EUROPEAN COMMISSION
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Directorate C – Public Health and Risk Assessment
C7 – Risk Assessment
Scientific Committee on Toxicity, Ecotoxicity and the Environment

OPINION OF THE SCIENTIFIC COMMITTEE ON TOXICITY, ECOTOXICITY AND THE ENVIRONMENT (CSTEE) ON

THE LGC'S REPORT ON
"RISKS OF SENSITISATION OF HUMANS TO NICKEL BY PIERCING POST ASSEMBLIES"
Final report 31 March 2003 - Contract No. EDT/FIF.2001592

Adopted by the CSTEE during the 40th plenary meeting
of 12-13 November 2003

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INTRODUCTION

Directive 94/27/EC 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 products that might lead to sensitisation such as post assemblies which are inserted into pierced parts of the human body and other jewellery.

The European Commission supported a study on "The risks of sensitisation of humans to nickel by piercing post assemblies", undertaken by LGC, to evaluate the scientific knowledge 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.

LGC measured nickel release from similar stainless steels with different surface finish or from a number of different stainless steels using three fluids likely to be in contact with the post assemblies during the period of epithilization (artificial sweat, blood plasma and urine).

To limit the risks of sensitisation of humans to nickel by piercing post assemblies, the LGC report eventually proposed to establish a regulatory approach for piercing post assemblies by the specification of a maximum nickel release value determined under controlled conditions. The composition, metallurgical structure and surface finish of the products, for which specification could present technical difficulties, would not have to be considered.

LGC recommended that the existing requirement for the maximum nickel content of 0.05% by mass in post assemblies as described in the Directive 94/27/EC is replaced by a nickel migration limit for all post assemblies of 0.2 µg/cm^2/week using the methodology specified in the European Standardised method EN 1811:1999 ('Reference Test Method for Release of Nickel from Products Intended to come into Direct and Prolonged Contact with the Skin').

Terms of reference

The CSTEE is requested to assess the overall scientific quality of the LGC report. In considering this, the CSTEE is asked to comment on the findings, conclusions and recommendation of the report.

CONCLUSION

The CSTEE finds the overall scientific quality of the report insufficient, the report is not very well structured and the justification of the migration limit recommended rather poor.

Nevertheless, the CSTEE agrees with the report that the current legislation based on nickel content by mass may induce higher risks than if it would be based on a nickel migration limit. Setting a limit on release makes the issue of composition, metallurgical structure and surface finish essentially irrelevant.

The CSTEE agrees with the recommendation in the report that the maximum nickel **content** of 0.05% in post assemblies as described in the Nickel Directive of 1994 is replaced by a nickel **migration** limit of 0.2 µg/cm2/week.

GENERAL COMMENTS

The report is poorly structured and therefore is not very easy to read. Chapter 5 includes the reference list for chapters 4 and 5; chapter 6 and 8 have their own list. Chapter 7 concerns experimental work on nickel release from high grade stainless steels and includes methodology, samples investigated, results and experimental assessment. Besides discussion of the experimental work covered in chapter 7, the discussion is in two parts (chapter 6, p. 26 and chapter 9, p. 64), which is not very coherent. It seems that the report has been produced in two separate steps.

It is never questioned in the report whether other metals that may be present at high levels in stainless steels (such as chromium) may play a role in the allergy, so-called concomitant allergy (*e.g*. van Hoogstraten *et al*., 1992a; Uter *et al*., 1995; Wong *et al*., 1998).

SPECIFIC COMMENTS

Chapter 1 - Introduction

The term allergic reactions is not properly defined: “mild irritation” should be replaced by “mild skin reaction”.

Chapter 2 – European Directive 94/27/EC - ‘The Nickel Directive’

This chapter gives clear explanations on the objective and requirements of the Directive 94/27/EC on the restriction of the use of nickel and its compounds in products that come into close and prolonged contact with the skin. According to this directive, for post assemblies the **concentration** of nickel should be less than 0.05%, and for products intended to come into direct and prolonged contact with the skin the nickel **release** should be less than 0.5 µg/cm2/week

Chapter 3 – Stainless steels

This chapter describes the categorisation and composition of the existing stainless steels.

The CSTEE noticed that a very high level of nickel content can nevertheless result in a very low nickel release.

The CSTEE questions the reproducibility of release values with regards to the variability of the products made in plants and factories.

No explanation is given how the different elements in the stainless steels may influence the release of nickel. If this information is known, it should have been provided.

Chapter 4 – Metabolism and Toxicology of Nickel

Metabolism is not really addressed in this chapter. The title does not reflect its content, which focuses on kinetics and toxicology.

The sentence "Orally administrated nickel can cause a dermatitis ..." is misleading (p.15, 1st§), as high oral doses can induce elicitation in sensitised people but do not cause primary dermal reactions.

The working group agrees that occupational exposure to nickel can cause rhinitis, asthma and dermatitis (p.15, 2nd§). However, references should have been provided to support this statement. In addition, it seems contradictory with the statement that symptoms of nickel have been rarely reported in workers (p.58).

As mentioned in the report nickel has indeed pre-inflammatory (pre-immune) effects, but it would have been relevant to expand on this. In addition, what is missing in the report is a description of the mechanisms of sensitisation (p.15, 3rd§), including the role of dermal antigen presenting cells.

Chapter 5 – Demography of Nickel Dermatitis

The reference (Peltonen, 1979) supporting the level of population (10% of women and 1% of men) affected by nickel allergy is old and is not included in the list of references (p.16, 1st§). More recent data indicate that around 12% of women and 2% of men are affected (Andersen *et al*., 2001).

Chapter 6 – Nickel Sensitisation and Release from Stainless Steel

Literature search

In this chapter studies on nickel sensitisation and release from stainless steels are discussed one by one, which contrasts to the format of the other chapters. The review seems extensive, but two studies (Fisher *et al.*, 1984 and Gawkrodger, 1996) that are cited in chapter 9 (p. 65) should have been included here as they apparently confirm that sensitised people may react to levels around 0.5 µg/cm2/week.

The report clearly shows that it is indeed quite difficult to get solid data on the risks of sensitisation by metal and no peer-reviewed papers have been published as mentioned in the report (p.26, 1st§).

The last paragraph in p. 27 gives a wrong impression that more studies on primary sensitisation are needed in man. It should be clear that for ethical reasons the risk of primary sensitisation should be deducted from data on elicitation. Animal models have in fact been used to determine the ratio of doses needed for sensitisation versus elicitation (see comments on chapter 8).

There is neither real discussion nor conclusion in the discussion and conclusion sections (p.26-30) of this chapter. As a basis for the final discussion and recommendation (Chapters 9 and 10) there should have been a real discussion of the most relevant studies to try to derive a threshold value of nickel release below it is unlikely that an allergic response is elicited in previously sensitised persons.

Chapter 7 – Evaluation of High Grade Stainless Steels

The title should clearly reflect that it provides experimental data on nickel release from high grade stainless steels. The section on methodology is very poor (*e.g.* number of samples investigated).

Results of the experimental release studies indicate i) that nickel releases in urine and plasma are approximately twice as much as in artificial sweat, a finding that is not explained by differences in pH as the range of the pH of the solutions is rather narrow (artificial sweat pH 6.5, urine pH 6 and blood plasma pH 7) but is perhaps due to complexing of the metal ion with organic components; and ii) the surface finish is a significant factor for the release of nickel ions irrespective of the composition: nickel release from polished articles and wires was mostly below the detection limit of 0.01 µg/cm2/week.

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

Introduction

It should be clear that, although it is difficult to determine thresholds for the induction of nickel sensitivity, available data could be used (p. 52, 3rd§).

Nickel hypersensitivity and allergic contact dermatitis

In the report both allergic contact dermatitis (ACD) (type IV hypersensitivity) and urticaria (type I, IgE mediated reactions ("urticaria") are mentioned as primary manifestations of nickel hypersensitivity, with ACD being more common. However it is very seldom to find IgE mediated reactions (in the cited paper by Estlander *et al.*, one single patient is reported) (p. 53, 1st§).

Nickel bioavailability

"Some evidence" on the elicitation by oral, inhalation, intravenous and dermal exposure in sensitised individuals, should be replaced by "abundant evidence" (p. 53, last §).

The process of sensitisation should be explained in an appropriate way (p. 54, 2nd§). The crucial point is the binding of nickel by the dermal Langerhans cells as antigen presenting cells but not how it is absorbed through the skin (see also comment regarding chapter 4)

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

In the report it is suggested that animals may not be good surrogates for studying nickel immunotoxicity in humans (p. 55, last §). An explanation for this is given in the next section. Animal models have in fact been used for the important issue to determine the ratio of doses needed for sensitisation versus elicitation in animals (see Polak, 1980). In the guinea pig, the optimal intradermal sensibilisation dose of nickel is 600 µg. This yields a ratio of 30 with an epicutaneous elicitation dose of 20 µg and a ratio of 24 with an intradermal elicitation dose of 25 µg (van Hoogstraten *et al.*, 1992b). In the mouse, a ratio of 100-300 has been reported (intradermal sensibilisation dose of 300 µg and intradermal elicitation dose of 1-3 µg) (van Hoogstraten *et al.*, 1993).

Immunotolerance

As mentioned in the report animal studies indeed show some limitations (p. 58, 1st§) because under normal conditions laboratory animals are already tolerant due to the contact with material from cages (covers, water nipples). More recent data are available regarding animal models for nickel allergy and nickel intolerance and should have been included (*e.g.* Artik *et al*., 1999; 2001; Roelofs-Haarhuis *et al*., 2003).

Non-dermal nickel exposure and elicitation of allergic contact dermatitis

Individuals "who have a propensity to develop allergic dermatitis" should be replaced by "who are already sensitised" (p. 59, 2nd§).

Chapter 9 – Discussion and Chapter 10 – Recommendation

Chapter 9 begins with mentioning an interim report that is neither quoted nor available to the working group. Here it again shows that the report is not very well structured. This chapter should have provided a better discussion of available data, identify key studies, describe uncertainties and then come up with a justification of the migration limit proposed.

In the discussion chapter, studies are cited indicating that 10 to 30% of sensitised individuals are likely to experience allergic contact dermatitis with a nickel release rate of 0.5 µg/cm2/week; some sensitised individuals may react to levels around 0.05 µg/cm2/week. These studies have apparently been the basis for the Nickel Directive of 1994 setting the release limit of 0.5 µg/cm2/week for products intended to come into direct and prolonged contact with the skin. Based on experiments reported in chapter 7, that nickel releases in blood plasma and urine are approximately twice as much as in artificial sweat, it is proposed that the release rate of 0.5 µg/cm2/week should be halved to 0.25 µg/cm2/week. According to the report, this limit would best protect the majority of the population and enable stainless steel piercing posts to be used during the period of epithelization. From the analytical perspective, using EN 1811 with artificial sweat, it is possible for most laboratories to measure a limit of quantification (LOQ) of <0.2 µg/cm2/week.

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 µg/cm2/week, it is recommended that the maximum nickel content of 0.05% in post assemblies as described in the Nickel Directive of 1994 is replaced by a nickel migration limit for all post assemblies of 0.2 µg/cm2/week when tested in accordance with EN 1811.

The CSTEE acknowledges that the nickel cut-off release value cannot be accurately defined based on the data available. However, it is clear that the figure of 0.5 µg/cm2/week used in the Nickel Directive of 1994 and subsequently used for recommending the 0.2 µg/cm2/week limit for post assemblies does not protect the whole population. For example, the study by Haudrechy *et al.* (1997) (p. 21) showed that in 4% of nickel-sensitised patients the high-sulphur AISI 303 elicited contact dermatitis (this stainless steel sample released 0.3 µg/cm2/week at pH 6.6, a value in the range of 6.45 to 6.55 of artificial sweat as described in the Standard EN 1811). However, following piercing epithelization of the wound will occur which will limit the release of nickel, an issue not addressed in the report. Finally, if in practice the level set at 0.2 µg/cm2/week appears not safe in every nickel-sensitive individual, allergic contact dermatitis can be cured by removing the post assembly, an issue also not addressed in the report.

The CSTEE agrees with the report that the current legislation based on nickel content by mass may induce higher risks than if it would be based on a nickel migration limit. Setting a limit on

release makes the issue of composition, metallurgical structure and surface finish essentially irrelevant.

In conclusion, although the justification of the migration limit is rather poor in the report, the CSTEE agrees with the recommendation that the maximum nickel **content** of 0.05% in post assemblies as described in the Nickel Directive of 1994 is replaced by a nickel **migration** limit of 0.2 µg/cm2/week.

N.B.: The CSTEE notes that the report does not discuss the use of the adjusted multiplication factor of 0.1 to the test result as required in the European Standard EN 1811 (7.1). This factor accounts for the imprecision of the method to measure the nickel release rate, including difficulties in the measurement of the surface area of intricately-shaped articles. Piercing studs, however, have very simple surfaces and there is no rationale to apply the adjustment factor.

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