

Review Article

Quantitative aspects of contact allergy to chromium and exposure to chrome-tanned leather

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The potential of trivalent and hexavalent chromium to induce and elicit allergic contact dermatitis and the degree of chromium exposure from leather products are reviewed. Chromium dermatitis is often due to exposure in the occupational environment, with cement being one of the most common chromium sources. However, consumer products such as chromium(III)-tanned leather products are also an important source of chromium exposure. Apart from Cr(III), which is used for tanning, leather often also contains trace amounts of Cr(VI), which is formed by oxidation of Cr(III) during the tanning process. In a recent study of the Cr(VI) content of leather products bought on the Danish market, 35% of such articles had a Cr(VI) content above the detection limit of 3 p.p.m., ranging from 3.6 p.p.m. to 14.7 p.p.m. Leachable Cr(III) was detected at levels of 430–980 p.p.m. An examination of available dose–response studies showed that exposure to occluded patch test concentrations of 7–45 p.p.m. Cr(VI) elicits a reaction in 10% of the chromium-sensitive patients. When reviewing repeated open exposure studies, it is seen that either exposure to 5 p.p.m. Cr(VI) in the presence of 1% sodium lauryl sulfate (SLS) or exposure to 10 p.p.m. Cr(VI) alone both elicit eczema in chromium-sensitive patients. The eliciting capacity of Cr(III) has not been systematically investigated but, compared to Cr(VI), much higher concentrations are needed to elicit eczema.

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Chromium, and the chronic allergic contact dermatitis that it can lead to, comprise a considerable health problem (1). In many countries, cement remains a major cause of allergic contact dermatitis. This is due to the formation of hexavalent chromium [Cr(VI)] from the trivalent chromium [Cr(III)] present in the raw material from which cement is produced (2). Occupational groups such as construction workers and bricklayers are therefore at risk of developing chromium allergy. Workers within the metal and tanning industry, offset printers and lithographers may also be exposed to chromium and develop chromium allergy (3–6). In Denmark, ferrous sulfate has been added to cement since 1981, resulting in a considerable reduction in the content of hexavalent chromium, and subsequently the frequency of chromium allergy among construction workers has decreased (2). As a consequence, the epidemiology of chromium dermatitis has changed. Leather products

have now become the most important known source of chromium exposure in Denmark and chromium allergy has primarily become a consumer problem (7). Other consumer products with a risk of causing chromium dermatitis, although more theoretically than practically, are cleaning products and make-up (8–10).

Since the most common source of chromium exposure changed in Denmark, the typical patient with chromium dermatitis is no longer a man with hand dermatitis due to contact with cement, but a woman presenting with foot dermatitis due to chromium exposure from leather footwear (Fig. 1) (7). Leather products, especially leather shoes, are also found to be a frequent source of chromate dermatitis in other countries (11–14). Therefore, we found it relevant to investigate and review the current literature concerning the content and release of chromium from leather. Moreover, results concerning induction and elicitation of allergic



Fig. 1. Allergic contact dermatitis of the foot and ankle of a chromium sensitive patient, due to leaching of chromium from leather boots.

contact dermatitis from trivalent and hexavalent chromium salts are presented.

Chromium Salts and Bioavailability

Chromium is an elemental metal that exists in oxidation states of -2 to $+6$. The existence of a particular oxidation state depends on various factors such as pH and temperature (15).

The ability to elicit allergic contact dermatitis depends among other things on the bioavailability of the chromium salts. As the water solubility of a chromium salt increases, its ability to penetrate the skin barrier and elicit allergic contact dermatitis also increases. The Cr(VI) salt potassium dichromate has high water solubility whereas most Cr(III) compounds have rather low water solubility (16). In a study by Gammelgaard et al. (17), permeation of chromium salts through human skin *in vitro* was investigated. Cr(VI) was found to have a greater ability to penetrate the skin than Cr(III), and Cr(VI) also had a higher degree of accumulation in the skin. Unequal skin absorption capabilities result in differences in bioavailability, which might explain why Cr(VI), compared to Cr(III), is more potent in eliciting dermatitis.

The chromium ion cannot elicit an immune response by itself but must be chemically linked to proteins in order to elicit a T-cell response (18). In contrast to Cr(VI), Cr(III) has rather a strong protein binding capacity (19). It has been speculated that Cr(III) is the actual hapten in that Cr(VI), after entering the skin cells, is reduced to Cr(III), which in turn binds intracellular proteins thereby forming immunogenic complexes (20).

Epidemiology

Patients are diagnosed as chromium-sensitive using either a patch test concentration of 5000 p.p.m.

potassium dichromate, corresponding to 1770 p.p.m. elemental Cr(VI), or a clinically equivalent dose of $23 \mu\text{g}/\text{cm}^2$ potassium dichromate (TRUE Test). The following results have been generated using these patch tests if nothing else is noted.

In an unselected Danish population of 193 males and 276 females, the prevalence of chromium allergy was 0.5% and 0.6%, respectively (calculated from results) (21). In Finland, the prevalence of Cr(VI) sensitivity among 822 human volunteers was found to be 1.7% (4) and in Germany the prevalence in an unselected population of 1141 adults was 1.1% (22).

Among consecutive eczema patients in the period 1989–94, the prevalence of chromium allergy was 1.8% in Denmark (7). In Germany, the frequency of consecutive patients with a positive reaction to potassium dichromate during the years 1993–97 declined from 5.8% to 4% for men and remained stable at about 3.6% for women (12). In addition, an increase in foot dermatitis was observed among chromium-sensitive women during 1993–97.

The prevalence of chromium allergy among consecutive patients has been found to be 7.5% in The United Arab Emirates (23) and 2.8% in North America. In the North American study, the test concentration of potassium dichromate was 0.25% (24).

The Skin Sensitization Potential of Chromium Salts

Predictive skin sensitization assays have been developed in order to identify potential contact allergens. Kligman (25) developed a human assay, the maximization test, which classifies substances into 5 classes according to their allergenic potentiality. Class 1 corresponds to weak allergens and class 5 to extreme allergens. Using this human assay, the hexavalent chromium salt, potassium dichromate, was identified as a class 5 allergen and trivalent chromium salts were recognized as grade 3 allergens.

Today, the sensitization potential of a substance is only investigated in animal models, the two most widely recognized models being the guinea-pig maximization test (26) and the local lymph node assay (LLNA) in mice (27). Using the guinea-pig maximization test, Magnusson & Kligman (26) identified potassium dichromate as being a strong allergen (class 4). This finding was confirmed by Basketter & Sholes (28). The mouse model, the LLNA, also predicts potassium dichromate to possess a significant ability to sensitize (29).

As regards to Cr(III), 2 guinea-pig maximization studies, using non-standard methods, consistently

Table 1. Interlaboratory comparison of dose-response patch test studies with dilution series of $K_2Cr_2O_7$.

Cr(VI) (p.p.m.)	MET response	No reaction	Reference
1770	3/14 (22%)		Allenby & Goodwin (31)
885	8/14 (57%)		
89	1/14* (7%)		
9	2/14 (14%)		
**		1/12 (8.3%)	
885	4/12 (33.3%)		Kosann et al. (32)
400	1/12 (8.3%)		
220	4/12 (33.3%)		
110	1/12 (8.3%)		
28	1/12 (8.3%)		

The minimal chromium concentration that gives a positive reaction in a patient is registered as the minimal eliciting threshold (MET) concentration for that patient. The response is registered as number of patients with a given MET out of total number of patients tested and as percentage. The allergen concentration tested is given as concentration (p.p.m.) of elemental Cr(VI), which may be converted to concentration (p.p.m.) of potassium dichromate by dividing by a factor 0.354.

*Adjusted to the table in that only 7 of the 14 patients were in fact tested with 89 ppm Cr(VI).

**The highest tested concentration by Kosann et al. (32) was 1770 ppm Cr(VI).

showed that the use of Cr(III) for both induction and elicitation gave a lower rate of sensitization than when using Cr(VI) (20, 30). Varying degrees of cross-reaction, that is inducing with one compound and challenging with the other, were reported in both studies.

Eliciting Concentration from Occluded Chromium Exposure

In order to evaluate the risk of developing contact dermatitis it is important to determine the threshold concentration that will elicit dermatitis in chromium-allergic subjects *versus* controls.

Threshold sensitivity for Cr(VI)

In a study by Allenby & Goodwin (31), the threshold concentration of Cr(VI) for eliciting a positive skin reaction in chromium-sensitive patients were determined by patch testing (Table 1). Allenby & Goodwin (31) found that the minimal eliciting threshold (MET) for Cr(VI) ranged from 1770 p.p.m. to 9 p.p.m. The MET may be defined as the minimal concentration of Cr(VI) that gives a positive patch test in an individual. In another dose-response study, performed by Kosann et al. (32), the MET concentrations ranged from 885 p.p.m. Cr(VI) to 28 p.p.m. Cr(VI) (Table 1). The dose-response relations are approximately the same for the 2 studies and are also in close agreement with other dose-response studies performed (33–36). When plotting the percentage of reacting patients against the concentration of Cr(VI), this agreement in dose-response relations between different studies becomes evident (Fig. 2). The concentration of Cr(VI) which results in 10% or 40% of the patients having a positive reaction are referred

to as MET_{10%} and MET_{40%}, respectively. For the above-mentioned studies, the MET_{10%} ranges from 7 p.p.m. Cr(VI) (31, 33) to 44 p.p.m. Cr(VI) (32) with a median value of 13 p.p.m. The MET_{40%} ranges from 51 p.p.m. Cr(VI) (32, 35) to 159 p.p.m. Cr(VI) (32) with a median value of 64 p.p.m. Among the 6 studies, 1 highly sensitive patient had a threshold concentration between 0.6 and 1.2 p.p.m. (31). Moreover, in 2 of the studies, the lowest Cr(VI) concentration found to be effective in eliciting an allergic response was 4 p.p.m. Cr(VI) (33, 35).

However, there are studies that find higher eliciting thresholds and thereby differ from the dose-response relationship depicted in Fig. 2 (8, 37).

The reported studies all give the minimal eliciting threshold in terms of applied patch test concentration of allergen (p.p.m.). However, to be used in risk assessment, it is important that the threshold data are reported in terms of mass of allergen per surface area of skin per time unit [$\mu\text{g Cr(VI)}/\text{cm}^2/2\text{ days}$]. In an investigation by Nethercott et al. (38), using the TRUE Test system, the MET dose ranged from $4.4\mu\text{g Cr(VI)}/\text{cm}^2/2\text{ days}$ down to $0.018\mu\text{g Cr(VI)}/\text{cm}^2/2\text{ days}$ (Table 2). The dose of $4.4\mu\text{g Cr(VI)}/\text{cm}^2$ corresponds clinically to a concentration of 2500 p.p.m. potassium dichromate (39). The MET_{10%} dose for Cr(VI) was determined to be $0.09\mu\text{g Cr(VI)}/\text{cm}^2/2\text{ days}$.

In order to compare the findings, the threshold concentrations for the studies in Fig. 2 may be converted to an estimated dose per unit area per time unit. The MET_{10%} concentration of 7 p.p.m. found by Allenby & Goodwin (31) is converted to a MET_{10%} dose of $0.35\mu\text{g}/\text{cm}^2/2\text{ days}$ and the MET_{10%} concentration of 45 p.p.m. found by Kosann et al. (32) is converted to a dose of $0.90\mu\text{g Cr(VI)}/\text{cm}^2/2\text{ days}$ (Table 3). The considerably

Dose–response studies with aqueous solutions of potassium dichromate.

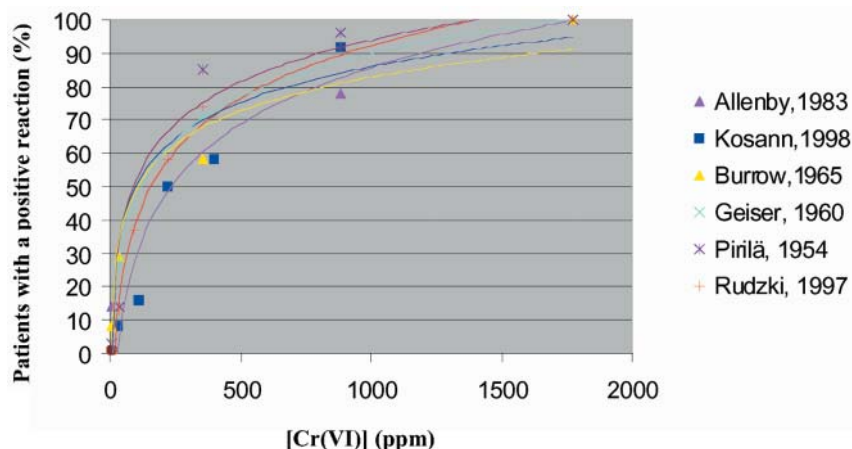


Fig. 2. Dose–response data from 6 different studies are presented in the diagram (31–36). Percentage of patients reacting is plotted against the concentration of elemental Cr(VI). A fitted logarithmic curve is superimposed on each data set. The MET_{10%} concentration ranges from 7 p.p.m. (31, 33) to 44 p.p.m. (32). The MET_{40%} concentration ranges from 51 p.p.m. (31, 35) to 159 p.p.m. (32).

lower MET_{10%} found by Nethercott et al. (38) may partly be explained by differences in the patch testing system used. In contrast to Allenby & Goodwin (31) and Kosann et al. (32) who used a Finn Chamber/Epitest with an aqueous potassium dichromate solution, Nethercott et al. (38) used the TRUE Test system. The TRUE Test system is known to have a higher degree of delivery of the applied dose to the skin surface (40). Moreover, the participants in the study by Nethercott et al. (38) may have been more chromium-sensitive because of differences in the criteria when enrolling the subjects for the dose–response studies. In con-

trast to Allenby & Goodwin (31) and Kosann et al. (32), who used a diagnostic test of 5000 p.p.m. potassium dichromate, Nethercott et al. (38) enrolled patients having a positive reaction to a patch test dose of 4.4 $\mu\text{g Cr(VI)}/\text{cm}^2$, corresponding to a clinically equivalent concentration of 2500 p.p.m. potassium dichromate.

Threshold sensitivity for Cr(III)

Cr(III) is a weak eliciting agent compared to Cr(VI). Allenby & Goodwin (31) found that 36% of the patients reacted to a Cr(III) concentration equal to or below of 8850 p.p.m. and 64% of the patients did not react to Cr(III) even at a concentration of 17 700 p.p.m. (Table 4). In a study by Samitz & Shrager (41), only 1 out of 5 patients (20%) reacted to 9750 p.p.m. Cr(III) (Table 4). To achieve a higher proportion of chromium-allergic patients with a positive reaction to Cr(III), the concentration must be much higher than for Cr(VI). Rudzki et al. (42) found that 46% of patients reacted to a Cr(III) concentration lower than or equal to 15581 p.p.m., and Fregert & Rorsman (44), found that 65% of patients reacted to a concentration of 26000 p.p.m. Cr(III) (Table 4) (43). In the investigation by Nethercott et al. (38) using the TRUE Test system, only 1 of the 54 chromium-sensitive patients tested had a response to Cr(III). This patient reacted weakly to the highest Cr(III) dose tested of 33 $\mu\text{g Cr(III)}/\text{cm}^2/2$ days.

Table 2. Dose–response study with potassium dichromate using the TRUE Test system

Cr(VI) ($\mu\text{g}/\text{cm}^2/2$ days)	Response (MET)
4.4	22/54 (41%)
0.88	22/54 (41%)
0.18	5/54 (9%)
0.088	4/54 (7%)
0.018	1/54 (2%)

A total of 54 chromium-allergic patients were patch tested with decreasing doses of Cr(VI). The allergen doses are given as dose of elemental Cr(VI)/ cm^2 . The MET_{10%} for Cr(VI) was determined to be 0.089 $\mu\text{g Cr(VI)}/\text{cm}^2/2$ days (38).

Table 3. Estimated MET_{10%} dose expressed as $\mu\text{g Cr(VI)}/\text{cm}^2/2$ days

MET _{10%} ($\mu\text{g Cr(VI)}/\text{cm}^2/2$ days)	Reference
0.09	Nethercott et al. (38)
0.35	Allenby & Goodwin (31)
0.90	Kosann et al. (32)

Based on the volume and area of the patch test chambers used, the MET_{10%} concentration of 7 p.p.m. found by Allenby & Goodwin (31) is converted to a MET_{10%} dose of 0.35 $\mu\text{g}/\text{cm}^2/2$ days and the MET_{10%} concentration of 45 p.p.m. found by Kosann et al. (32) is converted to a dose of 0.90 $\mu\text{g Cr(VI)}/\text{cm}^2/2$ days.

Eliciting Concentration from Non-occluded Chromium Exposure

Nielsen et al. (44) studied the effect of daily repeated exposures to low Cr(VI) concentrations on

Table 4. Interlaboratory comparison of patch test studies with chromium trichloride

Cr(III) (p.p.m.)	Cumulative response		
	Positive/total	Negative/total	Reference
*		9/14 (64%)	Allenby & Goodwin (31)
8850	5/14 (36%)		
89	1/14 (7%)		
9750	1/5 (20%)	4/5 (80%)	Samitz & Shrager (41)
15581	21/46 (46%)	25/46 (54%)	Rudzki et al. (42)
3100	6/46 (13%)		
1541	1/46 (2%)		
26000	11/17 (65%)	6/17 (35%)	Fregert & Rorsman (43)

The total number and percentage of patients having a positive reaction below or equal to a given Cr(III) concentration are listed in the 2nd column (cumulative response) (31, 41–43). The allergen concentration tested is given as concentration (p.p.m.) of elemental Cr(III), which may be converted to concentration (p.p.m.) of chromium trichloride hexahydrate by dividing by a factor 0.195

*The highest concentration tested was 17700 p.p.m. Cr(III).

the hands of 3 patients with chromium allergy. The patients exposed 1 finger to a 10-mg Cr(VI)/L solution (10 p.p.m.) for 10 min daily for the 1st week and to a 100-mg Cr(VI)/L (100 p.p.m.) solution for the 2nd week. After the 1st week, all the patients had a flare of hand eczema, which became worse in 2 of the patients during the 2nd week of exposure.

Fowler et al. (39) evaluated the potential for eliciting allergic contact dermatitis from contact with standing water containing Cr(VI). 38% of the chromium-sensitive subjects tested reacted when exposing 1 arm to a 25–29 mg Cr(VI)/L (25–29 p.p.m.) solution for 30 min per day over 3 consecutive days (39).

In addition, Basketter et al. (8) performed a repeated open application test with aqueous solutions of potassium dichromate containing 1% sodium lauryl sulfate (SLS). 20% of the patients tested developed eczema when exposed to a 5-p.p.m. Cr(VI) solution containing 1% SLS for 1 week.

Chromium and Leather Tanning

Only Cr(III) is used for tanning. During the tanning process, basic chromium(III) sulfate binds to the collagen thereby stabilizing the leather (45). However, even though no Cr(VI) is used, small trace amounts of Cr(VI) can often be found in leather articles (46, 47). This is due to oxidation of Cr(III) during leather manufacture leading to the formation of Cr(VI). Cr(VI) is a poor protein binder and it easily leaches out of the leather thereby coming into contact with the skin. The formation of Cr(VI) can be avoided by using the correct procedure at the relevant steps during leather manufacture (45).

Most of the Cr(III) is bound to the leather but there may be a considerable amount of Cr(III) in

excess due to improper washing procedures during leather preparation. Cr(III) may therefore also comprise a risk of causing chromium dermatitis, since this free unbound Cr(III) is capable of leaching out of the leather (47).

Since 80% of all leather is tanned with chromium it can be difficult to avoid exposure (45).

Chromium in Leather Products

In order to investigate the exposure to chromium from leather products, the content of Cr(VI) in 43 leather products bought on the Danish market have been analysed (45). The content of Cr(VI) was measured by the DIN 53314 method where

Table 5. The total content of Cr(VI) in 15 leather products bought on the Danish market.

Product	Cr(VI) content (p.p.m.)	mg/kg
Watch strap	3.6	
Watch strap	3.7	
Shoe	10.4	
Shoe	6.3	
Glove	8.6	
Baby shoe	6.4	
Working glove	14.7	
Working glove	4.0	
Working glove	6.2	
Jacket	10.6	
Jacket	6.8	
Leather top	4.9	
Leather top	5.0	
Skirt	8.5	
Hat	9.1	

The content of Cr(VI) in the 15 leather products with a Cr(VI) content above the detection level of 3 p.p.m. The content of Cr(VI) was measured by the DIN 53314 method where Cr(VI) is extracted out of a 2-g leather sample by incubating it in a dipotassium hydrogen phosphate buffer for 3 h. The content is given in mg Cr(VI)/kg leather (p.p.m.) (48).

Table 6. Amount of migrating chromium in the sole and the upper of two baby shoes bought on the Danish market. Total migrating chromium is in practice a measurement of the amount of free Cr(III) capable of leaching out of the leather. Migrating chromium was measured using ICP-AES as the detection method. The sole and the upper leather were analysed separately (48)

Material	Migrating chromium (p.p.m.)
Shoe 1 sole	430
Shoe 1 upper	560
Shoe 2 sole	980
Shoe 2 upper	370

Cr(VI) is extracted from a 2-g leather sample by putting it in a dipotassium hydrogen phosphate buffer for 3 h. The investigation showed that 15 (35%) of the products contained hexavalent chromium at levels above the detection limit of 3 mg/kg (p.p.m.) (Table 5). The content of Cr(VI) in the 15 leather products ranged from 3.6 mg/kg (p.p.m.) in a watch strap to 14.7 mg/kg (p.p.m.) in a pair of working gloves. 2 of the 5 shoes tested had a detectable content of hexavalent chromium of 10.4 mg/kg (p.p.m.) and 6.3 mg/kg (p.p.m.), respectively. Since all the hexavalent chromium is expected to leach out of the leather during use, significant Cr(VI) exposure will result.

In a time-dose-response study, a correlation has been found between the test concentration of a contact allergen and the median number of days passing until a positive reaction occurs (49, 50). Thus, the patients in the study by Nielsen et al. (44), reacting when exposed to 10 p.p.m. Cr(VI)/10 min daily, may react to lower concentrations of Cr(VI) if the exposure time is increased. Since leather products are often worn quite regularly for a long period, the Cr(VI) content in leather products may be even more significant.

2 baby shoes were also analysed for total content of migrating chromium in the above-mentioned investigation (Table 6) (48). In practice, this is a measurement of the amount of free Cr(III) capable of leaching out of the leather. Migrating chromium was found to be between 370 mg/kg (p.p.m.) and 980 mg/kg (p.p.m.). Cr(III) has been shown to elicit dermatitis at lower concentrations (31, 49) and this amount of Cr(III) capable of leaching out of the leather is therefore significant.

Other studies have also demonstrated that a significant amount of Cr(VI) and Cr(III) is capable of leaching out of leather products (46, 47, 50).

Conclusion and Perspective

Cr(III) and Cr(VI) are both able to sensitize and elicit allergic contact dermatitis, although much

higher concentrations of Cr(III) are needed. According to the literature, the most frequent known cause of chromium allergy in Denmark are consumer products containing chrome-tanned leather (7). Leather may contain amounts of leachable Cr(III) and Cr(VI) high enough to cause dermatitis in a chromium-sensitive patient. An investigation of leather products on the Danish market found that 35% of the products contained Cr(VI) at levels above the detection level of 3 p.p.m., ranging from 3.6 p.p.m. to 14.7 p.p.m. (48). Examination of the available dose-response studies gave information on threshold chromium concentrations for elicitation of chromium dermatitis. It was found that occluded patch test concentrations, ranging from 7 to 45 p.p.m. Cr(VI), elicited dermatitis in 10% of chromium-sensitive patients (32, 33). When reviewing open exposure studies, it was seen that either exposure to 5 p.p.m. Cr(VI) in the presence of 1% SLS or to 10 p.p.m. Cr(VI) alone both elicited dermatitis in chromium-sensitive patients (8, 44). Compared to Cr(VI), much higher concentrations of Cr(III) are needed in order to elicit dermatitis in chromium-sensitive patients. Fregert & Rorsman (43) elicited dermatitis in 65% of patients by exposing them to a patch test concentration of 26 000 p.p.m. Cr(III).

The content of Cr(VI) in cement has been reduced since the introduction of ferrous sulfate in 1981 in Denmark, followed by other Scandinavian countries (51). As a consequence, the prevalence of chromium allergy among men working in the construction industry has been reduced considerably in Denmark (2). Likewise, modifications in the leather manufacturing process can affect the amount of Cr(VI) and free Cr(III) present in the final leather product. In order to create guidelines for the acceptable amount and release of chromium from leather, research is needed. A strategy will be to expose chromium-sensitive patients to well-characterized leather samples in respect of chromium release per area per time unit. Thereby, the highest chromium release level which will not elicit allergic contact dermatitis in chromium-sensitized individuals can be determined. This may form the scientific basis for legislation on the content of Cr(VI) and free Cr(III) in leather products.

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