Letter to the Editor

Dear Editor,


We have serious concerns about the above paper, given the sensitivity of the issue of the potential risks from nanotubes. The paper claims to demonstrate that nanotubes have the potential to cause mesothelioma but we take issue with this in three main aspects.

1) The presentation of the dose

As shown in the paper itself, clumps of nanotubes were injected that were hundreds of microns in diameter. These would never have reached the part of the lung where macrophage phagocytosis, a key factor in determining fibre pathogenicity, would have occurred. To determine a long fibre effect (i.e. frustrated phagocytosis) the minimum requirement is that the fibres would be presented in a form thin enough to allow phagocytosis to be initiated. When this is the case, length becomes the important factor in dictating whether failed phagocytosis can occur, as for example with long thin crocidolite fibres. Undoubtedly frustrated phagocytosis would have occurred with the nanotube ‘clumps’ but this is not testing whether nanotubes caused mesothelioma in the way that asbestos fibres do. This seems a fatal flaw in the study.

2) The size of the dose

These workers injected 3mg or 3,000µg into each mouse. In our hands injecting nanotubes into mice produces an extremely sensitive response, with inflammation being detected down to 0.1µg (100ng), 30,000 times less than the mass dose used by Takagi et al. Whilst the idea of maximum tolerated dose is a difficult concept in the peritoneal cavity, it seems likely that a dose 30,000 times the NOEL for inflammation is far beyond what any reasonable person would take to be the maximum tolerated dose. The choice of 3mg seems to have been based on a misguided attempt to meet the fibre criteria of 10³ fibres (they cite Roller and Riego Sintes and Bernstein) which is a dosage defined by EU and was in common usage for detecting the carcinogenicity of fibres in rats. The size of the dose may have contributed to the faulty presentation of the material, since nanotubes are more likely to aggregate into clumps at such high concentrations.

3) The unvalidated nature of the p53 deficient mouse model for mesothelioma detection

Whilst the normal rat peritoneal cavity has been used extensively for detecting the mesothelioma hazard from fibres and is sensitive to fibre length, the sensitivity of the p53 deficient model is unknown; our concern is that it may be too sensitive. Irritant particles such as quartz do not cause mesothelioma in the normal rat peritoneal cavity and neither do short fibres, the model being essentially only sensitive to long fibres. The p53 deficient mouse model needs to be validated by demonstrating that irritants, in general, do not cause mesothelioma in the peritoneal cavity of p53-deficient mice. This mouse model is much more sensitive to carcinogenic effects, of course, and the danger is that an irritant effect, not a long fibre effect, is being detected here. There was no ‘irritant’ control in the Takagi study. Fullerene is not an irritant particle; indeed in many studies it is an anti-oxidant and thus not an appropriate control here.

In short we feel that this is a study where careful review should have identified the shortcomings of the design. According to the existing fibre pathogenicity paradigm, it may well be that some types of nanotube have the potential to cause mesothelioma if inhaled in sufficient dose, but the Takagi study does not contribute to this issue. Risk assessment is not aided, indeed it is confused, when flawed hazard data are published.

Yours sincerely

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