REVIEW   **Open Access**

Chromium and leather: a review on the chemistry of relevance for allergic contact dermatitis to chromium

Yolanda S. Hedberg

Abstract

As other causes decline in importance, chromium-tanned leather has become a more important source for chromium allergy, which affects around 1% of the general population. The aim of this review is to give suggestions on how to minimize the risk of leather-related allergic contact dermatitis, which can be elicited in chromium-allergic persons by hexavalent and trivalent chromium released from leather. Hexavalent chromium is the more potent chromium form and requires a lower skin dose to elicit allergic reactions. It is formed on the surface of some, antioxidant-free, leathers at dry conditions (< 35% relative humidity) and is influenced by the tanning process and other conditions, such as UV irradiation, contact with alkaline solutions, and leather age. Trivalent chromium is the dominant form released from chromium-tanned leather and its released amount is sufficient to elicit allergic reactions in some chromium-allergic individuals when they are exposed repetitively and over longer time (days – months). A low initial test result (< 3 mg/kg) for hexavalent chromium with the current standard test (ISO 17075) does not guarantee a low release of chromium from the leather or a low release of hexavalent chromium under typical exposure conditions during the service life of the leather. Information, labels, and certificates regarding leather products are often insufficient to protect chromium-allergic individuals. Correct labelling and information on the possible content of different allergens, as well as different tanning alternatives for certain leather products, are crucial.

Keywords: Hexavalent chromium, Chromium, Contact dermatitis, Allergy, Eczema, Relative humidity, Antioxidants, Exposure, Speciation, ISO 17075

1 Introduction

1.1 Chromium speciation – toxicological considerations

It is widely accepted that the chemical speciation of chromium matters for different toxicological outcomes in man and other species. However, its importance is different for different diseases and different species. For example, while hexavalent chromium is known to be by far more toxic and carcinogenic for man as compared to trivalent chromium species [1], this might be reversed for other species, such as bacteria and water organisms.

Trivalent chromium is more toxic to freshwater algae as compared to hexavalent chromium [2]. Predicted no effect concentrations of 3.4 μg/L for hexavalent chromium and of 4.7 μg/L for trivalent chromium for aquatic organisms have been estimated within the framework of environmental risk assessment in the European Union in 2005 [3]. This is in line with a recent biotoxicity study on *Photobacterium phosphoreum* of leachates from chromium-tanned leathers, that contained trivalent chromium bound to different organic ligands along with traces of other organic leachates [4]. The leachates were significantly more toxic as compared to control solutions of trivalent and hexavalent chromium, although the exact speciation and pH of these

Correspondence: yolanda@kth.se
Division of Surface and Corrosion Science, Department of Chemistry, School of Engineering Sciences in Chemistry, Biotechnology, and Health, KTH Royal Institute of Technology, Drottning Kristinas väg 51, SE-10044 Stockholm, Sweden

control solutions was not reported [4]. In the following, however, this review will only focus on man and skin allergies to chromium.

1.2 Chromium tanning

Tanning is a necessary process to preserve animal skins and hides and convert them into useful leather, which is a stable material resistant to microbial attack and with enhanced resistance to wet and dry heat [5]. Chromium-tanning is the most common tanning process worldwide, using a basic trivalent chromium sulfate salt, $Cr(OH)SO_4$ [5]. There are several advantages of chromium tanning as compared to other mineral tanning types, oil tanning, vegetable tanning, and aldehyde tanning: *i*) it results in higher heat resistance, *ii*) it is one of the cheapest and fastest tanning processes, *iii*) it is considered to be one of the environmentally most friendly and least toxic options, and *iv*) the raw material is readily available [5]. Trivalent chromium binds to the proteins, primarily collagen, of the skin/hide forming a complex [5, 6].

1.3 Chromium allergy and allergic contact dermatitis (ACD)

Chemically, the binding of a molecule to a protein is a common prerequisite for successful tanning, for skin allergy, and for one type of allergic asthma. Allergic asthma to chromium is relatively scarcely reported [7–12]. Respiratory illness, coupled with high immunoglobulin E (IgE) and chromium levels in the blood have been reported for tannery workers [13, 14], although it is not possible to rule out from these studies whether this was due to allergic asthma caused by chromium. This review will focus on skin allergy. The skin allergy discussed herein is a hypersensitivity of type IV, which is a delayed and T-cell-mediated type of skin allergy, and which can elicit allergic contact dermatitis (ACD) [15]. The word "contact" refers to the observation that ACD occurs at that skin area that has been in physical contact with the sensitizing substance. Type IV hypersensitivity consists of the sensitization step and the elicitation step, which take up to 30 days and 1–7 days, respectively, after skin contact with the sensitizing substance, to which the sensitization is specific. Once sensitized, the allergy is life-long, but contact eczema are only elicited after contact to the sensitizing substance. The reason for the long time between skin contact with the substance and visible skin reactions is a complicated cascade of immune reactions that involve dendritic cells (in the skin), T-cells, and lymph nodes [16]. To be sensitizing, chromium must bind to a protein. The chromium species/ion is in this context denoted hapten, and the protein to which it binds is the carrier, and together, as a conjugate, they form the antigen [17, 18]. The chromium species

changes the protein structure upon binding. The antigen is then processed and presented to T-cells by cutaneous dendritic cells (Langerhans cells) [18] during the sensitization step or recognized by circulating hapten-specific T-cells during the elicitation step [17–20]. Several common skin proteins, such as albumin and heparin, have been found to be able to be the carriers for the chromium antigen, and chromium binding as well as structural changes of these proteins have been confirmed [7, 21–29].

1.4 Relevant chemical speciation of chromium for ACD

Since hexavalent chromium forms exclusively negatively charged mono- or dichromates under the conditions of relevance for skin exposure and since these negatively charged chromates are not able to bind to proteins, it is only trivalent chromium that binds to proteins and forms the antigen [7, 30–32]. This means that hexavalent chromium first needs to be reduced prior to forming the antigen. Still, hexavalent chromium is considered to be the more potent skin sensitizer as compared to trivalent chromium species, since it *i*) penetrates the skin much more efficiently [7], *ii*) penetrates cell membranes at much higher rates [30, 32, 33], and *iii*) seems able, due to its oxidative properties, to induce some immunological responses that trivalent chromium is unable to cause [34, 35].

The extent of skin penetration and doses required in the sensitization and elicitation steps of chromium allergy are affected by the chemical speciation of chromium, in particular its size and charge, and the status of the skin (intact or damaged skin, state of skin barrier) [7, 36]. The tanning agent $Cr(OH)SO_4$ belongs to those chromium species of lowest skin penetration rates and lowest potency, which means that relatively high doses are required to elicit ACD to chromium [7, 37]. Still, a dose of 0.1 M (16.5 g/L) $Cr(OH)SO_4$ was able to elicit ACD in 70 of 94 tested chromium-allergic individuals [37]. In general, hexavalent chromium is found to be the most potent species, requiring lowest doses for elicitation (as low as 0.03 µg per cm^2 skin area or 1 µg/L) [38], followed by negatively charged trivalent chromium species, such as trivalent chromium oxalate [7, 36, 39]. Most importantly, the chromium speciation during leather tanning and that of relevance for consumer exposure to leather articles varies as a function of environmental parameters, such as pH, presence of complexing agents and antioxidants, relative humidity, temperature, and time [40–44]. Due to the acidic pH during chromium tanning and desired chemistry during the tanning process, exposure to $Cr(OH)SO_4$ and related trivalent chromium species seem most relevant for tannery workers. During production of $Cr(OH)SO_4$, however, there is exposure possible to the highly potent

hexavalent chromic acid, from which the spray dried powder $Cr(OH)SO_4$ is obtained by reduction by sulfur dioxide [5]. Tannery workers have been found to have a higher risk of ACD to chromium [13, 14, 45, 46] as compared to control groups. This review will however mostly focus on chromium allergy of relevance for consumers.

1.5 Prevalence of chromium allergy

Chromium allergy is relatively common. Chromium allergy becomes only clinically relevant upon sufficient skin exposure to chromium, which elicits ACD. Whether a person is chromium-allergic, can be tested by patch testing (further explained in section 2.2.). Estimates are approximately 1% of the general population in Europe, which is the region that has been studied most and has the lowest prevalence of chromium allergy among those countries and regions that have been studied, Table 1. Among clinical groups, which are mainly patients of specialized dermatology clinics, the prevalence of chromium allergy is about 4.2–4.8% in Europe and North America, while it is higher (6–10%) in other countries and continents, Table 1. Compared to other allergens, chromium is among the most frequent, usually among the top 1–20 most frequent allergens in different studies, see references in Table 1 and [91]. Over time, the prevalence of chromium allergy has declined in European and North American countries, but the fraction of leather related chromium allergy has increased. Most recent clinical data from Austria, Switzerland, and Germany suggests however an increase of the prevalence of chromium allergy after 2015 (from 4.2% in 2007–2010, to 3.3% in 2011–2014, to 4.5% in 2015–2018) [49], which requires further monitoring. Clinically, the leather related fraction of chromium allergy may be determined by asking the patient about the cause of his/her dermatitis, e.g. due to contact with certain shoes or a certain item, confirming the localization of the dermatitis related to a certain exposure, patch-testing the patient with that source confirming its relevance for the dermatitis, testing the leather for different allergens, and patch-testing the patient with different allergen series, e.g. the shoe series containing a number of shoe allergens covering, among others, glues, plastic chemicals, metal allergens, dyes, and preservatives. For example, Danish studies suggest that the leather related fraction of chromium allergy increased from about 24% in 1989–1994 [92] to 55% in 2010–2017 [50]. In other countries, work-related exposures and other consumer exposures, such as to cement, detergents, cleaning agents, chemicals, metal work, metal fumes, and chromated surfaces, remain dominant as cause of chromium allergy [7].

1.6 Severity and persistence of chromium allergy and ACD

Once sensitized, ACD to chromium can be elicited by relatively low doses of chromium [93]. Chromium allergy is characterized by that it more often causes chronic and severe eczema as compared to other type-IV allergies [94, 95], resulting in lower quality of life and higher unemployment rates. Also, the contact dermatitis to chromium is more often located on the hands and feet [96, 97]. ACD to chromium has been found to be very persistent [98–100] and to have a poor prognosis [94–96, 101–103].

This review focuses on chemical questions regarding chromium allergy of relevance for the leather industry, regulators, chromium-allergic persons, and consumers of leather articles. The aim of this review is to give suggestions on how to minimize the risk of chromium allergy related to leather articles.

Table 1 Summary of selected data on the prevalence of chromium allergy in the general population and different clinical/ occupational groups in different continents and countries. The data are merged for Europe, Asia, and North America. A detailed overview is given in the supplementary file, Table S1

Region	Type of tested persons	Years of testing	Prevalence of contact allergy to chromium (%)	Number of tested persons	References
Europe (merged)	General population	2008–2011	0.75	3119	[47]
Multi-national (mostly Europe)	General population	1967–2010	1.8	13,250	[48]
Europe (merged)	Clinical / occupational	1996–2018	4.2	260,676	[49–66]
North America (merged)	Clinical	2006–2019	4.8	39,570	[67–69]
Australia	Clinical	2001–2010	10	5180	[70]
Asia (merged)	Clinical / occupational	1990–2017	8.4	30,038	[71–88]
Ethiopia	clinical	2007–2008	6.4	514	[89]
Brazil	clinical	2003–2015	9.0	1386	[90]

2 Trivalent versus hexavalent chromium from an allergic perspective

2.1 Release of trivalent and hexavalent chromium from leather

Due to the different potency and skin permeability of trivalent and hexavalent chromium, it is important to understand the chemistry behind the release of trivalent and hexavalent chromium from leather articles in skin contact or under relevant exposure conditions. Figure 1 summarizes some data of studies investigating trivalent and hexavalent chromium release from different leathers under different pre-exposure and exposure conditions (for detailed information, see the supplementary file Table S2). For most leathers and exposure conditions, trivalent chromium is the predominant form of chromium that is released. The release of trivalent and hexavalent chromium from leather, even for the same leather, are strongly affected by pre-exposure conditions and exposure conditions. To date, a number of factors has been investigated both during the tanning and manufacturing steps and during pre-exposure and exposure from a consumer perspective. These factors and their influence on trivalent and hexavalent chromium release from leather are summarized in Table 2.
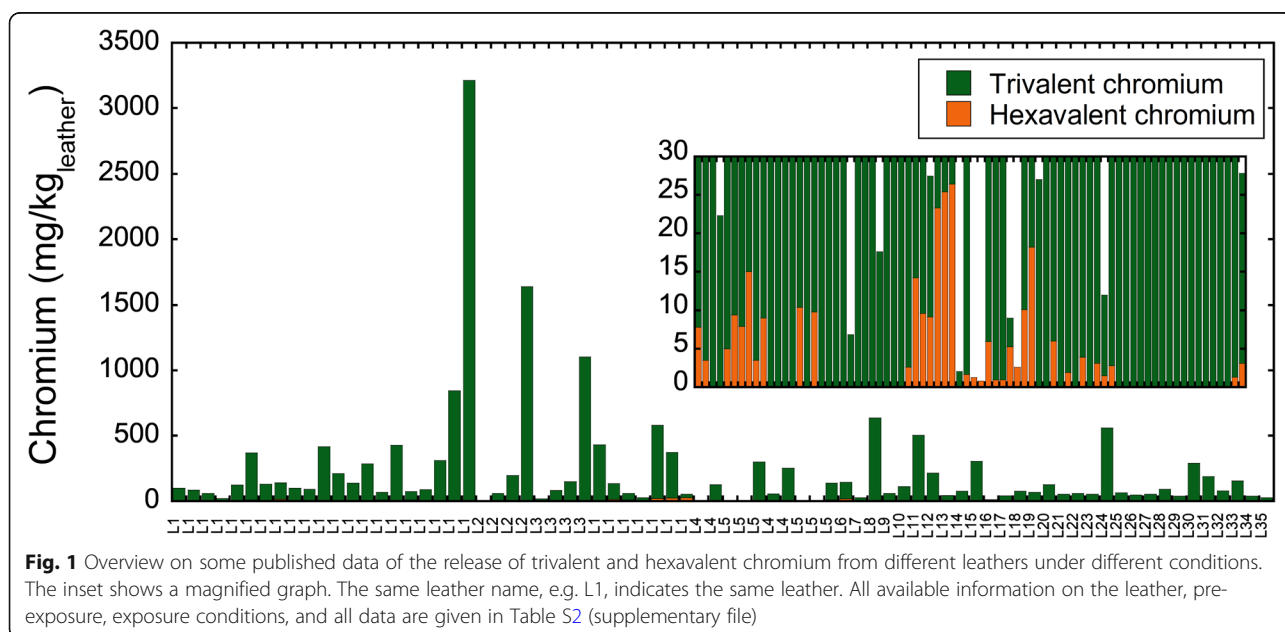
The release of total (trivalent and hexavalent) chromium is highest for new leather since excess chromium is released. Further, it is highest at acidic and alkaline conditions and after exposure to dry (< 35% relative humidity) air. The release of hexavalent chromium from leathers is affected by a larger number of parameters. The initial leather chemistry, which is largely determined by the tanning process, plays an important role as well

as pre-exposure and exposure conditions. In the absence of antioxidants, which is the case for some leathers and/or for old/used leathers, the most important factor is exposure to dry air (< 35% relative humidity) prior to exposure to any solution or the skin. For antioxidant-free and old/used leather, hexavalent chromium can even be detected in artificial sweat (pH 5–6.5) [133], while it is otherwise only detected at neutral and alkaline pH. This agrees with early studies on extraction of hexavalent chromium by human sweat [40]. The risk for release of hexavalent chromium from leathers increases for:

- Purely chromium-tanned leathers without any antioxidants, vegetable tannins, or reducing acids
- Tanning or manufacturing at too high pH or with oxidative species
- Exposure to dry air (< 35% relative humidity) prior to skin contact or exposure
- Exposure to UV irradiation and dry air prior to skin contact or testing / exposure
- Pre-exposure or exposure to alkaline media (pH 12 or higher), such as contact with cement
- Age / usage of leather.

2.2 Allergic reactions to trivalent and hexavalent chromium, and chromium-tanned leather

When comparing clinical studies on ACD to chromium as a function of trivalent and hexavalent chromium skin doses, it is important to consider the chemical speciation of the applied chemical substance. Many trivalent chromium salts induce a low pH that is not suitable for skin patch testing. Patch testing means that a small amount

Fig. 1 Overview on some published data of the release of trivalent and hexavalent chromium from different leathers under different conditions. The inset shows a magnified graph. The same leather name, e.g. L1, indicates the same leather. All available information on the leather, pre-exposure, exposure conditions, and all data are given in Table S2 (supplementary file)

Table 2 Most important tanning, leather, and exposure factors/conditions for the release of trivalent and hexavalent chromium from chromium-tanned leather

Factor	Release of trivalent chromium	Release of hexavalent chromium	Reference
Factors during tanning / manufacturing			
Total content of chromium	Possible increase in release	Unclear or contradictive effects	[104–111]
Fatty acids	–	Potential increase for mono- or polyunsaturated (free or esterified) acids, such as natural oils (fish oils etc.)	[104, 108, 111–119]
Vegetable tannins	–	Possible decrease, more decrease for higher contents and certain tannins (tara, sumac)	[42, 104, 105, 116, 117, 120–123]
Synthetic tannins	–	No effect, decreasing effect for polyhydroxyphenol	[104, 105, 122]
Reducing agents (antioxidants)	–	Decrease	[43, 104, 112, 121, 124–128]
Complexing agents	–	Can hinder the oxidation of trivalent chromium in solution	[104, 115]
Hide constituents, protein degradation products or cationic fatliquors	–	No effect	[104, 105]
pH in neutralization	–	Increase, if over-neutralization. Otherwise no effect.	[104, 108, 120, 129, 130]
Washing/rinsing	–	No effect. If too extensive, increased release possible due to removal of formic acid residues.	[104]
Alkaline adhesion binders	–	Increase	[105]
Relative humidity, leather water content	–	Possible decrease for increased relative humidity and leather water content	[43, 104, 106, 116, 125]
Storage time	–	Strongly dependent on relative humidity. Extended storage time can reduce the Cr(VI) content if relative humidity > 30–35%, otherwise a possible increase.	[41, 43, 104]
Dry heating (oxygen gas present)	–	Possible increase	[43, 104–106, 117, 121, 124, 125, 130, 131]
Vacuum drying	–	No effect	[104, 112]
UV irradiation at dry conditions	–	Possible increase	[104, 112, 117, 120, 121, 124, 125, 131]
Buffing	–	No effect	[129]
Leather factors during exposure			
Surface area to mass ratio	If increased, more release	Surface area that has been in contact with dry (< 35% relative humidity) air prior to exposure: if increased, more release. Increased surface area at > 35% relative humidity may result in decreased release due to co-released antioxidants/acids.	[41, 132]
Relative humidity and temperature prior to testing	Most release at 35% relative humidity. Slightly less release at lower humidity, and strongly reduced release at higher humidity. Minor importance of temperature.	The lower relative humidity (and longer storage time), the higher release. Relative humidity above 35% results in very low / non-detectable release. Minor importance of temperature.	[41, 43]
UV irradiation (at dry conditions) prior to exposure	No effect	Increase possible for certain exposure conditions	[41, 123]
Temperature during exposure (immersion or skin contact)	Increased release for higher temperature (even 5 °C higher)	–	[132]
Solution pH	Lowest release at neutral pH. Increased release for acidic (< 5) and alkaline (> 10) pH	Increased release for more alkaline pH. Very low release for pH < 7.	[41, 44]

Table 2 Most important tanning, leather, and exposure factors/conditions for the release of trivalent and hexavalent chromium from chromium-tanned leather *(Continued)*

| Factor	Release of trivalent chromium	Release of hexavalent chromium	Reference
Exposure time, repeated exposure, leather usage / age	Most release initially. Decreasing release rates with time / age.	Decreasing release rates when immersed / at humid conditions. Increased release after dry storage conditions and for older / used leather.	[132–134]
Co-released antioxidants	No effect	Decrease / non-detectable values	[42]
UV irradiation during exposure or at humid conditions	No effect	No effect	[132]
Wear	No effect	No effect	[41]

-, not investigated; *UV* ultraviolet

of the chemical substance is applied on the skin in an occluded chamber and kept there for usually 2 days [135]. The allergic skin reaction is then read by a dermatologist after additionally 1–5 days. The pH of the chemical substance applied should be in the range between 4 and 9. Most trivalent chromium salts are not stable in solution above pH 4 and would precipitate, which hence would reduce the actual, bioaccessible, skin dose during patch testing. However, trivalent chromium species bound to organic ligands can be stable under conditions relevant for leather and skin contact. Relevant chemical speciation of clinically important chromium species is illustrated as a function of pH in Fig. 2a. When the line of a certain species is on the top of that figure, all of it is in solution (in its aqueous phase) and when it is at the bottom, it is precipitated from solution (in a solid phase). From Fig. 2a, it can be deduced that it is not possible to design a clinical study that investigates stable trivalent and hexavalent chromium species at the same pH. The pH is an important factor for skin permeability [136] and skin charge [137]. In a recent study [36], trivalent and hexavalent chromium salts were chosen that would form similarly charged (negatively charged) and relatively stable species over the entire concentration range of the patch test study, Fig. 2b-c. The trivalent chromium solution was buffered to a pH of 4.1 and the hexavalent chromium solution to a pH of 8.5. The majority of chromium-allergic individuals in that study reacted to both trivalent and hexavalent chromium, although the required dose for a positive and stronger reaction was significantly lower for hexavalent chromium as compared to trivalent chromium, Fig. 2d-f, which is in agreement with a number of previous studies [37–39, 97, 137–140].

Figure 3 shows the lowest skin doses of the trivalent and hexavalent chromium during patch testing that the ten chromium-allergic individuals in the clinical study [36] reacted to. The asterisks in Fig. 3a-b mark those four chromium-allergic individuals that also reacted to a chromium-tanned leather bracelet within 3 weeks of use

(12 h per day like a normal bracelet). Only one of these individuals reacted to the same leather when tested on the back in an occluded patch test for 48 h. As also confirmed in other studies [97, 141], a lower elicitation threshold and positive reactions to trivalent chromium increased the risk of reacting to the chromium-tanned leather bracelet within the study period. In a Danish study on 2211 dermatitis patients, 71 (3.1%) had a positive reaction to hexavalent chromium (0.5% potassium dichromate), of which 31 also had a positive reaction to trivalent chromium (13% chromium trichloride) [97]. An increased risk of foot dermatitis was found for those patients reacting to both trivalent and hexavalent chromium. This increased risk of foot dermatitis was not caused by a higher degree of sensitivity to hexavalent chromium, suggesting that trivalent chromium played a role for shoe dermatitis for these patients, along with other shoe allergens [97]. The deposited amount of chromium from the chromium-leather bracelets on the skin of the participants in the bracelet study [36] was very low and no hexavalent chromium was detectable on the chromium-tanned leather bracelets after the three-weeks use test, Fig. 3d. These findings suggested that repeated skin exposure to very low amounts of chromium from chromium-tanned leather items and released trivalent chromium are sufficient to elicit ACD to chromium from leather items in chromium-allergic individuals. This observation is in agreement with other use test and repeated open application test studies and allergens, suggesting that lower doses are required if the exposure occurs repeatedly over longer time as compared to an occluded patch test during 48 h [141–144]. In that bracelet study [36], the two leathers were also tested for traces of other metals present (there were none). Both leathers were non-finished to avoid the presence of dyes or other allergens originating from the finishing process. The chromium-tanned leather was not tanned with other tannins. It is hence unlikely, but not completely impossible, that another organic allergen that might have been present in the chromium-tanned leather and absent
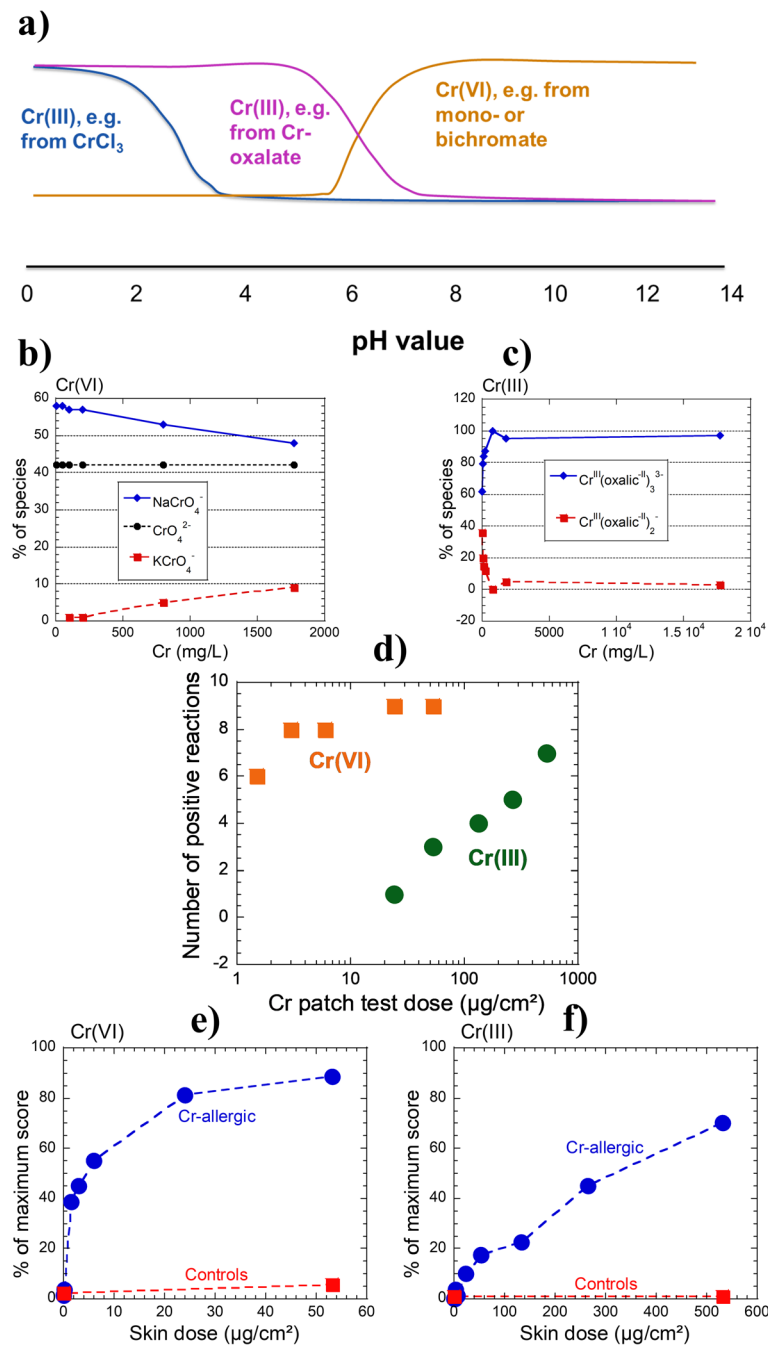
Fig. 2 Schematic overview on chemical speciation of different trivalent and hexavalent chromium species as a function of pH (**a**), calculated chemical speciation of hexavalent chromium from a dichromate salt at pH 8.5 (**b**) and of trivalent chromium from a chromium(III) oxalate salt at pH 4.1 (**c**) as a function of concentration covering the range of concentrations used in the clinical patch test study [36], number of positive skin reactions in ten chromium-allergic individuals as a function of patch test dose (**d**), from [36], and severity of skin reactions, expressed as percentage of the possible maximum score, of ten chromium-allergic individuals and 22 non-allergic controls, when tested with hexavalent chromium (**e**) or trivalent chromium (**f**) in the same study. Cr – chromium; Cr(VI) – hexavalent chromium; Cr(III) – trivalent chromium; skin or patch test dose is expressed as μg chromium species per cm^2 skin area
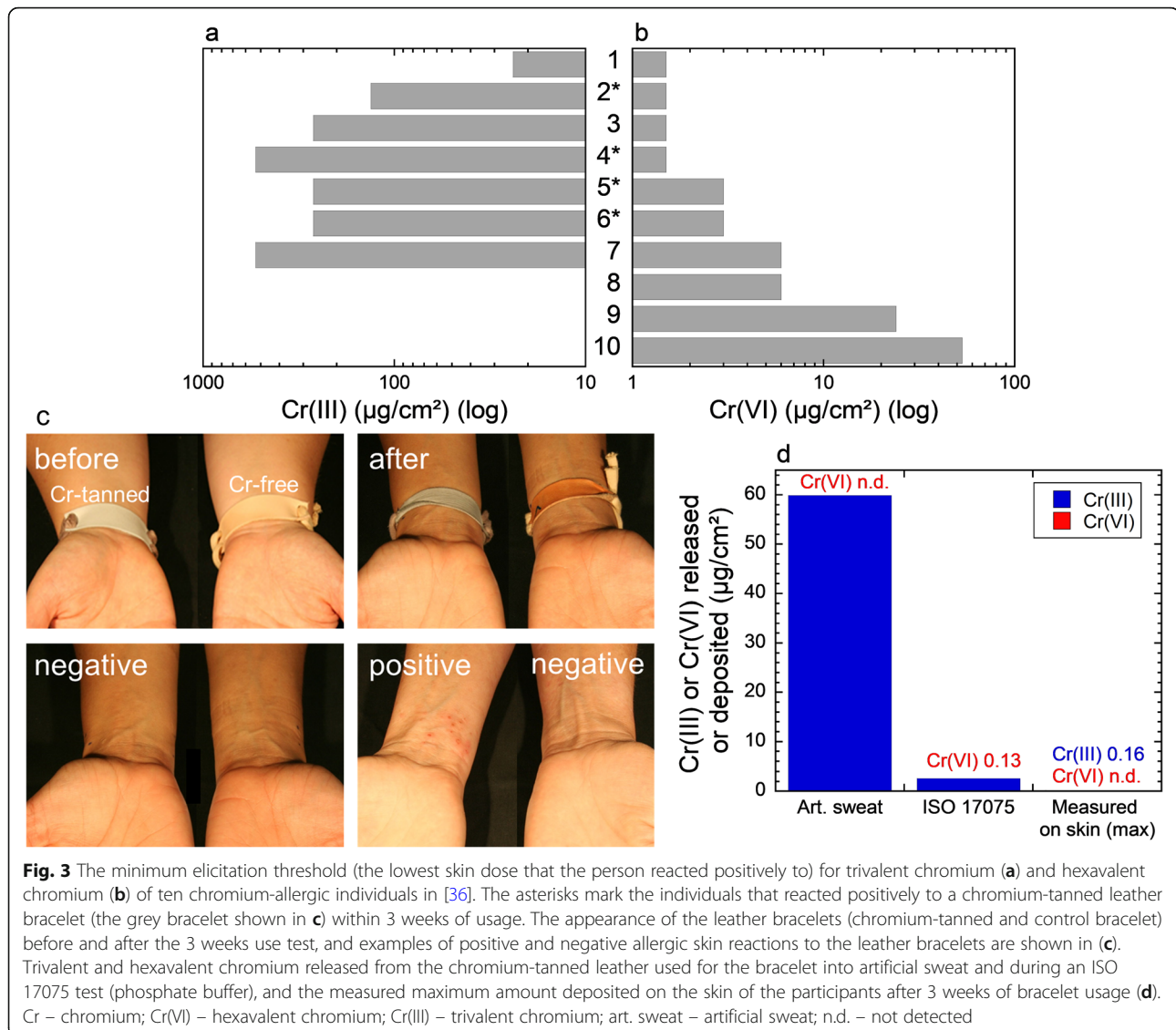
Fig. 3 The minimum elicitation threshold (the lowest skin dose that the person reacted positively to) for trivalent chromium (**a**) and hexavalent chromium (**b**) of ten chromium-allergic individuals in [36]. The asterisks mark the individuals that reacted positively to a chromium-tanned leather bracelet (the grey bracelet shown in **c**) within 3 weeks of usage. The appearance of the leather bracelets (chromium-tanned and control bracelet) before and after the 3 weeks use test, and examples of positive and negative allergic skin reactions to the leather bracelets are shown in (**c**). Trivalent and hexavalent chromium released from the chromium-tanned leather used for the bracelet into artificial sweat and during an ISO 17075 test (phosphate buffer), and the measured maximum amount deposited on the skin of the participants after 3 weeks of bracelet usage (**d**). Cr – chromium; Cr(VI) – hexavalent chromium; Cr(III) – trivalent chromium; art. sweat – artificial sweat; n.d. – not detected

in the vegetable-tanned leather would have elicited the reactions in the four chromium-allergic individuals, but not in the 20 controls. None of the ten chromium-allergic individuals in that study has been allergic to formaldehyde.
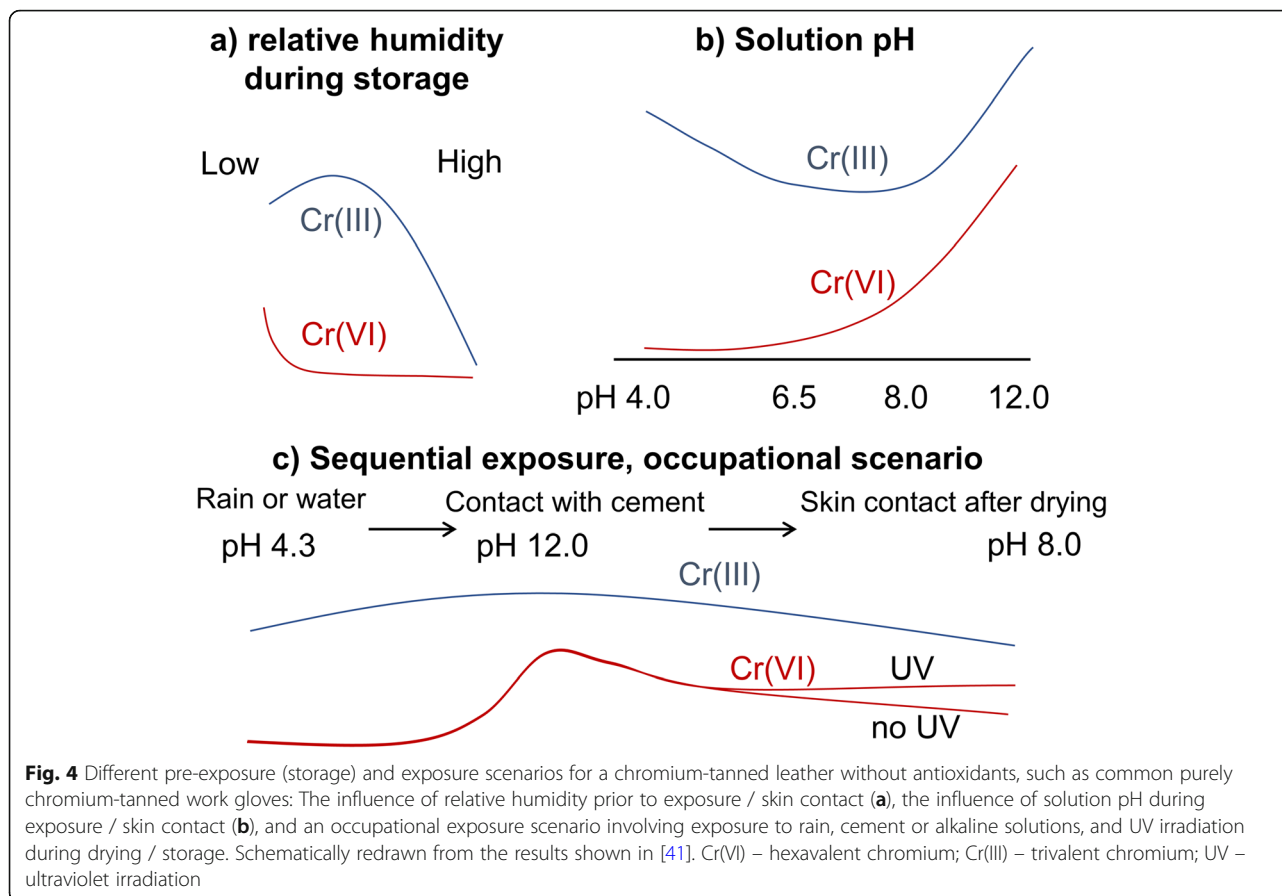
3 The formation of hexavalent chromium during use of chromium-tanned leather

While there is today enough evidence that released trivalent chromium from chromium-tanned leather is a problem for chromium-allergic individuals, the avoidance of the formation of hexavalent chromium in, or more exactly on, chromium-tanned leather remains the most important measure regarding chromium-tanned leathers for both chromium-allergic individuals and those that should be protected from sensitization.

3.1 Age of chromium-tanned leather article in use
There are reports that show that the extent of released hexavalent chromium from chromium-tanned leather increases with age/use [43, 133, 134], most probably since antioxidants, acids, and colors are washed out. The chromium-allergic participant number 2 in Fig. 3a-b reported that new leather shoes did not cause any problems, but old shoes did. A similar observation was reported in [145]. Instead, a study investigating the effect of different stable inhibitors for chromium oxidation found that leathers that were prepared with this inhibitor mixture did withstand the formation of hexavalent chromium (under dry conditions) even after 12 months of storage, while chromium-tanned leathers without that inhibitors could re-form hexavalent chromium after a heating step [43].

Fig. 4 Different pre-exposure (storage) and exposure scenarios for a chromium-tanned leather without antioxidants, such as common purely chromium-tanned work gloves: The influence of relative humidity prior to exposure / skin contact (**a**), the influence of solution pH during exposure / skin contact (**b**), and an occupational exposure scenario involving exposure to rain, cement or alkaline solutions, and UV irradiation during drying / storage. Schematically redrawn from the results shown in [41]. Cr(VI) – hexavalent chromium; Cr(III) – trivalent chromium; UV – ultraviolet irradiation

3.2 Environmental factors during use of leather articles

For those chromium-tanned leathers that lack antioxidants due to the tanning process or their age, hexavalent chromium can be formed as a function of environmental factors, such as relative humidity and UV irradiation during storage, solution pH, and contact with alkaline solutions (such as contact with cement), illustrated in Fig. 4. There is generally a high risk of the formation of hexavalent chromium for work gloves in contact with alkaline solutions or cement, especially if they are used repetitively and in regions with low relative humidity, such as Northern countries in the wintertime. It should be emphasized that the total chromium release from chromium-tanned leather items is even more important and that the total chromium release is primarily influenced by the amount of sweat and therefore highest in warm countries or during summertime [40, 133, 146–148].

4 Obstacles related to the standard test for hexavalent chromium in leather (ISO 17075)

Since 2015, all leather items in the European Union are required to comply to the regulation Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) [149, 150] and to have a lower test result than 3 mg/kg hexavalent chromium according to the standard test ISO 17075 [151].

However, an initially compliant test result with < 3 mg/kg hexavalent chromium does not mean that the leather item is not able to release hexavalent chromium later under different environmental conditions. The reasons are several.

First, it has been reported that manufacturers by intention spray the leather items prior to testing or retesting occasions with antioxidants, such as ascorbic acid [152]. These sprayed-on antioxidants prevent a test result that would prohibit the leather item to be placed on the market, but may not necessarily hinder the formation of hexavalent chromium on the leather item in the long term (if washed out). In contrast, stable inhibitors of hexavalent chromium formation may be useful, as they have been shown to be intact even after long-term storage [43].

Second, as discussed in the previous sections, the relative humidity prior to testing with ISO 17075 is crucial. If that relative humidity is greater than 35%, the test results will most probably be below the restriction limit of 3 mg/kg. In the current version of ISO 17075, it is

referred to ISO 4044 [153], which in turn refers to ISO 2419 [154]. In ISO 2419, the conditioning of dry leather samples is specified at 23 °C and 50% relative humidity (reference standard atmosphere) for 24 h for dry leather samples (dried at a temperature not exceeding 40 °C according to ISO 4044), after which the sample should be ground, cut, and stored (in a clean, dry, and airtight container, kept away from sources of heat) according to ISO 4044. Alternative atmospheric conditions are also specified and allowed, when reported, according to ISO 2419. The storage time and relative humidity during storage is not further specified. Several studies on hexavalent chromium in leathers pre-conditioned the samples by heating at 80 °C for at least 24 h [43, 123], which resulted in higher hexavalent chromium release as compared to other pre-conditioning. In one study, it was also confirmed that hexavalent chromium could be re-formed after up to 12 months of storage when heated again at 80 °C [43].

Third, ISO 17075 requires the leather to be tested to be cut/milled into small pieces. This increases largely the surface area to mass ratio, which increases the overall chromium release [132]. However, for hexavalent chromium, the increase of the specific surface area does not necessarily result in an increased release and may under some conditions even result in a slightly reduced release due to two reasons: *i*) co-released acids and antioxidants may decrease the amount of hexavalent chromium in solution [42, 132, 134], and *ii*) without new conditioning at low relative humidity, the increased surface area does not result in new formed hexavalent chromium all over the surface (hexavalent chromium is only found and formed on the surface in contact with oxygen at dry conditions) [41, 104, 116, 125, 132].

Several conditions of the ISO 17075 test are optimal for testing leathers for hexavalent chromium. The deaerated phosphate buffer, extraction time, and mass/solution ratio of the standard test of ISO 17075 can be considered ideal for the extraction of all surface-available hexavalent chromium of the test item [132]. There is no risk of oxidizing trivalent chromium to hexavalent chromium during the test procedure of ISO 17075 [115], hence avoiding false positive results.

It can be questioned how meaningful it is to test leather items for hexavalent chromium, without testing the release of trivalent chromium. From an allergic and exposure perspective, trivalent chromium is also important. The one-time testing of hexavalent chromium of a new leather product can rather be seen as a, relatively irrelevant, snapshot in a dynamic history of chromium speciation throughout the lifecycle of leather. It could be argued that the release of hexavalent chromium to some extent correlates with the total allergic potential of that leather item. But there is no relationship between released hexavalent and trivalent chromium, Fig. 5.
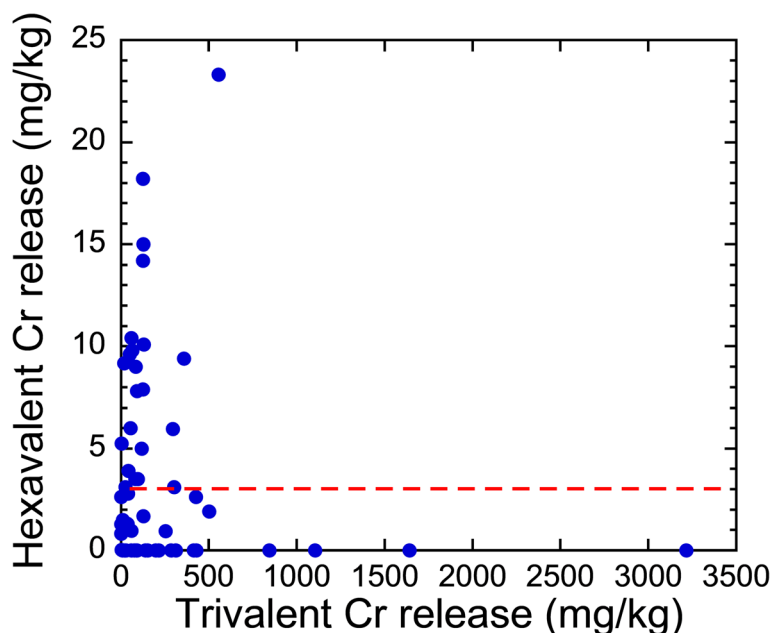
Fig. 5 Measured trivalent and hexavalent chromium release in mg/kg from different leathers and conditions of Fig. 1 (specified in Table S2), excluding non-measurable levels of hexavalent chromium due to color interferences. The red dotted line marks the restriction limit of 3 mg/kg for hexavalent chromium. Only leather items below that restriction limit are allowed to be placed on the market in the EU. Cr – chromium

5 Practical implications for chromium-allergic individuals as consumers of leather products

ACD to chromium can be severe and chronic. Its severity and persistency depend on the extent of exposure to chromium. If a chromium-allergic individual learns about his/her ACD to chromium and which sources of chromium exist, the person can avoid sources of chromium and the eczema will improve over time. Also, the elicitation threshold can increase in the long-term if chromium exposure is avoided for long time. Not all chromium-allergic individuals report problems with leather items. Some chromium-allergic persons report issues only for some types of leather items or occasions, such as for direct skin contact or certain types of shoes (e.g. old shoes). Other chromium-allergic individuals need to strictly avoid all skin contact with all chromium-tanned leather items.

For all chromium-allergic persons, clearly labelled leather products would be helpful. Information on whether the leather has been chromium-tanned or not is not easily available and sometimes wrong. Chromium-allergic persons in Sweden in the clinical study [36] reported that it was difficult to find some chromium-free leather products, such as special shoes. So far, most standards/labels only consider hexavalent chromium tested by ISO 17075, but not the release of trivalent chromium. The OEKO-TEX label, which has been initiated in 1992 in Germany, Austria, and Switzerland, requires testing for both hexavalent chromium (by ISO 17075) and for trivalent chromium extracted in artificial sweat for 4 h at 37 °C (by ISO 17072) with restriction limits of < 2 mg/kg for leather products intended for babies and of < 200 mg/kg for other leather products intended for direct skin contact [155]. For comparison, the leather that elicited allergic reactions in the bracelet study [36] released 313 mg/kg trivalent chromium into artificial sweat after 3 h at room temperature [132].

ACD to chromium is not specific to chromium-tanned leather but elicited by any sources of soluble chromium. These include cement, chemicals, chromated metals, metal fumes, detergents, and bleaching agents. A comprehensive overview is given in [7, 156]. Many occupations involve exposure to chromium, e.g. metal work and construction work, which makes it difficult for chromium-allergic persons to avoid long-lasting eczema and consequences.

6 Alternatives to chromium-tanning from an allergy perspective

Alternative methods to chromium-tanning exist, such as aldehyde-tanning, mineral tanning (other metal ions), and vegetable-tanning [5]. The allergenic potential of vegetable-tanning is so far relatively unknown. Vegetable-tanning has been claimed to have considerable disadvantages as compared with chromium-tanning [5]. Many attempts have been made to overcome these disadvantages and find alternative tanning methods [157–161]. The allergic potential for aldehyde-tanned leather is known: ACD to aldehyde-tanned leather has been reported [162, 163]. Of other practically possible mineral tanning methods, aluminium(III), titanium, zirconium, and iron have been named [5] and have a relatively low, but not totally absent, allergic potential [15].

From an allergic perspective, it is important to clearly label tanned leathers for any allergenic substances and to provide alternatives to chromium-tanned leathers, which today are dominating the market.

7 Conclusions

1. Chromium-tanning is the dominant tanning method for leathers today. Chromium-tanned leather increases in importance as cause for allergic contact dermatitis to chromium in some European and North American countries with a declining number of other chromium sources.

2. Around 1% of the general population, and more in some occupations and regions, are allergic to chromium. This means, that these chromium-allergic individuals can develop ACD upon sufficient skin exposure to chromium-releasing items.

3. ACD to chromium-tanned leathers can be elicited in chromium-allergic persons by both hexavalent and trivalent chromium released from chromium-tanned leather. Positive allergic reactions to trivalent chromium are more common for chromium-allergic persons that react to chromium-tanned leather as compared to other chromium-allergic individuals, which should further be investigated in future studies.

4. Hexavalent chromium is the more potent chromium form and requires a lower amount to elicit allergic reactions. It is formed on the surface of some, antioxidant-free, leathers at dry conditions (< 35% relative humidity) and is influenced by the tanning process and other environmental conditions, such as UV irradiation or contact with alkaline solutions. Hexavalent chromium can be released to a higher extent for older / aged leather as compared to new leather.

5. Trivalent chromium is the dominant form released from chromium-tanned leather and its amount released is sufficient to elicit allergic reactions in some chromium-allergic individuals when they are exposed repetitively and over longer time (days – months). Trivalent chromium is mostly released

initially, and its release is significantly lower for older or used leather.

6. A low test result (< 3 mg/kg) for hexavalent chromium with the current standard test ISO 17075 does not guarantee a low release of total chromium from the leather or low release of hexavalent chromium at another timepoint under certain exposure conditions. This means that certain leathers that have a negative test result in ISO 17075 at one time point can form hexavalent chromium later under certain environmental conditions, such as low relative humidity during storage and exposure to alkaline solutions.

7. Current information, labels and certificates of leather products are insufficient to protect chromium-allergic individuals.

8. Alternative tanning methods might not necessarily be better from an allergic, environmental, toxic, or economic point of view. Correct labelling and information regarding the content of potential allergens, as well as different tanning alternatives, are crucial.

8 Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s42825-020-00027-y.

> **Additional file 1.**
>
> **Additional file 2.**

Abbreviation
ACD: Allergic contact dermatitis

Author's contributions
Y.S. Hedberg prepared this review. The author(s) read and approved the final manuscript.

Availability of data and materials
All data generated or analysed during this study are included in this published article and its supplementary files (Table S1 and Table S2).

Competing interests
The author declares that she has no competing interests.

References

1. Nordberg GF, Fowler BA, Nordberg M. Handbook on the toxicology of metals. London: Academic press; 2014.
2. Vignati DAL, Dominik J, Beye ML, Pettine M, Ferrari BJD. Chromium(VI) is more toxic than chromium(III) to freshwater algae: a paradigm to revise? Ecotox Environ Safe. 2010;73(5):743–9.
3. EC. European Commission, Summary Risk Assessment Report, Chromium trioxide, sodium chromate, sodium dichromate, ammonium dichromate and potassium dichromate. Luxembourg: Institute for Health and Consumer Protection; 2005. Special Publication I.05.16.
4. Peng L, Li Y, Han W, Long W, Zhang W, Shi B. Investigation into the hazards of finished Cr-tanned leather as both product and waste. J Soc Leath Tech Ch. 2019;103(1):43–8.
5. Covington AD. Modern tanning chemistry. Chem Soc Rev. 1997;26(2):111–26.
6. Williams-Wynn D. Consideration of the vegetable tannin/chromium-collagen system. J Soc Leather Trades Chem. 1970;54:27–35.
7. Hedberg YS. Metal allergy: chromium. In: Chen JK, Thyssen JP, editors. Metal allergy: from dermatitis to implant and device failure. Cham: Springer International Publishing; 2018. p. 349–64.
8. Nemery B. Metal toxicity and the respiratory tract. Eur Respir J. 1990;3(2):202–19.
9. Fernández-Nieto M, Quirce S, Carnés J, Sastre J. Occupational asthma due to chromium and nickel salts. Int Arch Occ Env Hea. 2006;79(6):483–6.
10. Hannu T, Piipari R, Tuppurainen M, Nordman H, Tuomi T. Occupational asthma caused by stainless steel welding fumes: a clinical study. Eur Respir J. 2007;29(1):85–90.
11. Novey HS, Habib M, Wells ID. Asthma and IgE antibodies induced by chromium and nickel salts. J Allergy Clin Immun. 1983;72(4):407–12.
12. Keskinen H, Kalliomäki P-L, Alanko K. Occupational asthma due to stainless steel welding fumes. Clin Exp Allergy. 1980;10(2):151–9.
13. Islam LN, Rahman MF, Hossain MA. Serum immunoglobulin levels and complement function of tannery workers in Bangladesh. J Health Pollut. 2019;9(21):190308.
14. Hossain MA, Laila NI. Effect of occupational exposure on allergic diseases and relationship with serum IgE levels in the tannery workers in Bangladesh. Biores Communications-(BRC). 2016;2(1):158–63.
15. Chen JK, Thyssen JP, editors. Metal allergy - from dermatitis to implant and device failure. 1st ed. Cham: Springer International Publishing; 2018.
16. McKee AS, Fontenot AP. Interplay of innate and adaptive immunity in metal-induced hypersensitivity. Curr Opin Immunol. 2016;42:25–30.
17. Lepoittevin J-P. Molecular aspects in allergic and irritant contact dermatitis. In: Johansen J, Frosch P, Lepoittevin JP, editors. Contact Dermatitis. Berlin: Springer; 2011. p. 91–110.
18. Saint-Mezard P, Rosieres A, Krasteva M, Berard F, Dubois B, Kaiserlian D, et al. Allergic contact dermatitis. Eur J Dermatol. 2004;14(5):284–95.
19. Sinigaglia F. The molecular basis of metal recognition by T cells. J Invest Dermatol. 1994;102(4):398–401.
20. Forte G, Petrucci F, Bocca B. Metal allergens of growing significance: epidemiology, immunotoxicology, strategies for testing and prevention. Inflamm Allergy - Drug Targets. 2008;7(3):145–62.
21. Hedberg YS, Dobryden I, Chaudhary H, Wei Z, Claesson P, Lendel C. Synergistic effects of metal-induced aggregation of human serum albumin. Colloid Surface B. 2019;173:751–8.
22. Österberg R, Sjöberg B, Persson D. Cr (III)-induced polymerization of human albumin. Biol Trace Elem Res. 1981;3(3):157–67.
23. Hedberg YS, Pettersson M, Pradhan S, Odnevall Wallinder I, Rutland MW, Persson C. Can cobalt(II) and chromium(III) ions released from joint prostheses influence the friction coefficient? ACS Biomater Sci Eng. 2015;1(8):617–20.
24. Yang J, Black J. Competitive binding of chromium, cobalt and nickel to serum proteins. Biomaterials. 1994;15(4):262–8.
25. Friedberg F. Effects of metal binding on protein structure. Q Rev Biophys. 1974;7(01):1–33.
26. Thulin H, Zachariae H. The leucocyte migration test in chromium hypersensitivity. J Invest Dermatol. 1972;58(2):55–8.
27. Cohen HA. Carrier specificity of tuberculin-type reaction to trivalent chromium. Arch Dermatol. 1966;93(1):34–40.

28. Cohen HA. Tuberculin-type reaction to heparin-chromium complex: heparin—a specific carrier of chromium sensitivity. Arch Dermatol. 1966; 94(4):409–12.

29. Cohen HA. Hyaluronic acid: a specific carrier of chromium sensitivity. Arch Dermatol. 1968;98(2):148–51.

30. Polak L, Frey JR. Studies on contact hypersensitivity to chromium in the Guinea pig. Int Arch Allergy Imm. 1973;44(1):51–61.

31. Samitz M, Katz S. A study of the chemical reactions between chromium and skin. J Invest Dermatol. 1964;43(1):35–42.

32. Siegenthaler U, Laine A, Polak L. Studies on contact sensitivity to chromium in the Guinea pig. The role of valence in the formation of the antigenic determinant. J Invest Dermatol. 1983;80(1):44–7.

33. Rytter M, Haustein UF. Hapten conjugation in the leucocyte migration inhibition test in allergic chromate eczema. Brit J Dermatol. 1982;106(2):161–8.

34. Buters J, Biedermann T. Chromium(VI) contact dermatitis: getting closer to understanding the underlying mechanisms of toxicity and sensitization! J Invest Dermatol. 2017;137(2):274–7.

35. Adam C, Wohlfarth J, Haußmann M, Sennefelder H, Rodin A, Maler M, et al. Allergy-inducing chromium compounds trigger potent innate immune stimulation via ROS-dependent inflammasome activation. J Invest Dermatol. 2017;137(2):367–76.

36. Hedberg Y, Erfani B, Matura M, Lidén C. Chromium(III) release from chromium-tanned leather elicits allergic contact dermatitis: a use test study. Contact Dermat. 2018;78(5):307–14.

37. Fregert S, Rorsman H. Patch test reactions to basic chromium (III) sulfate. Arch Dermatol. 1965;91(3):233–4.

38. Hansen MB, Johansen JD, Menné T. Chromium allergy: significance of both Cr(III) and Cr(VI). Contact Dermat. 2003;49(4):206–12.

39. Fregert S, Rorsman H. Allergic reactions to trivalent chromium compounds. Arch Dermatol. 1966;93(6):711–3.

40. Samitz M, Gross S. Extraction by sweat of chromium from chrome tanned leathers. J Occup Environ Med. 1960;2(1):12–4.

41. Mathiason F, Lidén C, Hedberg Y. Chromium released from leather – II: the importance of environmental parameters. Contact Dermat. 2015;72(5):275–85.

42. Hedberg Y, Lidén C, Odnevall WI. Correlation between bulk- and surface chemistry of Cr-tanned leather and the release of Cr(III) and Cr(VI). J Hazard Mater. 2014;280:654–61.

43. Ogata K, Kumazawa Y, Hattori S, Yoshimura K, Takahashi K. Self-conversion of hexavalent chromium formed in chrome-tanned leather during long-term storage and perfect inhibition with a combination of inhibitors. J Soc Leath Tech Ch. 2018;102(2):53–8.

44. Ogata K, Kumazawa Y, Koyama Y. Measurement of hexavalent chromium in chroma-tanned leather: comparative study of acidic extraction with alkaline extraction. J Soc Leath Tech Ch. 2015;99(6):293–6.

45. Ateeq M, Zareen S, Rehman HU, Zaman H, Nadirullah, Ali T, et al. Occupational allergic contact dermatitis in tannery workers of Peshawar KP Pakistan: An under estimated health issue. J Entomol Zool Stud. 2016;1(97.5):1.4.

46. Kvitko E. Occupational contact dermatitis in the tanning industry. Contact Dermat. 2001;45(4):256.

47. Diepgen T, Ofenloch R, Bruze M, Bertuccio P, Cazzaniga S, Coenraads PJ, et al. Prevalence of contact allergy in the general population in different European regions. Brit J Dermatol. 2016;174(2):319–29.

48. Alinaghi F, Bennike NH, Egeberg A, Thyssen JP, Johansen JD. Prevalence of contact allergy in the general population: a systematic review and meta-analysis. Contact Dermat. 2019;80(2):77–85.

49. Uter W, Gefeller O, Mahler V, Geier J. Trends and current spectrum of contact allergy in Central Europe: results of the Information Network of Departments of Dermatology (IVDK) 2007–2018. Brit J Dermatol. 2020. https://doi.org/10.1111/bjd.18946.

50. Alinaghi F, Zachariae C, Thyssen JP, Johansen JD. Temporal changes in chromium allergy in Denmark between 2002 and 2017. Contact Dermat. 2019;80(3):156–61.

51. Schwensen JF, Menné T, Veien NK, Funding AT, Avnstorp C, Østerballe M, et al. Occupational contact dermatitis in blue-collar workers: results from a multicentre study from the Danish contact dermatitis group (2003–2012). Contact Dermat. 2014;71(6):348–55.

52. Uter W, Larese Filon F, Rui F, Balato A, Wilkinson M, Kręcisz B, et al. ESSCA results with nickel, cobalt and chromium, 2009–2012. Contact Dermat. 2016;75(2):117–21.

53. Fall S, Bruze M, Isaksson M, Lidén C, Matura M, Stenberg B, et al. Contact allergy trends in Sweden – a retrospective comparison of patch test data from 1992, 2000, and 2009. Contact Dermat. 2015;72(5):297–304.

54. Mahler V, Geier J, Schnuch A. Current trends in patch testing–new data from the German contact dermatitis research group (DKG) and the information network of departments of dermatology (IVDK). JDDG. 2014; 12(7):583–92.

55. Fida M, Topi G, Qirko E, Kellici S, Shehu E, Dervishi O, et al. The use of patch testing for the diagnosis of contact dermatitis: an Albanian experience. J Health Sci. 2015;5(2):65–71.

56. Machovcová A, Dastychová E, Kostalova D, Vojtechovska A, Reslova J, Smejkalova D, et al. Common contact sensitizers in the Czech Republic. Patch test results in 12,058 patients with suspected contact dermatitis. Contact Dermat. 2005;53(3):162–6.

57. Tichy M, Karlova I. Allergic contact dermatitis and changes in the frequency of the causative allergens demonstrated with patch testing in 2008-2012. Biomed Papers. 2015;159(3):480–8.

58. Reduta T, Bacharewicz J, Pawłoś A. Patch test results in patients with allergic contact dermatitis in the Podlasie region. Postep Derm Alergol. 2013;30: 350–7.

59. Beliauskiene A, Valiukeviciene S, Uter W, Schnuch A. The European baseline series in Lithuania: results of patch testing in consecutive adult patients. J Eur Acad Dermatol. 2011;25(1):59–63.

60. Rui F, Bovenzi M, Prodi A, Belloni Fortina A, Romano I, Corradin MT, et al. Nickel, chromium and cobalt sensitization in a patch test population in North-Eastern Italy (1996–2010). Contact Dermat. 2013; 68(1):23–31.

61. García-Gavín J, Armario-Hita J, Fernández-Redondo V, Fernández-Vozmediano J, Sánchez-Pérez J, Silvestre J, et al. Epidemiology of contact dermatitis in Spain. Results of the Spanish surveillance system on contact allergies for the year 2008. Actas Dermo-Sifiliográficas (English Edition). 2011;102(2):98–105.

62. Aguilar-Bernier M, Bernal-Ruiz A, Rivas-Ruiz F, Fernández-Morano M, de Troya-Martín M. Contact sensitization to allergens in the Spanish standard series at Hospital Costa del Sol in Marbella, Spain: a retrospective study (2005–2010). Actas Dermo-Sifiliográficas (English Edition). 2012;103(3):223–8.

63. Bordel-Gómez MT, Miranda-Romero A, Castrodeza-Sanz J. Isolated and concurrent prevalence of sensitization to transition metals in a Spanish population. J Eur Acad Dermatol. 2008;22(12):1452–7.

64. Lejding T, Mowitz M, Isaksson M, Bruze M, Pontén A, Svedman C, et al. A retrospective investigation of hexavalent chromium allergy in southern Sweden. Contact Dermat. 2018;78(6):386–92.

65. Tagka A, Stratigos A, Stavropoulos P, Rigopoulos D, Chatziioannou A. An epidemiological study of allergic contact dermatitis in Greece: prevalence of sensitization to an adapted European baseline series' allergens. Int J Res Dermatol. 2018;4(4):460–70.

66. Brans R, Schröder-Kraft C, Skudlik C, John SM, Geier J. Tertiary prevention of occupational skin diseases: prevalence of allergic contact dermatitis and pattern of patch test results. Contact Dermat. 2019;80(1):35–44.

67. Warshaw EM, Maibach HI, Taylor JS, Sasseville D, DeKoven JG, Zirwas MJ, et al. North American contact dermatitis group patch test results: 2011–2012. Dermatitis. 2015;26(1):49–59.

68. Wentworth AB, Yiannias JA, Keeling JH, Hall MR, Camilleri MJ, Drage LA, et al. Trends in patch-test results and allergen changes in the standard series: A Mayo Clinic 5-year retrospective review (January 1, 2006, to December 31, 2010). J Am Acad Dermatol. 2014;70(2):269–75.e4.

69. Scheman A, Patel KR, Roszko K, Severson D, Brod B, Jacob SE, et al. Relative prevalence of contact allergens in North America in 2018. Dermatitis. 2020; 31(2):112–21.

70. Toholka R, Wang YS, Tate B, Tam M, Cahill J, Palmer A, et al. The first Australian baseline series: recommendations for patch testing in suspected contact dermatitis. Australasia J Dermatol. 2015;56(2):107–15.

71. Boonchai W, Thanomkitti K, Kasemsarn P. Occupational contact dermatitis in tertiary university hospital: a 5-year retrospective study. J Med Assoc Thail. 2014;97(11):1182–8.

72. Kridin K, Bergman R, Khamaisi M, Weltfriend S. Chromate allergy in northern Israel in relation to exposure to cement and detergents. Dermatitis. 2016; 27(3):131–6.75.

73. Ertam I, Turkmen M, Alper S. Patch-test results of an academic department in Izmir. Turkey Dermatitis. 2008;19(4):213–5.

74. Boonchai W, Iamtharachai P. Risk factors for common contact allergens and patch test results using a modified European baseline series in patients tested during between 2000 and 2009 at Siriraj Hospital. Asian Pac J Allergy. 2014;32(1):60.

75. Goon AT, Goh C. Metal allergy in Singapore. Contact Dermat. 2005;52(3): 130–2.

76. Bajaj A, Saraswat A, Mukhija G, Rastogi S, Yadav S. Patch testing experience with 1000 patients. Indian J Dermatol Ve. 2007;73(5):313.

77. Yin R, Huang XY, Zhou XF, Hao F. A retrospective study of patch tests in Chongqing, China from 2004 to 2009. Contact Dermat. 2011;65(1):28–33.

78. Dou X, Zhao Y, Ni C, Zhu X, Liu L. Prevalence of contact allergy at a dermatology clinic in China from 1990-2009. Dermatitis. 2011;22(6):324–31.

79. Woo JY, Choi YW, Byun JY, Choi HY. Clinical characteristics of patients with chromium allergy in a single university hospital in Korea. Korean J Dermatol. 2016;54(1):34–42.

80. Sukakul T, Chaweekulrat P, Limphoka P, Boonchai W. Changing trends of contact allergens in Thailand: a 12-year retrospective study. Contact Dermat. 2019;81(2):124–9.

81. How KN, Tang MM, Kaur R, Johar A. Contact sensitisation in adults: a 5-year retrospective review in hospital Kuala Lumpur. Med J Malaysia. 2017;72(2):113–8.

82. Lam WS, Chan LY, Ho SCK, Chong LY, So WH, Wong TW. A retrospective study of 2585 patients patch tested with the European standard series in Hong Kong (1995–99). Int J Dermatol. 2008;47(2):128–33.

83. Kim DS, Bae JM, Jee H, Lee H, Kim D-Y, Kim SM, et al. Analysis of contact allergens in korean polysensitized patients by patch testing: a pilot study. Acta Derm-Venereol. 2014;94(1):80–1.

84. Bhachech HT, Jaiswal CSRP, Mehta HH. A study of patch testing in subjects with hand eczema of different occupational groups. Int J Community Med Public Health. 2016;3(9):2566–70.

85. Qayoom S, Rather SR, Khan K. Patch testing in hand eczema: a cross-sectional study from a teaching hospital of North India. Int J Res Med Sci. 2018;6(2):567–71.

86. Aithal V, Jacob M. Foot eczema and footwear dermatitis: role of patch test using Indian standard series and footwear series. Clin Dermatol Rev. 2019;3(1):62–7.

87. Cheng TY, Tseng YH, Sun CC, Chu CY. Contact sensitization to metals in Taiwan. Contact Dermat. 2008;59(6):353–60.

88. Nonaka H, Nakada T, Iijima M, Maibach HI. Metal patch test results from 1990–2009. J Dermatol. 2011;38(3):267–71.

89. Bilcha KD, Ayele A, Shibeshi D, Lovell C. Patch testing and contact allergens in Ethiopia – results of 514 contact dermatitis patients using the European baseline series. Contact Dermat. 2010;63(3):140–5.

90. Duarte I, Mendonça RF, Korkes KL, Lazzarini R, MdFS H. Nickel, chromium and cobalt: the relevant allergens in allergic contact dermatitis. Comparative study between two periods: 1995-2002 and 2003-2015. An Bras Dermatol. 2018;93:59–62.

91. Goon A. Metal allergy in Asia. In: Chen JK, Thyssen JP, editors. Metal Allergy. Cham: Springer; 2018. p. 515–20.

92. Thyssen JP, Jensen P, Carlsen BC, Engkilde K, Menné T, Johansen JD. The prevalence of chromium allergy in Denmark is currently increasing as a result of leather exposure. Brit J Dermatol. 2009;161(6):1288–93.

93. Fischer LA, Menné T, Voelund A, Johansen JD. Can exposure limitations for well-known contact allergens be simplified? An analysis of dose–response patch test data. Contact Dermat. 2011;64(6):337–42.

94. Hald M, Agner T, Blands J, Ravn H, Johansen JD. Allergens associated with severe symptoms of hand eczema and a poor prognosis. Contact Dermat. 2009;61(2):101–8.

95. Bregnbak D, Thyssen JP, Zachariae C, Johansen JD. Characteristics of chromium-allergic dermatitis patients prior to regulatory intervention for chromium in leather: a questionnaire study. Contact Dermat. 2014;71(6):338–47.

96. Dooms-Goossens A, Ceuterick A, Vanmaele N, Degreef H. Follow-up study of patients with contact dermatitis caused by chromates, nickel, and cobalt. Dermatology. 1980;160(4):249–60.

97. Hansen MB, Menné T, Johansen JD. Cr(III) reactivity and foot dermatitis in Cr(VI) positive patients. Contact Dermat. 2006;54(3):140–4.

98. Avnstorp C. Follow-up of workers from the prefabricated concrete industry after the addition of ferrous sulphate to Danish cement. Contact Dermat. 1989;20(5):365–71.

99. Thormann J, Jespersen N, Joensen H. Persistence of contact allergy to chromium. Contact Dermat. 1979;5(4):261–4.

100. Dittmar D, Ofenloch RF, Schuttelaar MLA. Persistence of contact allergy: a retrospective analysis. Contact Dermat. 2018;78(2):143–50.

101. Bang Pedersen N. CHAPTER 11 - The effects of chromium on the skin. In: Langård, editor. Biological and Environmental Aspects of Chromium. Amsterdam: Elsevier Biomedical Press; 1982. p. 249–75.

102. Wall LM, Gebauer KA. A follow-up study of occupational skin disease in Western Australia. Contact Dermat. 1991;24(4):241–3.

103. Fregert S. Occupational dermatitis in a 10–year material. Contact Dermat. 1975;1(2):96–107.

104. Graf D. Formation of Cr (VI) traces in chrome tanned leathers: causes, prevention, and latest findings. J Am Leather Chem As. 2001;96(5):169–79.

105. Hauber C. Sources, detection and avoidance of hexavalent chromium in leather and leather products, UNIDO report; 1999.

106. Nickolaus G. Untersuchungen zur Entstehung und Vermeidung von Chrom VI-Verbindungen im Verlauf der Lederverarbeitung [Investigations on the formation and avoidance of hexavalent chromium during leather production]. 52 VGCT meeting. Aachen: German Union of Leather Technologists and Chemists; 2000.

107. Nygren O, Wahlberg JE. Speciation of chromium in tanned leather gloves and relapse of chromium allergy from tanned leather samples. Analyst. 1998;123(5):935–7.

108. Fuck W, Gutterres M, Marcílio N, Bordingnon S. The influence of chromium supplied by tanning and wet finishing processes on the formation of Cr (VI) in leather. Braz J Chem Eng. 2011;28(2):221–8.

109. Sammarco U. Aspectos tecnológicos, ambientais e toxicológicos no moderno trabalho do couro. Int Tannery. 2004;183:51–68.

110. Basaran B, Isik N. Cr (VI) formation in double-face sheepskins: effect of chromium level and ironing temperature. J Soc Leath Tech Ch. 2007;91(1):4–10.

111. Chandra Babu N, Asma K, Raghupathi A, Venba R, Ramesh R, Sadulla S. Screening of leather auxiliaries for their role in toxic hexavalent chromium formation in leather—posing potential health hazards to the users. J Clean Prod. 2005;13(12):1189–95.

112. Hauber C, Germann H. Untersuchungen zur Entstehung und Vermeidung von Chromat in Leder. Leder Häute Markt. 1999;9:25–30.

113. Cory NJ, Hanna A, Germann H-P, Schneider S, Stanley A. A practical discussion session to deal with opportunities for improvement of customer/end user satisfaction. J Am Leather Chem As. 1997;92(5): 119–25.

114. Font J, Cuadros RM, Reyes MR, Costa-Lopez J. Influence of various factors on chromium (6) formation by photo-ageing. J Soc Leath Tech Ch. 1999;83(6):300–6.

115. Pastore P, Favaro G, Ballardin A, Danieletto D. Evidence of Cr(VI) formation during analysis of leather: proposal of an alternative method of analysis through the ion-chromatographic approach and post-column reaction. Talanta. 2004;63(4):941–7.

116. Graf D. The influence of the relative humidity of air during storage on the formation lowering of Cr(VI) in chrome tanned leathers. World Leather. 2000;13(5):38.

117. Long A, Cory N, Wood C. Potential chemical mechanisms causing false positive results in hexavalent chromium determination. J Soc Leath Tech Ch. 2000;84(2):74–8.

118. Palop R, Parareda J, Ballús O, Marsal A. Leather ageing and hexavalent chromium formation as a function of the fatliquoring agent. Part II: chrome retanned leathers. J Soc Leath Tech Ch. 2008;92(6):233–7.

119. Palop R, Parareda J, Ballús O, Marsal A. Leather ageing and hexavalent chromium formation as a function of the fatliquoring agent. Part I. chrome tanned leathers. J Soc Leath Tech Ch. 2008;92(5):200–4.

120. Font J, Cuadros R, Lalueza J, Orus C, Reyes M, Costa-Lopez J, et al. Presence of chromium (VI) in sheepskins: influence of tannery processes. J Soc Leath Tech Ch. 1999;83(2):91–5.

121. Meyndt R, Germann H. Relationships in the formation of hexavalent chrome [Cr(VI)]. World Leather. 2011.

122. Palop R, Ballús O, Manich A, Marsal A. Leather ageing and hexavalent chromium formation as a function of the fatliquoring agent. Part III: interaction with synthetic and vegetable retanning agents. J Soc Leath Tech Ch. 2010;94(2):70–6.

123. Kilicarislan Ozkan C, Ozgunay H, Kalender DA. Determination of antioxidant properties of commonly used vegetable tannins and their effects on prevention of Cr (VI) formation. J Soc Leath Tech Ch. 2015;99(5):245–9.

124. Gong Y, Liu X, Huang L, Chen W. Stabilization of chromium: an alternative to make safe leathers. J Hazard Mater. 2010;179(1–3):540–4.

125. Saddington M. Trivalent chromium to hexavalent chromium. Leather. 1999; 201:33.

126. Wolf G, Wegner B. Avoiding Cr (VI) in leather manufacture. World Leather. 2000;13(5):39.

127. Ogata K, Inatsugi T, Hattori S, Kagawa Y, Yoshimura K, Takahashi K. Pilot production of chrome-tanned leather without formation of hexavalent

chromium by treatment with a combination of inhibitors. J Soc Leath Tech Ch. 2019;103(1):1–5.

128. Ogata K, Hattori S, Takahashi K. Inhibitory mechanismof hexavalent chromium formation in chrome-tanned leather with combined inhibitors. J Soc Leath Tech Ch. 2019;103(5):253–9.

129. Hauber C. Formation, prevention & determination of Cr(VI) in leather - a short overview of recent publications, UNIDO report; 2000.

130. Bacardit A, Gonzalez M, Mir T, March R, Corbera J. Study of the chrome hexavalent content in commercial chromium salts. J Soc Leath Tech Ch. 2020;104(1):14–8.

131. Sammarco U. Formazione di Cr (VI) nelle pelli e possibilità di eliminazione. Cuoio, Pelli, Materie Concianti. 1998;74(2):83–94.

132. Hedberg Y, Lidén C, Odnevall WI. Chromium released from leather – I: exposure conditions that govern the release of chromium(III) and chromium(VI). Contact Dermat. 2015;72(4):206–15.

133. Hedberg YS, Wei Z, Matura M. High release of hexavalent chromium into artificial sweat in a case of leather shoe–induced contact dermatitis. Contact Dermat. 2020;82(3):179–81.

134. Hedberg YS, Lidén C. Chromium(III) and chromium(VI) release from leather during 8 months simulated use. Contact Dermat. 2016;75(2):82–8.

135. Johansen JD, Aalto-Korte K, Agner T, Andersen KE, Bircher A, Bruze M, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing–recommendations on best practice. Contact Dermat. 2015;73(4): 195–221.

136. Gammelgaard B, Fullerton A, Avnstorp C, Menné T. Permeation of chromium salts through human skin in vitro. Contact Dermat. 1992;27(5): 302–10.

137. Mali JWH, Van Kooten WJ, Van Neer FCJ. Some aspects of the behavior of chromium compounds in the skin. J Invest Dermatol. 1963;41(3):111–22.

138. Samitz M, Shrager J. Patch test reactions to hexavalent and trivalent chromium compounds. Arch Dermatol. 1966;94(3):304–6.

139. Fregert S, Rorsman H. Allergy to trivalent chromium. Arch Dermatol. 1964; 90(1):4.

140. Allenby C, Goodwin B. Influence of detergent washing powders on minimal eliciting patch test concentrations of nickel and chromium. Contact Dermat. 1983;9(6):491–9.

141. Hansen MB, Menné T, Johansen JD. Cr(III) and Cr(VI) in leather and elicitation of eczema. Contact Dermat. 2006;54(5):278–82.

142. Basketter D, Horev L, Slodovnik D, Merimes S, Trattner A, Ingber A. Investigation of the threshold for allergic reactivity to chromium. Contact Dermat. 2001;44(2):70–4.

143. Fischer LA, Voelund A, Andersen KE, Menné T, Johansen JD. The dose–response relationship between the patch test and ROAT and the potential use for regulatory purposes. Contact Dermat. 2009;61(4):201–8.

144. Yazar K, Lundov MD, Faurschou A, Matura M, Boman A, Johansen JD, et al. Methylisothiazolinone in rinse-off products causes allergic contact dermatitis: a repeated open-application study. Brit J Dermatol. 2015;173(1): 115–22.

145. Freeman S. Shoe dermatitis. Contact Dermat. 1997;36(5):247–51.

146. Roddy WT, Lollar RM. Resistance of white leather to breakdown by perspiration. J Am Leather Chem As. 1955;50:180–92.

147. Morris GE. "Chrome" Dermatitis: A study of the chemistry of shoe leather with particular reference to basic chromic sulfate. Arch Dermatol. 1958;78(5): 612–8.

148. Oumeish OY, Rushaidat QM. Contact dermatitis to military boots in Jordan. Contact Dermat. 1980;6(7):498.

149. Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/ EEC, 93/67/EEC, 93/105/EC and 2000/21/EC, (2006). Official Journal of the European Union. 2006; pp. L396:L136/133-L136/280.

150. European Union. EU 301/2014 COMMISSION REGULATION (EU) no 301/2014 of 25 March 2014 amending annex XVII to regulation (EC) no 1907/2006 of the European Parliament and of the council on the registration, evaluation, authorisation and restriction of chemicals (REACH) as regards chromium VI compounds. 2014.

151. ISO. ISO 17075-1, Leather -- Chemical determination of chromium(VI) content in leather -- Part 1: Colorimetric method. 2017.

152. Anderie I, Schulte K. Chromate testing in leather: EN ISO 17075. In: Chen JK, Thyssen JP, editors. Metal allergy. Cham: Springer; 2018. p. 31–8.

153. ISO. ISO 4044:2017, Leather – Chemical tests – Preparation of chemical test samples. 2017.

154. ISO. ISO2419:2012, Leather – Physical and mechanical tests – Sample preparation and conditioning. 2012.

155. OEKO-TEX Leather standard. https://www.oeko-tex.com/importedmedia/ downloadfiles/LEATHER_STANDARD_by_OEKO-TEX_R__-_Standard_en.pdf. Accessed 11 May 2020.

156. Bregnbak D, Johansen JD, Jellesen MS, Zachariae C, Menné T, Thyssen JP. Chromium allergy and dermatitis: prevalence and main findings. Contact Dermat. 2015;73(5):261–80.

157. Sundar VJ, Muralidharan C. An environmentally friendly mineral-free tanning of animal skins – sustainable approach with plant resources. Environ Processes. 2020;7(1):255–70.

158. Zhou Y, Ma J, Gao D, Li W, Zhang Y. Preparation and characterisation of sulfonated calix[4]arene and its application in chrome-free tanning. J Soc Leath Tech Ch. 2018;102(4):200–3.

159. Shi B. Combination tanning of vegetable tannin-metal salt. China Leather. 2007;7(1).

160. Pan H, Qi M, Zhang ZJ. Synthesis and study of MPNS/SMA nano-composite tanning agent. Chinese Chem Lett. 2008;19(4):435–7.

161. Plavan V, Koliada M, Valeika V. An eco-benign semi-metal tanning system for cleaner leather production. J Soc Leath Tech Ch. 2017;101(5):260–5.

162. Jordan WP Jr, Dahl MV, Albert HL. Contact dermatitis from glutaraldehyde. Arch Dermatol. 1972;105(1):94–5.

163. Kanerva L, Jolanki R, Estlander T. Allergic contact dermatitis from leather strap of wrist watch. Int J Dermatol. 1996;35(9):680–1.

Publisher's Note