Preliminary experimental findings using intraperitoneal assays to determine carcinogenic potential of man made mineral fibres: relevance to recent proposals for classification testing

Author's reply—I thank Rossignol for his comments, and apologise for having overlooked his paper on aircraft assemblers. His remarks highlight again the complex interaction between back pain and workplace and non-workplace factors. As there is a financial incentive to attribute health problems to the workplace, sorting out the various factors will be very difficult.

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The magnitude of the association, which compares with that reported by Finkelstein. The table shows the data for 247 male workers with a known parental status. The odds ratio obtained for parenthood in the multivariate logistic regression including age, smoking, work satisfaction (boredom), seniority at the task, and stressful life events was 1-6 (95% confidence interval 1-1-2-1).

Finkelstein suggested that back problems could occur more frequently among male parents due to parenting and recreational activities carried out with children. We would like to broaden the interpretation of that result to the work place as well. The work impairment that was reported by most workers in our study was limited to being bothered by back pain in doing the regular job and did not involve absenteeism. We could argue that the association between male parenthood and back problems could be confounded by other factors associated with being a father such as being less physically active in sports, being heavier, bringing to work family preoccupations as an additional source of stress, and even occupying different types of jobs that would contribute to back problems (maybe more sedentary in nature).

The corroboration of an association between male parenthood and back problems in two different studies re-enforces Finkelstein's recommendation of the importance of assessing parenthood (male or female) in epidemiological studies of back pain. The specific search for the “why” of such association might open new avenues for prevention.

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Table 1 Injection data from animals injected with MMVF11 and D6 fibres

<table>
<thead>
<tr>
<th>Material</th>
<th>Total mass of fibres injected (mg)</th>
<th>Total fibres injected (&gt; 10 μm)</th>
<th>WHO fibres injected (&gt; 10 μm)</th>
<th>Median length (μm)</th>
<th>Median diameter (μm)</th>
<th>Geometric mean diameter (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>MMVF 11</td>
<td>52</td>
<td>11-4</td>
<td>7-5</td>
<td>6-86</td>
<td>0-97</td>
</tr>
<tr>
<td></td>
<td>D6</td>
<td>36</td>
<td>12-0</td>
<td>8-8</td>
<td>7-84</td>
<td>0-80</td>
</tr>
<tr>
<td>Study II</td>
<td>MMVF 11</td>
<td>167</td>
<td>1-88</td>
<td>1-57</td>
<td>24-9</td>
<td>1-59</td>
</tr>
<tr>
<td></td>
<td>D6</td>
<td>172</td>
<td>3-05</td>
<td>2-53</td>
<td>20-1</td>
<td>1-50</td>
</tr>
</tbody>
</table>

Under our current project licensed by the United Kingdom Animals (Scientific Procedures) Act (1986), we are restricted to a maximum of 45 mg for a single IP injection of fibres or four weekly injections of <45 mg. Even if this limit were extended to allow an infinite number of weekly injections, the above masses would require in excess of 75 weeks to perform the injections.

We have found from peritoneal lavage studies, that the volume of the free space in the peritoneal cavity of a rat is about 10 ml in 10-12 week old animals, and would be lower in younger animals. Given that density of these fibre types is about 2-3 g cm⁻³, the minimum volume which 5300 mg could occupy is 2-3 cm³ or one quarter of the available free space in the peritoneal cavity. So even if the animals could be injected with this mass of material and survive, a significant fraction of the peritoneal free space would be filled with fibres.

Studies to determine the maximum mass that a rat could be injected with and survive have not been conducted, but I am certain that animals would not survive injection of the above masses. Even for masses used in our studies (<200 mg), we have seen significantly reduced life spans in animals that did not develop tumours, suggesting that the maximum tolerated dose for IP injection has been exceeded. The proposed regimen for testing fibres with IP injection would therefore not seem to be practical.

Our studies have also shown information on the sensitivity of the proposed IP test to fibre length. Table 2 shows for both studies, the doses given in terms of mass and fibre number, and the incidences of mesothelioma occurring in the animals. Results from studies on similar materials by Ritter and Pott are also given for comparison and were obtained by personal communication (1994).

For the stonewool fibre types, the three groups injected with longer fibres showed a similar response to the higher dose, suggesting that the maximum incidence had been achieved in all of these experiments. When shorter fibres were injected, even at a relatively high dose, the incidence of
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 × 10⁶) of 25 μm fibres obtaining a similar incidence of mesothelioma to that obtained with a higher dose (0.4 × 10⁶) 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 proposals 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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2 TGRS 905. Technische Regel für Gefahrstoffe. Verschmutzung krebserzeugender erbvererbender oder fortzuleitender Stoffe. 2.3 Faserstäube (und andere mineralische Stoffe).

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 mass loading in a unit area (μg Cr(VI)/cm²). Mass per unit 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 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 conditions. We think that in such cases, the loading of allergen on the skin surface is not an operate 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.3 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 approach identifies 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 path across this CIs of conditions. Wester et al found that for a constant soil loading on skin, cadmium retention in the skin increased with increasing cadmium loading (and consequently with increasing cadmium concentration) but transport of cadmium through the skin was independent of cadmium loading.4 When the concentration of cadmium in the skin was kept constant and the soil loading (and consequently mass per surface area) 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 suggested they found that at least under 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, 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 al4 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.1,7,8 One 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 how they support the contention of Nethercott et al. Fischer and Maibach considered inaccur-
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