



Commentary

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



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ABSTRACT

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

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1. Introduction

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

Both CrIII and CrVI present in leather can be released and consequently be deposited on the skin surface. The risk of systemic effects of Cr can be readily excluded based on the toxicological characteristics of CrIII and on the very low doses of CrVI (for an extensive review e.g. ATSDR, 2012; EFSA, 2014). The question is to what extent the amount released and the local skin conditions in

subjects wearing leather goods such as shoes, belts and clothing and the condition of use pose a risk of developing either irritative or allergic contact dermatitis (ACD) to CrVI or CrVI plus CrIII.

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

2. Chromium and skin irritation

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

3. Chromium and induction of allergic contact dermatitis

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

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

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

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

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

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

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

of their shoes and were negative to all tested shoe allergens that included rubber chemicals, potassium dichromate, BFP (p-t-butyl-formaldehyde resin), colophony, and paraphenylenediamine, and to the European standard series. Similarly, [Goossens and Taylor \(2011\)](#) support the hypothesis that ACD linked to shoes is not necessarily due to Cr, and report other allergens related to either other non-leather components of the shoe or other chemicals present in leather such as formaldehyde and nickel.

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

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

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

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

Table 2

New cases of CrVI allergy observed in Denmark. Adapted from [Table 1](#) in [Thyssen et al. \(2009\)](#).

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

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

Table 1

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

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

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

indication of the quality and provenience of the leather goods, nor a precise identification of the induction of sensitisation and on the onset of the ACD (see below for further comments). On the other hand, Caroe et al. (2010) did not find such change in another area in Denmark.

5. What is the potency of CrIII and CrVI to induce and elicit allergic contact skin reaction?

While there are no quantitative data to determine the concentration necessary to induce sensitisation to Cr, there are some reports in the literature that may help in defining the concentration of CrVI and CrIII that elicits an allergic skin reaction in sensitised subjects.

Hansen et al. (2002) reviewed six dose-response studies with CrVI (conducted between 1954 and 1997) and concluded that 10% of chromium-allergic patients will react to 7–44 ppm CrVI when patch tested. Not enough details were available in all studies to convert the concentration of the test material to actual concentration per unit of skin surface, which is the relevant metrics for assessing allergic potency (Nethercatt et al., 1994). Table 3 reports the conversions based on the size of the patch used and on the volume of the test compound applied, when the information was available (Alleby and Goodwin, 1983; Kosann et al., 1998) or could be hypothesised (Rudzki et al., 1997). Combining the studies, the benchmark concentration (BMC) (<http://www.epa.gov/ncea/bmds/>) for 10% and 50% respondent (BMC₁₀ and BMC₅₀, respectively) were 2 and 9 µg/cm² (for 48 h), corresponding to about 40 and 180 ppm, respectively. Also Basketter et al. (2001) report a dose-response curve (in ppm), but they do not provide enough details to calculate the concentration per surface unit. However, Fischer et al. (2011) reported the transformation to surface unit and calculated an ED₁₀ (BMC₁₀) of 1.04 µg/cm² with a very large confidence interval (0.003–5.55 µg/cm²). Assuming that this transformation is correct, the BMC₁₀ is consistent with the pooled BMC₁₀ calculated in this paper. For comparison, Liden et al. (2008) report chromium deposition on the hands of locksmiths, carpenters and cashiers (estimated chromium means of 0.045–7 µg/cm² per h) and handling of chromated metal products elicited skin contact responses in chromium sensitised subjects (Geier et al., 2011).

Table 4 reports the same approach for patch tests with CrIII. In

this case, precise calculations could not be performed because the details of the test systems (surface and volume of the applied solution) could not be retrieved in all publications, and pooled data were not suited for the determination of the BMC₅₀. However, when analysing separately the data from Allenby and Goodwin (1983), for which the transformation per surface units could be done, the difference with “pooled” BMC₁₀ was not significant, indicating that probably the differences in the test system did not give a large difference in concentration per surface unit. By comparing the BMCs for CrVI and CrIII, it can be concluded that the potency of CrVI is 120–240 times higher, as based on BMC₁₀ or BMC₅₀, respectively, that of CrIII in eliciting an allergic dermal reaction. An even higher ratio of >370 was determined by Nethercott et al. (1994), using the TRUE test system that cannot be directly compared with the other test systems, being the Minimal Eliciting Threshold (MET) in 10% of the subjects (same as the BMC₁₀) 0.089 µg/cm² for Cr(VI) and >33 µg/cm² for CrIII. In conclusion, available data indicate that CrVII is at least 120, but possibly more, times more potent than CrIII in eliciting allergic skin reaction in sensitised subjects (Kosann et al., 1998).

6. Release of Cr from leather and the role of sweat

Since it is not the content of Cr in leather, but the Cr released from leather that is relevant for the skin reaction, a number of studies have been carried out to determine the release. It is not intended to discuss here the methodology, which is still debated (see e.g.: Hedberg et al., 2014), but to present available data in the light of the above considerations on potency.

Hedberg et al. (2015) report a release of CrIII from leather treated with artificial sweat of 1–2 µg/cm² per h during the first 10 h; subsequently the rate of release slows down to less than 0.5 µg/cm² per h at 168 h. Therefore, wearing leather goods for a day (say for 10 h) will cause a maximum release of 20 µg/cm², which is about six times lower than the calculated pooled BMCL₁₀ (Table 4) for sensitised subjects exposed for 48 h during patch testing. In the same conditions, the authors found that CrVI was minimally, if at all, released unless leather had been exposed to very dry environment, UV radiation, and/or oxidising or alkaline species. Therefore, even in extreme conditions, sweat is unlikely to cause the release of enough CrIII to elicit an allergic skin reaction in sensitised subjects.

Table 3

Concentrations of CrVI that elicit allergic skin reactions in 10% (BMC₁₀) or 50% (BMC₅₀) of tested subjects, with their respective 95%ile lower confidence interval (BMCL). Data have been pooled from (A) Allenby and Goodwin (1983), (K) Kosann et al. (1998) and (R) Rudzki et al. (1997). Given the lack of some details, the data used from Allenby and Goodwin (1983) and from Rudzki et al. (1997) may underestimate the concentration by a factor of about 2.8.

Dose (µg/cm ²)	Respondents (N)	Tested (N)	Respondents (% tested)	Reference
0, 45	2	14	14	A
1	1	12	8	K
1, 3	5	38	13	R
4	3	14	21	A
4, 5	14	38	37	R
4, 5	2	12	17	K
6, 5	22	38	58	R
8	6	12	50	K
13	28	38	74	R
16	7	12	58	K
32	11	12	92	K
32	35	38	92	R
44, 2	11	14	79	A
64	11	12	92	K
64	14	14	100	A
88, 5	38	38	100	R

Calculated BenchMark Concentrations were:

BMC₁₀: 2.0 µg/cm².

BMCL₁₀ (95%): 1.1 µg/cm².

BMC₅₀: 9.0 µg/cm².

BMCL₅₀ (95%): 7.4 µg/cm².

Table 4
Concentrations of CrIII that elicit allergic skin reactions in 10% (BMC₁₀) or 50% (BMC₅₀) of tested subjects, with their respective 95%ile lower confidence interval (BMCL). Data have been pooled from (A) Allenby and Goodwin (1983), (F) Fregert and Rorsman (1964), (R) Rudzki et al. (1997), and (S) Samitz and Shrager (1966).

Dose (ppm)	Respondents (N)	Tested (N)	Respondents (% tested)	Reference
88, 5	1	14	7	A
443	1	14	7	A
885	1	14	7	A
1541	1	46	2	R
3100	6	46	13	R
4425	1	14	7	A
8850	5	14	36	A
9750	1	5	20	S
15,581	21	46	46	R
17,700	5	14	36	A
26,000	6	17	65	T

Calculated BenchMark Concentrations, assuming that the test systems gave the same concentrations per surface unit, were:

BMC₁₀: 2420 ppm.

BMCL₁₀ (95%): 1631 ppm.

BMC₅₀: unreliable, because of the shape of the dose-response curve.

Using only data from Allenby and Goodwin (1983):

BMC₁₀: 4801 ppm corresponding to 240 µg/cm².

BMCL₁₀ (95%): 2680 ppm corresponding to 134 µg/cm².

BMC₅₀: 43211 ppm corresponding to 2160 µg/cm².

BMCL₅₀ (95%): 23,095 ppm corresponding to 1150 µg/cm².

For comparison, release of CrIII from leather in phosphate buffer was lower by a factor of about 2 and that of CrVI was 5–10 lower than that of CrIII. Therefore, extrapolating to surface units, a release of 0.5–1 µg/cm² in 10 h can be estimated for CrVI, which is just below the BMCL₁₀ for eliciting an allergic skin reaction to patch testing in sensitised subjects. Note that shortened exposure times to CrVI were associated with an increase of the MET of 2–32 times, or even lack of reaction in 5/11 subjects.

Despite the fact that sweat may increase the release of CrIII and, possibly, CrVI from leather, such an environment will be slightly acidic, a condition which will favour the reduction of CrVI to CrIII (Hansen et al., 2003; van Lierde et al., 2006; Mathiason et al., 2015; Hedberg et al., 2015). This condition greatly reduces the allergenic potential of Cr, but the combination of occlusion and high humidity that characterises the microenvironment of leather shoes/gloves tends to favour elicitation of dermatitis, by somewhat facilitating CrIII skin penetration that would be otherwise very limited. Therefore, a “protective” effect of sweat by interfering with the amount of free CrVI likely balances the enhanced extraction of Cr from leather (Thyssen et al., 2012).

7. Epidemiology of Cr sensitisation

Thyssen et al. (2007) estimated that the median prevalence of contact allergy (i.e.: positivity to patch testing not actual ACD) to at least one skin allergen is about 20% of the general population, a value confirmed by Dotterud and Smith-Sivertsen (2007). The European Surveillance System on Contact Allergy Network found that 3.64–4.13% of the patient with non occupational contact dermatitis tested positive for CrVI as compared to 5.12–6.03% of those with occupational contact dermatitis (Pesonen et al., 2015).

Thyssen et al. (2009) conducted two consecutive cross-sectional patch test studies from the same general population in Denmark and showed that the prevalence of Cr allergy decreased between 1990 and 2006, significantly in men (from 0.7 to 0%) and slightly in women (from 0.4 to 0.3%).

Bregnbak et al. (2014b) and Thyssen et al. (2009) report that, between 1989 and 1994, 24.1% of the patients sensitised to CrVI reported exposure to leather goods compared to 45.5% in the years 1995–2007. They concluded that the increase in CrVI sensitised subjects was due to the increased use of leather goods. However, it should be noted that 56.9 and 48.5% of the patients, respectively, were not able to identify possible sources of contact with CrVI. As it

can be seen from Table 2, the number of subjects involved was quite low, and this both does not provide strong support to the statement, and indicates that the problem is, in any case, limited to a small number of subjects. As rightly pointed out by Thyssen et al. (2009), this increase may also be spuriously due to increased focus on leather allergy among dermatologists, that resulted in enhanced diagnostic work-out of patients, or on increased awareness about leather articles as sources of Cr rather than increased use of leather articles (Bregnbak et al., 2014b). Were this effect related to leather exposure, it cannot be determined if this is due to a more frequent exposure to leather goods or by exposure to higher concentrations of chromium released by leather. In contrast, Caroe et al. (2010) did not find any change over the years 1992–2009 in the possible sources of Cr exposure of the patients. Temporal evolution of sensitisation to various allergens have been described, and rarely a clear explanation of increased or decreased prevalence could be found (Nguyen et al., 2008; Goon and Goh, 2005; Lindberg et al., 2007).

Bregnbak et al. (2014b) found that CrVI-sensitised subjects had leather exposure, mainly from leisure time activities, as compared to controls with dermatitis not due to CrVI. However, the questionnaire was not very detailed on the type of shoes or gloves, or other leather products, used during these activities, and hence it is not known what was the quality those leather products as sources of CrVI. In addition, they did not enquire on the date of onset of the disease.

8. Discussion and conclusions

CrVI is certainly an allergen, which is responsible for a number of cases of occupational and non-occupational ACD; however, there are no data on the concentrations required for induction of sensitisation. These concentrations appear to be higher than those necessary to elicit the skin reaction in a sensitised subject, but it is not known to what extent. In reality, as stated by Caroe et al. (2010), there is no direct proof whether CrVI (or even CrIII) in leather-induced Cr sensitisation in all or a fraction of sensitised subjects, or rather it may just have elicited an allergic reaction in previously sensitized patients.

With respect to Cr in leather, it is important to define both the conditions that may elicit the skin reaction in sensitised subjects and the amount/concentration of CrVI/CrIII released by leather and not leather content of CrVI/CrIII. Combining the data from the

literature the MET₁₀ (BMC₁₀) for CrVI can be set at around 2 µg/cm² for a 48 h test. As discussed above, this should not be intended as the concentration that induces sensitisation in healthy individuals, but as the concentration that elicits a skin reaction in already sensitised subjects. In any case, this CrVI concentration appears to be higher than any concentration that can be released from leather. In addition, duration of exposure much shorter than 48 h occurs in normal life, and shorter duration of patch testing has been shown to be associated with lack of reaction or higher threshold (Kosann et al., 1998). CrIII is at least 120 times less potent than CrVI, and even if it is released from leather in amounts larger than CrVI, yet the amounts released seem to be generally lower than those necessary to elicit an allergic skin reaction. Based on these assessments of exposure, there is no clear evidence that all allergic reaction, or even irritation, associated with wearing leather goods can be associated to Cr released by leather, even in the presence of CrVI sensitisation.

It has been claimed that there has been an increase of Cr allergies associated with increased uses of leather goods, and, conversely that there was an increase of allergies to leather that are due to Cr that is released. However, in controlled studies no correlation could be found between the amounts of chromium, either CrIII or CrVI, released from leather and the elicitation of an allergic reaction after application of the leather sample to the skin of already sensitised subjects. It has been claimed that this lack of correlation indicates the inadequacy of the method of analysis for both CrVI and CrIII. While this can be, at least partially, true and does not reject a connection between the contact with Cr released from leather and the development of skin reaction, it points out to the need of enquiring for other possible allergens present in leather that have not been investigated in those leather samples (Hansen et al., 2006). In addition, metal co-reactivity is common among dermatitis patients. Thyssen and Menné (2010) reported that 79% of cobalt-allergic patients, 39% of chromium-allergic patients, and 95% of palladium-allergic patients, respectively, also reacted to nickel, 23% of nickel-allergic patients, 31% of chromium-allergic patients, and 36% of palladium-allergic patients, respectively, also reacted to cobalt and 5% of nickel-allergic patients and 15% of cobalt-allergic patients also displayed a positive reaction to chromium. This can be a consequence of either cross-sensitization (e.g., nickel and palladium) or concomitant sensitization (e.g., nickel and cobalt). Therefore, critical interpretation of positive patch test reactions and determination of their clinical relevance is always needed.

In the general population, the problem of Cr allergic skin reaction associated with leather contact appears to be small in absolute terms since it requires a combination of factors such as leather releasing sufficient amounts of Cr, prolonged occlusive and high humidity conditions, direct contact with the skin, and, probably, in a number of individuals, previous Cr sensitisation from other exposures (Thyssen et al., 2012). Other potential sources of Cr for which there are no specific quantitative data on exposure include cosmetics, tattoo ink, paint, detergents and bleaches, mobile phones, and metal alloys used in various consumer products and medical implants (Hamman et al., 2013).

In conclusion, the issue of allergic skin reactions associated with use of leather goods relates mainly to sensitised subjects that are a minority of the population. In addition, there is no evidence that skin reactions in all those subjects are due to the CrVI and/or CrVI plus CrIII released from leather and the role of other chemicals has not always been thoroughly examined. Certainly, there is a need to improve current methods and methodologies to measure and assess the role of Cr released from leather that, at the moment, are not fully adequate. In any case, this issue involves a few subjects in the whole population and appears to be of minor relevance if the leather industry avoids the use of CrVI and properly uses CrIII for

tanning. Moreover, in most of these subjects it appears that use of new, good quality material, proper use modalities, such as avoiding prolonged direct contact, hyperhidrosis, and use of socks help reducing the risk.

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