

Chromium allergy and dermatitis: prevalence and main findings

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Summary

The history of chromium as an allergen goes back more than a century, and includes an interventional success with national legislation that led to significant changes in the epidemiology of chromium allergy in construction workers. The 2015 EU Leather Regulation once again put a focus on chromium allergy, emphasizing that the investigation of chromium allergy is still far from complete. Our review article on chromium focuses on the allergen's chemical properties, its potential exposure sources, and the allergen's interaction with the skin, and also provides an overview of the regulations, and analyses the epidemiological pattern between nations and across continents. We provide an update on the allergen from a dermatological point of view, and conclude that much still remains to be discovered about the allergen, and that continued surveillance of exposure sources and prevalence rates is necessary.

Key words: allergic chromium dermatitis; allergy; chromium; chromium allergy; dermatitis; leather; metals; potassium dichromate; screening; spot test.

Chromium is a transition metal with the atomic number 24. Industrialization and modern living have resulted in increased exposure to chromium ions for more than a century. Chromium salts can induce skin irritation and allergic contact dermatitis. These manifestations have been the basis for multiple studies, reports, and regulations (Table 1). We review chromium allergy from a dermatological perspective, providing an update combined with a historical perspective.

Materials/Methods

For the epidemiological part of this review article, a PubMed/MEDLINE literature search was performed on 10 December 2014, with the following search terms:

'((((chromium or chromate or chrome or potassium dichromate) and (patch test or

dermatitis or allergy or sensitivity or sensitization or allergic contact dermatitis))) AND English [Language]) AND ("2004"[Date - Publication]; "2015"[Date - Publication])'

For a study to be included in the prevalence calculation, the prevalence rate had to be obtained from patch test clinics where the primary indication was dermatitis and not, for example, prosthesis insertion. Studies needed to report prevalence rates that would allow for calculations. Finally, we decided to only include studies published from 2004 and onwards, with the primary intention of performing an up-to-date review analysis on prevalence rates and trends during the last 10 years.

The information for the remaining sections of this review article originated from a similar PubMed/MEDLINE literature search performed with relevant search terms for the respective topics, focusing mainly on newer publications, but not neglecting older studies. The historical perspective of chromium allergy was mainly based on the doctoral theses by the Scandinavian dermatologists Bonnevie (7) and Høvdig (8). Retrieved clinical case reports, clinical trials, original research and review

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Table 1. Historical milestones regarding allergic contact dermatitis caused by chromium

1908	The first detailed description of cement dermatitis by Martial (1). During the construction of the Paris Metro system during 1900–1905, one-third to one-half of the workers experienced itching eruption of the hands. Because of the similarity of the eruption to scabies, he called the condition 'la gale du ciment'
1931	Patch testing with potassium dichromate 0.5% pet. was introduced (2)
1950	The association between cement dermatitis and chromium allergy was shown by Jaeger and Pelloni (3)
1964	Fregert and Rorsman (4) showed that allergy to chromium implies sensitivity to both chromium(III) and chromium(VI)
1971	Addition of 0.3% ferrous sulfate to cement reduced the risk of allergic contact dermatitis (5)
1981	Aalborg Portland A/S patented a method whereby the amount of chromium in the cement could be reduced with the method suggested by Fregert et al. in 1979 (6)
1983	Legislation made the addition of ferrous sulfate compulsory in Denmark. The content of water-soluble chromium in dry cement must not exceed 2 ppm (arbejdstilsynetsbekendtgørelse 1983)
2005	European legislation on chromium(VI) in cement (2003/53/EC)
2010	German regulation on leather. Eighteenth amendment to the Regulation of the German Ordinance on Commodities
2015	European regulation on leather. Commission regulation (EU) No. 301/2014

articles were evaluated, and the reference lists of relevant articles were checked for additional relevant studies.

Statistics

Data were analysed with IBM® SPSS™ Statistics (SPSS Inc., Chicago, IL, USA) for Windows™ (Release 19.0). Comparisons were made by use of the χ^2 -test. A χ^2 trend test was used to test for possible significant trends across test years (linear-by-linear association). The weighted average of prevalence rates was calculated as $[(n_1 \times \%_1) + (n_2 \times \%_2) + (n_n \times \%_n)] / (n_1 + n_2 + n_n)$. Statistical significance was predefined as a *p*-value of < 0.05.

Results

The literature search resulted in a total of 1066 potential studies for the epidemiological part. Abstracts were then screened, and 132 articles were found to be relevant for further analysis. For the epidemiological comparison between Europe, North America, and Asia, a total of 31 studies were relevant.

The Passivating Effects of Chromium

Chromium as a metal in its pure form is not useful for many applications. However, chromium is widely used as an alloying element in stainless steel alloys, where it provides superior corrosion resistance. With >10.5 wt% chromium as the alloying element, a tenacious passivating surface film is formed on the surface of stainless steel, preventing oxidation (and corrosion) of iron in the bulk material. Accordingly, an increased content of chromium as an alloying element provides further protection against corrosion (9).

Chromium is also used for plating purposes; chromium-plated layers appear as bright shiny metal

surface layers, typically on steel, copper, brass, or plastic, and a sub-layer of nickel is often applied before the chromium layer. Such chromium-plated layers can be made in plating baths containing chromium salts, which will dissolve as either chromium(III) or chromium(VI). Any left-over chromium salts are washed off after plating. Currently, mainly chromium(III) salts are being used, in order to minimize the use of chromium(VI) (9).

Chromium is also used as a thin conversion coating of aluminium, zinc, tin, etc. The chromating treatment results in a thin surface layer consisting of chromates and hydroxides, providing enhanced corrosion resistance. The chromate layers can appear in various colours, such as black, yellow, or green. Plating bath chemistry can be based on chromium(VI) or chromium(III). Aluminium has traditionally been coated with chromium(VI), with the brand name Alodine®. For many years, this process has been recognized to be a good basis for subsequent application of paint, as it offers good adhesion and corrosion resistance.

A number of other passivation products without chromium have been introduced over the last 5–10 years and have gradually gained a foothold in the market, because of the Restriction of Hazardous Substances Directive and a general desire to minimize the use of chromium(VI). In Denmark and Western Europe, the trend is towards passivation without the use of chromium(VI). Until recently, chromium(VI) as a passivation layer was primarily used for so-called yellow and olive passivation in Eastern Europe, Asia, and Africa (9).

Corrosion of stainless steel or chromium-plated items can cause the release of chromium in various oxidation states, the most common being II, III, and VI. The equilibrium potential between chromium and various oxidized species as a function of pH is plotted in Fig. 1. The stability region for water is marked by the two dashed lines. If the pH is below 4, Cr^{3+} ions and HCrO_4^- ions

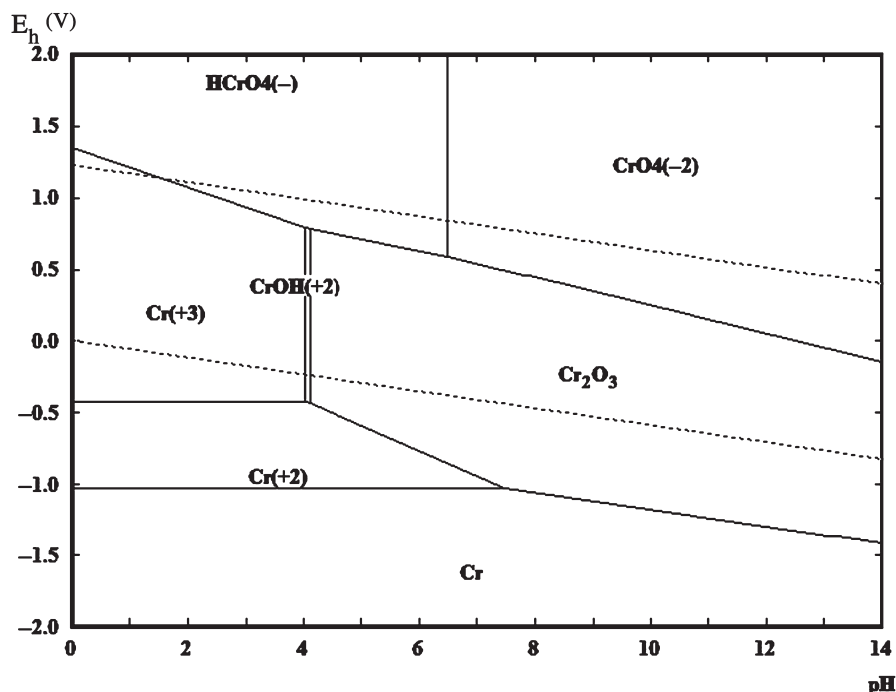


Fig. 1. Electrochemical potential–pH equilibrium diagram for the system chromium–water at 25°C, 1 atm pressure, and a chromium concentration of 1×10^{-6} M. The electrochemical potential is given in volts standard hydrogen electrode [E_h (V)]. The diagram was produced with HSC CHEMISTRY 7.1™ software.

are thermodynamically most stable. At higher pH values, chromium will exist as Cr_2O_3 or as chromium in oxidation state VI as HCrO_4^- or CrO_4^{2-} . The potential pH diagrams show that chromium(III) is the most stable oxidation state, and forms as Cr^{3+} , $\text{Cr}(\text{OH})^{2+}$, and Cr_2O_3 (10). Chromium in oxidation state VI, $(\text{CrO}_4)^{2-}$, can be released in a strong oxidizing environment (high electrochemical potential) and at high pH.

The influence of conditions such as pH, surface area, relative humidity, temperature, ultraviolet (UV) irradiation, repeated exposure, wear, alkaline solutions and sequential wet and dry exposures on chromium release was recently examined in larger studies on leather (11, 12). Several of the parameters significantly influenced the oxidation state of chromium, and further studies are needed.

Chromium Exposure Sources

A review of the published literature going back >100 years showed multiple exposure sources for chromium (13). A non-exhaustive list is shown in Table 2. In the text below, we introduce the most relevant sources of chromium exposure today.

Cement

Cement has historically been the most common and important cause of chromium allergy and dermatitis. The

association was first established in 1949 (3, 24). However, 10 years earlier, chromium allergy was suspected as a likely cause of dermatitis in cement workers (7). Cement regulations have now changed the epidemiology of chromium allergy among EU nations (Fig. 2), but, in other countries, occupational chromium dermatitis remains a major occupational health concern among construction workers (25–27). A recent Australian retrospective analysis showed a stable prevalence of allergic contact dermatitis caused by cement as opposed to the decrease observed in many European countries (28). The authors concluded that there is a need for regulation of chromium in cement similar to the European directive. Notably, cement exposure still causes allergic chromium dermatitis in Europe (29), and knowledge about adequate protective equipment and careful occupational hygiene remains crucial for prevention and work safety in construction workers. In a recent survey from Denmark, it was shown that 10% of chromium-allergic patients still reported a history of cement dermatitis (30).

Leather goods

It is estimated that 90% of the leather produced globally is tanned with chromium sulfates (60), the consequence being that chromium exposure may occur from prolonged contact with various leather products, for example belts, leather covers for car steering wheels, footwear, furniture, gloves, jackets, and watch straps. Chromium(III) is used

Table 2. Non-exhaustive list of chromium sources

Chromium source	Reference(s)
Anti-rust coatings*	(13, 14)
Ashes*	(13, 15)
Bleaches and detergents*	(13, 15–23)
Cement*	(3, 7, 13, 24–30)
Electroplating*	(13, 14)
Fabrics*	(13–15)
Food laboratory*	(13)
Foundry sand*	(13)
Galvanized sheets*	(13, 15)
Glass polishes*	(13)
Glass stains and glazing*	(13)
Implants/prostheses	(31–35)
Leather articles	(30, 36–39)
Magnetic tapes*	(13)
Matches*	(13, 14)
Make-up/cosmetics	(40–44)
Metal alloys	(45–49)
Mobile phones	(50–53)
Milk testers*	(13)
Oils*	(13, 15)
Paints*	(13, 14)
Paper industry*	(13)
Photographic chemicals*	(13, 14)
Primer paints*	(13, 14)
Printing*	(13–15)
Sutures	(54)
Tattoo ink	(55–59)
Wood preservatives*	(13)

Sources in bold are described further in the text.

*Reviewed by Cronin (13).

in leather tanning to provide softness, durability and flexibility following binding to collagen fibres, whereas chromium(VI) is an impurity resulting from oxidation of chromium(III) during manufacturing, and hypothetically also following usage (36, 61). An increase in the rate of allergic contact dermatitis caused by chromium as a result of skin contact with leather products was recently observed in Denmark (37). Moreover, a recent German survey performed between 2000 and 2006 examined 850 leather items, and showed that more than half released >3 ppm chromium(VI), and one-sixth released >10 ppm (<http://www.bfr.bund.de/cd/9575>). A Danish survey from 2009 examined 60 pieces of leather footwear, and showed that chromium was present in nearly all of the examined products, with a median content of 1.7%; 44% of 18 products evaluated with the ISO 17075 standard method showed release of chromium(VI) (38). We recently examined 121 Danish patients with chromium dermatitis diagnosed between 2003 and 2012, and showed that 66% reported dermatitis following exposure to leather products (30). As with cement, it is expected



Fig. 2. A picture from 2007 taken in Lanzarote, Spain, showing a bag of cement without chromium(VI). The EU Directive restricting the marketing and use of cement containing >2 ppm chromium(VI) came into force in January 2005 (2003/53/EC).

that the European regulation on leather will change the epidemiological pattern in the EU, and a decrease in the rate of chromium allergy resulting from leather exposure is expected. For the management of chromium-allergic patients with foot dermatitis, a recommendation to use chromium-free footwear is given. However, in a recent report, three pairs of allegedly 'chromium-free' footwear all contained chromium (62). Hedberg et al. (63) recently examined four leather samples from three European tanneries. They showed chromium release in different extraction solutions of all of the samples, but their results did not make it evident whether the surface of the samples released chromium(III) or chromium(VI), owing to the shifting oxidation state. Studies on the same leather samples showed that, previously, analysis according to ISO 17075 might underestimate the released chromium(VI) content, and environmental parameters not accounted for in ISO 17075 might be of significance for estimating the content of chromium released from leather goods (11, 12).

Mobile phones

Multiple case reports of mobile phone-associated allergic contact dermatitis have been published over the past 10 years. Seishima et al. reported the first case of allergic contact dermatitis caused by a chromium-containing phone in 2002 (50). The patient was a 35-year-old female with left-sided pre-auricular pruritic dermatitis. She had positive patch test reactions to 0.05%, 0.1% and 0.5% potassium dichromate, but did not react to other metals. A component of her mobile phone was plated with

chromium, and a diagnosis of allergic contact dermatitis caused by chromium was established, leading to her dermatitis resolving 10 days after avoidance of skin contact with the mobile phone. In 2003, Seishima et al. published a report on 8 additional cases of chromium-induced mobile phone allergic contact dermatitis from Japan, all of whom were patch test-positive to potassium dichromate and had auricular or pre-auricular facial dermatitis; their dermatitis cleared ~10 days after avoidance of the allergenic mobile phone (51). A similar case was published by Tan and Nixon from Australia in 2011 (52). A recent review article (53) of mobile phone dermatitis from 2014 showed that 10 of 37 published patient cases had a positive patch reaction to potassium dichromate; 6 of these test results implicated allergic contact dermatitis caused by chromium alone, whereas the remaining 4 patients had concomitant allergy to either nickel or cobalt, and these could therefore have played an additional role.

Make-up/cosmetics

The EU banned the use of chromium and other metals in cosmetic products in 1976 (Cosmetics Directive 76/768/EEC), but metals are still permitted in very low quantities as impurities. Despite this, only a few studies have evaluated the presence of chromium in cosmetics. In 2000, Sainio et al. examined 88 eye shadows bought in Finland; all contained chromium, and nine had concentrations of water-soluble chromium of >2 ppm, with the highest value being 318 ppm (40). Recent studies (41–43) representing the Asian and European market have found similar results, and concluded that, even though there may be chromium in cosmetics, it does not pose a significant health risk regarding the carcinogenic effect of chromium(VI), but that it could potentially contribute to allergic contact dermatitis morbidity. A recent study from 2009 examined toy make-up from Italy. This type of make-up is intended for the skin of children's faces. Among 52 samples investigated with atomic absorption spectrometry, chromium was found at >5 ppm in 28 samples, and at >1000 ppm in three eye shadows (44).

Tattoo ink

Tattoo dyes are not officially controlled, and could potentially contain various unknown substances (64). Most of the published cases lack information on relevant ink ingredients, because few manufacturers release the documentation (55). In a recent market survey from Italy, Forte et al. (55) showed that allergenic metals such as chromium, nickel and cobalt were present at above the safe allergological limit of 1 ppm in 35 cases, nine cases,

and one case, respectively, among a total sample size of 56 inks. The prevalence of tattooing among people aged 18–50 years in the United States was recently estimated to be close to 25% (56). Pigments that contain chromium are used mostly in green tattoos, but the yellow colour may rarely contain chromium salts as well. Allergic reactions to chromium pigments in green tattoos have been reported in older cases (57–59) and also in a light blue tattoo (65). In a recent case series, 3 patients with positive patch test reactions to potassium dichromate experienced a flare-up in the green portions of their tattoos during testing (66).

Detergents and bleaches

Washing detergents and bleaches have been associated with allergic chromium dermatitis. Historically, a French bleaching agent, 'Eau de Javel', caused allergic chromium dermatitis in Belgium, France, Israel, and Spain (16–19). Chromium salts were added to contribute to the colour and act as staining agents and stabilizers, but were later replaced with other chemicals (17). In modern formulations, chromium is often present in the trivalent form, and is thus less bioavailable (20). In a study from 1988 concerning US household bleaches, the authors found only trace levels of chromium, which were no different from those in other consumer products (21). In a study from 1997 of Swedish detergents, Wahlberg et al. (22) found similar low chromium concentrations when they examined 19 detergents, with 16 of 19 products containing <1.0 µg/g and no product containing >4 µg/g. However, in 1998, Ingber et al. (23) examined detergents and bleaches in Israel. They found chromium concentrations of >5 ppm in 56% of the products tested. No similar reports have been published recently.

Chromated metal alloys

As explained above, the surfaces of many metal products made from iron or zinc, such as screws, fittings, and other materials used in construction, are chromated to prevent rust or surface oxidation (45, 46). Fregert et al. (47) described hand dermatitis in 5 metal-workers who handled chromated metal sheets, emphasizing the clinical relevance of chromium exposure. The content of water-soluble chromium was between 0.03 and 0.44 µg/cm², and, of this, 22–86% was chromium(VI). Rycroft and Calnan (48) reported a metal-worker who was sensitized to chromium following contact with wet cement. However, hand dermatitis was induced by the handling of a chromated metal sheet releasing 0.03–0.10 µg/cm² chromium(VI). Hjerpe (49) observed

a small outbreak of hand dermatitis in 5 assembly workers in a Swedish automobile company, caused by chromated metal products; they had direct skin contact with screws, nuts, discs and other metal components covered with a yellow chromate layer. His conclusion was that yellow chromation is unsuitable for components that are manually handled. Wass and Wahlberg (67) published an experimental patch test study with 5 patients, and found that all 5 patch tested chromium-allergic individuals reacted to chromated discs releasing $0.060 \mu\text{g}/\text{cm}^2$ chromium(VI) from the surface within 20 min. Patch testing with discs releasing lower amounts of chromium(VI) failed to elicit positive test reactions. On the basis of their results, they recommended that the mean release of chromium(VI) from chromated products should not exceed $0.30 \mu\text{g}/\text{cm}^2$. Geier et al. (45) patch tested 95 patients with proven ($n=11$) or suspected ($n=84$) chromium allergy. They were patch tested with potassium dichromate 0.5% pet., and exposed to chromated rings (black, olive, and yellow); 52% (49/95) reacted to potassium dichromate 0.5% pet. and 26% (25/95) reacted to at least one chromated ring. They concluded that chromium metal products must be regarded as a hazard to chromium-sensitive individuals, in particular those with a strong allergy potential. In Sweden, Kettlerij et al. (31) recently examined used unwashed dental tools for chromium release; in total, 21 tools were examined, all releasing non-negligible amounts of chromium, and seven releasing high amounts ($30\text{--}160 \mu\text{g}/\text{cm}^2/\text{week}$).

Implants/prostheses

With increasingly ageing populations, metal implants and devices are widely used in medical treatment. All metals in contact with biological systems undergo some degree of corrosion, leading to the formation of metal ions, which may activate the immune system by forming complexes with endogenous proteins. Orthopaedic implants that contain chromium include stainless steel, cobalt–chromium alloys, and vitallium. The most widely used materials for vascular and cardiac stents are stainless steel or cobalt–chromium alloys, both of which contain significant amounts of chromium (32). It has been shown that the prevalence of metal allergy is higher among patients who have functional implants, and even higher in those with failed implants (33, 34). The extent to which metal sensitivity contributes to implant failure is a controversial topic. Dental implants also contain and release chromium. This has been summarized in a recent review by Basko-Plluska et al. (35) from 2011. In a Swedish study by Kettlerij et al. (31), five of five dental alloys released chromium in small amounts.

Regulations

Although chromium is widely found in our environment, and complete allergen avoidance can be difficult, regulatory interventions seem to limit excessive exposure. The potential source of chromium(VI) in cement is the trivalent compound in the raw materials from which it is produced. Chromium(III) compounds are oxidized to chromium(VI) compounds during the manufacturing process. In 1971, Burckhardt et al. (5) reported 62 of 78 chromium-allergic patients who did not react to a solution of 40% cement in water to which 0.3% ferrous sulfate had been added. Fregert et al. (6) further explored how the addition of 0.35% ferrous sulfate to cement could reduce the water-soluble chromium content of 20 ppm to undetectable concentrations. In 1981, ferrous sulfate was therefore added to cement manufactured by Aalborg Portland, Denmark. This lowered the water-soluble chromium content to <2 ppm. Legislation made the addition compulsory in Denmark from 1983. Finland followed in 1987, and Sweden in 1989. An EU Directive restricting the marketing and use of cement containing >2 ppm chromium(VI) came into force in January 2005 (2003/53/EC) – see Table 3.

Chromium exposure from leather has also been regulated stepwise. In 2003, the content in protective gloves was limited to <10 ppm chromium(VI) in the EU (EN 420:2003), and in 2009 it was further limited to <3 ppm chromium(VI) (EN 420:2009). In Germany, the 18th amendment to the Regulation of the German Ordinance on Commodities came into effect on 14 August 2010. This regulation limited the level of chromium(VI) in materials made of leather intended to come into prolonged contact with the skin to be not detectable (<3 ppm). Influenced by the German regulation and the increasing leather problem observed in Denmark (37), the Danish government submitted a dossier with information about the chromium leather problem to the European Chemicals Agency in January 2012. This was adopted by the EU Commission [Commission regulation (EU) No. 301/2014] and is a part of REACH, which is the Regulation on Registration, Evaluation, Authorization and Restriction of Chemicals in the EU. Thus, from May 2015, leather articles placed on the markets of European countries that come into contact with the skin should not contain >3 ppm chromium(VI) – see Table 4.

Chromated copper arsenate (CCA) is a wood preservative containing arsenic, chromium, and copper. In many countries, such as Canada, the United States, the United Kingdom, Australia, and Norway, regulations have limited the use of CCA as a wood preservative, because of concerns about its allergenic and toxic capacity (68). In Canada and the United States, manufacturers

Table 3. Summary of the EU Directive (2003/53/EC) and reference method

	From 17 January 2005	CEN standard
Part 1	Cement and cement-containing preparations may not be used or placed on the market, if they contain, when hydrated, more than 0.0002% soluble chromium(VI) of the total dry weight of the cement.	EN 196-10: A test portion of cement is used to make a standard mortar with CEN Standard sand and water in accordance with current standard EN 196-1. The mortar is mixed for a specified time and then filtered. An aliquot of filtrate is first treated with diphenylcarbazide reagent, and then acidified within a narrow range of pH (2.1–2.5). In acid solution, chromium(VI) forms a red–violet complex with the reagent, and its absorption/colour is measured with a visible light spectrophotometer set at a wavelength of 540 nm, although other instrumental/end-point procedures are permitted.
Part 2	If reducing agents are used, the packaging of cement or cement-containing preparations should be marked with information on the period of time for which the reducing agent remains effective (i.e. packing date, storage conditions, and storage period).	
Part 3	Part 1 and Part 2 do not apply when it is for use in totally automated and fully enclosed processes, where there is no possibility of contact with the skin.	

CEN, European Committee for Standardization; EN, European Norm.

Table 4. Summary of the Commission regulation (EU) no 301/2014 and reference method

	From 1 May 2015	ISO standard
Part 1	Leather articles coming into contact with the skin shall not be placed on the market if they contain chromium(VI) in concentrations equal to or greater than 3 mg/kg (0.0003% by weight) of the total dry weight of the leather.	ISO 17075:2007: Soluble chromium(VI) is leached from the sample in phosphate buffer at pH 7.5–8.0, and substances that influence the detection are removed by solid-phase extraction if necessary. Chromium(VI) content is determined with diphenylcarbazide reagent at a wavelength of 504 nm with a spectrophotometer or a filterphotometer. The method described is suitable for quantifying the chromium(VI) content in leathers down to 3 mg/kg.
Part 2	Articles containing leather parts coming into contact with the skin shall not be placed on the market if any of those leather parts contains chromium VI in concentrations equal to or greater than 3 mg/kg (0.0003% by weight) of the total dry weight of that leather part.	
Part 3	Part 1 and 2 shall not apply to the placing on the market of second-hand articles that were in end-use in the EU before 1 May 2015.	

CEN, International Organization for Standardization; EN, European Norm.

of wood-treatment chemicals voluntarily agreed to cease the use of CCA on lumber for non-industrial purposes as of 31 December 2003 (Health Canada Pest Management Regulatory Agency (HCPMR) 2002; U.S. Environmental Protection Agency (EPA) 2002a). Nevertheless, a recent study examined chromium on the hands of children after they had been playing on playgrounds built on CCA-treated wood. They found a significantly higher amount of accumulated chromium among the group from CCA playgrounds (69). Various other regulations concerning the carcinogenic effect of chromium(VI) exist, but they are beyond the scope of this review.

It is emphasized that the above description of regulations is non-exhaustive. Further descriptions of regulations are beyond the scope of this review.

Contents and Release Methods

Measuring the amount of chromium that is released from items can provide an estimate of potential chromium exposure. The different compositions of items require different methods to determine the release. Below, we present selected methods.

X-ray fluorescence (XRF)

The results obtained by screening with XRF indicate which elements are present and their approximate proportional distribution. It is a semiquantitative screening method that can only determine whether an element is present, and not whether it is released from the item or its oxidation.

Artificial sweat test – EN 1811:2011 (70)

The artificial sweat test (reference test method EN1811) is a test on metals that correlates, as far as possible, with the variable human reactions that occur when metallic articles are in direct and prolonged contact with the skin. The release of chromium can be studied quantitatively by immersing items in artificial sweat for 1 week according to the reference test method for the EU nickel regulation (EN 1811: 2011) (70). The concentration of dissolved metal ions in the solution is determined with an appropriate analytical method, for example inductively coupled plasma mass spectrometry (ICPMS) for total chromium content and photometric analysis for detection of chromium(VI). The result is expressed in micrograms per square centimetre per week ($\mu\text{g}/\text{cm}^2/\text{week}$). However, problems regarding correct measurements when the concentrations of the different oxidation states are determined can be a problem, as the evidence suggests that chromium may be both oxidized and reduced in artificial sweat (71).

ISO 17075:2007

ISO 17075:2007 is a test method for determining the chromium(VI) content in solutions leached from leather, and is suitable for all leather types to determine contents down to 3 mg/kg (3 ppm). The principle of the procedure is that a leather piece is sampled and ground according to written procedures (72). Afterwards, it is placed in an extraction solution of phosphate buffer for 3 hr. Chromium(VI) in the solution oxidizes 1,5-diphenylcarbazine (DPC) to 1,5-diphenylcarbazone to give a red–violet complex with chromium, which can be quantified photometrically at 540 nm. The method measures the mass fraction, expressed in milligrams per kilogram (mg/kg). There is no attempt to make the environmental conditions of the test imitate human physiology, with a pH of 8.0 ± 0.1 , room temperature ($20\text{--}25^\circ\text{C}$), and no UV light. Recently, Hedberg et al. (12) investigated the influence of stipulated test conditions of ISO 17075:2007. They concluded that several test parameters of the standard affect the amount of detectable chromium(VI), among others the cutting/grinding of the sample, which can possibly result in an underestimation of the release of chromium(VI). Furthermore, the standard does not consider the influence of temperature and UV irradiation, which have been shown to be significant factors for chromium release from leather articles (11, 12).

Inductively coupled plasma mass spectrometry

ICPMS is a type of mass spectrometry that is capable of detecting metals at low concentrations. The current

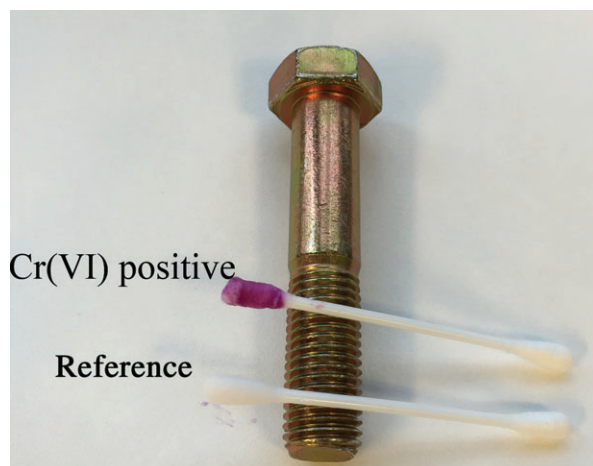


Fig. 3. A positive diphenylcarbazine spot test reaction on a chromated screw. (1) A cotton stick is soaked in the pre-made diphenylcarbazine solution, and then rubbed firmly against the screw for 30 seconds. (2) In the presence of chromium(VI), oxidation of 1,5-diphenylcarbazine to 1,5-diphenylcarbazone will give a reddish purple-coloured cotton stick; the final reading should be performed after 2 min.

technology does not normally allow separation between the different oxidation states. It is therefore a useful tool with which to determine the total chromium content of solutions, but other methods are needed in order to distinguish between chromium(III) and chromium(VI) contents, such as photometric detection.

Testing with the DPC spot test

The diphenylcarbazine (DPC) reagent is used for spectrometric determination of chromium(VI) content in ISO 17075:2007. Chromium release from leather and metals can also be detected with a DPC spot test (Fig. 3) (39). It is a semiquantitative direct screening method that can detect chromium(VI) content down to 0.5 ppm. The clinical role of the DPC spot test has not yet been defined, but it has shown the ability to screen leather, screws/nails, and earrings.

Chromium Deposition on the Skin

Skin exposure can be regarded as an interactive process of deposition of a source on the skin, and is defined as the mass of chemical reaching the body barrier and available for absorption per unit time (73). Most studies on chromium allergy lack data on how much chromium the skin has been exposed to. However, a wide range of methods have been developed to determine the deposition of metals on the skin in occupational settings, for example washing techniques (74), tape stripping (75), the acid

wipe test (76), and visualization by spot tests (77, 78). The washing techniques often involve washing the entire surface of the hands and collecting the washing liquid. Tape stripping, the acid wipe test and spot tests have the advantage of being able to examine a specified area of particular interest or exposure, and they can therefore assess the possible amount deposited per unit time.

Acid wipe sampling was developed for the quantitative assessment of nickel, chromium and cobalt deposition on the skin. The technique has been applied in several studies (76–82), and may be a valuable tool in the diagnostic workup of occupational hand eczema. It has been used to assess metal exposure in different occupations, is reproducible, and has the highest sampling efficiency of the mentioned techniques [~93% for nickel, chromium, and cobalt (76)]. It was developed in 2006 by Lidén et al. (76), and validation (81) was initially performed on workers performing normal work tasks. Here, chromium was deposited on the skin of carpenters, cashiers, and locksmiths, but to a much lesser degree on the skin of secretaries. In 2010, Julander et al. (80) examined skin deposition of chromium on the hands of workers producing components for gas turbines and space propulsion. Their results showed that, even though the chromium-exposed workers washed their hands several times during a workday, they would still be exposed to chromium on the skin, which may contribute to deposition and a risk for allergy.

Ideally, a rapid, inexpensive and direct-reading method for dermal exposure measurement should be developed. At present, most studies seem to use the acid wipe sampling technique for measuring the deposition of metals on the skin.

Chromium Penetration

Chromium penetration of the stratum corneum (SC) is a prerequisite for activation of the skin immune apparatus. The outermost barrier of the human body consists of layers of cornified keratinocytes with intercellular spaces sealed with lipids. It is the principal barrier against permeation, and represents an external barrier against foreign insults, as well as an internal barrier to keep the skin hydrated. The electrophilic nature of many metals and their water solubility determine their protein reactivity and penetration, which can result in intracellular depot formation in the SC (83). It is the bioavailability of the chromium salts that is essential for sensitization and induction of allergic contact dermatitis.

In vitro permeation studies with a variety of analytical techniques have been applied in the past, involving both animal and human skin. Early studies, mostly focusing on exogenous factors, showed that crucial factors

regarding the permeation of chromium salts include the following. (i) The oxidation state of chromium, because chromium(VI) can pass more easily through the skin barrier than chromium(III) (84–88). Chromium(III) tends to form stable complexes within the epidermis, and a smaller degree of permeation could also be attributable to greater rejection of the positively charged chromium(III) ions by the skin barrier (71, 87). (ii) Increasing the concentration of chromium(VI) results in an increased concentration in the skin, with a maximum peak, presumably as a result of the limited binding capacity of the skin (71, 86–89). (iii) Exposure time is an important factor, and longer exposure time results in higher amounts of chromium being absorbed by and permeating through the skin (71, 87). In agreement with these results is a recent study (71) on porcine and human skin, with evaluation by capillary electrophoresis–inductively coupled plasma-sector field mass spectrometry. They reconfirmed that chromium(III) has strong affinity for the skin, whereas the affinity of chromium(VI) for the skin is less pronounced, as it passes more easily through it. Although chromium(VI) ions pass more easily through the epidermis than chromium(III) ions, the condition of the skin barrier appears to play a critical role. Thus, Basketter et al. showed that, on normal skin, the patch test threshold level for potassium dichromate was 10 ppm, but, in the presence of an irritant, it was closer to 1 ppm (90).

A recent study on skin penetration using a Franz chamber showed that metallic chromium cannot permeate the skin in artificial sweat at pH 6.5 (91). Metallic cobalt and nickel could be oxidized when suspended in synthetic sweat, but not chromium. Nevertheless, lowering the pH of the sweat to 4.5 allowed chromium to penetrate the skin (92). In an *in vitro* permeation experiment with intact and damaged human skin, Larese et al. (93) showed that cobalt and nickel powders can permeate through damaged skin more easily than chromium powder, probably as a result of its stronger binding to skin proteins. Finally, a recent study by Kubo et al. showed that the SC comprises three layers with distinct metal ion barrier properties, owing to variation in amino acids (94).

Dose–Response Relationship

The specific dose of an allergen causing elicitation can be identified by experimental dose–response studies performed on allergic individuals. There have been several dose–response studies on chromium (61, 90, 95–102), but most of these have focused mainly on chromium(VI), and not chromium(III). An article by Hansen et al. (103) from 2002 reviewed results from previous studies on thresholds for elicitation. They calculated the minimal eliciting threshold (MET) in 10% of the

chromium-sensitive patients, and found that the MET_{10%} for chromium(VI) ranged from 7 ppm (100, 102) to 45 ppm (96), with a median value of 13 ppm. Regarding chromium(III), they did not systematically investigate the dose–response relationship, as a result of their data, but concluded that it is a weaker eliciting agent than chromium(IV).

An experimental study focusing on both chromium(III) and chromium(VI) was performed in 2003 by the same authors (61). For chromium(VI), they found a MET_{10%} of 1 ppm and a MET_{50%} of 5 ppm. For chromium(III), they found a MET_{10%} of 6 ppm and a MET_{50%} of 89 ppm. These results highlight the significance of chromium(III) for chromium contact dermatitis, and show a lower chromium(III) elicitation threshold than previously assumed. The results regarding chromium(VI) were in agreement with previous studies (103). The chromium(III) result is in contrast to most other studies (4, 97, 98), which all showed elicitation results of >1000 ppm. Allenby and Goodwin (100) found a similar MET in their study from 1983, with 1 individual reacting to solutions containing only 49 ppm chromium(III). A study from India found no elicitation of dermatitis among 18 chromium-allergic individuals exposed to 50 ppm chromium(III), but the duration of exposure to the allergen was only 4 hr (104). The synergistic effect regarding a lower threshold in the presence of both chromium(III) and chromium(VI) has, to our knowledge, only been examined once, but the authors did not test with low enough concentrations to show a potential synergistic effect (61). A study from 2001 by Basketter et al. (90) investigated the dose–response relationship in chromium allergy. They found a MET_{10%} of 34 ppm (95%CI: 0.1–182 ppm) both by testing under closed patch test conditions and with repeated open application, in order to mimic more realistic conditions of exposure. The conclusion of their study was that chromium-allergic individuals can react upon repeated exposure to very low levels of chromium. The results were not very different from those of a study from 2000 indicating that 10 ppm chromium may elicit hand dermatitis with immersion of a finger for 10 min daily for 2 weeks (105). The MET values for the different oxidation state forms and their interaction still seem to be incompletely explored, and further studies are probably needed in order to shed further light on this topic.

Genetics

Although only a few studies have investigated a genetic predisposition to chromium allergy, several studies have investigated nickel, cobalt and chromium in combination.

A thorough review of genetic factors in contact allergy was recently performed by Schnuch et al. (106).

Several different approaches have been used to investigate the genetic background of chromium allergy. In 1993, Ishii et al. (107) showed that genetic control of delayed-type hypersensitivity reactions in mice was antigen-specific for chromium, thus indicating a genetic component. Several studies have been performed with the human leukocyte antigen (HLA) encoded by the major histocompatibility complex (MHC) class I (HLA-A/HLA-B/HLA-C) and MHC class II (HLA-DP/HLA-DQ/HLA-DR) genes as serological immunogenetic markers (108–112). None of these studies found significant differences in the distribution of HLA alleles between chromium-sensitive individuals and controls. In 2008, Schnuch et al. reviewed evidence indicating that patients with polysensitization to contact allergens could represent a group with increased genetic susceptibility for the development of contact allergy (113). They found that the probability of being sensitized to an index allergen gradually increased with the number of additionally diagnosed allergens from the baseline series, including chromium. Their conclusion was that polysensitized individuals may represent a subgroup of patients in whom genetic risk factors are more prominent. Later in 2008, Carlsen et al. (114) published a study examining associations of 21 allergens in the European baseline series with polysensitization. They found that the individuals in their allergic population had already shown the ability to acquire contact allergies but sensitization to specific baseline allergens could not be used as risk indicators for polysensitization. Wang et al. examined the genetic polymorphisms of DNA from 153 cement workers, and found a significant association with the tumour necrosis factor (TNF)- α promoter-308 heterozygous and GST-T1 null genotype among the chromium-sensitive workers (115).

In conclusion, chromium allergy is a complex multifactorial disease, and the general view is that genetics do play a role, but that their importance as compared with environmental influences is probably very small.

Immunology

Although chromium(VI) penetrates the biological membranes more easily than chromium(III), it does not react with proteins to form haptens. It is first reduced to chromium(III) within the skin (116), which explains why chromium(III) is considered to be the actual hapten forming the complex recognized by T cells (117). A crucial distinct feature for the development of allergic contact dermatitis is the involvement of specific T cells. Allergens are bound, internalized, processed, and

transported by Langerhans cells or macrophages to the regional skin-draining lymph node, where they present the contact allergen in the context of MHC molecules to specific naïve T cells that become activated and clonally expand to memory T cells (118). Re-exposure to the relevant allergen initiates the efferent phase and clinical expression of allergic contact dermatitis (119). Apart from the antigen-specific T cell-activating signal, a second pro-inflammatory stimulus is required for efficient sensitization (120). This second stimulus delivers the danger signal to the immune system, upregulating extracellular matrix proteins that serve as endogenous ligands for the extracellular Toll-like receptors (TLRs), and in particular TLR4. The stimulation of the TLR receptors triggers the production of pro-inflammatory cytokines, which, in turn, promote the acquisition of skin sensitization, and subsequently the elicitation of allergic contact dermatitis (121). Recently, nickel was shown to be able to bypass the need for a second stimulation, and to induce an inflammatory response by directly activating human TLR-4 (120). This discovery has resulted in investigations on whether other metals have the same stimulatory effect or other unique response patterns. A recent investigation by Rachmawati et al. (122) studied a panel of allergens including chromium, cobalt, and palladium, and came to the conclusion that chromium may rather depend on microbial or tissue-derived cofactors to induce contact sensitization. In another recent study, they examined the different immunological pathways of hypersensitivity specifically caused by chromium(VI) (123). They suggested that chromium allergy might be prevented if anti-oxidative agents could reduce the formation of reactive oxygen species and their effects on cytokines [e.g. TNF- α and interleukin (IL)-1]. In a recent study on the concepts in cutaneous allergy the underlying immunological mechanisms are reviewed (124). Their conclusion was that, for prevention, diagnosis, treatment, hazard identification, and risk assessment, understanding the immunological mechanisms is crucial.

Concomitant test reactions

The finding of no cross-reactivity between cobalt, chromium and nickel was described in 1966, when Fregert and Rorsman (125) examined a total of 5416 patients, and came to the conclusion that concomitant allergies to these metals can be explained by the co-occurrence of various metals in sensitizing products. Several studies using guinea-pigs have shown no cross-reactivity between chromium and nickel (126–128). A later evaluation study using both guinea-pigs and the local lymph node assay in mice

showed no cross-reactions between chromium, nickel, titanium and zirconium salts (129). The topic was also examined in guinea-pigs with chromium and cobalt, and no indication of cross-reactivity was found (126). Guinea-pig sensitization rates seem to be practically identical between the sexes (130).

Potassium dichromate has been shown to be a strong sensitizer both in human models and in animals, with the two most widely recognized models being the guinea-pig maximization test and the local lymph node assay in mice. Kligman (131) developed a predictive human assay, the maximization test, which classifies allergens into five classes according to their potency. Potassium dichromate showed extreme allergenic potential, and was classified as a class 5 hapten. Magnusson and Kligman (132) reported potassium dichromate as a grade IV (of V) allergen, sensitizing 75% of the guinea-pigs in the maximization test. Basketter and Scholes (133) reported potassium dichromate to be an extreme sensitizer, according to the local lymph node assay.

Epidemiology

Patient characteristics

The characteristics of chromium-allergic patients show variations between different continents. In a recent questionnaire study, we characterized Danish chromium-allergic patients for the period 2003–2012 (30). We found that almost three-quarters of patients were women, with an age of >58 years. Occupational causation of chromium dermatitis was found for only one-quarter of patients. Similar trends have been seen in other European countries, with approximately two-thirds of the chromium patch test-positive populations being women in, for example, the Czech Republic (134), Italy (135), Poland (136), and Spain (137). Regulations and laws have existed in European nations for many years, beginning with the Danish cement regulation of 1983 (see Regulations). These interventions appear to have changed the aetiology and epidemiology of chromium allergy, from an occupational problem caused mainly by cement exposure (138–140) affecting primarily males, to a consumer problem caused by exposure to leather articles and primarily affecting females (30, 37, 141). A high age of chromium-allergic patients could be recognized when cement was the main cause of chromium allergy. In a thesis regarding cement dermatitis and chromium allergy from 1970, the chromium-positive study population had an average age of >50 years, implying that the development of clinical chromium allergy was a protracted process, usually requiring many years of exposure

(8). This could be a physiological phenomenon or a result of longer disease duration before diagnosis. Climatic and cultural differences probably play important roles as well. In 1985, Olumide (142) observed a prevalence of contact allergy to potassium dichromate of 7.8% in Nigeria, with the main causes being cement and leather. The leather exposure could very well be a result of the high usage in Nigeria of sandals with no shoe lining or socks, and thereby bio-available chromium(VI) (38).

In general, the characteristics of chromium-allergic patients appear to have been sparsely investigated outside Europe. In countries without regulation of chromium in cement, the aetiology and epidemiology resemble those in Europe before regulations came into force; that is, chromium allergy is mainly observed in male construction workers (27, 143, 144).

Atopic dermatitis

The relationship between allergic contact allergy and atopic dermatitis is inconclusive, and past findings have been contradictory. Regarding allergic contact dermatitis caused by chromium, published studies have mainly shown positive associations with atopic dermatitis (145–148). Nevertheless, these findings could be attributable to false-positive test reactions that may have occurred as a result of irritating properties of the chromium patch test preparation (145). Other factors, such as characteristics of the chromium-allergic patient, could potentially bias the data, making it difficult to detect an association, for example age, sex, and concurrent sensitizations. As mentioned above, Kubo et al. (94) recently found the SC to be composed of three layers with distinct metal ion barrier properties, by using both regular and flaggrin-knockout mice. The discovery of such a metal ion barrier does make a positive association between atopic dermatitis and allergic chromium dermatitis likely. In another recent study by Malajian and Belsito (149), a strikingly higher prevalence of chromium allergy among atopic dermatitis patients than in a non-atopic dermatitis group was found.

Although atopic dermatitis may, in some cases, lead to false-positive reactions upon patch testing, atopic dermatitis cannot be ignored as a potential risk factor for the development of allergic contact dermatitis caused by chromium or other allergens.

Temporal trends: historical and recent

Most data concerning prevalence rates are obtained from patch test clinics, and may give an inaccurate estimate, owing to selection bias. The causes of chromium-allergic

contact dermatitis are different from one country to another, and are influenced by regulations, fashion trends, technological developments, socio-cultural factors, and different patch test referral patterns. During the 1970s, an increase in the number of patients with occupational chromium dermatitis led to an increasing number of persons with permanent disability in Denmark (150). The legislation regarding compulsory addition of ferrous sulfate in 1983 resulted in a decreasing prevalence of chromium allergy in Denmark (139). The prevalence of chromium then decreased until 1995, and then increased again until 2007, presumably because of increased leather exposure (37). The reported prevalence rates from 1950 to 1996 have been reviewed by Proctor et al. (151). The reported clinical prevalence trends from Europe and North America are shown in Fig. 4. There was a notable rise from the late 1960s to the mid-1970s, and later similar fall in prevalence rates from the late 1980s, peaking in the mid-1990s.

We performed a literature search with the purpose of describing recent temporal trends regarding global chromium allergy prevalence rates (see Materials/Methods for details). The data reported are prevalence rates from 2002 and onwards, in an attempt to compare trends from three continents: Europe, North America, and Asia.

The European Surveillance System on Contact Allergies (ESSCA) started to collect patch test data from different centres in 2001. This European collaboration has so far resulted in four ESSCA analyses, reporting clinical prevalence rates and current temporal trends for the years 2002–2003, 2004, 2005–2006, and 2007–2008 (152–155). The authors observed an overall significant decline in the prevalence of chromium allergy from 5.3% in 2002–2003 to 4.2% in 2007–2009 (linear-by-linear association $p_{\text{trend}} < 0.001$). A similar temporal trend was observed when the weighted average of the individual countries' (134–137, 152, 156–165) prevalence rates across Europe in the period 2002–2012 ($p_{\text{trend}} < 0.001$) were examined. This general decrease in the prevalence of chromium allergy among European countries corresponds well with a possible effect of the European cement regulation.

The only continents outside Europe that have enough reported prevalence rates for estimation of temporal trends are North America and Asia. The data from North America show a significant decrease in prevalence from 2002 to 2010 ($p_{\text{trend}} = 0.003$). Asian clinics generally report much higher prevalence rates of chromium allergy than those in Europe and North America. However, no significant trend was observed from 2002 to 2012 ($p_{\text{trend}} = 0.131$) (Table 5).

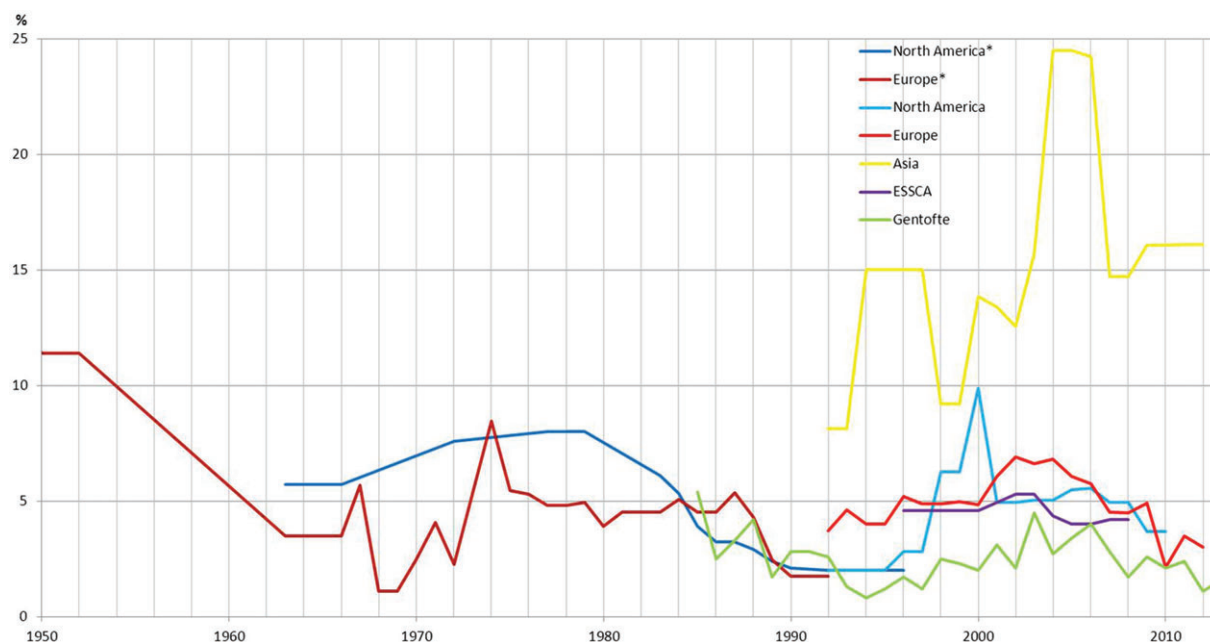


Fig. 4. Prevalence rates of positive patch test reactions to chromium among dermatitis patients: a weighted average from a literature search on general clinical studies from 2003 to 2014 on published prevalence rates (see Table 5). *Prevalence rates from the review by Proctor et al. (151). ESSCA, European Surveillance System on Contact Allergies.

Table 5. The weighted average of prevalence rates of chromium(VI) contact allergy from general clinical studies from 2002 and onwards

Region	Reference	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Temporal trend
Asia	(166–174)	n 1686	1343	967	967	841	615	615	788	–	–	85	→
		% 12.6	15.7	24.5	24.5	24.2	14.7	14.7	15.4	–	–	16.1	
Europe	(134–137, 152, 156–165)	n 1900	2047	1937	2046	1633	14 850	15 907	1867	15 142	14 156	13 048	↘
		% 6.9	6.6	6.8	6.1	5.7	4.5	4.5	4.9	2.1	3.5	3.0	
North America	(175–179)	n 3125	3433	3433	3086	2937	3253	3253	2866	2866	–	–	↘
		% 5.0	5.0	5.0	5.5	5.6	4.9	4.9	3.7	3.7	–	–	
ESSCA	(152, 160)	n 5256	5256	9987	9273	9273	12 911	12 911	–	–	–	–	↘
		% 5.3	5.3	4.4	4.0	4.0	4.2	4.2	–	–	–	–	

n, total number of patients examined in the study; %, percentage of positive patch test reactions to potassium dichromate; ESSCA, European Surveillance System of Contact Allergies.

Temporal trends are defined as χ^2 trend test with <0.05 ; ↘, significant fall; →, no significant change. Notice that the Europe and ESSCA results include some duplicate data.

The decrease in the prevalence rates appears to be a general trend in European and North American clinical populations. The frequency of chromium allergy is dependent on the level of exposure in the population, and the fact that different regulations regarding chromium exposure and an awareness of protective measures in occupational settings have been in focus for many years might explain the observed differences. It is plausible that regulations such as the German regulation and the upcoming European regulation have already had an impact, as a result of the industry's early awareness.

Clinical Aspects

From a clinical point of view, chromium allergy may often manifest as severe, sometimes widespread, very persistent dermatitis, and is considered to have a relatively poor prognosis, as dermatitis is often chronic (180–183). In 1960, Calnan (184) described the disease with prominent features of chronicity, recurrences, and therapeutic recalcitrance. In 1975, Fregert (183) published a study examining 14 chromium-allergic patients over a 10-year period. Only 7% of the patients remained

free of disease during the examination time, 43% had intermittent episodes of dermatitis, and 50% had chronic disease. In 2009, Hald et al. (180) examined the disease severity of 799 consecutive hand dermatitis patients assessed by the dermatologist with the Hand Eczema Severity Index. Their study showed that severe symptoms of hand dermatitis at baseline were associated with a positive patch test reaction to chromium, and evaluation 6 months after initial examination showed that patients with chromium contact allergy had the worst prognosis. A 7-year follow-up study on the same patient cohort was recently published, supporting the perception of hand dermatitis as a chronic disease and poor prognosis being associated with severity of hand dermatitis at baseline (185).

In a recent study characterizing a Danish cohort of chromium patch test-positive patients, we showed that the hands and the feet are most prone to be involved both in the acute phase and in the chronic phase of allergic contact dermatitis caused by chromium (30). Other investigations have supported the idea that these manifestations are the most frequent. Avnstorp (138) described primarily the clinical patterns of chromium allergy caused by cement, and found erythema and hyperkeratosis on the dorsal aspects of the hands and fingers, but also on the wrists, to be the most prevalent findings. Another Danish study (37) showed similar results, with the hands being the most frequent locations of dermatitis, and nearly half of the chromium-positive patients suffering from foot dermatitis.

Chromium allergy has been linked to recurrent, vesicular hand dermatitis (186, 187). In both studies, double-blind, placebo-controlled oral challenge with tablets of 2.5 mg of chromium and placebo were given. Of the 61 patients, 28 experienced flare-up of dermatitis after ingestion of chromium, and 6 experienced flare-up of dermatitis after ingestion of the placebo tablet. In a recent published case, a chromium-allergic patient with treatment-resistant dermatitis had his lesions completely resolved after stopping daily intake of vitamin pills containing 150 µg of chromium chloride (188). After 3 months without dermatitis, he experienced immediate flare-up after one tablet a day for three consecutive days. Sharma et al. recently reviewed the role of a low-chromium diet among chromium-allergic patients (189). They reported that careful selection of food with a relatively low chromium concentration can result in a reduction in the total dietary intake of chromate per day. A diet with a low chromium concentration may improve the outcome of the disease, especially chronic vesicular hand eczema caused by chromium sensitivity.

Patch Testing

Patch testing with potassium dichromate 0.5% pet. was introduced in 1931 (2). Currently, it is present in the European baseline patch test series, and it is used at 0.25% in North America. The European Environmental and Contact Dermatitis Research Group (190, 191) conducted trials comparing 0.5% potassium dichromate with 0.375% and 0.25%. The conclusion was that patch testing with lower concentrations of potassium dichromate results in fewer irritant reactions, but that, at lower concentrations, some allergic reactions may be missed. Potassium dichromate is an allergen that may produce a positive test reaction after the D2 reading. Shehade et al. (192) examined 4721 patch tested patients with D2 and D4 readings. A total of 3.4% had positive reactions to potassium dichromate, but 18.9% of these reactions were negative at the D2 reading. Macfarlane et al. (193) examined patch test reactions at D7 and D9. This study concluded that D9 readings were of limited value, and that paired patch test readings on D4 and D7 were more reliable than those on D2 and D4.

Lymphocyte proliferation testing is an *in vitro* assay that evaluates lymphocyte antigen recall (194). Recent studies have suggested that production of the cytokine IL-13 may be used to diagnose chromium-allergic contact dermatitis, and that interferon- γ , IL-2, IL-5 and IL-12 may serve to further establish an accurate diagnosis (195, 196). It was recently suggested that cellular *in vitro* responses, determined with the lymphocyte transformation test, could discriminate between sensitized individuals with and without clinically manifest allergy (197). These tests could potentially supplement patch testing.

Future Investigations

A reduction in the amount of chromium exposure remains an important health consideration. As previous regulations on chromium in cement have decreased the prevalence of chromium allergy, novel regulations on chromium in leather are expected to have a similar impact on the epidemiological pattern. We recommend epidemiological monitoring of current interventions to measure the magnitude of effect.

According to the European leather regulation, control of compliance regarding chromium(VI) release levels has to be performed according to ISO 17075:2007, and only once. This could be a problem, given that environmental factors such as pH change, temperature and tear from the environment could change the oxidation state of chromium, thus giving different release levels. The standard should be refined.

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