CORRESPONDENCE

Fibrogenic effect of wollastonite compared with asbestos dust and dusts containing quartz

Editor—I would like to comment on a recent paper by Cambelova and Juck on the fibrogenic effect of wollastonite compared with asbestos dust and dusts containing quartz.1

Having studied the biological effects (actually lack thereof—no fibrosis or neoplasia) after long-term (10 mg/m3 for 6 a day, 5 days a week for 12 months plus 12 months observation, or for a full 24 months) inhalation exposure of wollastonite in rats (McConnell et al, 1991), I was surprised to find the authors of this article reporting pulmonary fibrosis after intratracheal (IT) instillation. I offer the following comments and possible explanation for this unexpected result.

It is difficult to determine from the report what their rats were actually exposed to or the total exposure. The authors reported that they obtained their wollastonite sample by crushing quartz particles (crushing, comminution, etc)1 and reported a geometric mean length × diameter of 11.57 × 1.34 µm (wollastonite-China) and 9.22 × 1.21 (wollastonite-NYCO). Although this size of fibre is above the alveolar clearance range of the lung through inhalation, the authors do not report what else was present in the sample injected into the lung—such as, the number, size, and other characteristics of these particles that would also be produced by “crushing” and would also be injected into the lung. Was any effort made to clean up the sample of wollastonite so that only particulates of relevant size were injected? Most of a crushed sample would not be in an aerosol and all of these particulates >1.5 µm diameter in the aerosol would be filtered by the nose and upper airways and never reach the alveolar region. Also, although the authors report that each instillation contained “about 3 × 106 particles sample” and that the “Exposure lasted three months”, it is impossible to determine the number of exposures—that is, 1, 2, or 3 instillations a week for 1, 2, 3 weeks of the full 3 months?

Notwithstanding the lack of adequate description of the protocol, I offer the following in an effort to explain the findings of Cambelova and Juck. Before conducting our inhalation studies of wollastonite we also attempted IT instillation (20 mg/rat/week for 13 weeks), but had to abandon it in favour of inhalation because of early deaths, which we ascribed to severe acute bronchiolitis obliterans. It seemed that the sample of wollastonite we used (NYCO No. 6) did not include masses of non-fibrous as well as fibrous particles that plugged the small airways. There was an immediate attempt by the host to deal with these clumps of wollastonite with a foreign body fibrogenous reaction type reaction. The fibres and non-fibrous particulates were clearly visible in these lesions. Interestingly, there was minimal alveolar reaction, except in areas where the airway had been completely occluded with resultant atelectasis. I have also noted this phenomenon after IT injection of other types of particulates and fibres. I am confident that if rats are given a high enough dose of most particulates by IT injection, a similar inflammatory response will be found.

Although we did conduct hydroxyproline measurements in our study, I am sure these would have been increased due to the collagen in these foreign body granulomas in the airways. Unfortunately (and importantly), the authors did not report any histopathological findings in their study that would settle the question of the location of the increased amounts of collagen. One normally uses the lung for histopathology and the other half or even a single lobe for quantifying collagen. This is of utmost importance because the pathology induced by inhaled fibres (all types) is not in the airways, but almost exclusively found in the terminal bronchioles and proximal alveolar ducts or alveoli. In contrast, IT instillation of particulates often causes these bolus type lesions higher up in the airways, which are irrelevant to potential hazard assessment because they cannot occur after inhalation; the route of human exposure of most concern. After inhalation, only respirable-sized wollastonite fibres are found in the alveolar region and they are diffusely distributed. But, also distributed, where we believe a fibrogenic reaction with collagen. The authors refer to the consensus paper published by the WHO health authorities in the field of fibre toxicology (McClellan et al) as giving credibility to IT instillation as a potential “... gauge of fibrogenic potential ... “. One of the more important conclusions of the workshops that impact directly on the interpretation of the Cambelova and Juck study states that “Numerous studies have demonstrated that inhalation models best simulate the harmful mechanisms of only respirable-sized fibres reach the parenchymal regions of the lung. Physiological mechanisms of fibre clearance and/or inflammation depend on deposition, translocation, and clearance routes. Alternate routes, including intracavitary and intratracheal methods of fibre exposures, can provide useful information on the potential toxicity of fibres. However, the results obtained using these artificial routes can differ from those observed following inhalation exposures.” They also pointed out that “Studies using injections routes of exposure may indicate the pathogenic potential of fibres; however, normal clearance mechanisms are either overloaded through a bolus effect or simply bypassed, bringing into question the role of such studies for assessing human risk.”

Finally, the results of this study are in conflict with the results of intraperitoneal (IP) injection studies (Pott et al).3 These authors injected the same types and similar amounts (>20 mg) of wollastonite into the abdomen of rats and failed to produce either a significant amount of fibrosis or tumours. The IP model is very sensitive and readily reacts to asbestos as well as induction of mesotheliomas. In fact, it has been suggested that the IP model is over-sensitive and therefore, like the IT model, is not appropriate for hazard or risk assessment. Nevertheless, a negative IP result would be incongruous in the light of a positive (fibrosis) result after IT instillation.

In summary, I am convinced that what the authors actually produced in their studies was a fibrogenomulatous bronchiolitis (probably osseous) that did not occur if the fibres were given by inhalation, and therefore these results have no relevance for determining the potential health effects of wollastonite in humans.

ERNEST T MCCONNELL
3028 Ethan Lane, Durham, North Carolina 27713, USA


Methods in cohort studies

Editor—Callas, Pastides, and Hosmer perform a valuable service in examining current practices in the analysis of occupational cohorts.1 They find standardised mortality ratio (SMR) analyses remain the preferred choice of most investigators despite well known bias from transposing exposure and/or reference populations, as in the healthy worker effect. This limitation is further appreciated with recognition that healthy worker bias affects malignant as well as non-malignant disease. A host of investigators persist in denial.2 Whereas SMRs on average may underestimate point estimates of cancer relative risks in industrial cohorts by only 10% to 15%, the impact on hypothesis testing is greater, particularly in studies of limited statistical power. Effect estimates with lower confidence limits between 0 and 1.0 are called non-significant even though the lower limit could substantially exceed 1.0 in a non-biased analysis.

The authors favour local comparison populations (when the study cohort is an immortal part of the population and local rates are stable). Local comparison helps control bias from a variety of sources, such as general environmental conditions, medical practices, life style, and ethnic risk factors. Social class is another likely determinant of risk and industrial cohorts, representing a relatively select employment, may diverge substantially from local populations for educational, family history, income, and health care. Moreover, local populations often share the occupa-