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Commentary

Hexavalent and trivalent chromium in leather: What should be done?

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ABSTRACT

Trivalent chromium compounds are used for leather tanning, and chromium may be released during use of leather goods. In certain instances, small amounts of hexavalent chromium can be formed and released. Both trivalent and hexavalent chromium can elicit allergic skin reaction in chromium sensitised subjects, the latter being significantly more potent. Induction of sensitisation only occurs after exposure to hexavalent chromium. A minority of subjects are sensitised to chromium, and in a fraction of these subjects allergic skin reaction have been described after wearing leather shoes or, less frequently, other leather goods. The evidence that in all these cases the reaction is related to hexavalent chromium is not always strong. The content of hexavalent chromium in leather is regulated in European Union, but rate of release rather than content is relevant for allergic skin reaction. The role of trivalent chromium appear much less relevant if at all. Modern tanning procedure do not pose significant risk due to either hexavalent or trivalent chromium. Dismissing bad quality and worn-off leather goods is relevant in reducing or eliminating the skin reaction. It should also be pointed out that shoe components or substances other than chromium in leather may cause allergic/irritative skin reactions.

1. Introduction

Trivalent chromium (CrIII) is commonly used for leather tanning, usually as sulphate salt. As a consequence, leather contains CrIII, which is mostly bound to proteins and in minor part maybe free. Hexavalent chromium (CrVI) is not used for tanning, but small quantities of CrVI may be present in the tanning mixture (although not in modern mixtures) (Tegtmeyer and Rabe, 2014), or can be formed in leather under particular conditions (see e.g. Hedberg et al., 2014; Meyndt and Germann, 2011).

Both CrIII and CrVI present in leather can be released and consequently be deposited on the skin surface. The risk of systemic effects of Cr can be readily excluded based on the toxicological characteristics of CrIII and on the very low doses of CrVI (for an extensive review e.g. ATDSR, 2012; EFSA, 2014). The question is to what extent the amount released and the local skin conditions in subjects wearing leather goods such as shoes, belts and clothing and the condition of use pose a risk of developing either irritative or allergic contact dermatitis (ACD) to CrVI or CrVI plus CrIII.

Recently the EU passed a regulation (EC, 2014) based on an opinion by EChA (EChA, 2012), that limited the content of CrVI in leather to <3 ppm (i.e.: the detection limit). This review points out some issues related to both CrVI and CrIII as causal agent(s) of ACD associated with contact with leather, and to the role of CrIII and to its potency related to CrVI.

2. Chromium and skin irritation

CrIII is not a skin irritant, even when high concentrations are applied on the skin, while CrVI causes irritation, though at relatively high concentrations. There are no quantitative data in humans that indicate the threshold for such effects. Skin lesions have been reported in humans, following accidental high exposure (ATSDR, 2012), that are not expected from contact with even grossly improperly tanned leather goods.

3. Chromium and induction of allergic contact dermatitis

CrVI is a known allergen and, in the past, several cases of allergy in construction workers have been related to the use of cement

Abbreviations: ACD, Allergic Contact Dermatitis; BMC, BenchMark Concentration; BMCL, BenchMark Concentration Low (lower bound of the BMC, CI 95%); CrIII, trivalent chromium; CrVI, hexavalent chromium; MET, Minimum Eliciting Threshold.

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containing CrVI, and the incidence of occupational ACD in Europe has been declining after legislation was introduced to reduce the CrVI content in cement (see e.g.: Athavale et al., 2007; Bensefa-Colas et al., 2014; Bock et al., 2003; Geier et al., 2011).

Whether CrIII can induce sensitisation is questionable, since evidence could not be found that CrIII alone was responsible of such an effect. On the other hand, it is well established that very high concentrations of CrIII can elicit skin reaction in a minority of CrVI-sensitised subjects (Nethercott et al., 1994) (see below).

4. What is the evidence that chromium is the cause of allergic reactions to leather goods?

The literature contains several reports that claim the induction and elicitation of ACD to wearing leather goods, especially shoes, that is attributed to the presence of Cr.

Sometimes, ACD or positivity to patch test have been attributed, as a "default" option, to Cr present in shoes but without either measuring Cr in the "incriminated" shoes or hypothesising other allergens in the footwear material (see e.g. Thyssen et al., 2014). For instance, Van Coevorden et al. (2002) showed that shoes with low or even without Cr, cause ACD due to other, sometimes unknown, components of leather (e.g.: dyes or other tanning agents). This may, at least in part, explain the lack of correlation between CrIII and/or CrVI content in leather and skin reaction to leather patch test as reported by Hansen et al. (2006). These authors carried out patch tests on 15 CrVI sensitised subjects, with 14 different chromate-tanned leather samples and one vegetable-tanned leather, as a control. As it can be seen from Table 1, they found no correlation between either CrVI or CrIII extracted from the leather and the reaction to the patch test with leather samples. In fact, only 5/14 samples caused positive reaction, and in particular the sample that caused reactions in most subjects (3/15) contained the less CrVI and CrIII. Also, wearing for 14 days a bracelet made with the leather sample containing the highest level of CrVI (16.9 ppm) (and 209 ppm CrIII) caused an allergic skin reaction in 3/12 subjects: to be noted the fact that these 3 subjects did not react to the 48 h patch test, whereas 2 subjects who reacted to the 48 h patch test did not react to the bracelet. These authors concluded that the lack of correlation may be attributable to the fact that the method to measure Cr released by leather (DIN 53314) is not appropriate, although they admitted that other non-Cr allergens may have caused the observed allergic skin reactions following sensitisation concomitant with Cr. For instance, Freeman (1997) reports that less than 25% of the subjects with shoe allergy showed positive reaction to patch test with CrVI, the commonest allergens being rubber antioxidants, such as mercaptobenzothiazole. The sources of rubber allergy in shoes were reported to be most commonly rubber adhesives used for shoe linings, and, less so, rubber innersoles and elastics present in the uppers of shoes. She also indicates that 80% of the 55 patients reported the presence of hyperhidrosis, suggesting that excessive sweat might either have helped to leach out chemicals from shoes, thus contributing to sensitization, or modified skin condition that favoured Cr absorption. It is of particular interest that 14.5% of patients had positive patch tests to a sample of their shoes and were negative to all tested shoe allergens that included rubber chemicals, potassium dichromate, BFP (p-t-butyl-formahaldeyde resin), colophony, and paraphenylenediamine, and to the European standard series. Similarly, Goossens and Taylor (2011) support the hypothesis that ACD linked to shoes is not necessarily due to Cr, and report other allergens related to either other non-leather components of the shoe or other chemicals present in leather such as formaldehyde and nickel.

On the other hand, Bajaj et al. (1991) reported that about 75% of the subjects with shoe allergy in India tested positive to CrVI. In addition to the unknown quality of the shoes, high temperature and humidity, rainy season and lack or rare use of socks may have facilitated the development of the allergic reaction. More recently, Chowdhuri and Ghosh (2007) from India report that positivity to CrVI was found in 46% of the subjects with footwear dermatitis, and also these authors point out that the quality of Indian shoes is not properly controlled. In more recent reports, from other parts of the world, the percentage of CrVI positivity was lower than 30%, sometimes lower that 20% in subjects with shoe dermatitis (Holden and Gawkrodger, 2005, and references therein).

Quality of leather appears to be relevant for the allergy. In fact, Freeman (1997) reported that 3 subjects with shoe allergy, who tested positive to CrVI, had resolved at follow-up despite the fact that they continued to wear leather shoes, because "they wore good quality, new leather shoes". Among other, also Nardelli et al. (2005) report improvement by wearing good-quality new leather shoes.

Several authors pointed out that sensibilisation to cobalt may also be relevant (Bregnbak et al., 2014a; Landeck et al., 2012; Thyssen et al., 2013; Nardelli et al., 2005). Nardelli et al. (2005) reported that 89 subjects (out of 1168) with "shoe allergy" tested positive to colophony which is used for leather treatment. Although prohibited in EU, cases of ACD associated with the presence of dimethylfumarate in leather are still reported in Europe (e.g.: Svecova et al., 2013; D'Erme et al., 2012; Toledo et al., 2011; Silvestre et al., 2011; Susitaival et al., 2010).

Thyssen et al. (2009) state that, in Denmark, chromium allergic patients who reported relevant leather exposure increased from about 24% during 1989–1994 to 45.5% during 1995–2007 ($p < 0.02$), whereas those with clinically relevant cement exposure decreased from about 13% in 1989–1994 to 3.0% in 1995–2007 ($p < 0.01$). Moreover, most cases of dermatitis and Cr allergy were associated to contact with leather footwear and/or leather gloves, based on data from 1995 to 2007. However, this conclusion was based on a low number of cases (see Table 2) and there was neither

Table 2
New cases of CrVI allergy observed in Denmark. Adapted from Table 1 in Thyssen et al. (2009).

year	N/year – all	N/year – males	N/year – females
1985–1990	18, 1	7, 8	10,3
1991–1996	12, 6	4, 6	8
1997–2001	16, 8	3, 8	13
2002–2007	21, 6	8	13, 6

Total cases of skin allergy were 16,228 (705/year).

Table 1
Lack of correlation between the content of soluble CrIII and/or CrVI in 14 leather samples and allergic skin reaction in 15 Cr sensitised subjects (modified from Hansen et al., 2006). Subjects have been tested by applying a sample of leather on the skin for 48 h in occlusive conditions.

	Cr (III) (ppm) measured in leather	Cr (VI) (ppm) measured in leather	Subjects with (+) patch test/tested subjects
9 samples	93–209	<3–16, 9	0/15
1 sample	112	9.2	1/15
3 samples	90–591	<3–4.6	2/15
1 sample	12	<3	3/15

NOTE: the total number of subjects who tested positive was 4/15.