## REFERENCES

Chirch LM, Cataline PR, Dieckhaus KD, Grant-Kels JM. Proactive infectious disease approach to dermatologic patients who are taking tumor necrosis factor-alfa antagonists: Part I. Risks associated with tumor necrosis factor-alfa antagonists. J Am Acad Dermatol 2014;71:1.e1–8.

Dávila-Seijo P, Dauden E, Descalzo MA, Carretero G, Carrascosa JM, Vanaclocha F, et al. Infections in moderate to severe psoriasis patients treated with biological drugs compared to classic systemic drugs: Findings from the BIOBADADERM registry. J Invest Dermatol 2017;137:313–21.

Garcia-Doval I, Carretero G, Vanaclocha F, Ferrandiz C, Dauden E, Sanchez-Carazo JL, et al. Risk of serious adverse events associated with biologic and nonbiologic psoriasis systemic therapy: patients ineligible vs eligible for randomized controlled trials. Arch Dermatol 2012;148:463–70.

Garcia-Doval I, Cohen AD, Cazzaniga S, Feldhamer I, Addis A, Carretero G, et al. Risk of serious infections, cutaneous bacterial infections, and granulomatous infections in patients with psoriasis treated with anti-tumor necrosis factor agents versus classic therapies: prospective meta-analysis of Psonet registries [e-pub ahead of print]. J Am Acad Dermatol 2016; http://dx.doi.org/10.1016/j.jaad.2016.07.039 (accessed 15 November 2016).

Gliklich RE, Dreyer NA, Leavy MB, editors. Registries for evaluating patient outcomes: a user's guide. 3rd ed. AHRQ Publication No 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality; 2012.

Kalb RE, Fiorentino DF, Lebwohl MG, Toole J, Poulin Y, Cohen AD, et al. Risk of serious infection with biologic and systemic treatment of psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). JAMA Dermatol 2015;151:961–9.

Moride Y, Abenhaim L. Evidence of the depletion of susceptibles effect in non-experimental pharmacoepidemiologic research. J Clin Epidemiol 1994;47:731–7.

Nijsten T, Spuls PI, Naldi L, Stern RS. The misperception that clinical trial data reflect long-term drug safety: lessons learned from Efalizumab's withdrawal. Arch Dermatol 2009;145:1037–9.

Pichler WJ. Adverse side-effects to biological agents. Allergy 2006;61:912–20.

Yiu ZZN, Exton LS, Jabbar-Lopez Z, Mustapa FM, Samarasekera EJ, Burden AD, et al. Risk of serious infections in patients with psoriasis on biologic therapies: a systematic review and meta-analysis. J Invest Dermatol 2016;136:1584–91.


*See related article on pg 367*

# Chromium(VI) Contact Dermatitis: Getting Closer to Understanding the Underlying Mechanisms of Toxicity and Sensitization!

Jeroen Buters[1,2] and Tilo Biedermann[3]

**Various haptens trigger innate immune pathways and/or induce cytotoxicity as a part of sensitization. Adam et al. decipher in vitro the mechanisms by which chromium(VI) induces inflammation, the likely prerequisites for toxicity, sensitization, and allergic contact dermatitis against chromium(VI). Importantly, and in line with other observations, chromium(VI), but not chromium(III) (or Ni(II)), induces mitochondrial reactive oxygen species accumulation. Mitochondrial reactive oxygen species in turn activate the NLRP3 inflammasome, allowing increased IL-1β processing and secretion, which likely underlies both chromium(VI)-induced cutaneous toxicity and sensitization. Interrupting this mechanism, perhaps with reducing agents or inhibitors of the NLRP3/IL-1 axis, may be a new option to prevent occupational chromium toxicity and allergy.**

*Journal of Investigative Dermatology* (2017) **137,** 274–277. doi:10.1016/j.jid.2016.11.015

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## Chromium toxicity and contact dermatitis

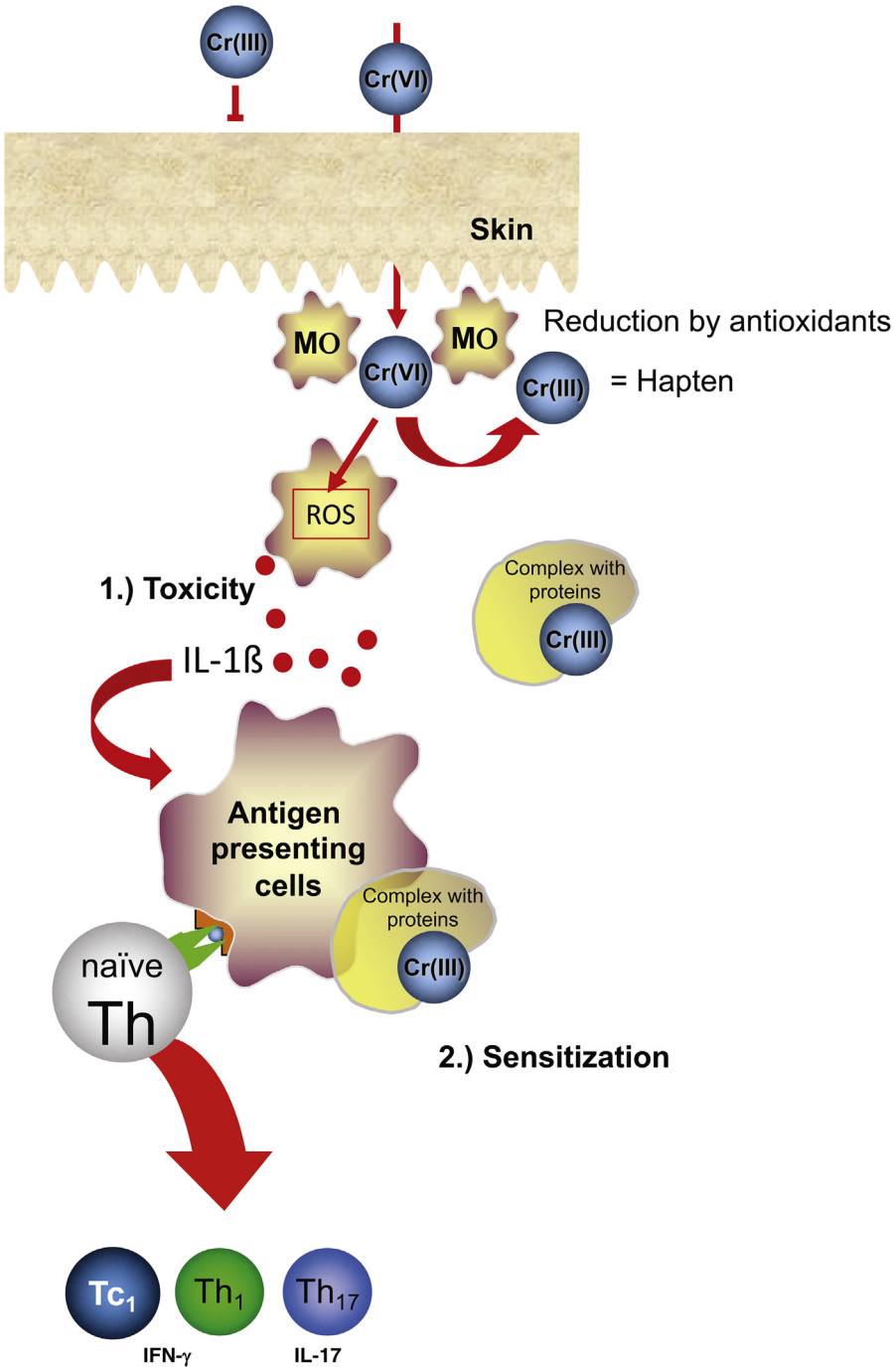
Humans are exposed to chromium from elemental chromium and its many chromium salts. Chromium ions occur in several valences, but two of these, trivalent chromium(III) and hexavalent chromium(VI), are of major health concern (Bregnbak et al., 2015). Chromium as the hexavalent ion (Cr(VI), $Cr^{6+}$, chromates, dichromates) causes the most harm (Bregnbak et al., 2015; Nethercott et al., 1994), as it is a known skin sensitizer and irritant. Repeated exposure to chromium(VI) can even result in chrome ulcers (Bradberry and Vale, 1999; Bregnbak et al., 2015; MAK. Chrom(VI)-Verbindungen, 2012; Nethercott et al., 1994). Chromium(VI) has been classified by legislative organizations as a known human lung carcinogen (IARC, 1990; MAK. Chrom(VI)-Verbindungen, 2012).

Chromium(III) is less toxic and evokes less skin irritation than chromium(VI), and it has been believed that this is due mainly to a lower bioavailability of chromium(III), because chromium(III) does not penetrate cellular walls or skin very well (MAK. Chrom(III), 2012; MAK. Chrom(VI)-Verbindungen, 2012). The basis of chromium(VI) toxicity seems to relate to its strong oxidative capacity, which leads to cell death. The toxicity of chromium(III) and chromium(VI) is well reviewed by governmental committees. In Germany, defining the maximum workplace concentrations has a relatively long history (MAK) (IARC, 1990; MAK. Chrom(III), 2012; MAK. Chrom(VI)-Verbindungen, 2012).

Most human chromium exposure is to chromium(III). Chromium(III) can be oxidized to or is concomitantly present in mixtures that include chromium(VI). In contrast to chromium(III), chromium(VI) penetrates the skin easily. After penetration, chromium(VI) is reduced by proteins or intracellular antioxidants to chromium(III), which then intercalates into DNA or proteins, resulting in its effects (Bregnbak et al., 2015; MAK. Chrom(VI)-Verbindungen, 2012). Although chromium(III) is the mechanistic ingredient for chromium sensitization, chromium(VI) is the biological transportable form and the major practical problem (Figure 1).

## Clinical Implications

- The mechanisms of chromium-induced toxicity, and most likely sensitization, involve activation of the NLRP3 inflammasome, leading to IL-1β release.
- This mechanism is specific for chromium(VI) as chromium(III) and Ni(II) do not activate it.
- Chromium contact dermatitis may perhaps be prevented with antioxidants, because NLPR3 activation relies on chromium(VI)-induced reactive oxygen species accumulation.




**Epidemiology of contact dermatitis**

Approximately 1–3% of the European population is allergic to chromium (Hedberg et al., 2015). Most exposure to chromium occurs in occupational settings especially in industrial processes such as chrome-plating and leather production, but especially in the construction industry, as cement contains chromium salts (Stocks et al., 2012). Occupational skin diseases represent more than 30% of all recorded occupational diseases in Europe (Pesonen et al., 2015) and in much of the rest of the world (Bregnbak et al., 2015). The most common occupational skin diseases are irritant contact dermatitis and allergic contact dermatitis. Chromium causes both. Of all type IV sensitizations, nickel(II) is the most frequent (23%) followed by cobalt(II) (9.3%) and chromium(VI) (5.6%) as diagnosed by patch testing. Obviously, professions that include more frequent exposure to chromium show an even higher prevalences. Approximately one-third of bricklayers and stonemasons who are in frequent contact with cement and 1 in 10 metal operators who have an occupational disorder received a diagnosis of chromium(VI) skin disease (Bregnbak et al., 2015; Bruynzeel et al., 2005; Pesonen et al., 2015).

Because the new EU cement regulations on limiting the amount of chromium(VI) in cement became effective, the next major exposure source causing sensitizations to chromium(VI) comes from contact with leather. Also because chromium contact dermatitis is more severe and more chronic than other contact allergies (Bregnbak et al., 2014), chromium sensitization is a substantial

**Figure 1. Schematic representation of the mode of action of chromium allergic sensitivity.** Chromium(VI) penetrates the skin, and chromium(III) penetrates much less. In the skin, chromium(VI) is reduced by antioxidants such as glutathione to chromium(III). Chromium(III) is the hapten that intercallates with proteins to form complete allergen(s). At the same time, chromium(VI) leads to accumulation of reactive oxygen species (ROS) as shown for monocytes. ROS, via K+ efflux, activate the NRLP3 inflammasome, resulting in IL-1β processing and release, potentially activating antigen presenting cells that process the allergen, which activate chromium-specific T cells, all resulting in the chromium hypersensitivity.

medical and economic problem that will not go away any time soon.

### Prevention of chromium contact dermatitis

To curb allergic skin sensitization to chromium the EU has focused its attention on reducing the amount of chromium(VI) in cement to 0.0002% (2 ppm chromium(VI)) and, if necessary by adding a reducing agent such as (nontoxic) 0.35% ferrous ($Fe^{2+}$) sulfate (European Commission, 2003; Scientific Committee on Toxicity, Ecotoxicity and the Environment, 2002). Reducing agents convert Cr(VI) to Cr(III), which does not penetrate the skin well and is thus less toxic. The threshold for chromium(VI) sensitization is approximately 10 ppm, and the concentration used in skin patch test preparations in Europe is approximately 0.5%, which is obviously much higher than this threshold (Bruynzeel et al., 2005). In wet, alkaline cement, the reduction of chromium(VI) to chromium(III) leads to its precipitation of insoluble and inactive chromium hydroxide (Scientific Committee on Toxicity, Ecotoxicity and the Environment, 2002).

Clearly, cement is a main sensitizing source. However, chromium(III) is also used extensively in leather tanning to improve the durability of leather through cross-linking of collagen (European Commission, 2014). However, as noted previously, chromium(III) can be oxidized to chromium(VI). After the reduction in allowable concentrations in cement, new EU regulations were also implemented to reduce the amount of chromium(VI) release from leather products (European Commission, 2014). Taken together, better understanding of how chromium elicits toxicity and sensitization is an important task with important implications for occupational disease prevention.

### Mechanism of chromium(VI) contact dermatitis

Previously the authors reported that Ni(II) contact dermatitis was mediated by toll-like receptor 4 (Schmidt et al., 2010). The article by Adam et al. (2017) has now addressed the mechanism of chromium contact dermatitis, toxic as well as allergic. The general hypothesis for chromium allergy is that chromium(VI), which penetrates the skin, is reduced to chromium(III), which, being a hapten, reacts with proteins (MAK. Chrom(VI)-Verbindungen, 2012), to which chromium-specific T cells react after antigen presenting cells present the complex (Figure 1). Together with its toxicity, chromium activates these specific T cells causing inflammation and, ultimately, symptoms (Bregnbak et al., 2015).

The authors show in vitro that chromium(VI) leads to reactive oxygen species (ROS) accumulation, which results in $K^+$ efflux, thereby activating the inflammasome, in this case the NLRP3 inflammasome. Inhibiting $K^+$ efflux by increasing extracellular $K^+$ eliminated the effects of chromium(VI) on IL-1β release, showing that the processes are sequential: first ROS generation, then $K^+$ efflux, followed by NLRP3 activation and IL-1β release. Importantly, this is effective only after appropriate priming of the NLRP3 inflammasome, which is known to react to several stimuli such as pathogen-associated molecular patterns or danger-associated molecular patterns (Gross et al., 2011). Thus, in their setting, increased IL-1β release by chromium(VI)-induced ROS generation requires concomitant innate stimulation by lipopolysaccharide or the phorbol ester 12-*O*-tetradecanoylphorbol-13-acetate.

There is a small caveat: chromium(VI) is reduced in vivo to chromium(III), probably by sulfur-containing amino acids such as methionine, cysteine, or glutathione (MAK. Chrom(VI)-Verbindungen, 2012). Chromium(III) inside of the cells is then thought to be the active intercalating component. N-acetylcysteine used in the experiments of the authors is a compound that reacts directly with chromium(VI), forming stable complexes (Brauer et al., 1996). The finding that N-acetylcysteine, a well-known ROS scavenger, eliminates the ROS generated by chromium(VI) stimulation of mitochondria could also be due to direct complexation of N-acetylcysteine with chromium(VI), perhaps even direct reduction of chromium(VI) to chromium (III) by N-acetylcysteine. This could also circumvent the ROS-generating potential of chromium(VI), not by scavenging the generated ROS (Brauer et al., 1996).

However, the authors show clearly that the inflammasome is involved in translating exposure to chromium(VI) into inflammation. They provide evidence that ROS from mitochondria are involved, leading to $K^+$ efflux that is capable of activating the inflammasome, given appropriate priming. The next steps would be to identify the relevant stimulus of the priming for chromium inflammasome activation and to show the clinical relevance of their findings. This would create new avenues for the prevention of chromium(VI) contact dermatitis.


### CONFLICT OF INTEREST

JB and TB are governmental employees of the Technical University Munich. JB is supported by grants from the Bavarian Government, Helmholtz, and the Christine Kühne Stiftung. TB is supported by grants from Deutsche Forschungsgemeinschaft (BI696/10-1, B1696/5-1, BI696/5-2, SFB 685, SFB 824), Helmholtz, Novartis, and Phadia; has received payment for the development of educational presentations from Phadia; and has consultant arrangements with or received honorarium from Alk-Abello, Astellas, Bencard, Biogen, Janssen, Leo, Meda, MSD, Novartis, and Phadia-Thermo Fisher.


### REFERENCES


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

Bradberry SM, Vale JA. Therapeutic review: is ascorbic acid of value in chromium poisoning and chromium dermatitis? J Toxicol Clin Toxicol 1999;37:195–200.

Brauer SL, Hneihen AS, McBride JS, Wetterhahn KE. Chromium(VI) forms thiolate complexes with gamma-glutamylcysteine, N-acetylcysteine, cysteine, and the methyl ester of N-acetylcysteine. Inorg Chem 1996;35:373–81.

Bregnbak D, Johansen JD, Jellesen MS, Zachariae C, Menne T, Thyssen JP. Chromium allergy and dermatitis: prevalence and main findings. Contact Dermatitis 2015;73:261–80.

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

Bruynzeel DP, Diepgen TL, Andersen KE, Brandao FM, Bruze M, Frosch PJ, et al. Monitoring the European standard series in 10 centres 1996-2000. Contact Dermatitis 2005;53:146–9.

European Commission. Commission Regulation (EU) No 301/2014. OJEU L90/1–3; 2014.

European Commission. Directive 2003/53/EC of the European Parliament and of the Council. OJEU L178/24; 2003.

Gross O, Thomas CJ, Guarda G, Tschopp J. The inflammasome: an integrated view. Immunol Rev 2011;243:136–51.

Hedberg YS, Liden C, Odnevall Wallinder I. Chromium released from leather—I: exposure conditions that govern the release of chromium(III) and chromium(VI). Contact Dermatitis 2015;72:206–15.

IARC (International Agency for Research on Cancer). Chromium (VI) compounds. Monograph 100C. WHO; 1990.

MAK. Chrom(III) und seine anorganischen Verbindungen [MAK Value Documentation in German language, 2009]. The MAK-Collection for Occupational Health and Safety: Wiley-VCH; 2012.

MAK. Chrom(VI)-Verbindungen [MAK Value Documentation in German language, 2010]. The MAK-Collection for Occupational Health and Safety: Wiley-VCH; 2012.

Nethercott J, Paustenbach D, Adams R, Fowler J, Marks J, Morton C, et al. A study of chromium induced allergic contact dermatitis with 54 volunteers: implications for environmental risk assessment. Occup Environ Med 1994;51:371–80.

Pesonen M, Jolanki R, Larese Filon F, Wilkinson M, Krecisz B, Kiec-Swierczynska M, et al. Patch test results of the European baseline series among patients with occupational contact dermatitis across Europe—analyses of the European Surveillance System on Contact Allergy network, 2002-2010. Contact Dermatitis 2015;72:154–63.

Schmidt M, Raghavan B, Muller V, Vogl T, Fejer G, Tchaptchet S, et al. Crucial role for human Toll-like receptor 4 in the development of contact allergy to nickel. Nat Immunol 2010;11:814–9.

Scientific Committee on Toxicity, Ecotoxicity and the Environment. Risks to health from chromium(VI) in cement. European Commission Directorate-General Health and Consumer Protection. Chromium VI 270622002. Brussels; 2002.

Stocks S, McNamee R, Turner S, Carder M, Agius R. Has European Union legislation to reduce exposure to chromate in cement been effective in reducing the incidence of allergic contact dermatitis attributed to chromate in the UK? Occup Environ Med 2012;69:150–2.

*See related article on pg 484*

# Imatinib in Dermatofibrosarcoma: Targeted Therapy or Immunotherapy?

Selma Ugurel[1] and Jürgen C. Becker[1,2]

**There is increasing evidence that certain kinase inhibitors are able to foster two strategies, i.e. inhibition of oncogenic activated molecular pathways and modulation of immunological processes. In this respect, the study of Tazzari et al. is of great interest because it shows both effects for the kinase inhibitor imatinib in dermatofibrosarcoma protuberans.**

*Journal of Investigative Dermatology* (2017) **137,** 277–279. doi:10.1016/j.jid.2016.10.027

Current advances in anticancer therapy rely mainly on two independent strategies: (i) targeted therapy with small molecule inhibitors modulating signaling pathways constitutively activated because of cancer-specific driver mutations and (ii) immune-modulating therapy aiming at efficient T-cell–mediated tumor cell eradication. The cancer entity in which both strategies were pioneered is melanoma, with BRAF and mitogen-activated protein kinase/extracellular signal-regulated kinase inhibitors targeting the mitogen-activated kinase (MAPK) pathway in BRAF V600-mutated tumors and anti-CTLA-4 and anti-PD1 checkpoint blocking antibodies activating and/or boosting melanoma-specific T-cell–mediated immune responses (Ugurel et al., 2016). Recent observations suggest that these two strategies have more in common than initially anticipated.

Indeed, there is increasing evidence that certain kinase inhibitors are able to foster both strategies, that is, inhibition of oncogenic activated molecular pathways and modulation of immunological processes. In this respect, the study of Tazzari et al. (2017) is of great interest because it shows both effects for the kinase inhibitor imatinib in dermatofibrosarcoma protuberans (DFSP) (Tazzari et al., 2017) (Figure 1).

> There is increasing evidence that certain kinase inhibitors are able to foster two unique strategies, inhibition of oncogenic activated molecular pathways and modulation of immunological processes.

The authors collected and analyzed a panel of tissue samples of DFSP with sarcomatous transformation (FS-DFSP) obtained before and/or after treatment with imatinib. FS-DFSP is a rare subgroup of DFSP, and it is known for its more aggressive growth pattern and higher potential for metastasis when compared with regular nontransformed DFSP (Hoesly et al., 2015; Liang et al., 2014). Imatinib is a multikinase inhibitor targeting, among others, the platelet-derived growth factor receptor (PDGFR) pathway. The PDGFR pathway is pathophysiologically relevant in DFSP, because it is activated constitutively because of a translocation and fusion of the genes encoding PDGFB and COL1A1 (Simon et al., 1997). On the basis of this molecular aberration, imatinib was tested successfully and was subsequently approved for the systemic treatment of locally advanced or metastatic DFSP, showing objective response rates of

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