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—toxic or neoplastic) after long-term (10 mg/m³ for 8 h 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 unclear 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 (crushing, fragmentation, etc.) 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 fibres reaches the alveolar region 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 the foreign bodies 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 those 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 week, 2, 3 weeks, or for 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 Wollastonite LP, Dallas, TX) was contaminated with 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 fibrogenomatosus 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 not conduct hydroxyproline measurements in our study, I am sure that there would have been increased due to the collagen in these foreign body granulomas in the airways. Unfortunately (and unpredicted by the authors) we did not report any histopathological findings in our study that would settle the question of the location of the increased amounts of collagen. One normally uses the lung for siatopathology 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 alveoli, and almost exclusively is 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, while the authors failed to provide potential hazard assessment because they cannot occur after inhalation; the route of human exposure of most concern. After inhalation, only respirable wollastonite fibres are found in the alveolar region and they are diffusely distributed. Also, distributed evenly wollastonite is highly soluble in lung fluids and tissues (Bellemann et al).

Fibrous authors refer to the consensus paper produced by national authorities in the field of fibre toxicology (McClaien et al) as giving credence to IT instillation as a potential "... gauge of fibrogenic potential ..."). One of the most important conclusions of the workshop that impacts directly on the interpretation of the Cambelova and Juck study states that "Numerous studies have demonstrated that inhalation models best simulate the clinical responses because only respirable-sized fibres reach the parenchymal regions of the lung. Physiological mechanisms of fibre clearance and/or inflammation depend on deposition, translocation, aggregation, and clearance routes including intratracheal 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, fibrogenic 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). These authors injected the same types and similar amounts (>20 mg/kg) of wollastonite into the abdomens 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 and other fibrous 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 fibrogenomatosum bronchiolitis (probably occlusive) that had not occurred if the fibres were given by inhalation, and therefore these results have no relevance for determining the potential health effects of wollastonite in humans.

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Methods in cohort studies

Editor—Cassels, Passides, and Hosmer perform a meticulous 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 non-comparable 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 diseases, and that investigators persist in denial. 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 0-9 and 0-0 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 immigrant 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, lifestyle 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 education, family history, income, and health care. Moreover, local populations often share the occupa-
tional exposures of the study cohort. For example, heavy metalworking industrial concentrations are found in the United States, especially around cities such as Cleveland or Detroit; petroleum and petrochemical industry is dense in certain counties of Texas or Louisiana. These considerations support the use of a national reference population.

In describing powerful multivariate modelling methods, which perform internal comparisons while incorporating external population experience, the authors cited Poisson and Cox regression examples. Not mentioned was modelling mortality (or incidence) odds with logistic regression, in well enumerated cohorts, which also inserts expected mortality (incidence) odds from an external population.7,8 Like Poisson and Cox regression, this approach estimates relative (but not absolute) rates for exposure effects, and has some notable advantages. Unlike Poisson or Cox methods, control information is required only for decedents (or incident cases). For example, date of birth or race, retrievable from death certificates or cancer registries, are often not available for a large proportion of younger general populations. Restriction of work history retrieval to the decedent (or incident cancer) subpopulation is a major advantage, compared with traditional cohort designs that may require numerous efforts to follow. The method is actually a case-control design with the controls (for mortality study) consisting of all decedents with causes of death thought to be unrelated to exposures under study. The advantages and disadvantages of the use of deceased controls has been debated without clear resolution.9,10 In an incidence study with a cancer registry, controls would be all incident cancer at selected sites.

The actual computation of mortality (incidence) odds by logistic regression is relatively simple compared with Poisson or Cox regression on the full population at risk. It can readily accommodate complex risk factor specifications, including cumulative exposures adjusted for latency, demographic dependencies of the healthy worker effect, imbalances in mortality odds with employment duration independent of exposures.11

The concern of Callas et al on the appropriateness of multiplicative and non-linear exposure-response structures imposed by logistic (and Poisson) regression can be assessed by goodness of fit. In several studies, logistic models performed well.11,12 There is, however, some additional biological basis for this finding. For example, multifactor carcinogenesis implies a higher than linear dependence in time (or exposure duration) that an exponential function can approximate over the ranges of effects found.

NOTICES


The British Association for Lung Research (BALR) was founded in 1981, and is the premier UK organisation for workers researching into medical and non-medical aspects of the lung. The last 5 years has seen exciting new insights into the effects of particles on the lung.

Fibres—The publication of the RCC study data; the completion of the first phase of the Colt Programme; the increasing importance of bio-persistence.

Environmental particles—Association with disease; the role of particle size.

Overload—The mechanisms; impact on the interpretation of inhalation toxicity studies.

Key note speakers: Dr Gunter Oberdorster, Rochester, New York; Dr Brooke Mossman, Burlington, Vermont; Dr Tom Hesterberg, Denver, Colorado.

Colt fibre programme reports: Dr JMG Davis; Dr A Searle; Dr A Jones; Dr K Donaldson.

Open sessions: Fibres; Particles; General lung research.

Young scientist competition: this session is open to younger BALR members. The prize will enable the winner to travel to a major scientific meeting of their choice.

The BALR summer meeting is sponsored by the Colt Foundation.

For further information contact: Dr R Cullen, Institute of Occupational Medicine, 8 Roxburgh Place, Edinburgh EH8 9SU. Tel 0131 447 8460, Fax 0131 447 2822.


Aims and objectives:
• To consider the need for occupational health services and workplace health and surveillance systems.
• To raise awareness about occupational diseases, injuries and disability; their impact on individuals, families, businesses and society; and the system for compensating victims.
• Discuss recent initiatives in industry and the NHS aimed at promoting the health and the wellbeing of working people and meeting the occupational health needs of under served working groups.

Speakers and topics include:
• Occupational health services in economically stringent times—Dr Michael Baxendale, Director of Occupational Health Services, United Biscuits.


15 Offspring sex ratios as an index of pollution hazard in residential environments.

Author’s reply—Your correspondent suggests that the negative findings for exposure to generalised air pollution on the sex ratios of births reported in our paper may conceal positive, but opposing, effects of the pollutants on male and female parents. He advances the analogy with the changes in the sex ratio of the offspring of parents with multiple sclerosis, when the direction of the change of sex ratio depends on the sex of the parent sufferer. It is indeed possible that such a cryptic scenario might result from exposure to general air pollution and an answer to this hypothesis might well come through follow-up studies as he suggests. That approach, however, would require extremely expensive ad hoc studies to generate the data. The main purpose of our investigation was to ascertain whether the sex ratio was a sensitive barometer of exposure to generalised environmental pollution in residential communities. Whether or not the sex ratios of offspring in exposed parents differ from those of the control groups. This has been our concern. We have used the sex ratio in this study as an index of air pollution from specific industrial processes.

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Methods in cohort studies.

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*Occup Environ Med* 1995 52: 621-622
doi: 10.1136/oem.52.9.621-a

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