A study of chromium induced allergic contact dermatitis with 54 volunteers: implications for environmental risk assessment

Editor—In their recent paper, Nethercott et al proposed a dose-response relation for the elicitation of allergic contact dermatitis (ACD) in sensitised people by hexavalent chromium (Cr(VI)) based on mass loading of (Cr(VI)) per unit skin area (µg Cr(VI)/cm² skin).1 Nethercott et al then attempted to apply this approach to the derivation of soil clean up guidance for Cr(VI). They present their dose-response relation with the unqualified assertion that to perform health risk assessments, patch testing data must be presented in terms of mg of chemical per skin area. We have previously presented a risk assessment approach to the derivation of soil clean up guidance for Cr(VI) based on an ACD dose-response relation derived from historical patch test data with Cr(VI) in aqueous solution on the patch (µg Cr(VI)/cm²). In this approach, a standard extraction procedure is applied to the soil to calculate the soil concentration of Cr(VI) retrospectively corresponding to the target Cr(VI) solution concentration.

We agree that the potential for a material to elicit an ACD in a sensitised person may be related to, among other things, the mass of allergen delivered over a given surface area, as well as to the concentration of allergen at the skin surface. Under certain circumstances, this can be described in terms of mass loading of allergen in skin area (µg Cr(VI)/cm² skin area) per unit mass area is most appropriately applied to descriptions of exposure that potentially elicit ACD in situations where the contact between soil and skin is static and uptake of the allergen is governed by equilibrium processes of extraction from the soil and diffusion to the skin surface. Although it is possible to construct limited scenarios of environmental exposure scenarios that meet these criteria, other realistic environmental exposure scenarios cannot be adequately described in these terms. Two such cases are exposure to allergen in solution on the soil surface—for example, a puddle—and continuous replenishment of soil on the skin surface such as can occur in gardening. In the first case, the contact of a liquid film with the skin precludes description in terms of variable loading per unit area. In the second case, continuous replenishment of soil on the skin surface can produce large but essentially indeterminate loading and precludes assumption of equilibrium scenarios. We think that in such cases, the loading of allergen on the skin surface is not an operative concept and the interaction of allergen and skin occurs largely at the interface of solution containing allergen and the skin surface. Such surface processes are most appropriately described in terms of the solution concentration of allergen that is presented to the skin surface.

The data relating ACD response to hexavalent chromium (Cr(VI)) in solution measured by traditional patch test methods are numerous and consistent.2 For the types of exposure scenarios described above, the most meaningful question for a patch test analogy to soil is: can environmental conditions (rain, sweat, etc in contact with contaminated soil) produce a concentration of Cr(VI) in solution equal to that known to elicit an ACD response? If soil conditions and Cr(VI) concentrations are such that a Cr(VI) solution concentration is equal to or greater than the threshold for producing an ACD response, then an adverse response in exposed sensitised people may result.

Even for those scenarios where a mass per surface area loading of soil has been identified the range of variability in the conditions of soil loading on the skin is quite large. This variability is a function of specific activity patterns, the rate of soil replacement on the skin, soil type, inherent moisture content of the soil, extent of soil hydration by sweat, and skin surface area exposed to soil. It is not clear to what extent mass per surface area is critical to prediction of potential ACD across this wide range of conditions. Wester et al found that for a constant soil loading on skin, cadmium retention in the skin increased with cadmium loading (and consequently with increased cadmium concentration) but transport of cadmium through the skin was independent of cadmium loading.4 When the concentration of cadmium in the soil was kept constant and the soil loading (and consequently the skin load) was varied, cadmium retention in the skin increased with increased cadmium loading, but cadmium transport through the skin was again independent of cadmium loading. The data of Yang et al suggest that under at least some conditions of soil loading, percutaneous absorption of a contaminant from soil is derived solely from the monolayer of soil directly in contact with the skin and its absorption is thus independent of the total mass of contaminant loaded over a given surface area of skin.5 Furthermore, there are data to suggest that, unlike the classic dose-response paradigm for ingestion and inhalation toxicity, ACD response may not follow a simple relation with administered dose (mass of allergen applied per unit area of skin). For example, Upadhye and Maibach suggested that within a range of exposure concentrations the number of Langerhans cells bearing many molecules of allergen is a more potent activating stimulus for the immune system than a large number of Langerhans cells bearing a few molecules of allergen.6 Nethercott et al cited four papers by other authors in support of the use of mass loading per skin surface area as the only valid measure of ACD potential.8 Of these papers (Andersen et al, 1992)9 is unavailable to us despite widespread attempts to locate it. For the three remaining papers, despite careful reading, we are at a loss to understand in what way they support the contention of Nethercott et al. Fischer and Maibach considered inaccur-
cies and inconsistencies in the preparation of commercial patch test solutions and the implication for diagnostic patch testing. Upadhye and Maibach dealt with the importance of area of allergen application. Data they recently presented to another journal in their reply to that letter,1 we presented what we think is a clear and concise definition of the problem and its resolution. We appreciate this opportunity to continue the discussion and present another opportunity to further describe the factors that predict the risk of elicitation of allergic contact dermatitis (ACD) through dermal contact with Cr(VI) in soils.

The position we have presented in our paper is that the only valid measure of dermal dose is mass of chemical per unit surface area of skin (μg/cm² skin), and that knowing the applied concentration of the chemical permits understanding the validity of the response of the contactant applied (I), cannot provide a measure of the mass of chemical contacting the stratum corneum. As simple as the rationale for this concept may seem, Hazen and Stem have provided a lengthy rebuttal that only exemplifies that they do not appreciate the significance of the available data.

The issue at hand concerns the appropriate method to determine the standard for ACD upon exposure to Cr(VI) that protects against elicitation of ACD in people sensitised to Cr(VI). Stem and Hazen originally took the position that 10 ppm Cr(VI) in solution should be the standard for ACD, because belief that a (a) 10 ppm Cr(VI) in solution is a threshold dose for elicitation (based on their interpretation of historic patch test data) and (b) 10 ppm Cr(VI) in solution on skin might generate 10 ppm Cr(VI) in solution on the skin surface.2 We undertook numerous studies to test the legitimacy of their assumptions. Firstly, we showed that, at sweat/solvent ratios that they thought to represent an environmentally relevant condition, human sweat does not extract sufficient Cr(VI) from the soil to generate 10 ppm Cr(VI) in solution on the skin surface. In fact, much less than 0.1 ppm is generated even when the concentration of Cr(VI) in soil is above 500 ppm. Once this was established, they abandoned the soil on skin argument in favour of what might be termed the mud puddle hypothesis. This hypothesis suggested that in an unlimited reservoir of soil containing 10 ppm Cr(VI) (rather than a thin layer of soil on skin) could generate 10 ppm Cr(VI) in solution in the environment—for example, in the form of puddles after rain. Although this change in reasoning failed to support the notion that on skin issue, it still failed to correct the major data gap, namely, the measurement of dose-response with a dose measure that involved mass of Cr(VI) delivered to the skin (applied dose). Our second major research effort, wherein 54 people sensitised to Cr(VI) were patch tested, corrected this issue. Specifically, we obtained data on the applied dose that is necessary to sensitize people to Cr(VI). When these results were presented to Stem and Hazen two years ago, they proceeded to recalibrate the applied dose threshold of 0.089 μg Cr(VI)/cm² by converting the patch test dose (from μg Cr(VI)/cm²) to concentration in ppm (based on some unsubstantiated assumptions about the patch dimensions). Not surprisingly, the recalculated threshold was once again 10 ppm Cr(VI). In short, although Stem and Hazen's technical bases and reasoning have changed as their assumptions are challenged, the Cr(VI) soil standard has remained.

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Authors' reply—We are pleased to have this opportunity to respond to the letter by Stem and Hazen. Most of their letter is repeated verbatim in another letter to the editor they recently sent to another journal. In our response to that letter,1 we presented what we think is a clear and concise definition of the problem and its resolution. We appreciate this opportunity to continue the discussion and present another opportunity to further describe the factors that predict the risk of elicitation of allergic contact dermatitis (ACD) through dermal contact with Cr(VI) in soils.

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