The glass fibre was glass fibre, no high associated results in the incidence of carcinogenic risks. The proposed test for contact Cr(VI) chromium elicitation risk, from historical data, could result in ambiguous results depending on the fibre length used; and that the classification in terms of WHO definitions or fibres with size distributions typical of those found occupationally are not suitable for describing the biological activity of the fibres.

### Table 2 Influence of fibre length on incidence of mesothelioma

<table>
<thead>
<tr>
<th>Material</th>
<th>Total fibre* (n x 10^9)</th>
<th>Mass (mg)</th>
<th>Medium length (µm)</th>
<th>Mesothelioma (%)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stonewool fibre:</td>
<td>0.82</td>
<td>37</td>
<td>7.8</td>
<td>56</td>
<td>Study I</td>
</tr>
<tr>
<td>D6</td>
<td>0.02</td>
<td>172</td>
<td>20.1</td>
<td>76</td>
<td>Study II</td>
</tr>
<tr>
<td>MMVF 21</td>
<td>0.04</td>
<td>60</td>
<td>16.9</td>
<td>84</td>
<td>Roller and Port 1994</td>
</tr>
<tr>
<td>MMVF 21</td>
<td>1.0</td>
<td>150</td>
<td>16.9</td>
<td>76</td>
<td>Roller and Port 1994</td>
</tr>
<tr>
<td>Glass fibre:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMVF F11</td>
<td>0.03</td>
<td>55</td>
<td>6.9</td>
<td>0</td>
<td>Study I</td>
</tr>
<tr>
<td>MMVF F11</td>
<td>0.13</td>
<td>167</td>
<td>24.9</td>
<td>33</td>
<td>Study II</td>
</tr>
<tr>
<td>MMVF F11</td>
<td>0.04</td>
<td>70</td>
<td>14.6</td>
<td>38</td>
<td>Roller and Port 1994</td>
</tr>
<tr>
<td>MMVF F11</td>
<td>1.0</td>
<td>180</td>
<td>14.6</td>
<td>74</td>
<td>Roller and Port 1994</td>
</tr>
</tbody>
</table>

*Length > 5 µm; diameter < 2 µm; aspect ratio > 5.

mesothelioma was significantly lower. For the glass fibre, a near maximal response was only obtained at the highest dose of longer fibres; lower doses of long fibres resulted in lower incidences of mesothelioma, but a relatively high dose of shorter fibres resulted in no mesotheliomas. A difference in sensitivity could even be seen between fibres of 25 µm and 15 µm in length, with a dose (0.13 x 10^6) of 25 µm fibres obtaining a similar incidence of mesothelioma to that obtained with a higher dose (0.4 x 10^6) of 15 µm fibres. Hence, even in the range of fibre lengths found in occupational situations, the results of the proposed IP test may be influenced by the length of the fibre.

Our recent studies are completed and a full publication of the results is in preparation. This letter highlights some of the problems associated with the recent proposal on IP testing of fibres, namely that the masses proposed for fibres to be classified as non-carcinogenic are unworkably high; that the proposed test displays sensitivity to fibre length that could result in ambiguous results depending on the fibre length used; and that the classification in terms of WHO definitions or fibres with size distributions typical of those found occupationally are not suitable for describing the biological activity of the fibres.

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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).2 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 the exposure that a person is given such that the 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 to make these criteria, other realist 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.2 In the first case, the contact of a liquid film with the skin precludes desorption 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 equil-
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 were reviewed and we compare the importance of the area of allergen application with, in some cases, solution concentration at the skin surface, and in other cases with mass loading per surface area. Unwarranted importance of solution concentration and mass loading is not considered. Finally, Fischer and Maibach dealt with a comparison between the TRUE-test patch (similar to that used by Netherton et al.) and the TRUE-test with iodine per iodine in tests for nickel sensitivity. The TRUE-test was found to eliminate problems of uneven delivery of allergen that specifically arose from the use of petrolatum. Rather than allowing solution concentration to be the only valid measure of potential ACD, this study found that the results from the two methods compared well with each other across a large range of serial dilutions. A comprehensive model of ACD risk from exposure to contaminated soil has not yet been developed. In the absence of such a model, we think that Netherton et al are unwarranted in their assertion that mass per surface area is the only valid predictor of potential ACD from environmental contamination. Furthermore, we think that the analysis in Stern et al, based on numerous studies of solution concentration vs ACD response, provided a reasonable empirical basis for estimation of ACD risk.

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**Authors' reply—**We are pleased to have this opportunity to respond to the letter by Stern and Maibach. 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, 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 of the specific issue raised in their letter and to provide 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 that we have presented in this 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 (or mass of chemical volume of the contactant applied) 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 Stern 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 of ACD risk assessment, in particular, the standard for Cr(VI) that protects against elicitation of ACD in people sensitised to Cr(VI). Stern and Hazen originally took the position that 10 ppm Cr(VI) in soil should be the standard for Cr(VI) and that the belief that "(a) 10 ppm Cr(VI) in solution on skin is a threshold for elicitation (based on their interpretation of historic patch test data) and (b) 10 ppm Cr(VI) in soil on skin generate 10 ppm Cr(VI) in solution on the skin surface." We undertook numerous studies to test the legitimacy of their assumptions. Firstly, we showed that, at sweat:solids ratios that they thought to be representative of environmental conditions, 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. That hypothesis suggested that 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 circumvented the soil 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) and not dose per unit surface area. 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 threshold for elicitation of Cr(VI). When these results were presented to Stern and Hazen two years ago, they proceeded to recalculate the applied dose threshold of 0.089 μg Cr(VI)/cm² by converting the patch test dose (from μg Cr(VI)/cm²) to patch concentration in ppm (based on some unsubstantiated assumptions about the patch dimensions). Not surprisingly, the threshold concentration was once again 10 ppm Cr(VI). In short, although Stern and Hazen’s technical bases and reasoning have changed as their assumptions are challenged, the Cr(VI) soil standard has remained unchanged.

In their letter to *this* *Journal*, Stern and Hazen continue to side step the critical dis-
tinction between applied concentration (ppm) and applied dose (μg Cr(VI)/cm² skin). We think it is clear that applied dose not applied concentration dictates elicitation. In our paper we identified the threshold dose concentration to Cr(VI) (the dose below which elicitation is unlikely to occur) as approximately 0.089 μg Cr(VI)/cm² skin, with little or no response occurring at lower doses. A typical dose-response curve was shown at successively higher doses. Stern and Hazen continue to assert that an understanding of applied dose is not necessary, and that applied concentration provides sufficient information to predict contact sensitisation. We stand by the validity of their position, consider an analogous situation with a volume of water containing one part per thousand arsenic. One cannot conclude whether ingestion of the solution would cause death unless there is some understanding of the volume to be ingested—that is, the dose. The outcome depends on whether the ingested dose is above or below the lethal dose. Regardless of the outcome, however, the concentration of arsenic would remain constant. Similarly, one cannot predict the effects of the application of a cutaneous allergen when only the allergen concentration is known; there must be some understanding of the amount of that concentration applied.

As shown in the figure, the validity of applied dose as the correct dose measure holds true for elicitation of ACD. As described in our paper, we tested nine people for applied concentration of Cr(VI) 0.88 μg Cr(VI)/cm². We found that 0.88 μg Cr(VI)/cm² is the elicitation threshold for 0.88 μg Cr(VI/cm²) patch test. Hence, it is clear that applied dose, not applied concentration, governs elicitation. Further, these results alone refute the claim of Stern and Hazen that 10 ppm Cr(VI) is the elicitation threshold as a 175 ppm Cr(VI) patch test did not elicit a response.

We must disagree with the suggestion that ACD may not always follow a classic dose-response relationship. We referred to this in our study and numerous other patch test studies where there is a clear dose-response relationship between applied Cr(VI) dose and elicitation of ACD. Furthermore, Stern and Hazen’s basis for a 10 ppm Cr(VI) response threshold rests entirely on a dose-response relation they have generated from a variety of disparate studies, some of which are more than 30 years old. Hence, to suggest that ACD may not follow a classic dose-response paradigm is not consistent with their own published analysis. Stern and Hazen’s position was shown referencing of four papers that support their applied dose concept. We did not claim that these papers state that mass loading per skin surface area is the only valid measure; these papers were cited because they acknowledged the importance of the applied dose concept. Rather than be diverted into a lengthy rebuttal as to why these papers are relevant, we direct Stern and Hazen once again to their more recent and incontrovertible evidence to date: the figure shows the results. Although these data have been presented to Stern and Hazen numerous times in the past two years, they have not engaged the issue as to how their position can be valid in the face of these results. Indeed, they have