# 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/m$^3$ for 6 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 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 "mechanical treatment (crushing, sedimentation, etc)" and reported a geometric mean length × diameter of 11·57 × 1·34 $\mu$m (wollastonite-China) and 9·22 × 1·21 (wollastonite-NYCO). Although this size of fibres could clearly reach 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 non-fibrous particulates 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 $\mu$m 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 $3 \times 10^9$ 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, 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 NYAD-G) agglomerated into 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 fibrogranulomatous 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 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 one half of 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 is 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 have no relevance to 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, when distributed evenly wollastonite is highly soluble in lung fluids and tissues (Belleman and Muhle).[3]

The authors refer to the consensus paper produced by leading authorities in the field of fibre toxicology (McClellan *et al*) as giving credibility to IT instillation as a potential " . . . gauge of fibrogenic potential . . . ".[4] One of the more 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 human exposures because 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 patterns. 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*).[5] These authors injected the same types and similar amounts ($\geq$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 fibres with fibrosis and the induction of mesotheliomas. In fact, it has been suggested that the IP model is oversensitive 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 injection.

In summary, I am convinced that what the authors actually produced in their studies was a fibrogranulomatous bronchiolitis (probably occlusive) that would not have 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—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 use of 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,[2] although many investigators persist in denial.[3] Whereas SMRs on average may understate 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 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 insignificant part of that population and local rates are stable). Local comparison helps control bias from a variety of sources, such as general environmental conditions, medical practices, some life style, and ethnic risk factors. Social class is another likely determinant of risk[2] and industrial cohorts, representing a relatively select employment, may diverge substantially from local populations for 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 in counties around cities such as Cleveland[4] or Detroit[5]; 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.[6-11] 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, complete 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 occupational cohorts or 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 enormous efforts.[5] 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.[12-15] In an incidence study with a cancer registry, controls would be all incident cancers at selected other 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, and variation in mortality odds with employment duration independent of exposures.[12]

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.[9 10] There is, moreover, some biological basis for this finding. For example, multistage carcinogenesis implies a higher than linear dependence in time (or exposure duration) that an exponential function can reasonably approximate over the ranges of effects found.

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## 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 pollution on male and female parents.[1] 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 has suggested. 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 of generalised environmental pollution in residential communities. Whether or not the sex ratios of offspring in exposed parents differ was really beyond the design of this investigation. Our conclusions therefore are unaltered: the **routinely** available data on sex ratios of births do not betray the presence of potential toxins in general industrial air pollution in the same way as was apparent for air pollution from specific industrial processes.

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1 James WH. Offspring sex ratios as an index of pollution hazard in residential environments. *Occup Environ Med* 1995;52:556.

# NOTICES

**Fibres, particles, and the lung: New perspectives. 11–12 September 1995. Edinburgh Conference Centre, Heriot Watt University, Edinburgh.**

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 toxicology 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 Searl; 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.

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**Royal Society of Health National Conference—Caring for the working population. 10 October 1995. The Society of Chemical Industry, 14–15 Belgrave Square, London.**

Aims and objectives:

- To consider the need for occupational health services and workplace health and surveillance systems.
- 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 Baxendine, Director of Occupational Health Services, United Biscuits.