

Can reducing cosmetic substances help prevent chromate contact allergy?

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Abstract

Background: Allergic contact dermatitis caused by Cr(VI) is often severe and difficult to treat. Therefore, primary prevention is a main goal, but secondary prevention can be valuable to ease the symptoms or prevent relapse of Cr(VI) dermatitis when sensitization has occurred. Barrier creams have been tried for many chemical substances, but until now there is no successful barrier cream against Cr(VI).

Objectives: To investigate the ability of reducing agents to transform Cr(VI) into Cr(III) in an experimental situation, in order to find suitable chemicals to investigate for possible use in a barrier cream.

Methods: The capacity to reduce the amount of Cr(VI) was analyzed in water solutions of acetylcysteine, cysteine, dihydroxyacetone, glutathione, and iron sulfate heptahydrate. Thereafter the reducing capacity of acetylcysteine, dihydroxyacetone, glutathione, and iron sulfate on the amount of Cr(VI) in cement extracts was investigated. The content of Cr(VI) in the test solutions and in the cement extracts was estimated by the diphenyl carbazide spot test.

Results: All of the chosen chemicals reduced the amount of Cr(VI) in the test solutions and in the cement extracts to some extent. The reducing capacity was most prominent for iron sulfate.

Conclusion: A reducing capacity was found for all chosen chemicals.

KEYWORDS

allergic contact dermatitis, barrier cream, chromate, Cr(VI), hexavalent chromium, reducing chemicals

1 | INTRODUCTION

Metallic chrome (Cr) is not considered a contact allergen but several chromium compounds are well-known contact allergens. This is especially true for Cr(VI) compounds. Common Cr(VI) compounds are dichromates ($\text{Cr}_2\text{O}_7^{2-}$) and chromates (CrO_4^{2-}). When using the word “chromate” in this study, we consistently refer to “monochromate.” Contact allergy to chromium compounds is generally detected by

patch testing with potassium dichromate ($\text{K}_2\text{Cr}_2\text{O}_7$) in petrolatum. The contact allergy is considered to be caused by the Cr(VI) atom in chromates as well as in dichromates and other Cr(VI) compounds. Contact allergy to Cr(VI) compounds can, owing to this, have a number of names: chromate allergy, dichromate allergy, chromium(VI) allergy, Cr(VI) allergy, and not rarely the somewhat improper name chromium allergy. However, chromium allergy has the advantage of not excluding the chromium(III) (Cr(III)) compounds, which probably

cause the same contact allergy as Cr(VI) compounds do. In fact it is likely that the Cr(III) ion is the most important allergen but that it does not penetrate the skin easily and therefore is not considered a strong allergen. The Cr(VI) ions penetrate the skin easier, oxidize skin components, and are converted into Cr(III) ions, which act as the contact allergen. As long as it is noted that metallic chromium, chromium-plated objects, and chrome in stainless steel practically can be considered nonallergenic it can be useful to use the expression chromium allergy.^{1,2}

The primary exposure causing sensitization to chromate used to be cement with a high content of Cr(VI).^{3,4} Historically, allergic contact dermatitis (ACD) from Cr(VI) in cement affecting construction workers was the most common cause of invalidity due to skin disease in Sweden. The epidemiology has changed, and nowadays we rarely see ACD caused by cement in Sweden. This is due to intense work in the 1970s by Sigfrid Fregert and Birgitta Gruvberger at the Department of Occupational Dermatology in Lund, Sweden, which resulted in a method in which Cr(VI) could be reduced to a less allergenic form, that is Cr(III), by addition of iron sulfate to cement.⁵ In Sweden iron sulfate has been added to cement since 1983 and in 1989 legislation was implemented stating that the maximum concentration of Cr(VI) in

cement should not exceed 2 ppm. Since January 2005, the same rule applies in the EU.⁶

Today ACD due to exposure to cement in construction workers is rarely found where the legislative measures are followed. However, the frequency of contact allergy to Cr(VI) is still relatively high, about 3% in consecutively tested patients with dermatitis in southern Sweden and in the patch test cohort of hospitals associated with the German Contact Dermatitis Research Group and the Information Network of Departments of Dermatology consortium.^{7,8} The exposure to Cr(VI) nowadays has been attributed to leather goods, such as shoes and gloves. The epidemiology may change again, at least in Europe, since there is now legislation regulating the release of Cr(VI) also from leather, enforced in the EU since May 2015.⁹

There is still a problem with Cr(VI) dermatitis in those countries without legislation concerning Cr(VI) content in cement, and even in countries with the legislation a few individuals may get allergic to Cr(VI) from iron sulfate-treated cement.^{10,11} The aim of this study was to investigate the capacity of selected chemicals to reduce Cr(VI) in order to find suitable chemicals to investigate further in a barrier cream, mainly to protect construction workers.

TABLE 1 Names and chemical structures of the reducing cosmetic substances investigated

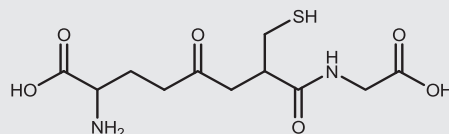
Glutathione (GSH)

CAS no.: 70-18-8

MW: 307

log $P_{o/w}$: -2.03

Conc*: 1.6 mmol/5 mL = 0.32 M



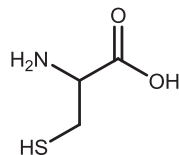
Cysteine

CAS no.: 52-90-4

MW: 121

log $P_{o/w}$: -0.92

Conc: 4.1 mmol/5 mL = 0.82 M



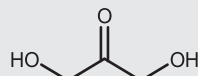
Dihydroxyacetone (DHA)

CAS no.: 96-26-4

MW: 90

log $P_{o/w}$: -1.86

Conc: 5.6 mmol/5 mL = 1.1 M



Iron(II) sulfate heptahydrate (FeSO₄)

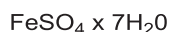
CAS no.: 7782-63-0

MW: 278

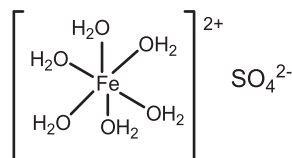
Water solubility: 29.5 g/100 mL (25°C)

Conc: 1.8 mmol/5 mL = 0.36 M

Formula:



In solution:



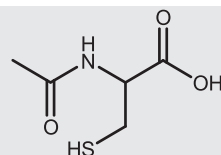
Acetylcysteine

CAS no.: 616-91-1

MW: 163

log $P_{o/w}$: -0.99

Conc: 3.1 mmol/5 mL = 0.62 M



Abbreviations: CAS no., Chemical Abstracts numbers; MW, molecular weight; log $P_{o/w}$ = logarithm of the partition constant of the substance between octanol and water; * = Concentration at start in the 10% w/v test and the cement samples. (Added Cr(IV) = 0.0009 mmol/5 mL = 0.00018 M.).

2 | MATERIALS AND METHODS

2.1 | Reducing substances

The CosIng database¹² was used to select substances functioning as reducing agents in cosmetic products. The following cosmetically approved reducing substances were found: glutathione, dihydroxyacetone, iron(II) sulfate heptahydrate, cysteine, and acetylcysteine. The chemical structures of these substances are shown in Table 1.

2.2 | Preparation of test solutions

A 10.0% w/v stock solution of each reducing chemical: glutathione (GSH; ICN Biomedicals, Aurora, Ohio) pH 3; dihydroxyacetone (DHA; Merck, Darmstadt, Germany) pH 5.5; iron(II) sulfate heptahydrate (FeSO_4 ; Sigma-Aldrich Chemie, Steinheim, Germany) pH 6.5; and cysteine (ICN Biomedicals) pH 5, was prepared in water (MilliQ water, Millipore, Molsheim, France). From the 10.0% stock solutions a dilution series of each chemical with the concentrations of 5.0%, 1.0%, 0.010%, and 0.0010% was prepared. The solution with the highest concentration of acetylcysteine (Sigma-Aldrich, St Louis, Missouri) pH 2 that could be achieved was 5.0%, and the dilution series was prepared from it. The acetylcysteine solutions were used only for analysis on Day (D) 0.

Three sets of each test solution with 5.0 mL in each test tube were prepared. To each test solution, 100 μL of 1000 ppm CrO_4^{2-} (corresponding to 448 ppm Cr(VI)) stock solution of Cr(VI) (K_2CrO_4 , Merck), was added on D0. One set was used for spot test immediately on D0, the second set on D2, and the third set on D7, in order to investigate the Cr(VI) content after storing. The resulting test solutions and concentrations are provided in Table 2. There might be an adsorption of Cr(VI) on the walls of glass vessels. After comparing the results in solutions prepared in glass vessels and plastic vessels (by measuring the content of Cr(VI) with the spot test as described below) without any difference, we went on using glass vessels for all solutions.

2.3 | Spot test procedure

The diphenyl carbazide spot test¹³ was used to assess the concentrations of Cr(VI) in the tested samples. The following reagents were used: (i) sym-diphenylcarbazine (Acros Organics, Geel, Belgium) 1.0% (w/v) in 99.5% ethanol (Kemetyl, Haninge, Sweden) (a fresh solution was prepared each new day of analyses); and (ii) sulfuric acid 18 M (Merck, Darmstadt, Germany) diluted with water to 1.0 M.

To perform the spot test, reference solutions with known Cr(VI) content (expressed as CrO_4^{2-}) need to be prepared. The reference solutions of Cr(VI) were prepared as follows: first a 100 ppm CrO_4^{2-} solution was prepared from a 1000 ppm stock solution. The 100 ppm CrO_4^{2-} solution was further diluted in water to 5 ppm (5 $\mu\text{g}/\text{mL}$), 2, 1, and 0.5 ppm. The study was designed to choose the most effective reducing chemicals; therefore we did not calibrate

higher than to 5 ppm. To these solutions three drops (around 60 μL) of 1.0 M H_2SO_4 and three drops (around 30 μL) of 1.0% diphenyl carbazide were added. A fresh set of Cr(VI) reference solutions was prepared for each new analysis, that is, also on D2 and D7. A set of reference solutions is shown in Figure 1.

2.4 | Spot tests of test solutions

On D0, three drops of 1.0 M H_2SO_4 and three drops of 1.0% diphenyl carbazide were added to the first of the three sets of test tubes, that

TABLE 2 Spot test results of test solutions

Test solutions with 20 ppm Cr(VI) (as CrO_4^{2-})	Cr(VI) content, as CrO_4^{2-} (ppm) D0	Cr(VI) content, as CrO_4^{2-} (ppm) D2	Cr(VI) content, as CrO_4^{2-} (ppm) D7
GSH 10.0% pH 3	-	-	-
GSH 5.0%	-	-	-
GSH 1.0%	-	-	-
GSH 0.10%	2-5	-	-
GSH 0.010%	>5	>5	>5
GSH 0.0010%	>5	>5	>5
Cysteine 10.0% pH 5	-	-	-
Cysteine 5.0%	-	-	-
Cysteine 1.0%	-	<0.5	<0.5
Cysteine 0.10%	-	<0.5	<0.5
Cysteine 0.010%	>5	>5	>5
Cysteine 0.0010%	>5	>5	>5
DHA 10.0% pH 5.5	>5	-	-
DHA 5.0%	>5	-	-
DHA 1.0%	>5	-	-
DHA 0.10%	>5	>5	>5
DHA 0.010%	>5	>5	>5
DHA 0.0010%	>5	>5	>5
FeSO_4 10.0% pH 6.5	-	-	-
FeSO_4 5.0%	-	-	-
FeSO_4 1.0%	-	-	-
FeSO_4 0.10%	-	-	-
FeSO_4 0.010%	5	>5	>5
FeSO_4 0.0010%	>5	>5	>5
Acetylcysteine 5.0% pH 2	-	NT	NT
Acetylcysteine 1.0%	-	NT	NT
Acetylcysteine 0.10%	>5	NT	NT
Acetylcysteine 0.010%	>5	NT	NT
Acetylcysteine 0.0010%	>5	NT	NT

Abbreviations: DHA, dihydroxyacetone; FeSO_4 , iron(II) sulfate heptahydrate; GSH, glutathione; NT, not tested; -, no change of color observed, i.e., less than 0.5 ppm Cr(VI) (expressed as CrO_4^{2-}).

is, the spot test was performed. The color that developed in the test solution was compared to the colors of the set of reference solutions for assessment of the approximate concentration of Cr(VI) (expressed as CrO_4^{2-}).

The test solution analyses were repeated three times with solutions prepared on day D0. On both D2 and D7, fresh 1.0% diphenyl carbazide reagent and Cr(VI) reference solutions were prepared. Thereafter the procedure as on D0 was repeated with the second and third of the three sets of test tubes. The maximum time for storage of the solutions is 7 days. The solutions were kept sealed at room temperature and they were not exposed to direct sun light.

2.5 | Preparation and spot tests of the cement extract

The cement used in the preparation of cement extract was taken from a cement sample stored in our laboratory. The cement is originating from Sweden and it has a determined low content of Cr(VI). These extracts represent the typical cement milieu; the pH is around 11. Amounts of 10 g of this cement were placed in 23 separate beakers. To each beaker 200 μL of 1000 ppm CrO_4^{2-} was added to give the samples a Cr(VI) concentration corresponding to 20 ppm or 20 $\mu\text{g/g}$ cement (expressed as CrO_4^{2-}). Immediately thereafter, 10 mL of each solution of reducing chemicals described above were added to each beaker for a total of 23 solutions. The resulting mixtures were placed

in an ultrasonic bath for 5 minutes. Thereafter the samples were filtered in Munktell paper filters and transferred into test tubes.

The diphenyl carbazide spot test was performed, and any change of color noted. The resulting cement extracts and concentrations are given in Table 3. All analyses were performed once, immediately at D0.

3 | RESULTS

The spot test results of the test solutions are presented in Table 2 and the spot test results of cement extracts are presented in Table 3. In summary, all chosen chemicals showed a Cr(VI) reducing capacity. FeSO_4 showed the strongest reducing capacity in both test solutions and in cement extracts, and also the most longstanding capacity over time. Some of the reducing chemicals were difficult to dissolve. Cysteine was excluded from analyses in cement extract due to dissolving difficulties experienced when investigating the water solutions. Ten per cent acetylcysteine could not be used in the analysis due to dissolving problems.

TABLE 3 Spot test results of cement extracts

Cement extracts with 20 ppm Cr (VI) content (expressed as CrO_4^{2-}) + reducing chemical (% w/v)	Cr (VI) content as CrO_4^{2-} (ppm) D0
Cement+ GSH 10.0%	-
Cement+ GSH 5.0%	-
Cement+ GSH 1.0%	< 0.5
Cement+ GSH 0.10%	>5
Cement+ GSH 0.010%	>5
Cement+ GSH 0.0010%	>5
Cement+ DHA 10.0%	-
Cement+ DHA 5.0%	-
Cement+ DHA 1.0%	-
Cement+ DHA 0.10%	1
Cement+ DHA 0.010%	>5
Cement+ DHA 0.0010%	>5
Cement+ FeSO_4 10.0%	-
Cement+ FeSO_4 5.0%	-
Cement+ FeSO_4 1.0%	-
Cement+ FeSO_4 0.10%	-
Cement+ FeSO_4 0.010%	>5
Cement+ FeSO_4 0.0010%	>5
Cement+ acetylcysteine 5.0%	<1
Cement+ acetylcysteine 1.0%	1
Cement+ acetylcysteine 0.10%	>5
Cement+ acetylcysteine 0.010%	>5
Cement+ acetylcysteine 0.0010%	>5

Abbreviations: DHA = dihydroxyacetone; FeSO_4 = iron(II) sulfate heptahydrate; GSH, glutathione; – = no change of color observed, i.e. less than 0.5 ppm Cr (VI) (as CrO_4^{2-}).

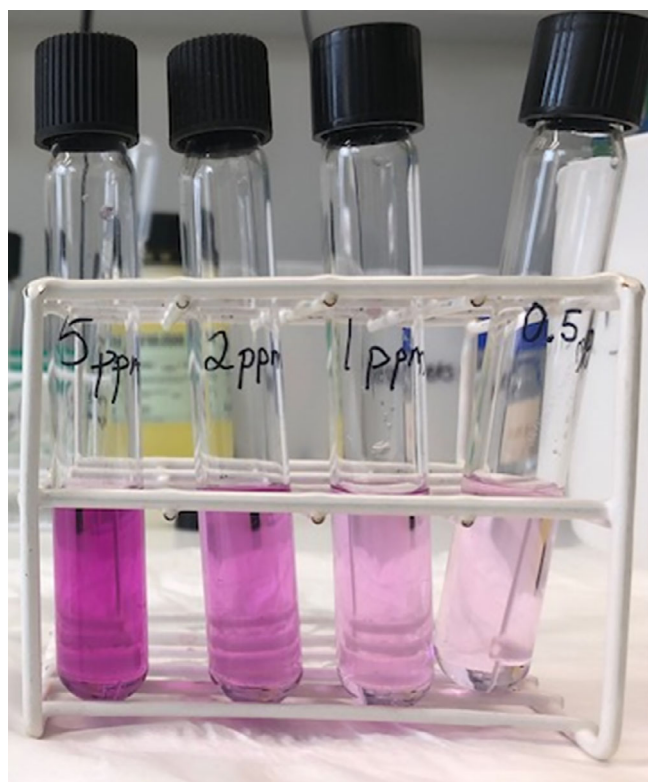


FIGURE 1 Reference solutions with known Cr(VI) content (expressed as CrO_4^{2-}) for estimation of the Cr(VI) content (expressed as CrO_4^{2-}) in the test tubes

4 | DISCUSSION

The objective of the present study was to find chemicals capable of reducing Cr(VI) and at the same time being appropriate to be applied and left on the skin without any adverse effects, in order to find chemicals to investigate further for use in a barrier cream. To be suitable for everyday use, any hand cream should have certain qualities such as good absorption and a tolerable odor. Even more it should not cause discomfort. It is known that a bad odor might develop from formulas containing GSH and attempts to solve this problem have been described.¹⁴ In addition, GSH is assumed to have a bleaching action on the skin.¹⁵ Furthermore, DHA has a characteristic odor. Moreover DHA tans the skin and is widely used for this purpose.¹⁶ In any cream, bad odor must be considered as an undesirable side effect, and in a barrier cream the property of tanning as well as bleaching of the skin must be as well. Despite this, those chemicals were included in this study because of other described properties, such as a reducing capacity and being innocuous to the skin.

For most of the reducing agents, the Cr(VI) content was the same when analyzed on D0, D2, and D7. For DHA, however, there was a marked change of color, that is, a poor reducing effect, in the immediate analyses on D0 but on D2 and D7 the Cr(VI) content in the 10.0%, 5.0%, and 1.0% test tubes was less than 0.5 ppm, indicating a successively developing reducing capacity over time.

In addition to FeSO₄, the results of analyses in this study indicated that GSH might be an alternative for further investigations as an ingredient in a barrier cream despite a bad odor. Compared to DHA, which in addition to tanning of the skin also has a characteristic odor as mentioned,¹⁶ the bad odor of GSH may be avoided if the cream is kept and stored in an airtight jar.

Cement extracts were analyzed to investigate if the chemical properties of cement might interfere with the reduction of Cr(VI). The reducing capacity of the chemicals was proven also in the cement extracts and most prominent for FeSO₄ and GSH. This is a valuable observation because the barrier cream in which these chemicals were chosen for further investigations is intended to be used for the protection of construction workers who are handling cement.

The function of barrier creams on the level of skin penetration has been evaluated earlier.¹⁷ In addition, barrier creams working directly against certain allergens have been described^{18,19} and in some cases also with successful results.^{20,21} There is a commercially available barrier cream promoted as to offer protection against chromium.²² However, to our knowledge there is still no barrier cream proven to be effective in protection against chromium in Cr(VI)-allergic individuals.

In conclusion, FeSO₄ showed the most promising Cr(VI) reducing capacity in these laboratory investigations. However, we also noted an acceptable reducing capacity of the other chemicals investigated. Because the main aim of this study was to find candidate chemicals for further investigations concerning barrier creams, we also considered other aspects such as solubility, tanning of the skin, and bad odor. FeSO₄ was chosen to be investigated further in a barrier cream study. In addition GSH was chosen, despite the risk of a bad odor,

since this problem may be avoided if the cream is kept in an airtight jar.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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