

# Allergic Contact Dermatitis to Metals over a 20 Year Period in the Centre of Portugal: Evaluation of the Effects of the European Directives



ARTIGO ORIGINAL

## Alergia de Contacto a Metais num Período de 20 Anos no Centro de Portugal: Implicações das Directivas Europeias

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### ABSTRACT

**Introduction:** Metals are a common cause of allergic contact dermatitis. After the introduction of the EU Nickel Directive (1994/27/CE; 2004/96/EC) and, more recently, the Cement Directive (2003/53/EC) there has been a significant decrease in sensitization to metals mainly in the Nordic countries. The applicability of these directives and their impact in the Portuguese population is unknown.

**Material and Methods:** A retrospective study (1992-2011) was carried out in our patch test clinic to assess the temporal trend of metal sensitization (nickel [Ni], cobalt [Co] and chromium [Cr]) along the last 20 years, particularly considering age, sex and its relation with occupational activity.

**Results:** Out of 5 250 consecutively patch-tested patients, 1 626 (31%) were reactive to at least one metal (26.5% to Ni; 10.0% to Co and 7.9% to Cr). Women had a higher prevalence of sensitization to Ni (34.4% vs 8.9%) whereas men were more reactive to Cr (11.5% vs 5.0%). Nickel sensitization did not decrease significantly over the years, although in recent years among women sensitized to nickel the percentage of younger patients (16-30 years-old) is significantly lower ( $p < 0.001$ ). Chromium sensitization significantly decreased, particularly in men ( $r = -0.535$ ), and mainly in the construction workers ( $r = -0.639$ ). Chromium reactivity associated with the shoe dermatitis has remained stable.

**Discussion:** We emphasize the higher and stable percentage of nickel sensitized individuals suggesting, so far, a low impact from the EU Ni directive, although a decreasing percentage in the younger group among Ni sensitized women may suggest a beneficial effect is becoming evident in this age group. On the contrary, the impact of the directive regarding the modification of Cr in cement seems to be effective. There is now a need to regulate chromium content in leather products, namely in shoes.

**Conclusions:** The regulation of interventional measures related either to the manufacture and trade of adornments or professional use will better protect the population of allergy to metals.

**Keywords:** Dermatitis, Allergic Contact; Chromium; Cobalt; European Union; Metals; Nickel; Patch Tests; Portugal.

### RESUMO

**Introdução:** Os metais são causa frequente de dermatite de contacto alérgica. Desde a introdução da Directiva Comunitária do Níquel (1994/27/CE; 2004/96/CE) e, mais recentemente, da Directiva do Cimento (2003/53/CE), nos países nórdicos tem havido uma diminuição da sensibilização aos metais. A aplicabilidade destas medidas e o seu impacto permanece por avaliar em Portugal.

**Material e Métodos:** Foi realizado um estudo retrospectivo (1992-2011) na Consulta de Alergologia Cutânea com o principal objectivo de analisar a variação dos padrões de sensibilização aos metais (níquel [Ni], cobalto [Co] e crómio [Cr]) ao longo de 20 anos, em particular no que se refere ao género, grupo etário e relação com a actividade profissional.

**Resultados:** Do total de 5 250 doentes estudados, em 1 626 (31%) observámos pelo menos um teste epicutâneo positivo a um metal (26,5% ao Ni; 10,0% ao Co e 7,0% ao Cr). A prevalência de sensibilização ao Ni era significativamente maior nas mulheres (34,4% versus 8,9%) e ao Cr nos homens (11,5% versus 5,0%). Não houve diminuição significativa da sensibilização ao Ni ao longo dos 20 anos, mas o contributo da faixa etária dos 16-30 anos no total de mulheres sensíveis a este metal decresceu de forma significativamente estatística ao longo dos anos ( $p < 0,001$ ). A sensibilização ao Cr decresceu sobretudo nos homens ( $r = -0,535$ ), muito particularmente nos casos relacionados com a construção civil ( $r = -0,639$ ), enquanto a reatividade ao Cr relacionado com o uso de calçado se manteve estável.

**Discussão:** A manutenção dos elevados níveis de sensibilização ao níquel denota ainda uma fraca implementação das Directivas comunitárias mas a redução da percentagem de mulheres jovens poderá significar já algum efeito positivo nesta faixa etária. Ao contrário, a Directiva referente à redução do Cr no cimento parece estar a ter os seus efeitos positivos. Há, contudo, necessidade de interferir com o conteúdo em Cr no couro natural utilizado no calçado.

**Conclusões:** A regulamentação da implementação de medidas interventivas relacionadas quer com o fabrico e comércio de adornos quer a nível profissional permitirá uma melhor protecção da população da alergia aos metais.

**Palavras-chave:** Dermatite de Contacto Alérgica; Metais; Níquel; Cobalto; Crómio; Testes Epicutâneos; Portugal; União Europeia.

### INTRODUCTION

Metals are a common cause of allergic contact dermatitis (ACD). Over the 20<sup>th</sup> Century, in industrialized countries, sensitization to nickel (Ni) became the most common cause of ACD in women.<sup>1,2</sup> This is related to a higher exposure to metallic ornaments in direct and prolonged contact with the skin, such as in the case of jewellery and metallic parts used in garments. Ni is also present in different daily use

metallic objects (keys, watches, lighters, scissors, thimbles, tweezers, eyeglass frames, mobiles, 1 and 2-euro coins, etc.), dental and orthopaedic prosthesis.<sup>3-8</sup> In sensitized individuals, skin exposure to Ni in concentrations above the recommended limit is capable of triggering ACD. In addition, contact with metallic orthopaedic or dental prosthesis may trigger local intolerance reactions and its absorption may

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cause systemic contact dermatitis.<sup>9</sup>

The EU Nickel Directive (1994/27/EC), issued in June 1994 and effective in Portugal since October 2000, establishes that Ni or its compounds may only be used: i) in any post-assemblies which are inserted, temporarily or not, into pierced ears and other pierced parts (earrings, piercings, etc.) in which the rate of nickel release is below 0.5 µg/cm<sup>2</sup>/week and, ii) in products intended to come into direct and prolonged contact with the skin, if the rate of nickel release from the parts of these products is below 0.5 µg/cm<sup>2</sup>/week<sup>10</sup>. In 2004, considering that the previously imposed limits were insufficient, this Directive was amended (2004/96/EC), restricting the marketing and use of piercing post-assemblies in contact with the skin, to a Ni release below 0.2 µg/cm<sup>2</sup>/week; such amendment was effective in Portugal by December 2005.<sup>11</sup> More recently, as several cases of ACD are related to contact with mobile metallic parts, their Ni content was also covered by the EU regulation.

Cobalt (Co) shares with Ni and chromium (Cr) the same exposure sources, namely within occupational context in construction related to cement manipulation, leather products, porcelain and greenish blue/blue and yellow paint pigment for ceramic, glass products, synthetic enamels and printing ink. It is also an important allergen in metallic ornaments (jewellery) and metallic parts used in garments, dental and orthopaedic prosthesis, tattoos, cosmetics and hair dyes (light brown colour). Therefore, Co allergy often goes along with Cr and/or Ni allergy, related to concomitant sensitization.<sup>3-5</sup>

Chromium is an important occupational allergen namely in construction due to cement handling, contact with leather products and in tanning industry and is a pigment in anti-corrosive industrial paints. In non-occupational exposure, it is important to consider contact with leather products (footwear, watch straps, gloves, belts, etc.), cleaning products handling (bleach), make-up products and orthopaedic metallic prosthesis.<sup>3</sup> The cement Directive (2003/53/CE), implemented in June 2003 in Europe and in Portugal in March 2005, establishes a 0.0002% Cr(VI) concentration limit in hydrated cement paste (two parts per million [ppm] of its total dry weight).<sup>12</sup>

These preventive measures aim to protect European consumers from Ni and Cr allergy which, as described, may have other consequences beyond ACD. Scientific evidence shows that, within these limits, we may have a reduction in sensitization and eventually we may avoid ACD in previously sensitized individuals.<sup>13</sup> Since the introduction of these EU Directives, a decrease in metal sensitization has occurred in the Nordic countries.<sup>14,15</sup> The applicability and level of impact of these measures is yet to be assessed in Portugal.

## OBJECTIVES

Our study analysed the prevalence of Ni, Co and Cr allergy in a group of patients who underwent epicutaneous patch testing (EPT) and their variation over a 20-year period

of time, in order to assess the potential impact of these measures in a population of the Central region of Portugal.

## MATERIAL AND METHODS

All patients with a diagnostic suspicion of ACD or any other skin hypersensitivity reaction that underwent EPT between January 1992 and December 2011 at the *Centro Hospitalar e Universitário de Coimbra* were included in our study. Metal sensitization was defined as a positive reaction to at least one of the three metals tested in the basic allergen series (Ni, Co, Cr).

Clinical relevance has been categorized as i) current relevance – the ET identified the allergen causing the dermatitis, ii) past relevance – the reaction has no relevance for current dermatitis, although it explained previous ACD events iii) non-relevant – there was no explanation found for the positive ET.

Metal reactivity variation was globally and separately assessed for each metal, in five-year groups spanning the 20 years study time and the patterns found were characterized according to gender, age and their occupational relevance.

### Patch (epicutaneous) tests

Metallic allergens tested in the basic series of the Portuguese Group for the Study of Contact Dermatitis (*Grupo Português de Estudo das Dermatites de Contacto*) included 5% nickel sulphate, 1% cobalt chloride and 0.5% potassium dichromate (Chemotechnique Diagnostics™, Vellinge, Sweden). These were applied onto the dorsal region within Finn Chambers on Scanpor Tape (Epitest Ltd, Almirall) or, more rarely, within *IQ chambers* (Chemotechnique Diagnostics™, Vellinge, Sweden) and removed 48h later. Reading and interpretation were made at day 2 (D2) and D4, D3 and D4 or eventually at D7, according to the recommendations of the International Contact Dermatitis Research Group<sup>16</sup>. The recommended semi-quantitative grading was used: + (erythema and papules or infiltrate) or the ++ and +++ (more intense) reactions were considered as positive.

### Statistical analysis

Statistical analysis involved the use of SPSS (Software Package for Statistical Science, version 18.0, Chicago, IL) software. Parametric and non-parametric tests were applied in order to analyse the patterns of sensitization to metals in the different 5-year periods. A *p*-value of 0.05 or below was considered significant.

## RESULTS

We studied 5,250 patients (3,636 female – 69.3% and 1,614 male – 30.7%) over 20 years of age, with a medium age of 37, 23.1% with an occupational disease, 35.9% with hand dermatitis, 6.5% with leg ulcer or lower limb chronic venous insufficiency, 20.6% with facial involvement and 24.1% with a clinical history of atopy.

From these, 1,626 (31%) presented at least one positive metal patch test: 1,392 (26.5%) to Ni, 524 (10.0%) to Co

**Table 1** - Demographic data and patch test results of our group of patients.

EPT: Epicutaneous patch testing; the variable 'Relevant reactivity' includes current and past relevance; PT/NPT: parametric/non-parametric tests, as indicated; when  $p < 0.05$ , Pearson correlation ( $r$ ) was applied in parametric tests and Spearman correlation ( $r_o$ ) in non-parametric tests, respectively. Note: for data presentation, these were grouped in 5-year periods; the statistical analysis was referred to the 20-year data.

	1992-1996 (n, %)	1997-2001 (n, %)	2002-2006 (n, %)	2007-2011 (n, %)	Total (n, %)	PT/NPT
	1,238	1,473	1,039	1,500	5,250	
<b>Male</b>	394 (31.8)	490 (33.3)	326 (31.4)	404 (26.9)	1,614 (30.7)	
<b>Female</b>	844 (68.2)	983 (66.7)	713 (68.6)	1096 (73.1)	3,636 (69.3)	
<b>Sensitization <math>\geq</math> 1 metal</b>	405 (32.7)	436 (29.6)	342 (32.9)	443 (29.5)	1,626 (31.0)	
<b>Other positive EPT</b>	325 (80.2)	351 (80.5)	263 (76.9)	326 (73.6)	1,265 (77.8)	
<b>Reactivity relevance</b>						
Relevant	376 (92.8)	402 (92.2)	313 (91.5)	367 (82.8)	1458 (89.7)	$r = -0.614$
Non-relevant	29 (7.2)	33 (7.6)	29 (8.5)	76 (17.2)	167 (10.3)	$r = 0.592$
<b>Nickel (Ni)</b>						
<b>Ni Total</b>	327 (26.4)	366 (24.8)	300 (28.9)	399 (26.6)	1392 (26.5)	-
Ni Men	29 (7.4)	37 (7.6)	41 (12.6)	36 (8.9)	143 (8.9)	-
Ni Women	298 (35.3)	329 (33.5)	259 (36.3)	363 (33.1)	1249 (34.4)	-
<b>Cobalt (Co)</b>						
<b>Co Total</b>	125 (10.1)	147 (10.0)	123 (11.8)	129 (8.6)	524 (10.0)	-
Co Men	36 (9.1)	48 (9.8)	33 (10.1)	24 (5.9)	141 (8.7)	$r_o = -0.492$
Co Women	89 (10.5)	99 (10.1)	90 (12.6)	105 (9.6)	383 (10.5)	-
<b>Chromium (Cr)</b>						
<b>Cr Total</b>	122 (9.9)	89 (6.0)	84 (8.1)	72 (4.8)	367 (7.0)	$r = -0.586$
Cr Men	62 (15.7)	59 (12.0)	41 (12.6)	23 (5.7)	185 (11.5)	$r = -0.535$
Cr Women	60 (7.1)	30 (3.1)	43 (6.0)	49 (4.5)	182 (5.0)	-
<b>Total Ni - age groups</b>						
$\leq 15$	12 (3.7)	10 (2.7)	7 (2.3)	9 (2.3)	38 (2.7)	-
16-30	153 (46.8)	153 (41.8)	109 (36.3)	120 (30.1)	535 (38.4)	$r = -0.820$
31-64	154 (47.1)	193 (52.7)	167 (55.7)	245 (61.4)	759 (54.5)	
$\geq 65$	8 (2.4)	10 (2.7)	17 (5.7)	25 (6.3)	60 (4.3)	-
<b>Ni - Men</b>						
$\leq 15$	1 (3.4)	0 (0.0)	1 (2.4)	3 (8.3)	5 (3.5)	
16-30	7 (24.1)	8 (21.6)	9 (22.0)	3 (8.3)	27 (18.9)	$r = -0.820$
31-64	20 (69.0)	25 (67.6)	25 (61.0)	26 (72.2)	96 (67.1)	$r = 0.783$
$\geq 65$	1 (3.4)	4 (10.8)	6 (14.6)	4 (11.1)	15 (10.5)	$r = 0.566$
<b>Ni - Women</b>						
$\leq 15$	11 (3.7)	10 (3.0)	6 (2.3)	6 (1.7)	33 (2.6)	-
16-30	146 (49.0)	145 (44.1)	100 (38.6)	117 (32.2)	508 (40.7)	$r = -0.823$
31-64	134 (45.0)	168 (51.1)	142 (54.8)	219 (60.3)	663 (53.0)	$r = 0.767$
$\geq 65$	7 (2.3)	6 (1.8)	11 (4.2)	21 (5.8)	45 (3.6)	$r = 0.603$

(continues)

and 367 (7.0%) to Cr (Table 1). The Ni sensitization was observed in 34.4% of female vs. 8.9% of male ( $p < 0.05$ ). These mainly occurred in the 30-64 age group. The Co reactivity occurred in 10.5% of female patients and in 8.7% of male. Cr reactivity was more frequent in male gender

(11.5% vs. 5.0%,  $p < 0.05$ ) and in older ages, in whom 76.8% of Cr-reactive patients were included in the >30 age group (Table 1).

Positive patch tests to three metals occurred in 120 (2.3%) patients. The association of positive patch tests to Ni

**Table 1** - Demographic data and patch test results of our group of patients (continued)

EPT: Epicutaneous patch testing; the variable 'Relevant reactivity' includes current and past relevance; PT/NPT: parametric/non-parametric tests, as indicated; when  $p < 0.05$ , Pearson correlation ( $r$ ) was applied in parametric tests and Spearman correlation ( $r_o$ ) in non-parametric tests, respectively. Note: for data presentation, these were grouped in 5-year periods; the statistical analysis was referred to the 20-year data.

	1992-1996 (n, %)	1997-2001 (n, %)	2002-2006 (n, %)	2007-2011 (n, %)	Total (n, %)	PT/NPT
	<b>1,238</b>	<b>1,473</b>	<b>1,039</b>	<b>1,500</b>	<b>5,250</b>	
<b>Total Co - age groups</b>						
≤ 15	5 (4.0)	5 (3.4)	1 (0.8)	2 (1.6)	<b>13 (2.5)</b>	$r = -0.505$
16-30	52 (41.6)	57 (38.8)	50 (40.7)	35 (27.1)	<b>194 (37.0)</b>	-
31-64	64 (51.2)	81 (55.1)	68 (55.3)	84 (65.1)	<b>297 (56.7)</b>	-
≥ 65	4 (3.2)	4 (2.7)	4 (3.3)	8 (6.2)	<b>20 (3.8)</b>	-
<b>Co - Men (N, %)</b>						
≤ 15	1 (2.8)	0 (0.0)	0 (0.0)	1 (4.2)	<b>2 (1.4)</b>	-
15-30	7 (19.4)	14 (29.2)	8 (24.2)	5 (20.8)	<b>34 (24.1)</b>	-
31-64	23 (63.9)	32 (66.7)	24 (72.7)	16 (66.7)	<b>95 (67.4)</b>	-
≥ 65	2 (5.6)	2 (4.2)	1 (3.0)	2 (8.3)	<b>7 (5.0)</b>	-
<b>Co - Women</b>						
≤ 15	4 (4.5)	5 (5.1)	1 (1.1)	1 (1.1)	<b>11 (2.9)</b>	$r = -0.494$
16-30	44 (49.4)	43 (43.4)	42 (46.7)	35 (33.3)	<b>164 (42.8)</b>	-
31-64	39 (43.8)	49 (49.5)	44 (48.9)	78 (74.3)	<b>210 (55.0)</b>	-
≥ 65	2 (2.2)	2 (2.0)	3 (3.3)	6 (5.7)	<b>13 (3.4)</b>	-
<b>Total Cr - age groups</b>						
≤ 15	4 (3.3)	1 (1.1)	1 (1.2)	0 (0.0)	<b>6 (1.6)</b>	-
16-30	40 (32.8)	31 (34.8)	29 (34.5)	15 (20.8)	<b>115 (31.3)</b>	-
31-64	80 (65.6)	54 (60.7)	52 (61.9)	54 (75.0)	<b>240 (65.4)</b>	-
≥ 65	2 (0.2)	3 (0.3)	2 (0.2)	3 (0.4)	<b>10 (2.7)</b>	-
<b>Cr - Men</b>						
≤ 15	1 (1.6)	0 (0.0)	1 (2.4)	0 (0.0)	<b>2 (1.1)</b>	-
16-30	11 (17.7)	15 (25.4)	10 (24.4)	5 (21.7)	<b>41 (22.2)</b>	-
31-64	47 (75.8)	42 (71.2)	29 (70.7)	17 (73.9)	<b>135 (73.0)</b>	-
≥ 65	3 (4.8)	2 (3.4)	1 (2.4)	1 (4.3)	<b>7 (3.8)</b>	-
<b>Cr - Women</b>						
≤ 15	3 (5.0)	1 (3.3)	0 (0.0)	0 (0.0)	<b>4 (2.2)</b>	-
16-30	25 (41.7)	16 (53.3)	19 (44.2)	10 (20.4)	<b>70 (38.5)</b>	$r_o = -0.526$
31-64	31 (51.7)	12 (40.0)	23 (53.5)	37 (75.5)	<b>103 (56.6)</b>	$r = 0.537$
≥ 65	1 (1.7)	1 (3.3)	1 (2.3)	2 (4.1)	<b>5 (2.7)</b>	-

(continues)

and Co occurred in 389 (7.4%), mainly in female (9.2%) and the association of Cr and Co was observed in 211 (4.0%), mainly in the male patients (6.6%). The association of Ni and Cr was more rare ( $n = 178$ , 3.4%) (Fig. 1).

As suggested by an analysis of the variation in metal sensitization according to the periods of time studied (Fig. 2), confirmed by statistical analysis, there was a significant global decrease in metal sensitization ( $p > 0.05$ ). Significantly, the sensitization to Ni, when considered on its

own, remained stable over these 20 years, with no different pattern between genders. When analysed in relation to age, we found that the 16-30 age group was responsible for 49% of sensitized women over the first five years and only 32.6% over the last five, standing for a significant decrease in young women sensitized to this metal ( $p < 0.001$ ) (Fig. 3). The changes in Co sensitization did not present any statistical significance, over these 20 years. Regarding Cr, sensitization decreased mainly in men ( $r = -0.535$ , Fig. 4a).

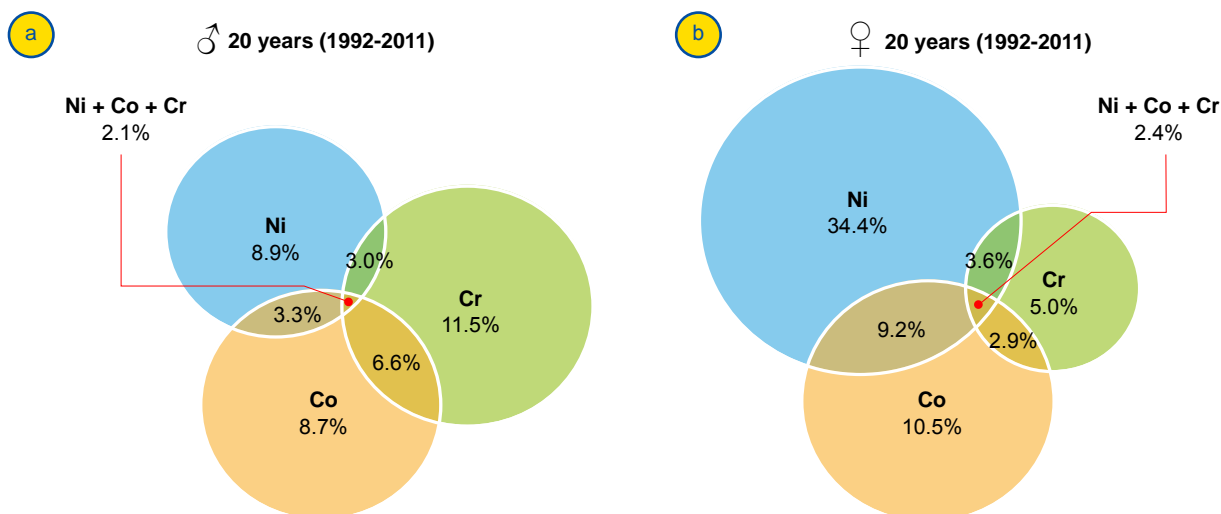
**Table 1** - Demographic data and patch test results of our group of patients (final section)

EPT: Epicutaneous patch testing; the variable 'Relevant reactivity' includes current and past relevance; PT/NPT: parametric/non-parametric tests, as indicated; when  $p < 0.05$ , Pearson correlation ( $r$ ) was applied in parametric tests and Spearman correlation ( $r_o$ ) in non-parametric tests, respectively. Note: for data presentation, these were grouped in 5-year periods; the statistical analysis was referred to the 20-year data.

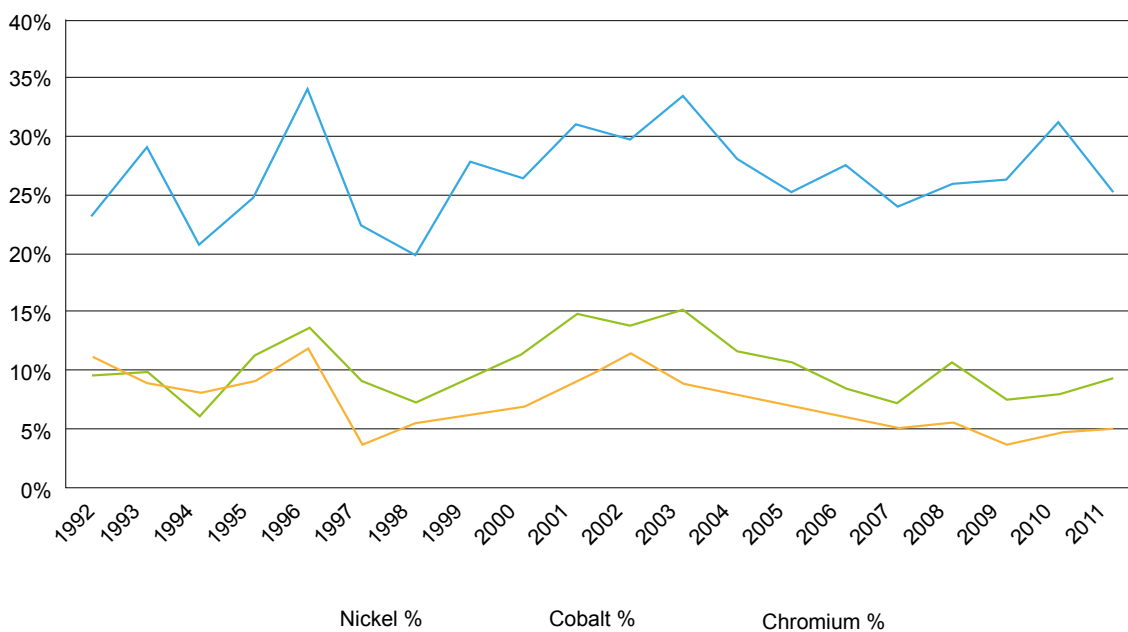
	1992-1996 (n, %)	1997-2001 (n, %)	2002-2006 (n, %)	2007-2011 (n, %)	Total (n, %)	PT/NPT
	1,238	1,473	1,039	1,500	5,250	
<b>Co-sensitization</b>						
<b>Ni + Co Total</b>	<b>91 (7.4)</b>	<b>103 (7.0)</b>	<b>96 (9.2)</b>	<b>99 (6.6)</b>	<b>389 (7.4)</b>	-
Ni + Co Men	11 (2.8)	14 (2.9)	17 (5.2)	11 (2.7)	53 (3.3)	-
Ni + Co Women	80 (9.5)	89 (9.1)	79 (11.1)	88 (8.0)	336 (9.2)	-
<b>Ni + Cr Total</b>	<b>50 (4.0)</b>	<b>30 (2.0)</b>	<b>50 (4.8)</b>	<b>48 (3.2)</b>	<b>178 (3.4)</b>	-
Ni + Cr Men	8 (2.0)	10 (2.0)	17 (5.2)	12 (3.0)	47 (3.0)	-
Ni + Cr Women	41 (4.9)	20 (2.0)	33 (4.6)	36 (3.3)	130 (3.6)	-
<b>Ni + Co + Cr Total</b>	<b>26 (2.1)</b>	<b>25 (1.7)</b>	<b>37 (3.6)</b>	<b>32 (2.1)</b>	<b>120 (2.3)</b>	-
Ni + Co + Cr Men	5 (1.3)	9 (1.8)	13 (4.0)	7 (1.7)	34 (2.1)	-
Ni + Co + Cr Women	21 (2.5)	16 (1.6)	24 (3.4)	25 (2.3)	86 (2.4)	-
<b>Cr + Co Total</b>	<b>54 (4.4)</b>	<b>58 (3.9)</b>	<b>56 (5.4)</b>	<b>43 (2.9)</b>	<b>211 (4.0)</b>	-
Cr + Co Men	28 (7.1)	40 (8.2)	27 (8.3)	12 (3.0)	107 (6.6)	-
Cr + Co Women	26 (3.1)	18 (1.8)	29 (4.1)	31 (2.8)	104 (2.9)	-
<b>Occupational metals-related ACD</b>	112 (9.0)	99 (6.7)	74 (7.1)	57 (3.8)	342 (6.5)	$r = -0.445$
<b>Cr-related ACD in construction</b>	45 (3.6)	48 (3.3)	22 (2.1)	8 (0.5)	123 (2.3)	$r = -0.639$
<b>Cr-related ACD in footwear</b>	12 (1.0)	17 (1.2)	16 (1.5)	16 (1.1)	61 (1.2)	-

Metal reactivity in patch tests was considered as relevant in 89.7% of the patients (Table 1), most of them related to a previous dermatitis and to the use of jewellery or metallic objects in contact with the skin. The reaction was considered as predominantly occupational in 342 patients (6.5%), a percentage that has decreased significantly over these 20 years ( $r = -0.445$ ;  $p = 0.005$ , Fig. 4b). This

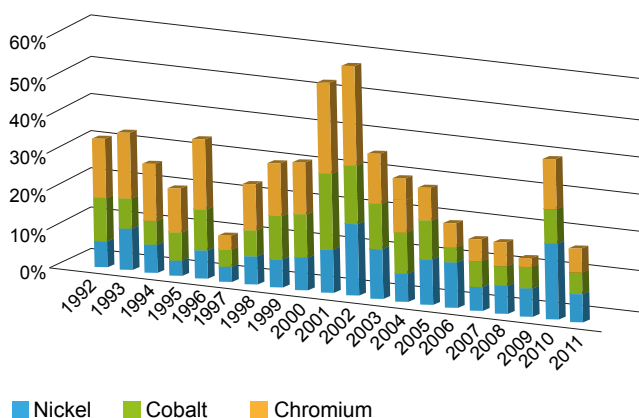
reduction is particularly significant regarding the number of patients with ACD to Cr in construction workers (3% of all patients tested in 1992 vs. 0.4% in 2011) (Fig. 5b). On the contrary, the number of patients with sensitization to Cr related to the use of footwear has remained stable over the years (approximately 1%) (Fig. 5a).

**Figure 1** - Prevalence of metal co-sensitization in male (a) and female gender (b).

**a** % Metal sensitization (♂ + ♀)



**b** % Metal sensitization - Men



**c** % Metal sensitization - Women

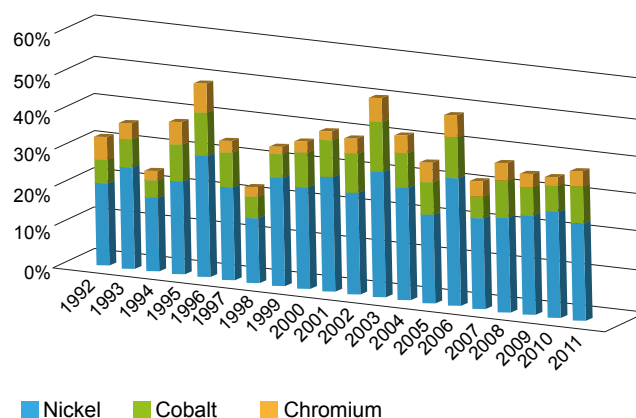


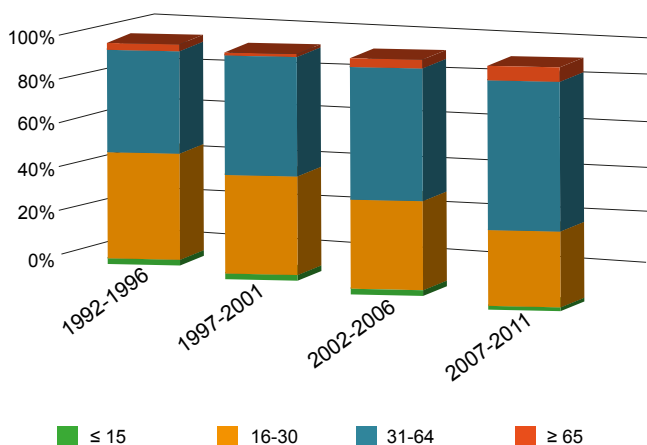
Figure 2 - (a) Variation patterns of metal sensitization over the last 20 years. Variation over time in nickel, cobalt and chromium sensitization in male (b) and female gender (c).

## DISCUSSION

Studies by the European Surveillance System on Contact Allergy show that Ni sensitization is more prevalent in Southern European countries.<sup>17</sup> In Spain, the prevalence of Ni allergy is about 25% and is considered as a public health issue.<sup>18,19</sup> The results from our study confirm that metals are an important cause of ACD in Portuguese population, mainly Ni allergy, affecting 26.5% of tested patients. ACD caused by Ni may occur in an occupational context (hairdressers, restaurants, metal industry, etc.), although non-occupational exposure is predominant, as

shown in the study by Rietschel *et al.* in which only 6% of Ni allergic patients had an occupational ACD.<sup>20</sup>

Sensitization to Ni has a multi-factorial aetiology (genetic predisposition, skin irritant exposure, exposure dose, duration and frequency, as well as anatomical location and exposure area) and possibly related to its intensity. Hence, some patients may present ACD to Ni even in doses below the limit established by the EU Directive and therefore it is not possible to establish a threshold assuring a full eviction of ACD to Ni in sensitized patients (except when Ni is completely abolished from objects).<sup>15,21-23</sup> However,



**Figure 3** - Percentage of women sensitized to nickel, according to age group. The 16-30 age group stood for a decreasing percentage of sensitized women to this metal over the last years ( $r = 0.823$ ,  $p < 0.001$ ).

the application of these preventive measures has produced positive effects on sensitization, significantly reducing the percentage of sensitized population to Ni, mainly in the Nordic countries, which were pioneer in this initiative.<sup>14,15,24</sup> The sensitization to Ni in Denmark is significantly lower in young women whose ears were pierced after the implementation of measures that regulate the Ni content released by metallic ornaments (*odds ratio* 1.20 vs. 3.34), demonstrating their importance.<sup>25</sup>

We believe, for the moment, that the Nickel Directive which has only been transposed to the Portuguese legislation in 2005 may already have started to show its effect in the case of young women. Nevertheless, its late implementation, the incertitude regarding its full compliance and an exposure to objects acquired before implementation

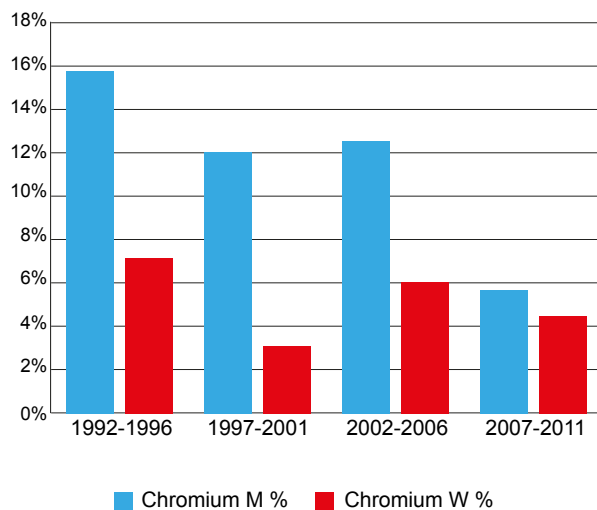
or in non-European countries where such regulations are not implemented, could explain new cases of sensitization and the persistence of the number of sensitized patients, delaying the emergence of beneficial effects of these measures on sensitization. In the younger age group (<16), in which the impact of this Directive could be more evident by reducing new sensitizations, we did not find any significant difference across these 20 years, despite numbers are too low to have a significant expression. The 16-30 age group is responsible for a decreasing total percentage of Ni-sensitized women; therefore, we believe this reflects a beneficial effect of EU measures regarding new sensitizations, although we still need to improve the implementation of this Directive in Portugal.

Sensitization to cobalt is frequently associated to an allergy to Ni (mainly in women) or to chromium (in men). In a retrospective study, Thyssen *et al.* showed that allergy to Ni has decreased in young women, while allergy to Co has remained stable. This study suggests that Ni replacement by Co in jewellery, for example, may probably explain this tendency, although the release of Co that was tested in these products was minimal.<sup>26,27</sup>

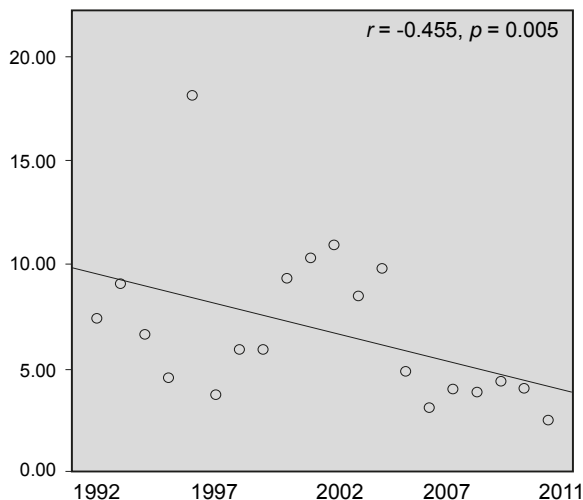
In Portugal, the number of occupational metal-related ACD has decreased over the last 20 years in a statistically significant way. This may be partly explained by the improvement of hygiene and safety work conditions (in factories, industry, construction, hairdressers), with a lower allergen-exposure, but also related to the cement EU Directive.

Although occupational ACD in construction workers may be caused by multiple factors (metals, epoxy resins, rubber, etc.), affecting the evaluation of this dermatitis, the cement is the most important product in this context. The addition of ferrous sulphate as reducing agent allows for

**a** Chromium



**b** Occupational ACD



**Figure 4** - (a) Decrease of the number of patients with an allergy to chromium, over the years ( $r = -0.586$ ,  $p = 0.007$ ), mainly in men (in blue) ( $r = -0.535$ ,  $p = 0.015$ ). (b) Decrease of the number of occupational ACD metal-related ( $r = -0.445$ ,  $p = 0.005$ ).

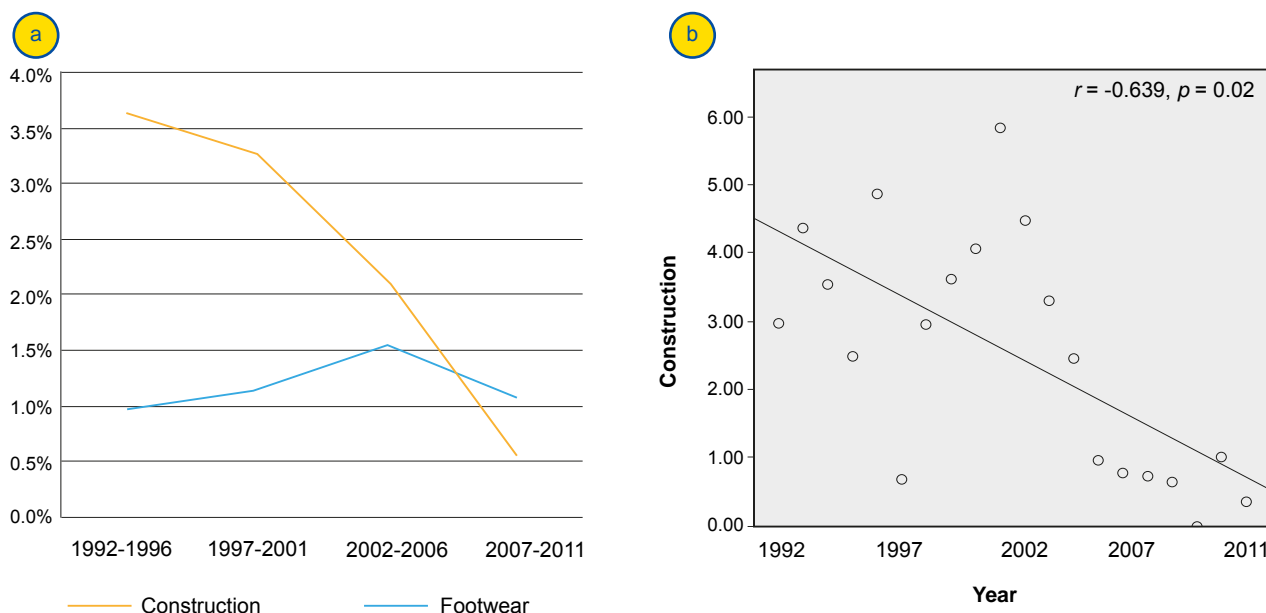


Figura 5 - (a) Relation between chromium-related ACD in construction workers (orange line) vs. footwear-related ACD (blue line). (b) Decreasing tendency of the number of chromium-allergy cases in construction workers ( $r = -0.639$ ,  $p = 0.02$ ).

the transformation of hexavalent chromium in its trivalent insoluble form, with less sensitizing potential. From 1983, this has become a compulsory procedure in Denmark, standing for an important reduction of the prevalence of allergy to Cr in this context, despite an increase of the cases related to the use of leather products.<sup>28,29</sup> In our study we found a significant decrease in the cases of ACD caused by Cr in construction workers, explaining the positive effects of this Directive, transposed to Portuguese legislation in 2005.

In addition, Cr is frequently used in tanning of animal skins, aimed to increase stability, resistance and durability of that material, to be used for instance in footwear, where it is a frequent cause of ACD. Risk of sensitization and ACD risk is generally considered with a Cr(VI) release from materials above 3 ppm.<sup>30</sup> However, under special conditions (humidity, pH, pre-existing dermatitis, etc.) lower levels from 1 ppm may cause sensitization. The available analytic methods only detect a Cr release above 3 ppm (3 mg/Kg). A recent Danish study analysed the level of Cr in 60 pairs of skin footwear bought in that country, some of which were imported, also from Portugal.<sup>30</sup> High hexavalent Cr levels were detected, mostly between 3-6 ppm, although some reaching 63 ppm. These results were presented to the European Chemicals Agency and, until the completion of our study, the situation is under assessment in order to implement measures over the EU also related to the Cr in footwear and other leather products intended to be used in contact with the skin. These measures will be based on the restrictions currently present in Germany (since Aug 2010), which consist of a prohibition of the sale of leather products that remain in contact with the skin for a long period of time

(footwear, gloves, garments, suitcases) with a Cr(VI) level above 3 mg/kg. In our analysis, the number of patients with an allergy to Cr related to the use of footwear did not change significantly over the years, assuring the absence of regulations regarding the Cr level in footwear also in Portugal.

Our study has some limitations, related to its retrospective nature and possible bias in the selection of our sample (patients with a predominant suspected ACD) and may not stand for general population. However, it may serve as a starting point for future research aimed to clarify this issue.

The implementation of regulation related to garment manufacturing and trade (jewellery, watches, etc.) as well as in an occupational context (construction, textile industry, etc.) will allow for a better protection from allergy to metals.

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#### CONFLICT OF INTERESTS

There was no conflict of interests in the writing of this manuscript.

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