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PROLONGED CONTACT WITH THE SKIN - DEFINITION BUILDING FOR NICKEL

Background

In the nickel (Ni) restriction (Entry 27 of Annex XVII to REACH) the release threshold has been set at 0.5 µg Ni/cm^2/week. This concerns articles which are intended to come into direct and prolonged contact with the skin. However, the restriction does not define the term "prolonged contact with the skin" and its possible interpretation has therefore been raised. A proposal for a definition was discussed in CARACAL in October 2010 (Questions and Answers on the restrictions in Annex XVII of REACH, Doc. CA/8/2010). However, Member States required more detailed information of the scientific background for the proposal. The Commission contacted ECHA on 8 February 2011 and requested ECHA to investigate the issue and provide to the Commission and to the Member States a justified value/definition or any additional information that could clarify how to understand this "prolonged contact" in relation to the Ni entry.

ECHA prepared a draft document with a proposal for a definition and its justification. The draft document was send to the Commission services (DG Enterprise and DG Environment) on 19 October 2012 and comments were received on 15 November 2012. Based on these comments the draft document was revised and an expert opinion was sought from the Karolinska Institutet/Prof. Carola Lidén on 21 December 2012. In addition the Commission services consulted the German mirror Committee for CEN/TC 347 "Methods for Analysis of Allergens" with the draft document. The expert opinion from the Karolinska Institutet/Prof. Lidén and her colleagues was received on 21 March 2013 and comments from German mirror Committee for CEN/TC 347 were received on 8 March 2013. The comments relevant to definition building with the focus on the contact time to articles releasing Ni above the release threshold of 0.5 µg Ni/cm^2/week have been taken into account in preparation of this document.

The aim of this document is to provide a proposal for a definition for "prolonged contact with the skin" in relation to nickel restriction with justification based on the scientific evidence available. A detailed description on the approach taken and scientific justifications are provided in Annex 1. The text in the Ni restriction with additional information is provided in Annex 2 and some further considerations related to conducted consultations during the process are in Annex 3.

Definition of "prolonged contact with the skin" in relation to nickel restriction (Entry 27 of Annex XVII to REACH)

After reviewing and evaluating the available relevant scientific information the following minimum contact time as a definition for "prolonged contact with the skin" in relation to nickel restriction (Entry 27 of Annex XVII to REACH) is provided:

> **Prolonged contact with the skin is defined as contact with the skin of nickel of potentially more than**
> - **10 minutes on three or more occasions within two weeks, or**
> - **30 minutes on one or more occasions within two weeks**.

The skin contact time of 10 minutes applies when there are three or more occasions of skin

contacts within a two-week time period. The skin contact time of 30 minutes applies when there is at least one occasion within a two-week time period.

Justification of the definition

Starting from the time-related information on Ni release from alloys combined with information on Ni-sensitised subject's reactions to different doses, and information on skin uptake and penetration, it was estimated which contact time would sufficiently protect Ni-sensitised and not yet sensitised subjects from contact dermatitis. Further assessment of impact of sensitivity of the skin area, size of the skin area, and repetition of exposure to skin contact time needed for skin reactions were done. A contact time of 30 minutes of an alloy releasing Ni at the rate of the legal threshold should be adequately protective towards skin reactions in most of the Ni-sensitised individuals. The repetition of exposure is taking into account as minimum 3 contact times per two weeks, reflecting the turnover time of one month for the epidermis and allergen retention for two weeks. This leads to the definition for "prolonged contact with the skin" of "more than 10 minutes on three or more occasions within two weeks, or 30 minutes on one or more occasions within two weeks".

Annex 1 Background information

1. The Nickel restriction and basis of the legislative threshold

Entry 27 of Annex XVII to REACH states that nickel (Ni) shall not be used "in articles intended to come into direct and prolonged contact with the skin…, if the rate of nickel release from the parts of these articles coming into direct and prolonged contact with the skin is greater than 0.5 µg/cm^2/week". The entire entry 27 is attached as an Annex 2.

In large patch test studies with a two-day skin contact time, Ni-allergic subjects were exposed to metallic discs of known composition with known release of Ni into artificial sweat (discussed in Thyssen et al., 2012). Alloys with a release rate between 0.2 and 0.5 µg/cm^2/week caused positive test reactions in 11-54% of the tested 173 Ni-sensitive individuals, while 56-81% of subjects were test positive to alloys with release above 1 µg/cm^2/week (Menné et al., 1987). In a smaller and limited study by Fischer and coworkers (1984, as referred in Fischer et al., 2005), all of the 18 Ni-sensitive subjects reacted to at least one white gold sample when tested with different unplated white-gold discs (total area 0.8 cm^2 releasing 0.09-0.82 µg Ni/week or with rhodium-plated white gold discs releasing 0.04-0.54 µg Ni/week. A further study (Lidén et al., 1996) indicates that 17% of the one hundred Ni-allergic subjects reacted to a white gold alloy (quality control material) which had a Ni release of 0.4 µg/cm^2/week.

The "direct and prolonged contact" is not defined in the restriction. The interpretation in this document is concentrating on the duration of the contact that can be expected from the items within the meaning of the Entry 27. It should be noted that the current restriction entry does not cover coins, even though the information on coins has been used as supporting evidence. Furthermore the European Union Risk Assessment Report on nickel (2008) did not find concern from coins or other nickel releasing objects e.g. tools for workers or consumers, even though addressed uncertainties in its assessment.

2. The proposal for a definition of "prolonged contact with the skin" discussed in CARACAL 2010

During previous discussion in CARACAL (2010) on a definition for "prolonged contact with the skin", the Commission proposal based an expert judgement (after discussion e.g., with Torkil Menné from DK) was the following:

> Daily overall contact with skin of more than 30 minutes continuously or 1 hour discontinuously.

3. Detailed approach and justification for the definition provided by ECHA

The definition on "prolonged contact with the skin" has been derived to support the implementation of the legislative threshold for Ni release of 0.5 µg/cm^2/week. An approach has been developed by ECHA which relies on measured time-related releases of Ni from alloys in concert with the information on nickel specific mechanisms and human data. According to the review of the recent scientific information relevant for the definition building for Ni, no measurements are reported which would provide direct information on the duration, minimum concentration and impact of repetitions that could be used to define the duration for "prolonged contact with the skin" necessary to cause allergic skin reactions. A detailed description on the approach applied and its justifications are provided in this Annex 1. The text in the Ni restriction with additional information is provided in Annex 2 and some further considerations related to conducted consultation during the process are in Annex 3.

The proposal is based mainly on the following information:

1) Information from dose-response relationships based on data from clinical patch tests (with two-day long exposure) with Ni-solutions ($NiSO_4$).
    a. 5% of the Ni-sensitised population are estimated to react to an occluded dose of 0.44 µg Ni/cm^2/2 days, and 1% to an occluded dose of 0.067 µg/cm^2/2 days (Fischer et al., 2005).

2) Information from patch tests with alloys releasing Ni at or below the legal threshold level.
    a. Reactions are noted in certain Ni-sensitive individuals when testing alloys releasing below 0.5 µg/cm^2/week (Menne et al., 1987).
    b. 17% of Ni-allergic individuals reacted to a white gold alloy with Ni release of 0.4 µg/cm^2/week (Lidén et al., 1996)
    c. Ni-sensitive individuals may react to alloys releasing very low amounts, such as 0.04 µg/cm^2/week (Fischer et al., 1984)

3) Information from time-related Ni release from alloys including coins (Julander et al., 2009; Lidén et al., 2008; Karolinska Institutet/Lidén C et al., 2013 unpublished opinion).

4) The amount and rate of Ni ($NiCl_2$ vs $NiSO_4$) permeation/absorption by the skin (Fullerton et al., 1986, Hostynek 2003) including information on skin area permeation/sensitivity (Hostynek 2003).

5) Repetitive contact and allergen specific memory of the skin
    a. Repetitive short exposure at low concentrations is a stronger stimulus than less frequent longer exposure at the same or higher concentrations (discussed in Fischer et al., 2007).
    b. Deposition/accumulation of Ni on the skin (Lidén et al., 2008; Staton et al., 2006) and in (epi)dermis (Fullerton and Hoelgaard, 1998, Fullerton et al., 1988).
    c. Turnover of epidermis (Bergstresser and Taylor, 1977), antigen-bearing Langerhans cells (reviewed in Boukhman and Maibach, 2001),
    d. At least one month allergen-specific memory of the skin (Hindsén and Bruze, 1998; Rustemeyer et al., 2011)

This information is described and discussed during the definition building Steps 1-5 below.

Step 1. Relationship between Ni concentration and skin reactions from clinical patch tests and tests using alloys

The patch test detects the highest proportion (89%) of Ni-sensitised subjects when using 5% $NiSO_4$ in petrolatum as the testing solution (this is generally used diagnostic patch testing in Europe) (Seidenari et al., 2005). In addition, 12.5% of the subjects reacted to 0.005% $NiSO_4$. Non-sensitised subjects are reported not to react to $NiSO_4$ exposure. The amount of Ni used in the clinical patch test is 184 µg/cm^2 for a 2-day exposure which is much higher than the legal threshold for Ni release from an item (0.5 µg/cm^2/week). Dose-response studies indicate a clear relationship between different concentrations of Ni and incidence of individuals with skin reactions (e.g. Seidenari et al., 2005; Fischer et al., 2005; 2007). The percentage of the Ni-sensitised subjects reacting to different concentrations in clinical patch tests were 10%, 5% and 1% at 0.530 (Staton et al., 2006), 0.44 and 0.067 µg/cm^2/2 days (Fischer et al., 2005), respectively.

However, also high incidences have been reported using alloys; 17% of the one hundred Ni-allergic subjects reacted to a white gold alloy (quality control material) which had a Ni release of 0.4 µg/cm^2/week (Lidén et al., 1996). Reactions are noted in certain Ni-sensitive individuals when testing alloys releasing below 0.5 µg/cm^2/week (Menné et al., 1987). Alloys with a release rate between 0.2 and 0.5 µg/cm^2/week caused positive test reactions in 11-54% of the tested 173 Ni-sensitive individuals, while 56-81% of subjects were test positive to alloys with release above 1 µg/cm^2/week (Menné et al., 1987). In addition, Ni-sensitive individuals may react after a two-day exposure to alloys releasing very low amounts, such as 0.04 µg Ni/week (assuming per square cm; Fischer et al., 1984).

Critical information taken for further calculations/estimations: Five and one percent of Ni-sensitised subjects react to Ni doses of 0.44 and 0.067 µg/cm^2/2 days in patch tests. In addition 17% of Ni-allergic subjects reacted after a 2-day exposure to an alloy releasing 0.4 µg/cm^2/week and 11-54% reacted to alloys releasing between 0.2 and 0.5 µg/cm^2/week; some individuals may react also to alloys releasing very low amounts, such as 0.04 µg Ni/week.

Step 2. Ni release from alloys at various time points

In order to evaluate the relationship between Ni release from an item and exposure duration leading to skin reaction, information on time-related Ni release from alloys into artificial sweat was reviewed. In some examples from hard metal alloys with weekly release comparable to that of the legal threshold, the release of Ni increased by approximately 10-fold from one hour measurement point to one day measurement point, and 2-fold from one day time point to one week time point (the release of Ni was 0.39 or 0.48 µg/cm^2/week, 0.17 µg/cm^2/day, 0.020 µg/cm^2/hour, and <0.001 µg/cm^2/2 minutes for sample D (Table 1, Figure 1; Julander et al., 2009)).

Table 1. Estimations of the factors describing the cumulative increase in Ni release from a hard metal alloy based on Julander et al., 2009.

	2 min	1 hour	1 day	1 week	1 week
Release (µg/cm^2)	<0.001	0.020	0.17	0.39	0.48
Factor			~10 x release at 1 hour (8.5x)	~2 x release at 1 day (2.3x)	(2.8 x release at 1 day)

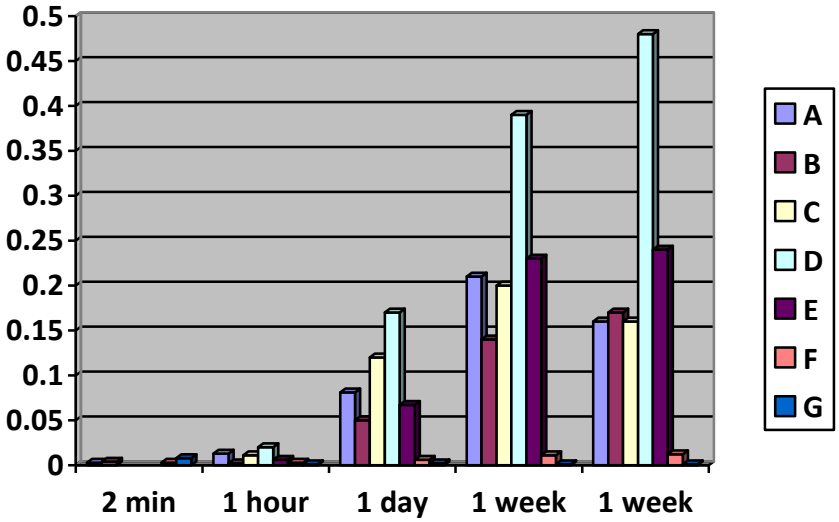

Figure 1. Ni release (µg/cm^2) from hard metal alloys in artificial sweat; A to G represents different alloys (based on information in Julander et al., 2009).

Using these approximations, release of Ni during one day would be approximately half of the weekly release. The release during the first hour would be around one tenth of the release during the first day (Table 1) indicating highest rate (speed) of release at the beginning. Based on this data, it can be estimated how much any weakly release would correspond to release at shorter time points. Taking the legal threshold of Ni release of 0.5 µg/cm^2/week from a hard metal item as a starting point, a release of 0.025 µg/cm^2 during the first hour and a release of 0.25 µg/cm^2 during the first day can be estimated (Table 2). Further, release during the first 30 minutes can be calculated by assuming linear increase of Ni release between 2 minutes and one hour time points and using interpolation to 30 minutes time point. An estimation of release value of 0.013 µg/cm^2/30 min for an item releasing 0.5 µg/cm^2/week is obtained (Table 2).

Similar release pattern, although with higher values, has been reported by Lidén et al. (2008) from coins indicating that 1 SEK coin would release around 121 µg/cm^2 per week (range 117-129), approximately one half of that during one day (mean of 52, range 35-60 µg/cm^2) and one tenth of that during one hour (mean of 4.3, range 2.9-5.1 µg/cm^2). During the first 2 minutes, the release was 0.11 µg/cm^2 (range 0.06-0.15 µg/cm^2) (Table 2 and Figure 2). Information from Lidén et al. (2008) from coins would lead to a higher estimate due to higher Ni content and release from coins but the ratios of measured cumulative releases at different time points are in line with the results from Julander et al., (2009) supporting the estimated values. There is further yet unpublished relevant information on Ni release from the surface-abraded quality control material in EN1811:2011 (white gold; Ni 6%) with higher release values than published in Julander and co-workers (2009) and again, the ratios of cumulative releases support the values presented in Table 2. From surface–abraded quality control material Ni release on the first day is 55% of the 1 week value and 1 hour value is 22% of 1 day value (Prof. Carola Lidén, personal communication and expert opinion Karolinska Institutet/Lidén C et al., 2013, unpublished) which adequately support the approximated ratios of 50% (35-44%) and 10% (8.3-12%) based on information in Julander et al. (2009) and Lidén et al. (2008)(Table 2). Taking also the unpublished information into account, the ranges of the releases are 35-55% of the weekly release during the first day and 8-22% of the first day release during the first hour (or 4-12% of the weekly release during the first hour).

The abraded quality control material seems to release slightly higher amounts of Ni than

materials used by Julander et al., 2009. From abraded quality control material release seem to be already quite high (0.025 µg/cm^2) at 2 min and 0.068 µg/cm^2 at 1 hour with weekly release of 0.56 µg/cm^2 (Table 2; Prof. Carola Lidén, personal communication and expert opinion Karolinska Institutet/Lidén C et al., 2013, unpublished). This suggests very rapid Ni release at the very beginning of the exposure. The EN1811:2011 quality control material has shown to have a Ni release value of 0.4±0.2 µg/cm^2/week (Lidén et al., 1996) showing variation and suggesting a slightly lower mean value than from an abraded item used in unpublished work of Carola Lidén's research group (0.56 µg/cm^2).

Using the data from metal alloys and a linear interpolation to approximate the release rate during the first 30 minutes from the data provided by Julander and co-workers (2009) and unpublished information from Prof. Carola Lidén, an estimated release of 0.01-0.046 µg/cm^2/30 min could be expected from an item releasing 0.5 µg/cm^2/week (legal threshold; Table 2). Linear interpolation between 1 hour and 2 min time points is considered justified based on the almost linear increase in the cumulative release curve at the beginning of the release.

Table 2. Estimated cumulative releases (µg/cm^2) of Ni at various time points from an item releasing 0.5 µg/cm^2/week (legal threshold). Estimations are based on measured values in Julander et al., 2009, Lidén et al., 2008b and unpublished information from Karolinska Institutet/Lidén C et al., in their expert opinion.

	2 min	30 min[a)]	1 hour	1 day	1 week
Legal threshold		0.013	0.025 (estimated)	0.25 (estimated)	0.5
Julander et al., 2009	<0.001 (measured)	0.01 (estimated)	0.020 (measured)	0.17 (measured)	0.39/0.48 (measured)
Lidén et al., 2008	0.11 (measured)	2.2 (estimated)	4.3 (measured)	52 (measured)	121 (measured)
Karolinska Institutet/Lidén et al., 2013 unpublished	0.025 (measured)	0.046 (estimated)	0.068 (measured)	0.31 (measured)	0.56 (measured)

a) interpolation assuming linear increase between 2 min and 1 hour time points

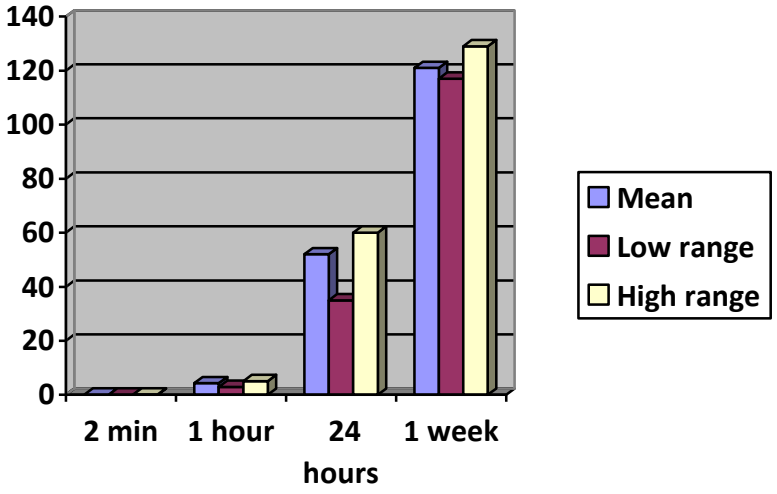

Figure 2. Ni release (µg/cm^2) from 1 SEK coins in artificial sweat (based on information in Lidén et al., 2008).

It is acknowledged that the Ni release depends on the composition of an alloy and especially on the composition of an items surface where the conditions of an alloy is dynamic and can be altered by skin contact affecting the skin deposition of the Ni (Julander et al., 2013). However, for the purpose of this proposal, it is considered that the estimated values are accurate enough for items releasing low amounts of Ni.

Critical information taken for further calculations/estimations: Information from Table 2, especially measured and estimated Ni releases of 0.01-0.046 µg/cm^2/30 minutes and 0.02-0.068 µg/cm^2/1 hour corresponding to a weekly release of approximately 0.5 µg/cm^2 (0.39-0.56 µg/cm^2/week).

Step 3. Penetration rate/skin absorption of Ni-ions from solutions

Ni-ions are taken up by the skin following a skin contact of metallic Ni and Ni-salts dissolved by sweat (reviewed by Hostynek 2003). $NiCl_2$ is formed from the metallic Ni with the sweat. The diffusion rate of Ni through stratum corneum (the horny layer) is the main factor determining the dermal penetration/absorption, which is influenced by several factors including sweat, counter ions, solvents, detergents, occlusion and the condition of the skin (Grandjean et al., 1989; Fullerton et al., 1988; Fischer 1989; Filon et al., 2009; Hostynek 2003; Thyssen and Menné 2010). Ni-ions can also penetrate the skin faster at sweat ducts and hair follicles (discussed in Hostynek 2003). Experiments with radioactively labelled $NiSO_4$ have indicated Ni absorption of 55-77% through the human skin *in vivo* under occlusion within 24 hours (Norgaard 1955). There was no difference between normal and Ni-sensitive individuals. The absorption rate strongly depends on the counter ion, and Ni-ions penetrated human skin *in vitro* about 50 times faster from a $NiCl_2$ solution than from a $NiSO_4$ solution which is used in the patch tests under occlusion (Fullerton et al., 1986). This suggests that the penetration of a certain amount of Ni from $NiCl_2$ would need less time than from $NiSO_4$, e.g., the same amount of Ni penetrating from $NiSO_4$ during 48 hours (2880 minutes) would require only one hour (57.6 minutes; 2880 minutes per 50) penetration time from $NiCl_2$. The diffusion rate is inversely dependent of the square root of the molecular weight and the smaller chloride ion has a faster diffusion rate than the sulphate ion (Hostynek, 2003). Several counter ions are potentially available in the biological systems and $NiCl_2$ can be considered as a worst case since its diffusion is likely to be fastest.

Elicitation of nickel allergy has been shown to be dependent on the dose and the size of the exposed area even though the same dose per unit area is applied (discussed in Boukhman and Mainbach, 2001). This means that the total amount of applied Ni is a driving factor and that the larger the skin contact area of an item is, it may increase the elicitation potency at the same level of Ni release. Some anatomical areas of the skin are considered to be thinner and more permeable than others; e.g. arm seems to be twice as permeable as back which is usually used in clinical tests (reviewed by Hostynek 2003). In addition, if the skin conditions are compromised, permeation of Ni particles increases significantly (Filon et al., 2009). To take into account the higher skin permeability/sensitivity of the areas where e.g. jewellery are generally worn compared to skin of the back which is used in clinical tests, a factor of 2 should be applied to cover higher skin permeability/sensitivity and area. This factor can be considered to cover also other uncertainties such as the area of the skin contact may be larger than in clinical tests (0.8 cm^2 is the normal area in clinical tests). It has been reported that due to difficulties in calculating complicated area sizes, an adjustment factor is allowed in the reference method for Ni release (EN 1811:1998) which factually increase the legal threshold from 0.5 up to 5 µg/cm^2/week (Thyssen et al., 2011). This method has now been superseded by EN1811:2011 with a measurement uncertainty interval which corresponds to an adjustment factor of less than 2. However, this further supports inclusion of a correction factor and suggest that underestimation of exposure is unlikely.

Critical information taken for further calculations/estimations: Ni-ions penetrate human skin about 50 times faster from $NiCl_2$ solution than from $NiSO_4$ solution. In addition, two times higher permeability/sensitivity of the skin areas where jewellery is generally worn should be taken into account.

Step 4. Amounts of Ni and contact period that can elicit a reaction

In this Step information from previous Steps (Steps 1-3) is combined. Based on the information on Ni release from alloys and coins at various time points, it can be estimated that the Ni release would be 0.01-0.046 µg/cm^2 during the first 30 minutes and 0.02-0.068 µg/cm^2 during the first hour from an item releasing 0.39-0.56 µg/cm^2/week (the legal threshold is 0.5 µg/cm^2/week; Table 2 above). In order to estimate how many of the Ni-sensitised subjects would react to amounts of Ni released during 30 minutes and 1 hour, the following comparisons and calculations were conducted applying information from previous sections.

A portion of 1% of the Ni-sensitised subjects react to applied Ni amount of 0.067 µg/cm^2/2 days in a clinical patch test and 5% of the subjects reacted to 0.44 µg/cm^2/2 days (using $NiSO_4$) as discussed in Step 1. These values would correspond to 0.067 µg/cm^2/1 hour and 0.44 µg/cm^2/1 hour for $NiCl_2$ based on information in Step 3 (50 times faster permeation of the Ni ion from $NiCl_2$) and further reduction of the contact time to 0.067 µg/cm^2/30 min and 0.44 µg/cm^2/30 min, respectively (based on twice as permeable skin areas than used in clinical tests leading to much shorter dermal uptake time). This would indicate that around 1% of the Ni-sensitised individuals may react to exposure to (alloys releasing) 0.067 µg/cm^2 which is slightly above the 30 minutes release range (0.01-0.046 µg/cm^2/30 min) and within the one-hour release range (0.02-0.068 µg/cm^2/1 hour) from an alloy releasing 0.39-0.56 µg/cm^2/week.

Information from skin reactions to alloys reveal that 17% of the Ni-sensitised individuals react to an alloy releasing Ni 0.4 µg/cm^2/week during 2-day exposure. This alloy can be estimated to release 0.23 µg Ni/cm^2/2 days (linear interpolation to 2 day time point between 1 week and 1 day values when 1 day value is 50% of the 1 week value). This means that 0.23 µg Ni/cm^2 has been available for skin uptake to induce skin reactions. Ni-sensitised individuals have reacted also to alloys releasing 10 times lower values (0.04 µg/cm^2/week) during two-day exposure (Fischer et al., 1984; Menné et al., 1987). It can be estimated, based on the release data above, that the Ni release during two days from this alloy would be at least 0.023 µg/cm^2/2 days. There is uncertainty towards a higher release value because the measurements in this study were done at a lower temperature than which is relevant to human exposure. Based on the available information from alloys show variable values (dependent on alloy and circumstances) but it can be estimated that release below of 0.023-0.23 µg/cm^2/2 days could cause skin reactions only in small part of Ni-sensitised individuals. The lower end of this range would be between the estimated release values during the first 30 minutes (0.01-0.046 µg/cm^2/30 min) from an alloy releasing 0.39-0.56 µg/cm^2/week and also within the range of the measured release values during the first hour (0.02-0.068 µg/cm^2/1 hour) but at lower end.

Taking together, the information from clinical patch tests with liquids and tests using alloys indicate that exposure to 0.023 – 0.067 µg Ni/cm^2 could cause skin reactions to low amounts of Ni-sensitised individuals. This value is within the range of measured release values of 0.02-0.068 µg/cm^2/1 hour from alloys. Taking into account the higher permeability of the skin areas where jewellery is generally worn compared to the area used in clinical patch test (e.g. arm is two times more permeable than back) and the uncertainties related to the area size (larger contact area of many jewellery than used in patch tests) and measurement, it is concluded that an exposure time of 30 minutes,

corresponding release values range of 0.01-0.046 µg/cm^2/30 min, would be adequately protective towards exposure to alloys releasing Ni 0.5 µg/cm^2/week.

Step 5. Repetitive contact

There is no information on repeated exposure on Ni such as how frequent and extensive exposure would be needed to elicit reactions. However, based on information on other chemicals very short instances at rather large intervals have been shown to cause allergy. Repetitive short exposure at low concentrations is a stronger stimulus than less frequent longer exposure at the same or higher concentrations (discussed in Fischer et al., 2007). For Ni the rapid transport to the epidermis and deposition/accumulation of Ni might be a critical factor (Thyssen et al., 2008; Julander et al., 2013). Ni has been shown to accumulate in the epidermis with a significant amount also in the dermis (Fullerton and Hoelgaard, 1988; Fullerton et al., 1988). The investigations using repeated open application (ROAT) support the importance of repeated low doses for elicitation of allergic contact dermatitis (Fischer et al., 2007). In a repeated open application test (ROAT), when Ni solution was applied twice a day for a week, 56% of Ni-allergic subjects reacted to Ni concentration of 0.35 µg/cm^2 and 22% to Ni concentration of 0.035 µg/cm^2 (Fischer et al., 2007) indicating that repeated dosing leads potentially to a lower threshold concentration than one longer exposure duration. In addition, coin handling increases the amount of Ni in the skin already within 2 minutes with a linear relationship between the exposure time and measured Ni levels (Staton et al., 2006). Unpublished information indicate that abraded EN1811:2011 quality control material releases 0.025 µg/cm^2/2 min (Karolinska Institutet/Lidén C et al., 2013, unpublished) which is close to the Ni concentration of 0.035 µg/cm^2 causing skin reactions to 22% of Ni-sensitised individuals in ROAT.

It has been hypothesised that a greater allergen concentration enhances cytokine induction leading to enhancement of the migration of Langerhans cells to lymph nodes and activation of the T-lymphocytes. Below a critical threshold level the absolute amount of antigen-bearing Langerhans cells might be too low to induce/elicit a reaction (reviewed in Boukhman and Maibach 2001). The turnover of epidermis is around 31 days and that for stratus corneum around 14 days (Bergstresser and Taylor, 1977). This would indicate that Ni-protein complex may cumulate and be available to antigen presenting dendrite cells at least for 14 days in the epidermis. In addition, local allergen retention for a two-week period is considered from short-lasting, low-dose contact generally as a maximum and enough to exceed the time required for active sensitisation (Rustemeyer et al., 2011).

There is evidence for allergen specific memory function in the skin (Hindsén and Bruze, 1998). Allergen specific T cells may persist for at least several months in the skin causing "local skin memory" (reviewed by Rustemeyer et al., 2011). Specifically for Ni, increased sensitivity was found one month later at the site with previous allergic contact dermatitis (Hindsén and Bruze, 1998). In earlier experiments, increased reactivity was found even after 8 months (as discussed in Hindsén and Bruze, 1998). The accumulation of Ni to epidermis and allergen specific memory function of the skin may explain why the induction threshold is generally considered to be higher than the elicitation threshold and also why repeated exposures seem to be more potent than single rare exposures. The detailed mechanism of allergic contact dermatitis is reviewed by Rustemeyer and coworkers (2011).

Considering the turnover rate of the epidermis of one month and allergen retention of a two-week period, it is estimated that 2-3 contact times within two weeks could be critical for eliciting reactions. Thus, a repeated exposure for 10 min 3 times within two-weeks (30 min/3 = 10 minutes) is selected as a criterion for prolonged contact with the skin representing a minimum contact time.

4. Conclusion

Starting from the time-related information on Ni release from alloys combined with information on Ni-sensitised subject's reactions to different doses, and information on skin uptake and penetration, it was estimated which contact time would sufficiently protect Ni-sensitised and not yet sensitised subjects from contact dermatitis. Further assessment of impact of sensitivity of the skin area, size of the skin area, and repetition of exposure to skin contact time needed for skin reactions were done. A contact time of 30 minutes of an alloy releasing Ni at the rate of the legal threshold should be adequately protective towards skin reactions in most of the Ni-sensitised individuals. The repetition of exposure is taking into account as minimum 3 contact times per two weeks, reflecting the turnover time of one month for the epidermis and allergen retention for two weeks. This leads to the definition for "prolonged contact with the skin" of "more than 10 minutes on three or more occasions within two weeks, or 30 minutes on one or more occasions within two weeks".

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Entry 27 of Annex XVII to REACH (see Annex 2)

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Annex 2. Restriction entry 27 (nickel and its compounds) of Annex XVII to REACH and agreed interpretations

Restriction entry 27

27. Nickel CAS No 7440-02-0 EC No 231-111-4 and its compounds

1. Shall not be used:

   (a) in any post assemblies which are inserted into pierced ears and other pierced parts of the human body unless the rate of nickel release from such post assemblies is less than 0,2 µg/ cm ²/week (migration limit);
   (b) in articles 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, rivets, zippers and metal marks, when these are used in garments,

   if the rate of nickel release from the parts of these articles coming into direct and prolonged contact with the skin is greater than 0,5 µg/cm²/week.
   (c) in articles referred to in point (b) where these have a non-nickel coating unless such coating is sufficient to ensure that the rate of nickel release from those parts of such articles 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 article.

2. Articles which are the subject of paragraph 1 shall not be placed on the market unless they conform to the requirements set out in that paragraph.
3. The standards adopted by the European Committee for Standardisation (CEN) shall be used as the test methods for demonstrating the conformity of articles to paragraphs 1 and 2.

Agreed interpretations

In addition to the non-exhaustive list of articles mentioned in the restriction entry, the Question and answers on restrictions[1] states that the use of mobile telephones fulfil the condition of "direct and prolonged contact with the skin" and thus they are covered by the restriction.

Coins are outside the scope of the entry. This is stated in the Council Regulation 975/98/EC on denominations and technical specifications of euro coins intended for circulation. The preamble 11 refers to the Directive 94/27/EC[2]; '… which limited the use of nickel in certain products in recognition that nickel could be cause of allergies under certain conditions; whereas coins are not covered by that Directive..', even though highlighting the desire to reduce the nickel content of coins when moving to a new coinage system.

[1] Questions and answers on ECHA's website. See restrictions from: http://echa.europa.eu/support/qas-support/qas

[2] European parliament and Council Directive 94/27/EC of 30 June 1994 amending for the 12th time Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations (original nickel restriction)

Annex 3. Consultations and further considerations

Comments for the ECHA's draft proposal were requested from German mirror Committee for CEN[3]/TC 347 "Methods for Analysis of Allergens" and from Karolinska Institutet/Prof. Carola Lidén et al. The proposal was revised taking the received comments related to the definition building into account and in addition the following concerns were raised in comments:

The current method measuring Ni release from an item contains considerable uncertainty related to complicated area sizes. In addition, the Ni release in contact with the skin does not reflect only the composition of the item but very complex dynamical conditions at the surface of the item. It could be considered and explored if Ni restriction could be based on Ni detection method (with a threshold) without measurements of release values per time unit and considerations of duration of the skin contact time. Restriction relying on detection of Ni would potentially make the enforcement easier when contact time would not be a critical factor. Another approach could be to shorten the duration of the release measurement time to address the release values at the beginning which may better reflect the critical release of Ni from an alloy.

Ni detection approach is supported by the new information suggesting that very short, a couple of seconds long, but repetitive contact with Ni containing items may cause building up deposition of Ni in the skin that could cause contact dermatitis. There are case studies on use of items coated with Ni which are used potentially on daily basis but for short times and causing contact dermatitis.

[3] CEN - The European Committee for Standardization