

# Role of different valence states of chromium in the elicitation of allergic contact dermatitis

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Chromium, a known contact sensitizer, is present at high levels in certain detergent bars (40–50 p.p.m.) sold in India. A concern was whether chromium present in such detergent bars could sensitize users or their use lead to the elicitation of allergic contact dermatitis. Chromium present in detergent bars was analyzed for its valence state. It was found to be trivalent [Cr (III)] and not hexavalent [Cr (VI)]. An elicitation test on normal volunteers, as well as on volunteers who were sensitive to chromium, was carried out to determine the elicitation potential of chromium (III) in the bars. Of the 48 volunteers who completed the study, 30 did not show any positive response to either potassium dichromate, the positive control, or the detergent bar containing chromium (III). 18 volunteers who were identified as chromium-sensitive showed a positive response to potassium dichromate but not to the detergent bar containing trivalent chromium. This study clearly showed that the detergent bar with 40–50 p.p.m. of trivalent chromium did not elicit any allergic contact dermatitis even in individuals known to be chromium-sensitive. Hexavalent chromium (potassium dichromate) did however, elicit allergic contact dermatitis in these subjects.

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The toxicity of chromium compounds has been well established through epidemiological studies as well as in animal models. The oxidation (valence) state is a critical factor in the evaluation of its toxicity. Hexavalent chromium compounds in general are more toxic than trivalent compounds (1). Tissue damage and cell-mediated allergic responses caused by hexavalent chromium are known. On the contrary, elicitation of allergic response by trivalent chromium is not well understood or characterized. It is believed that such a response to chromium (III) can occur only with very high concentrations (2).

Laundry bars/powders have been used in India for the past 3 decades without any known adverse effects. Some of these bars contain high levels of chromium (III) (40–50 p.p.m.). It was previously thought that chromium was a contact allergen irrespective of the valence state. The aim of this work was to identify and differentiate the valence states of chromium in terms of allergic responses, so as to explain the non-occurrence of allergic reactions to high levels of Cr (III) present in deter-

gent bars. An elicitation test was carried out on normal volunteers as well as on volunteers who were sensitive to chromium, to test for allergic responses to the high levels of chromium (III) in detergent bars.

## Materials and Methods

### *Test materials*

A marketed detergent bar containing chromium (III), potassium dichromate 0.5% (w/w) in petrolatum (pet.) (Systopic Laboratories, New Delhi, India), Finn Chambers, 3M Micropore adhesive tape.

### *Valence state of chromium in the detergent bar*

The valence state of chromium in the detergent sample was analyzed by solid phase extraction and detection by inductively coupled plasma emission spectrometer (ICP-ES) and graphite furnace atomic absorption spectrometer (GF- AAS) (3).

## Method

### Test system

49 healthy volunteers (33 male + 16 female), who were not on any medication and were without any skin disease at the treatment site, i.e. the upper arm, were selected. The study was cleared by the local Research Ethics Committee. Of the 49 volunteers, 18 (15 male + 3 female) were chromium – sensitive persons as per the records of the hospital, who had shown positive responses to a potassium dichromate patch test. All the volunteers were informed about the test procedure in detail and informed consent was obtained before start of the study.

### Test method

Finn Chamber on 3M Micropore adhesive tape was used as the patch for applying the test sample. 75% (w/w) of the test sample (detergent bar with chromium (III)) was prepared in distilled water and 0.1 mL of this solution/slurry was dispensed on the patch and applied on the left upper arm of 31 volunteers and on the right upper arm of 18 volunteers. A contact period of 4 h was allowed. Thereafter, the patch was removed and the treatment site wiped with a moist tissue to remove the sample residue. The treatment site was marked with a blue or black marker. All the volunteers also received a potassium dichromate patch [0.1 mL of 0.5% (w/w) in pet.] simultaneously for 72 h to confirm sensitivity to chromium.

### Observation and scoring

Observation and scoring was carried out at 72 h after patch application. The potassium dichromate patch was removed after 72 h contact and observed 30 min after patch removal. The treatment sites were scored according to the International Contact Dermatitis Research Group (ICDRG) scale (4). The number of volunteers showing positive response and the degree of reaction was recorded.

## Results

The valence state of chromium was found to be III and no hexavalent chromium was detected in the bars (detection limit for Cr (III) and (VI) was 0.5 (p.p.b.). Of the 48 (including 18 chromium-positive) volunteers who completed the study, 1 dropped out due to reasons not related to treatment, and none of the remainder showed any positive response to the detergent bar containing trivalent chromium. Of the 18 chromium-positive

Table 1. Individual reaction score

| Volunteer no. | Detergent bar containing chromium (III) | Potassium dichromate |
|---------------|-----------------------------------------|----------------------|
| 1             | Did not complete the study              |                      |
| 2             | –                                       | +                    |
| 3             | –                                       | –                    |
| 4             | –                                       | –                    |
| 5             | –                                       | ++                   |
| 6             | –                                       | –                    |
| 7             | –                                       | –                    |
| 8             | –                                       | –                    |
| 9             | –                                       | –                    |
| 10            | –                                       | –                    |
| 11            | –                                       | –                    |
| 12            | –                                       | –                    |
| 13            | –                                       | –                    |
| 14            | –                                       | –                    |
| 15            | –                                       | –                    |
| 16            | –                                       | –                    |
| 17            | –                                       | –                    |
| 18            | –                                       | –                    |
| 19            | –                                       | –                    |
| 20            | –                                       | –                    |

Table 2. Individual reaction score

| Volunteer no. | Detergent bar containing chromium (III) | Potassium dichromate |
|---------------|-----------------------------------------|----------------------|
| 21            | –                                       | –                    |
| 22            | –                                       | –                    |
| 23            | –                                       | –                    |
| 24            | –                                       | –                    |
| 25            | –                                       | –                    |
| 26            | –                                       | –                    |
| 27            | –                                       | +                    |
| 28            | –                                       | –                    |
| 29            | –                                       | –                    |
| 30            | –                                       | –                    |
| 31            | –                                       | –                    |
| 32            | –                                       | –                    |
| 33            | –                                       | ++                   |
| 34            | –                                       | –                    |
| 35            | –                                       | ++                   |
| 36            | –                                       | –                    |
| 37            | –                                       | +                    |
| 38            | –                                       | ++                   |
| 39            | –                                       | +                    |
| 40            | –                                       | +                    |
| 41            | –                                       | ++                   |
| 42            | –                                       | ++                   |
| 43            | –                                       | ++                   |
| 44            | –                                       | +                    |
| 45            | –                                       | ++                   |
| 46            | –                                       | +++                  |
| 47            | –                                       | ++                   |
| 48            | –                                       | +++                  |
| 49            | –                                       | +++                  |

volunteers (as per hospital records), 6 showed weak positive (+), 9 strong positive (++) and 3 extreme positive (+++) reactions to the chromium patch (Tables 1 and 2).

### Discussion

Some of the detergent bars used for fabric washing contain high levels of chromium. It was thought that the use of these detergent bars might induce contact sensitization among users or elicit allergic contact dermatitis among chromium-sensitized people. Complaints of allergy to such products had not been received. We hypothesized that the lack of complaints could be due to the valence state of chromium [being in the Cr (III) form]. As a first step, chromium present in the detergent bars was analyzed for their valence state. We found that detergent bars contained 40–50 p.p.m. of trivalent [Cr (III)] without any detectable level of hexavalent chromium [Cr (VI)]. A high frequency of contact allergy to Cr, probably from household consumer products has been reported, in Israeli housewives (5). But no indication was given whether this was caused by Cr (III) or (VI). In modern formulations, Cr is often present in the trivalent form and is less bioavailable. Much higher levels of Cr (III) than (VI) are normally required to elicit patch test reactions in Cr-sensitive individuals (2). Several investigators of chromate dermatitis were of the opinion that Cr (III) was not active in the elicitation of the allergic response.

The study was designed to give an exaggerated level of product contact with the skin. Normal consumers may use the detergent bar for a period of about 30 min to 1 h on a daily basis. In this study protocol, an exaggerated 4-h contact period was allowed with 75% detergent bar under occlusion, to allow maximum loading of chromium. The presence of surface active agent in the detergent bar would have further enhanced the penetration of any soluble chromium. Therefore, the conditions employed in this study should be considered as severe. Any further increase in the contact period would have resulted in irritant responses due to the surfactant system itself.

Of the 48 volunteers who completed the study, 30 did not show any positive response to either potassium dichromate or the detergent bar with chromium (III). 18 volunteers, who were earlier identified as chromium-sensitive, showed a positive response to potassium dichromate but not to the detergent bar containing chromium III. Thus, this study clearly showed that the detergent bar with 40–50 p.p.m. of trivalent chromium did not elicit any allergic contact dermatitis even in chromium-sensitive individuals, whereas hexavalent chromium (potassium dichromate) did elicit such allergic responses, indicating strongly the role of the valence state of chromium in elicitation of the allergic response. The detergent/laundry bars contain natural clay minerals and chromium can be

present as an impurity in those clay minerals. The main oxide and silicate ores of chromium are chromite ( $\text{FeCr}_2\text{O}_4$ ) and uvarovite [ $\text{Ca}_3\text{Cr}_2(\text{SiO}_4)_3$ ], respectively, both being chromium (III) compounds. The only naturally occurring chromium (VI) source is crocoite ( $\text{PbCrO}_4$ ), but this is a very rare material and highly insoluble in water (6, 7).

Cr (VI) is generally soluble in aqueous medium and is absorbed more easily through the skin. It can also cross the cell membrane more readily than insoluble trivalent chromium salts (8). Inside the cell it is reduced by intracellular reductase to reactive Cr (V) and Cr (IV) which are ultimately converted to stable Cr (III). It is believed that reduction of Cr (VI) is key factor in induction of DNA damage and cytotoxicity. In contrast, most Cr (III) compounds are insoluble and hence it is difficult for them to enter cells. Some soluble Cr (III) compounds can enter cells but they are in stable form and therefore unable to cause any toxic effect. Trivalent chromium is an essential element, while hexavalent chromium is allergenic and carcinogenic in nature.

The main reason for Cr (VI) toxicity has been found to be the reduction of Cr (VI) to other reactive lower valence states, and it was found recently that intracellular glutathione reductase plays an important role in Cr toxicity (9). Hexavalent chromium was found to induce the generation of superoxide anion, which may be involved in membrane lipid peroxidation, but no such data is available for Cr (III) (10).

Therefore, from the present work, it is clear that among the valence states of chromium the hexavalent form is the most toxic and allergenic while the trivalent form is the least toxic. The current recommendation is 5 p.p.m. as the maximum limit of chromium, with a target of 1 p.p.m. (11) for consumer products. This recommendation does not make any mention of the valence states. In view of the current findings, it is suggested that this recommendation may be reviewed to incorporate the valence state of chromium. It is also recommended that, wherever possible/necessary, chromium (VI) should be replaced with chromium (III) in consumer products.

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