be determined in the short term, as it would require deliberately sensitising humans to known concentrations of nickel and that is ethically unacceptable. In the future novel techniques using cell lines may be developed but to-date researchers have concentrated on the levels that sensitised individuals are likely to experience allergic contact dermatitis. These studies on sensitised populations use patch testing with solutions of known nickel concentration to elicit an allergic response. In these studies it has been suggested that 10% of sensitised individuals are likely to experience allergic contact dermatitis when the nickel release rate is 0.5 µg/cm^2/week (Liden *et al*., 1996). Other studies suggest that up to 30% of the sensitised population may react to a release rate of 0.5 µg/cm^2/week. Studies have reported that some sensitised individuals may react to levels around 0.05 µg/cm^2/week (Menne et al, 1987; Fischer *et al*., 1984; Gawkrodger, 1996). The Nickel Directive has set the rate of nickel release from those parts of such products coming into direct and prolonged contact with the skin will not exceed 0.5 µg/cm²/week for a period of at least two years of normal use of the product. In the absence of any other data on the level of nickel that will induce sensitisation the most logical approach would be to examine feasibility of adopting the existing requirement for nickel release of 0.5 µg/cm²/week that is intended to minimise the risk of eliciting allergic contact dermatitis in sensitised people. This would most likely provide the protection given that higher levels of nickel exposure are likely to

be necessary to induce nickel sensitisation compared with the elicitation of allergic contact dermatitis. However, the release rate of 0.5 µg/cm²/week applies to parts of such products coming into direct and prolonged contact with the skin using artificial sweat as migration media. During epithilization the release media is blood plasma rather than sweat and therefore consideration needs to be made as to whether a nickel release rate of 0.5 µg/cm²/week is applicable. As demonstrated in experiments in this report using EN 1811, the rate of release of nickel ions from stainless steel into blood plasma compared to artificial sweat is approximately double. It could be argued that for piercing posts that blood plasma or an equivalent solution should be used as the release media for stainless steel piercing posts to mimic the effect of epithilization. However, the use of biological fluids can cause problems in testing due to matrix and other interferences requiring specialist knowledge. Therefore, it would be sensible to continue to use artificial sweat but lower the limit by half to account for effect of blood plasma. This suggests that the release limit of 0.5 µg/cm²/week should be halved to 0.25 µg/cm²/week. As highlighted at the beginning there is no conclusive data that enables researchers to determine a value for nickel release that will induce sensitisation in humans and therefore this cannot be viewed as a risk assessment in its correct sense. A nickel release rate of 0.25 µg/cm²/week using EN 1811 should provide protection for the majority of the population using post assemblies.

The question of homogeneity has been raised and relates to metal posts and assemblies composed of layers of metals such as gold plating on the surface of the piercing post made of steel or some other alloy. Previously, it was found that gold plated stainless steel posts would release significant amounts of nickel above the limit for release of 0.5 µg/cm²/week. This was found to be due to the use of nickel as an inter-liner material that allows the gold to be deposited on the surface of the steel post. This question is important if a compositional requirement was specified rather than a release rate as not only would the stainless steel need to be specified but also the other materials used in manufacture and the finishing to ensure the product was of sufficient quality to prevent significant nickel release. This would cause difficulties in checking both for enforcement authorities as well

as industry itself. This gives weight to the argument that piercing posts and any other similar jewellery should be assessed on the nickel release rather than composition or finish.

The application of the current nickel-release test method, EN 1811, to ear and body piercing post assemblies using different simulants did not show any problems using urine or blood plasma although specialist equipment and staff was necessary to determine the nickel content in biological solutions. Higher nickel release values were obtained for blood plasma and urine compared to artificial sweat and it has been suggested that this is due to the nickel ions preferentially complexing with ammonium ions as in the case of urine. As already discussed, the use of solutions other than artificial sweat was likely to create difficulties for testing laboratories that are familiar using EN 1811 with artificial sweat and the need to re-validate the method for a different stimulant.

In conclusion, specifying a particular type of stainless steel as suitable as a piercing post is not practical as it has been shown that stainless steels with the same composition will release nickel at different rates mainly due to the surface finishing. Specifying the surface finishing would present technical difficulties with specialist facilities required by both industry and enforcement agencies with no guarantee that the nickel release rate was below any acceptable limit. The best approach for determining whether a piercing post made of stainless steel or any other alloy is likely to release nickel is to measure the nickel release under controlled conditions. It has been shown that laboratories using EN 1811 with artificial sweat and standard equipment can obtain a limit of quantification (LOQ) on a commercial stainless steel piercing post of <0.2 $\mu g/cm^2$/week. In the risk assessment it is suggested that a release limit of 0.25 $\mu g/cm^2$/week using EN 1811 with artificial sweat would best protect the majority of the population and enable stainless steel piercing posts to be used during the period of epithilization. As many commercial stainless steel products and wires were shown not to release nickel above the analytical detection limit of the test equipment and was below the limit of 0.25 $\mu g/cm^2$/week, it was decided to set the limit at 0.2 $\mu g/cm^2$/week for a high level of consumer protection.

10. Recommendation

It is recommended that the existing requirement for the maximum nickel content of 0.05% m/m in post assemblies as described in the Nickel Directive is replaced by a nickel migration limit for all post assemblies of 0.2 µg/cm^2/week when tested in accordance with EN 1811.