

Skin application of glutathione and iron sulfate can inhibit elicitation of allergic contact dermatitis from hexavalent chromium

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Abstract

Background: Allergic contact dermatitis (ACD) caused by hexavalent chromium, Cr(VI), is often severe and difficult to treat. The most common source of exposure to Cr(VI) in Sweden used to be cement, and more recently leather. The contact allergy can be diminished or inhibited if the exposure is decreased or ceases. Barrier creams against different kinds of allergens have been investigated for their protective properties which may offer protection against Cr(VI) exposure.

Objectives: To investigate the capacity of formulas containing glutathione (GSH) and iron sulfate to inhibit elicitation of ACD in Cr(VI)-allergic individuals when exposed to Cr(VI).

Methods: In 18 Cr(VI)-allergic volunteers the back was divided into eight patch test areas which were treated with preparations of possible barrier creams, prior to patch testing with a dilution series of potassium dichromate and a buffered extract of cement.

Results: A significant reduction in reactivity to Cr(VI) and cement extract on skin treated with formulas containing GSH or iron sulfate was noticed, compared with untreated skin.

Conclusion: Formulas containing GSH or iron sulfate in barrier creams inhibit ACD in individuals allergic to Cr(VI) when applied before exposure to Cr(VI) and cement extract.

KEYWORDS

allergic contact dermatitis, barrier cream, chromate, contact allergy, Cr(III), Cr(VI), delayed hypersensitivity, hexavalent chromium, patch testing, prevention, trivalent chromium

1 | INTRODUCTION

The primary cause of contact allergy toward chromium in Sweden used to be occupational exposure to cement containing Cr(VI).^{1,2} However, the epidemiology has changed and nowadays we rarely see allergic contact dermatitis (ACD) caused by cement in Sweden. This is due to the intense primary preventive work in the 1970s, performed

by Fregert and Gruvberger at the Department of Occupational Dermatology in Lund, Sweden, which resulted in a method in which Cr(VI) can be reduced to a less allergenic form, namely, Cr(III), by addition of iron sulfate to cement. In the practical use of concrete in construction, there is no negative influence of the stability when iron sulfate is added to concrete in a certain calculated amount.³ In Sweden, iron sulfate has been added to cement since 1983 and in 1989 a

legislation stating that the maximum concentration of Cr(VI) in cement should not exceed 2 ppm was implemented. In 2005 the same directive concerning cement was applied in the European Union.⁴ However, ACD due to cement is still sometimes found in construction workers in northern Europe and the frequency of contact allergy to Cr(VI) remains relatively high (about 3%).^{5,6} Despite the regulation, some individuals become allergic to Cr(VI).^{7,8}

A barrier cream limiting the amount of Cr(VI) penetrating the skin causing sensitization, or elicitation of ACD in those already allergic, might be effective in primary or secondary prevention. For ethical reasons and because the dose for elicitation is usually lower than that of sensitization, we intended to investigate the possible change in elicitation threshold that may be an effect of a barrier cream.

The aim of this study was to investigate the ability of glutathione (GSH) and iron sulfate in barrier cream formulas to decrease reactivity or inhibit elicitation in Cr(VI)-allergic volunteers when exposed to Cr(VI) and cement extract at patch testing. We chose these reducing chemicals based on observations in a study previously performed at our laboratory.⁹ Barrier creams may act as both physical and chemical shield. Our intention was to find a formula working in both ways.

2 | MATERIALS AND METHODS

The study was performed as a standard patch test using a dilution series. Prior to patch testing the skin was treated with formulas with and without GSH or iron sulfate dispersed in two different vehicles, that is, petrolatum (pet.) and Essex cream. This was done before application of the test chambers loaded with the respective test solution. On day 2, after removing the test chambers, the skin was treated with the same formulas again. We also patch tested the volunteers with Cr(III) on an untreated area. This was done because the reactivity to Cr(III) may be important as Cr(VI) is reduced to Cr(III) by GSH and iron sulfate (the reducing additives) in the formulas. We wanted to know whether there were differences in protective properties to Cr(VI) of the formulas if the volunteers reacted to Cr(III) or not.

The study sample consisted of 18 dermatitis patients (10 women and eight men, age range 31–81 years, mean age 57 years), previously tested at our department with the baseline series, showing strong or extreme allergic reactions (++, +++) to potassium dichromate (Cr₂K₂O₇) 0.5% pet. (Chemotechnique Diagnostics, Vellinge, Sweden). The study was approved by the Regional Ethical Review Board, Lund, Sweden (Dnr 2016/814, 161 108). Volunteers signed a paper of informed consent before the testing took place.

2.1 | Formulation of the barrier creams

Pet. (Vaselin; vitt APL, Stockholm, Sweden) and Essex cream (Schering-Plough, Heist-op-den-Berg, Belgium) were chosen as vehicles to have one lipophilic matrix and one oil-in-water emulsion formula. Based on a study previously performed at our laboratory,⁹ we chose GSH (ICN Biomedicals, Aurora, Ohio) and iron sulfate(III)

heptahydrate (FeSO₄; Sigma-Aldrich Chemie, Steinheim, Germany) as reducing additives.

Each of the two substances was mixed at a concentration of 10% (wt/wt) in both pet. and Essex cream. Thus, in total four formulas were prepared: 10% FeSO₄ in pet., 10% FeSO₄ in Essex, 10% GSH in pet., and 10% GSH in Essex. In addition to these, pet. and Essex as such, without any reducing additives, were used as vehicle controls. We also tested a commercially available formula, marketed as a barrier cream protecting against metals, on a separate test area on each volunteer's back. These results are presented elsewhere.¹⁰

2.2 | Patch test preparations

A dilution series of potassium dichromate (Cr₂K₂O₇; Janssen Chimica, Geel, Belgium) in water was prepared for evaluation of the various formulas. The dilution series consisted of nine preparations. A stock solution containing potassium dichromate 0.67% (wt/vol) aq. was further diluted by a factor of $\sqrt{10}$ down to the concentrations shown in Table 1. A preparation of chromium(III) chloride hexahydrate (CrCl₃·6H₂O; Fluka, Sigma-Aldrich Chemie) 1.21% (wt/vol) aq. was prepared in equimolar concentration to Cr(VI) (ie, Cr₂K₂O₇ 0.67% aq.).

In addition, a cement extract was prepared from approximately 200 g of a cement sample from India, to which no reducing agent had been added. The preparation was done by weighing approximately 25 g of cement each into eight plastic test tubes (50 mL; Sarstedt, Nümdrecht, Germany) adding 25 mL water (MilliQ water; Millipore, Molsheim, France) into each test tube. The test tubes were placed on a test tube rocker for 10 minutes and then centrifuged for 10 minutes at 2500 rpm. The water phases were collected and filtered, resulting in a total volume of 95 mL. Thereafter, it was evaporated to a volume of 3 mL. The pH was adjusted to 8.5 with 1 M HCl and 0.1 M NaOH. The total chromium content was determined to 84 ppm with atomic absorption spectrometry and the Cr(VI) content was determined to approximately 50 ppm with atomic absorption spectrometry and the diphenyl carbazide spot test.¹¹

2.3 | Application of formulas and patch testing

2.3.1 | Day 0

The back of each volunteer was divided into eight areas, of which six areas were treated with the aforementioned formulas; one area was treated with the commercially available formula and one area was left untreated (Figure 1).

When applying the formulas, templates made from laboratory paper (Disposable lab mat absorbent liner; Bel-Art products, Pequannock, New Jersey) were used to standardize the test area. The inner area of the template was 3.5 × 10 cm, corresponding approximately to a Finn chamber patch unit with 10 test chambers with a diameter of 8 mm (SmartPractice, Phoenix, Arizona), as used in our standard patch testing. Approximately 350 mg of each formula was applied on each area (except the untreated) corresponding to 10 mg/cm². Because the concentration and amounts of the chromium

TABLE 1 Patch test results on day 3/4 or day 7 in 18 volunteers tested to serial dilutions of $\text{Cr}_2\text{K}_2\text{O}_7$ (potassium dichromate), cement, and $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (chromium[III] chloride hexahydrate) on skin treated with different formulas and untreated skin

Treatment of skin	Concentration of $\text{Cr}_2\text{K}_2\text{O}_7\%$	Case number																
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Untreated	0.67	+++	(+)	++	++	+++	(+) ^a	++(+) ^a	-	-	++(+) ^a	+++	++	+++	+	-	++	++(+) ^a
	0.21	+++	-	+	++(+)	+++	-	+	-	-	++(+) ^a	++(+)	++	++(+)	(+)	-	+	-
	0.067	++(+)	-	++(+)	(+)	+++	-	-	-	-	++ ^a	(+)	++(+)	++	-	-	(+) ^a	-
	0.021	+	(+) ^a	(+)	(+)	++	-	-	-	-	+ ^a	(+)	+	++(+)	-	-	(+) ^a	-
	0.0067	+	-	(+) ^a	-	+	-	-	-	-	(+) ^a	-	(+)	(+)	-	-	-	-
	0.0021	+	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-
	0.00067	(+)	(+)	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-
	0.00021	(+)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	0.000067	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Cement	+++	-	-	++	++	-	(+)	-	-	++	+	-	++(+)	-	-	(+)	++
GSH pet.	0.67	(+) ^a	-	(+) ^a	(+)	+++	-	-	-	-	-	-	-	+ ^a	-	-	-	(+)
	0.21	-	-	-	-	(+)	-	-	-	-	-	-	-	(+) ^a	-	-	-	-
	0.067	(+)	-	-	-	(+)	-	-	-	-	-	-	-	-	-	-	(+)	-
	0.021	-	-	-	-	(+)	-	-	-	-	-	-	-	-	(+)	-	-	-
	0.0067	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	≤0.0021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Cement	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	(+)
	0.67	(+)	-	++(+)	-	+	-	(+)	-	-	+ ^a	(+)	+++	++(+) ^a	-	-	+ ^a	+
	0.21	(+)	-	+ ^a	-	++	-	-	(+)	-	+	-	(+)	(+)	-	-	(+)	++ ^a
	0.067	(+)	-	+ ^a	-	+++	-	-	(+)	-	(+) ^a	+	(+)	(+)	-	-	(+)	(+)
GSH Essex	0.021	(+)	-	(+)	-	+++	-	-	+	-	+ ^a	(+)	(+)	(+)	-	-	-	+ ^a
	0.0067	-	-	(+)	-	++	-	-	(+)	-	(+) ^a	(+) ^a	-	(+)	-	-	-	+ ^a
	0.0021	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
	0.00067	-	-	-	(+)	-	-	-	-	-	-	-	-	-	-	-	-	-
	≤0.00021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Cement	-	-	-	-	+	(+)	-	-	-	(+)	-	-	(+)	-	-	-	(+)
	0.67	++(+)	-	-	-	++	-	-	-	-	(+) ^a	(+) ^a	-	+	-	-	-	++ ^a
	0.21	(+) ^a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	≤0.067	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Cement	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

(Continues)

TABLE 1 (Continued)

Treatment of skin	Concentration of Cr ₂ K ₂ O ₇ %	Case number																	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
FeSO ₄ Essex	0.67	(+)	—	(+) ^a	—	+	—	—	—	—	(+) ^a	—	++(+)	++	—	—	—	—	++
	0.21	—	—	(+)	—	(+)	—	—	—	—	—	—	—	—	—	—	—	—	
	0.067	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
	0.021	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
	0.0067	—	—	—	(+) ^a	—	—	—	—	—	—	—	—	—	—	—	—	—	
	≤0.0021	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
	Cement	—	—	—	—	—	—	—	—	—	—	—	+	—	—	—	—	—	
pet.	0.67	++	—	+	—	++	+	—	—	—	++(+) ^a	+++	++(+) ^a	++	—	(+)	++	—	+++
	0.21	++	—	—	—	+	—	—	—	—	++ ^a	(+)	++ ^a	++ ^a	—	—	(+)	—	++
	0.067	—	—	(+) ^a	—	(+)	—	—	—	—	++(+) ^a	(+)	—	++ ^a	—	—	(+)	—	(+)
	0.021	—	—	—	—	(+)	—	—	—	—	(+)	—	—	(+) ^a	—	—	—	—	(+) ^a
	0.0067	—	—	—	(+)	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	0.0021	—	—	—	—	—	—	—	—	—	—	—	++(+)	—	—	—	—	—	—
	0.00067	—	—	—	—	—	—	—	—	—	—	—	(+)	—	—	—	—	—	—
	≤0.00021	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Cement	(+) ^a	—	(+)	—	(+)	—	—	—	—	(+) ^a	++(+)	—	—	—	—	—	—	—
	Essex	0.67	++(+)	(+)	++(+) ^a	(+)	+++	—	++	—	—	+++	+++	+++	++ ^a	+	(+)	++(+)	++ ^a
0.21		++(+)	—	++(+) ^a	—	+++	—	+	—	—	++(+)	++(+)	++(+)	++ ^a	—	—	++(+)	—	+++
0.067		(+)	—	(+) ^a	(+)	++	—	(+)	—	—	++(+) ^a	++ ^a	—	(+)	—	—	—	—	++ ^a
0.021		—	—	—	—	(+)	—	—	—	—	++ ^a	—	—	(+)	—	—	—	—	(+)
0.0067		—	(+)	—	—	—	—	—	—	—	—	—	—	(+)	—	—	—	—	(+)
0.0021		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	(+)
0.00067		—	—	—	—	—	++ ^a	—	—	—	—	—	—	—	—	—	—	—	—
0.00021		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
0.000067		—	—	—	—	—	—	—	—	—	—	—	—	—	(+)	—	—	—	—
Cement		—	—	—	+	++	—	(+)	—	—	++(+) ^a	(+)	—	++	—	—	—	—	++(+)
Untreated skin	CrCl ₃ ·6H ₂ O 1.21%	(+) ^a	—	(+)	—	+++	—	—	—	++(+) ^a	—	—	—	(+) ^a	—	—	—	++ ^a	

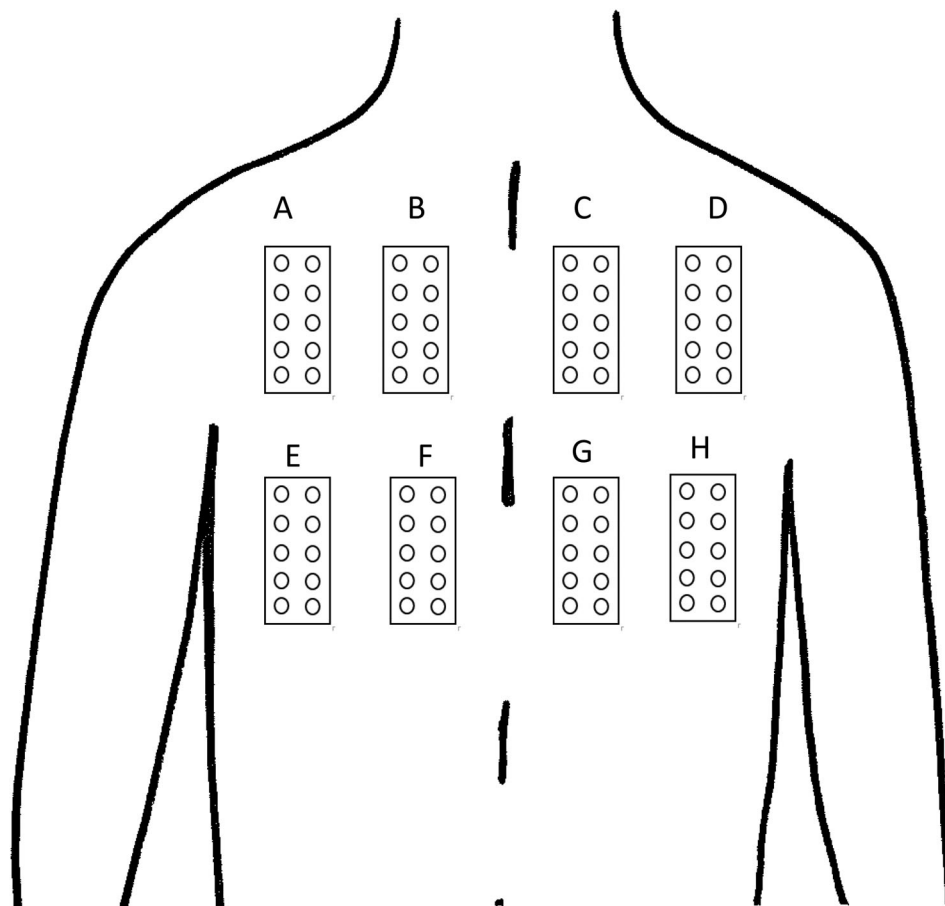
Negative = 0; (+) = 0.5; + = 1; ++ = 1.5; +++ = 2; ++(+)= 2.5; +++ = 3.

Note: Minimal eliciting concentration for every volunteer and formula given in bold.

Abbreviations: FeSO₄, iron sulfate(III) heptahydrate; GSH, glutathione; pet., petrolatum (+), a morphology in between the morphology that is marked +, (that is, tests were read according to International Contact Dermatitis Research Group and ESCD criteria but with some minor modifications).

^aSeen on test reading day 7.

FIGURE 1 A schematic picture of how the formulas were localized on each volunteers back, for example, volunteer X: A, untreated; B, GSH; C, pet.; D, commercial barrier cream; E, Essex; F, FeSO₄ Essex; G, FeSO₄ pet.; H, GSH Essex. The order in which the formulas and the untreated area were localized was the same for all volunteers, but rotated one step to create a blinded test reading (so that in volunteer Y the order was A, GSH pet.; B, pet., etc.). FeSO₄, iron sulfate(III) heptahydrate; GSH, glutathione; pet., petrolatum



were relatively high compared with a real-life situation in the test situation, we used an excess amount of the formulas to balance. The exact amount of the formulas applied was weighed. The order in which the formulas were applied to the test areas was the same for all volunteers but rotated one step in each volunteer to create a blinded test reading situation.

On each area the volunteers were patch tested with the dilution series of potassium dichromate and cement extract. Separately, at an untreated area of the back, a preparation of chromium(III) chloride hexahydrate ($\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$; Cr[III]) was applied. Patch testing was performed using the 8 mm Ø Finn chamber mounted on Scanpor tape (Norgesplaster, Vennesla, Norway) with 48 hours occlusion. The patch test dose for the liquid preparations was 15 μL and the solutions were applied to the filter paper using a micropipette.¹²

2.3.2 | Day 2

The test chambers were removed at the department and discarded before reapplication of the formulas. The same formulas in a smaller amount (70 mg; 2.0 mg/cm²) were weighed and reapplied on the same test areas.

2.3.3 | Day 3/4 and day 7

The patch tests were read by experienced dermatologists on day (D) 3 or D4 and on D7 according to International Contact Dermatitis

Research Group and ESCD criteria^{13,14} but with some minor modifications.¹⁵

The tests were blinded for the readers who did not know which formula had been used on each area. However, the readers knew that the highest concentration in the dilution series was placed apically.

2.4 | Statistics

The exact McNemar two-sided test was used to compare the number of volunteers showing positive reactions at the untreated area and each of the treated areas and when comparing the formulas with each other. Fisher's exact two-sided test was used for the statistical calculations concerning Cr(III) and cement extraction.

For statistical analysis scores were assigned the following reactions: negative = 0; (+) = 0.5; + = 1; +(+) = 1.5; ++ = 2; ++(+) = 2.5; +++ = 3. The patch test results were considered in respect to both the lowest concentration eliciting at least one + reaction, that is, minimal eliciting concentration (MEC), and the summarized test score (STS), that is, all skin reactions summarized.¹⁵

MEC was defined as the lowest positive reaction on either D3, 4, or 7 for statistical calculations. The positive patch test reactions were not always continuous. When the number of negative and/or doubtful reactions was followed by at least the same number of positive reactions, the lowest positive reaction was considered the MEC.

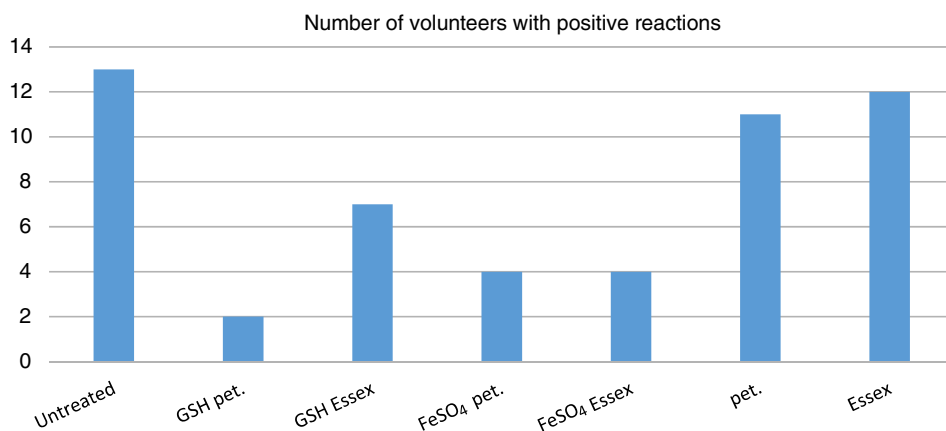


FIGURE 2 Number of volunteers with positive reactions on untreated skin, skin treated with vehicle + GSH/FeSO₄, and skin treated with vehicle only in the 18 volunteers. Number of volunteers reacting on the y axis. FeSO₄, iron sulfate(III) heptahydrate; GSH, glutathione; pet., petrolatum

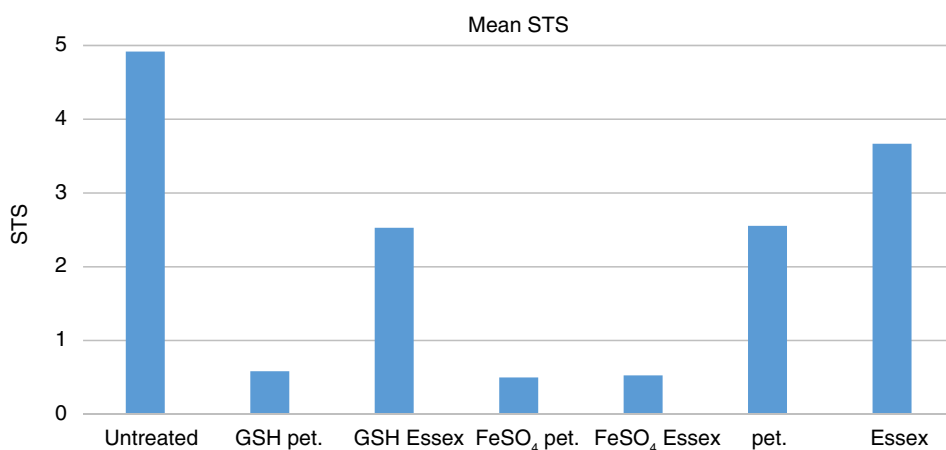


FIGURE 3 Mean summarized test score for the Cr(VI) dilution series tested on skin areas treated with the different formulas and on untreated skin in the 18 volunteers. FeSO₄, iron sulfate(III) heptahydrate; GSH, glutathione; pet., petrolatum; STS, summarized test score

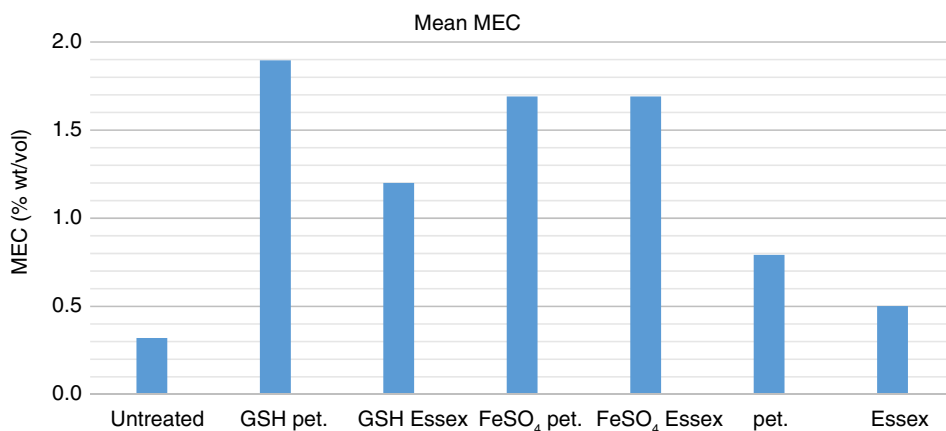


FIGURE 4 Mean minimal eliciting concentration (MEC) for the Cr(VI) dilution series tested on skin areas treated with the different formulas and untreated skin. The calculations are based on the results of the 13 volunteers who were positive on their untreated area. FeSO₄, iron sulfate(III) heptahydrate; GSH, glutathione; pet., petrolatum

In all other cases the concentration above the one eliciting the first negative or doubtful reaction was registered as the MEC.¹⁵

3 | RESULTS

All volunteers completed the study according to the protocol. We did not notice any unforeseen adverse effects in the volunteers. The results are presented in Table 1.

The most prominent reactions were seen on untreated skin followed by almost as prominent reactions on the skin treated with the Essex vehicle as such. The results are summarized by numbers of volunteers with positive reactions in Figure 2, by mean STS in Figure 3, and by mean MEC in Figure 4.

Three of the 18 volunteers showed positive reactions to Cr(III) on untreated skin. All of these three volunteers had a strong reaction (++/+++)

TABLE 2 *P*-values of number of volunteers showing positive reactions on skin treated with the formulas, vehicles as such, and untreated

	GSH pet. (n = 2)	GSH Essex (n = 7)	FeSO ₄ pet. (n = 4)	FeSO ₄ Essex (n = 4)	pet. (n = 11)	Essex (n = 12)	Untreated (n = 13)
GSH pet. (n = 2)	X	.063	.50	.50	.0039	.0020	<.001
GSH Essex (n = 7)	.063	X	.38	.25	.13	.063	.031
FeSO ₄ pet. (n = 4)	.50	.38	X	> .99	.016	.0078	.0039
FeSO ₄ Essex (n = 4)	.50	.25	> .99	X	.016	.0078	.0039
Pet. (n = 11)	.0039	.13	.016	.016	X	> .99	.63
Essex (n = 12)	.0020	.063	.0078	.0078	> .99	X	> .99
Untreated (n = 13)	<.001	.031	.0039	.0039	.63	> .99	X

Abbreviations: FeSO₄, iron sulfate(III) heptahydrate; GSH, glutathione; pet., petrolatum.

Note: The bold values refers to a significant *P*-value <.05.

volunteers with weak or negative reactions to Cr(VI) (three of 10 versus 0 of 8; *P* = .22).

Formulas containing GSH and FeSO₄ inhibited ACD in Cr(VI)-allergic individuals tested with a dilution series of Cr(VI) and cement. The differences were significant for both of the reducing additives. Volunteers also showed less reactivity on the areas of their backs treated with pet. vehicle as such only (Table 2).

The impact on reactivity to cement on skin treated with any formula was similar to the reactivity pattern in the dilution series of potassium dichromate.

4 | DISCUSSION

In this study the protective properties of the investigated formulas were examined under standardized conditions. By testing one lipid-based vehicle (pet.) and one oil-in-water emulsion (Essex) the physical barrier function could be investigated. Pet. showed some protective property when tested as such, that is, even without the addition of a reducing ingredient.

Formulas containing either GSH or FeSO₄ inhibited ACD in Cr(VI)-allergic individuals tested with a dilution series of Cr(VI) and cement. The differences between the formulas containing any of the actively reducing chemicals are not remarkable. A lipophilic matrix vehicle seems to be preferable, because the formulas with pet. all together seemed to be slightly superior with lesser skin reactions.

When considering the effect of a barrier cream it is necessary to take into account how the cream is intended to be used. If the purpose is secondary prevention, that is, to protect already sensitized individuals, the protective effect must be better than if the purpose is primary prevention because a lower dose of an allergen is needed for elicitation than for sensitization. This means that a barrier cream can be useful even if the decrease of reactivity in treated skin is, for example, twofold, compared with untreated skin. These ratios are familiar because the same works effectively when reducing the amount of Cr(VI) in cement by adding FeSO₄. Overall, at least eightfold decrease of reactivity in skin treated with any of the four formulas containing an active reducing ingredient compared with untreated skin was noted.

A barrier cream reducing the total exposure to Cr(VI) may offer protection against both sensitization and elicitation. A weakness in this study is that the volunteers tested all had a formerly known contact allergy toward Cr(VI). Consequently, it is not possible to prove a protection against sensitization. However, this appears most plausible because, as discussed before, even a minor decrease of Cr(VI) results in protection. Field studies need to be performed to investigate whether there is both a primary and a secondary preventive effect of any of these barrier creams.

Protection of individuals at risk of allergic chromium dermatitis in their work is desirable. In countries lacking regulations construction workers are at risk. A recent study from Australia mentioned ACD caused by Cr(VI) in cement as a significant occupational hazard with at least 24 new cases/year.¹⁶ There are examples from other countries too, including Singapore, Turkey, and Taiwan.^{17–19} As mentioned before, even in countries with a regulation concerning Cr(VI) some individuals get sensitized and develop ACD caused by Cr(VI).²⁰ For example, cement with the addition of FeSO₄ may contain an excess amount of Cr(VI), because the components in the cement can oxidize through exposure to air when the storage package is left open for more than 8 weeks.²¹ The situation for construction workers differs based on various factors, a worst case scenario probably being working without any physical protection at all and handling cement containing high amounts of Cr(VI).

Previous studies have investigated the preventive effect of barrier creams on ACD caused by different allergens.^{22,23} In a study from 1998, the reducing properties of GSH on the concentration of methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) in different emollients were examined. Using a high-performance liquid chromatography technique it was shown that the concentration of the preservative was reduced *in vitro*.²⁴ A case report from 2015 demonstrated successful inhibition of ACD caused by MCI/MI with topical application of GSH. A patient sensitized to MCI/MI was exposed occasionally to steam containing MCI/MI. When the patient knew he would risk such exposure, he rubbed an emollient containing GSH onto exposed areas prior to exposure, thereby inhibiting ACD.²⁵ In another case study, a male worker in a mechanical shop blocked his hand eczema from nickel using a barrier cream. With an application

four to five times daily after washing his hands they were free of eczema.²⁶ Another study proved a preventive effect on ACD to metals using the chelator diethylenetriaminepentaacetic acid (DTPA) in a cream. Individuals sensitized to various metals showed a significant decrease in positive patch test reactions after pre-treatment with the DTPA cream. However, it showed no protective effect against chromium (potassium dichromate).²⁷ To the best of our knowledge there is yet no barrier cream with a proven protective effect toward Cr(VI). In this study the formulas containing GSH and FeSO₄ showed protective properties and they did so despite the concentrations of Cr(VI) being considerably higher than in real-life situations.

Reducing the skin exposure to Cr(VI) is health promoting and the following examples clarify the benefit of further attempts to protect those still at risk. Data from a study carried out in the UK after the EU Directive 2003/53/EC (the legislation concerning Cr(VI) content in cement) was implemented have shown a significant decline in the incidence of chromate-attributed ACD since the legislation came in force.²⁸ The authors of another large study from Germany concluded that reducing the Cr(VI) content in cement was useful in preventing ACD caused by Cr(VI).²⁹ Another example is the Øresund (Öresund) bridge connecting Denmark and Sweden which was built in 1995–2000. None of the construction workers were found to suffer from ACD caused by Cr(VI) in cement.³⁰ Conversely, during the building of the Channel tunnel in 1990–1991, 17% of the grouters had ACD caused by Cr(VI).³¹

Only seven of 18 volunteers in the present study showed a positive reaction to cement extract. All of these had strong-to-extreme reactions (++, +++) ($P = .004$) to potassium dichromate (Cr₂K₂O₇). The limited reactivity to cement extract is probably explained by the relatively low content of Cr(VI) in the cement extract used (about 50 ppm), much less than in the Cr₂K₂O₇ dilution series. Reactivity to Cr(III) was demonstrated in three of the volunteers in this study. Cr(III) is recognized as having less potential to sensitize and cause ACD than Cr(VI). It is less toxic and evokes less skin irritation than Cr(VI). This is often explained to be mainly due to a lower bioavailability of Cr(III), because it does not penetrate the cell walls or skin very well. However, there might still be an influence on the skin, maybe not only to those allergic to Cr(VI),³² and Cr(III) is furthermore considered to be the actual hapten at the cellular level.³³ Despite that, and based on this study, we believe that there is a practical utility of a barrier cream directed against Cr(VI).

The finding of a method to reduce Cr(VI) in cement by adding FeSO₄ has been of great importance and is the most preferable way to decrease the risk of ACD caused by Cr(VI) in cement, as it does not impair the function of the cement nor demands an effort from the individual construction worker. However, unfortunately, this measure does not always seem to be sufficient. We find the results of this study promising enough to encourage further studies in which the protective effect of a barrier cream in worst case scenarios, as represented in, for example, countries lacking Cr(VI) regulation, can be investigated.

In conclusion, the protective capacity of formulas prepared to act as barrier creams was investigated in this study. Barrier creams

containing GSH and FeSO₄ inhibited elicitation of ACD in Cr(VI)-allergic individuals tested with a dilution series of Cr(VI) and cement extract. The differences in reactivity between treated and untreated skin were significant for both reducing additives. A protective effect of the lipophilic matrix vehicle per se as such was also noted.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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REFERENCES

1. Avnstorp C. Prevalence of cement eczema in Denmark before and since addition of ferrous sulfate to Danish cement. *Acta Derm Venereol.* 1989;69:151–155.
2. Hansen MB, Menné T, Johansen JD. Cr(III) reactivity and foot dermatitis in Cr(VI) positive patients. *Contact Dermatitis.* 2006;54:140–144.
3. Fregert S, Gruvberger B, Sandahl E. Reduction of chromate in cement by iron sulfate. *Contact Dermatitis.* 1979;5:39–42.
4. European Parliament, Council of the European Union. Directive 2003/53/EC of the European Parliament and of the Council of June 18, 2003 amending for the 26th time Council Directive 76/769/EEC relating to restrictions on the marketing and use of certain dangerous substances and preparations (nonylphenol, nonylphenol ethoxylate and cement). *Off J Eur Union.* 2003; p. L178/24–L178/27
5. Lejding T, Mowitz M, Isaksson M, et al. A retrospective investigation of hexavalent chromium allergy in southern Sweden. *Contact Dermatitis.* 2018;78:386–392.
6. Schmidt M, Goebler M. Immunology of metal allergies. *J Dtsch Dermatol Ges.* 2015;13:653–660.
7. Bruze M, Gruvberger B, Hradil E. Chromate sensitization and elicitation from cement with iron sulfate. *Acta Derm Venereol.* 1990;70:160–162.
8. Mowitz M, Zimerson E, Hauksson I, Pontén A. Chromate and amine contact allergies in workers manufacturing precast concrete elements. *Contact Dermatitis.* 2016;75:363–369.
9. Submitted. Lejding T, Engfeldt M, Bruze M, et al. Can reducing cosmetic substances help prevent chromate contact allergy?
10. Submitted. Lejding T, Svedman C, Engfeldt M, et al. Barrier creams may not always perform as expected.
11. Bregnbak D, Johansen JD, Jellesen MS, Zachariae C, Thyssen JP. Chromium (VI) release from leather and metals can be detected with a diphenylcarbazide spot test. *Contact Dermatitis.* 2015;73:281–288.
12. Frick-Engfeldt M, Gruvberger B, Isaksson M, Hauksson I, Pontén A, Bruze M. Comparison of three different techniques for application of water solutions to Finn Chambers®. *Contact Dermatitis.* 2010;63:284–288.
13. Fregert S. *Manual of contact dermatitis.* 2nd ed. Copenhagen: Munksgaard; 1981 138p.
14. Johansen JD, Aalto-Korte K, Agner T, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing – recommendations on the best practice. *Contact Dermatitis.* 2015;73:195–211.

15. Hindsén M, Bruze M, Christensen OB. The significance of previous allergic contact dermatitis for elicitation of delayed hypersensitivity to nickel. *Contact Dermatitis*. 1997;37:101-106.
16. Wong CC, Gamboni SE, Palmer AM, Nixon RL. Occupational allergic contact dermatitis to chromium from cement: estimating the size of the problem in Australia. *Australas J Dermatol*. 2015;56:290-293.
17. Goon ATJ, Goh CL. Metal allergy in Singapore. *Contact Dermatitis*. 2005;52:130-132.
18. Lim YL, Goon A. Occupational skin diseases in Singapore 2003-2004: an epidemiologic update. *Contact Dermatitis*. 2007;56:157-159.
19. Akasya-Hillenbrand E, Özkaya-Bayazit E. Patch test results in 542 patients with suspected contact dermatitis in Turkey. *Contact Dermatitis*. 2002;46:17-23.
20. Hedberg YS, Gumulka M, Lind ML, Matura M, Lidén C. Severe occupational chromium allergy despite cement legislation. *Contact Dermatitis*. 2014;70:321-323.
21. D. Bregnbak and C. Avnstorp. *Kanerva's Occupational Dermatology*, Springer International Publishing AG; 2018.
22. Teichmann A, Jacobi U, Waibler E, Sterry W, Lademann J. An in vivo model to evaluate the efficacy of barrier creams on the level of skin penetration on chemicals. *Contact Dermatitis*. 2006;54:5-13.
23. Romaguera C, Grimalt F, Vilaplana J, Carreras E. Formulations of a barrier cream against chromate. *Contact Dermatitis*. 1985;13:49-52.
24. Gruvberger B, Bruze M. Can glutathione-containing emollients inactivate methylchloroisothiazolinone/methylisothiazolinone? *Contact Dermatitis*. 1998;38:261-265.
25. Isaksson M. Successful inhibition of allergic contact dermatitis caused by methylchloroisothiazolinone/methylisothiazolinone with topical glutathione. *Contact Dermatitis*. 2015;73:126-128.
26. Isaksson M, Niklasson B. Allergic contact dermatitis from Nickel is prevented using a novel barrier cream. *Contact Dermatitis*. 2016;75:68.
27. Wöhrl S, Kriechbaumer N, Hemmer W, et al. A cream containing the chelator DTPA (diethylenetriaminepenta-acetic acid) can prevent contact allergic reactions to metals. *Contact Dermatitis*. 2001;44:224-228.
28. Stocks SJ, McNamee R, Turner S, Carder M, Agius RM. Has European 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;69:150-152.
29. Geier J, Krautheim A, Uter W, Lessmann H, Schnuch A. Occupational contact allergy in the building trade in Germany: influence of preventive measures and changing exposure. *Int Arch Occup Environ Health*. 2011;84:403-411.
30. Fregert S, Björkner B, Bruze M, Gruvberger B, Isaksson M, Zimerson E. *Yrkesoch Miljödermatologi. Andra upplagan*. Lund: Studentlitteratur; 2011.
31. Irvine C, Pugh CE, Hansen EJ, Rycroft RJ. Cement dermatitis in underground workers during construction of the Channel Tunnel. *Occup Med*. 1994;44:17-23.
32. Buters J, Biedermann T. Chromium(VI) contact dermatitis: getting closer to understanding the underlying mechanisms of toxicity and sensitization! *J Invest Dermatol*. 2017;137:274-277.
33. Siegenthaler U, Laine A, Polak L. Studies on contact sensitivity to chromium in the guinea pig. The role of valence in the formation of the antigenic determinant. *J Invest Dermatol*. 1983;80:44-47.

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