Meeting Report

Low dose exposure to natural and man made fibres and the risk of cancer: towards a collaborative European epidemiology

Report of a workshop held in Paris, 10-12 June, 1991

Alain-J Valleron, Jean Bignon, Janet M Hughes, Thomas W Hesterberg, Thomas Schneider, Garry J Burdett, Patrick Brochard, Denis Hémon

Introduction (*A-J Valleron and J Bignon*)

Assessment of risk of cancer associated with low doses of natural and man made fibres has been discussed in depth in the past four years at at least two international meetings. The subject is still clearly topical in the United States where, since this symposium took place, the 5th Circuit Court of Appeals¹ has vacated the Environmental Protection Agencies 1989 ruling² pending further investigation, and the Health Effects Institute-Asbestos Research has published a review and synthesis of current knowledge.³ In Europe the EC countries still express differing

policies and are trying to establish a common position. Many questions remain unanswered, however, such as: are the present regulatory industrial thresholds (for example, in France 0.5 fibre/ml of chrysotile) low enough? What does low enough mean? Is it the level below which there is no risk? What about the risks of non-occupational exposure to asbestos? What is the rationale for remedy or removal of sprayed asbestos in buildings with asbestos containing materials? What future risks are possibly associated with new fibrous materials that could replace asbestos? How do we guarantee that efficient alarm systems are now available to avoid putting or keeping on the market products that may also be dangerous? What epidemiological surveys should be organised on which to base a rational approach? The answers (if any) to these questions can be extrapolated to other carcinogenic hazards, either chemical or physical. Whatever the environmental carcinogen under consideration, the difficulties lie in assessing the risk for very low doses, setting a maximum exposure threshold, and finding good surveillance systems. The conflicts between persons, groups, and interests are also the same. It was therefore extremely interesting to discuss in depth the case of mineral fibres, where so much expertise has been obtained, and see what can be extrapolated to the epidemiology of other hazards.

Therefore the aims of the symposium reported here were firstly to provide an update on the risks of cancers associated with low dose exposure to mineral fibres, secondly to outline the most suitable methodological tools in the field of environmental epidemiology for risk of cancer associated with exposure to low repeated concentrations of carcinogens. This workshop was limited in size to guarantee true discussions between scientists from 13

Unité de Recherches Biomathématiques et Biostatistiques (INSERM) B₃E—Faculté de Médecine St Antoine, 27 rue Chaligny, 75571 Paris Cedex 12 France

A-J Valleron

Unité de Recherches sur la Biopathologie et la Toxicologie, Pulmonaire et Rénale (Inserm), Hôpital Henri Mondor, 51 Ave du Maréchal de Lattre de Tassigny 94010 Créteil Cédex France

J Bignon, P Brochard

Tulane Medical Center, Pulmonary Diseases Section, 1700 Perdido Street, New Orleans, Louisiana 70112, USA

J M Hughes

Manville Technical Center, PO Box 625005, Denver, CO 80162-5005, USA

T W Hesterberg

National Institute of Occupational Health, Lerso Parkallé 105, DK-2100 Copenhagen, Denmark

T Schneider

Health and Safety Executive, 403 Edgware Road, Cricklewood, London NW2 6LN, UK

G J Burdett

Unité de Recherches Epidémiologiques et Statistiques sur l'Environnement et la Santé (Inserm), 16 Avenue Paul Vaillant Couturier, 94807 Villejuif Cedex, France

D Hémon

European countries, north and south America, Japan, and Africa.

M Tubiana opened the meeting with a keynote address on the general problem of epidemiology and decision making associated with low dose exposures (see editorial in this issue of the journal). The meeting was organised around seven themes with suitably long discussion times, to each of which was allocated a moderator to report on the consensus or lack of it. All the documents that the moderators considered important for discussion were previously circulated. The themes and moderators were: *Dose-effect relationships at low exposure* (J Hughes), *interest of laboratory approaches for evaluating the effects of low doses* (T W Hesterberg), *measurement of dose* (T Schneider, G Burdett), *rational approaches for determining exposure standards* (P Brochard), *identification and assessment of co-factors* (J Bignon), *methodology needed for collaborative epidemiology* (D Hémon), and *tools for pooling data and for pooling knowledge* (A-J Valleron). Also, a single session was devoted to a presentation of 10 ongoing studies in Europe (M Albin, Lund (Sweden); J Ameille, Paris (France); Y I Baris, Ankara (Turkey); K Browne, Northfolk (UK); S H Constantopoulos, Ionnina (Greece); S A Jaffrey, London (UK); C Magnani, Turin (Italy); F Mollo, Turin (Italy); M Neuberger, Vienna (Austria); C G Ohlson, Örebro (Sweden).

Dose-effect relations at low exposure (J Hughes)

Three state of the art papers were presented. These were *Exposure-response in asbestos related lung cancer* by J C McDonald, *mesotheliomas without identifiable exposure to asbestos* by J Bignon, and *man made fibres and cancer* by R Saracci.

Numerous epidemiological and experimental studies have established that all asbestos mineral types are carcinogenic, with risk increasing with exposure. Few studies have been able to examine risk in relation to quantitative estimates of exposure, however; these have all involved workers occupationally exposed to asbestos (see for example⁴). Current concern involves potential cancer risk from exposures far lower, often orders of magnitude lower, than those of workers studied. One approach to estimating risks for low exposures is the extrapolation of exposure-response data to these lower levels using mathematical modelling.

For asbestos related lung cancer, risk has generally been linearly related to cumulative exposure but with great variability in the slopes of the lines. This variability is consistent with extensive evidence that other aspects of exposure are major risk factors; these include fibre type, dimension, and durability in human lung tissue.

The evidence increasingly indicates that, fibre for fibre, risk is appreciably greater for amphibole than

for chrysotile exposure, and greater for long fibres than short. Apart from asbestos textile manufacturing, the shallowest slopes were found for chrysotile exposures (mining and manufacturing), intermediate for mixed fibre manufacturing, and steepest for amphiboles (mining and manufacturing). For the three asbestos textile cohorts (one using only chrysotile, the others using both amphiboles and chrysotile) slopes were similar and steep. The relatively steep slopes for textile manufacturing might be explained by a greater percentage of long fibres than in other industries, an explanation consistent with the evidence from animal experiments of greater risk from long fibres.

The basic question of the appropriateness of extrapolating results for past workers to much lower exposure levels, an approach which assumes that any amount of exposure, no matter how small, increases risk of cancer. There is also the practical question as to whether concentrations of asbestos exist at which risk is sufficiently low as to be acceptable to those exposed. Such decisions are societal but must be based on scientifically valid data regarding risk. Possibly relevant to risk of lung cancer are several studies indicating that asbestos induced lung cancer may be a complication of lung fibrosis, as there is general agreement that very low exposure will not result in identifiable fibrosis.

Among men, incidence of mesothelioma has been increasing in industrialised countries for several decades, most, if not all, of this increase being attributed to the increased use of asbestos beginning 50 years ago. Incidence among women has not exhibited a clear trend, suggesting that non-occupational risks are too low to be detected. Virtually every investigation of mesothelioma cases has identified persons without known exposure to asbestos, and comparisons of lung fibre burdens of cases with controls have found cases without raised fibre concentrations. The difficulty is in determining whether these cases are due to low environmental exposures or to other factors.

Based on several studies showing that incidence of mesothelioma increases as a power of time since the beginning of exposure, and that risk increases with intensity and duration of exposure, a mesothelioma model has been derived that can be used for estimating risk at low exposure. Although there are considerable uncertainties regarding the model, it has been shown to provide a reasonably good fit to the available data.

The long term health effects of man made mineral fibres (MMMFs) have been the object of epidemiological and experimental investigation over the past 15 years (see for example,^{5,6}). There have been three large mortality studies, including over 40 000 workers, some hired over 30 years ago. No excess risk of mesothelioma was seen in these cohorts

and lung cancer risks were not significantly increased for glass wool workers. Rock wool and slag wool workers showed raised risk for lung cancer, however, probably related to these industrial exposures, especially those during the early production processes. Because quantitative exposure-response relations have not been found, no quantitative estimates of risk for MMMF exposures can be made with confidence. No results of mortality among ceramic fibre workers have been published. An IARC Working Group⁷ classified all three categories of man made mineral fibres as "possibly carcinogenic (2B)". The classification for glass wool fibres remains particularly controversial, as it is not supported by the epidemiological evidence and the experimental data are not clearcut.

Laboratory approaches to evaluating the effects of low doses (T W Hesterberg)

Three state of the art papers were presented. These were *utility of the animal experimentation approach in the evaluation of the effects of low exposure* by J M G Davis, *relevance of in-vitro assays for the evaluation of low dose effects* by M C Jaurand, and *chronic inhalation toxicity study of an experimental man made vitreous fibre* by T W Hesterberg.

Several laboratory models have been developed to study the toxicology of natural and man made fibres. Intracavity injection studies in animals have shown the importance of fibre dimension in the induction of mesotheliomas.^{8,9} Cell culture studies have identified a number of plausible mechanisms by which fibres could cause cancer.¹⁰ These in vitro studies have shown that neoplastic transformation of cells in culture by fibres is associated with structural and numerical changes in the chromosomes.¹¹ These types of systems will continue to provide valuable insight into biological mechanisms and those fibre properties that are their determinants. They may also be useful as screening tests for determining the relative toxicity of fibres.

Injection of fibres into animal cavities bypasses all respiratory defence mechanisms of the lung and could produce excessive or overload doses in the target tissue. When fibres are injected into the pleura or peritoneum of an animal, not only is the natural pathway of the respiratory tract bypassed, thus eliminating innate anatomical fate and any potential for normal clearance, but the concomitant leaching, degradation, fragmentation, or other transformations are unlikely to be the same as after inhalation. The pathogenicity of fibres is known to be influenced by some of these transformations. Thus fibres injected into the pleura or peritoneum may be qualitatively and quantitatively different from fibres that have been inhaled and translocated to the target issue. These weaknesses of intracavity injection studies severely limit their relevance for quantitative human risk assessment.¹²

Inhalation is the only route of exposure to fibres that has been associated with disease in humans. Thus animal inhalation models are the most relevant for assessing the potential carcinogenic risk of fibres to humans. The animal model must be capable of reproducing the asbestos related lung diseases observed in humans, including fibrosis, lung cancer, and mesothelioma.

A chronic inhalation study in animals should include adequate exposure of the target tissues and animals should be monitored for tumour formation throughout their lifetime or until 20% survival occurs. The dimensions of the fibres used in these studies should allow deposition into the deep lung regions, which are the primary target for lung toxicity. Therefore, it is important that fibres used are preselected for their size and that the aerosol generation equipment does not alter this, or increase the non-fibrous particulate fraction. At least three exposure concentrations should be used to determine the dose-response relation of any changes induced and also to determine the no effect level. The effects of the lower concentrations in animal lungs can provide information on the potential effects of low dose fibre exposure in humans.

A number of chronic inhalation studies have been conducted using man made fibres and several more are in progress. The results of these studies vary, depending on protocol and fibre type, but they have provided a very useful insight into the factors that may be important in assessing the potential for adverse effects. For example, the durability of MMMFs within the lung seems to be one of the critical determinants of their chronic toxicity and tumorigenicity. Extremely durable fibres such as refractory ceramic fibres are tumorigenic after chronic animal inhalation.^{13,14} Less durable fibres, such as fibrous glass, have not been shown to be tumorigenic after chronic inhalation.¹²

Measurement of dose (T Schneider, G Burdett)

Two state of the art papers were presented. These were *lung fibre analysis as an internal dose marker of low level exposure* by B Case and *critical review of the results and methodologies for evaluating mineral and man made fibres in buildings* by G Burdett.

EXPOSURE AND DOSE

Exposure can be defined as the presence of a potentially noxious substance available for interaction with host, whereas *dose* is the total integrated amount of exposure that is received by the host.

Exposure to airborne fibres can be characterised quantitatively by the use of time-concentration profiles, where the time integral of the concentration $\int_{t_1}^{t_2} C(t)dt$ is referred to as cumulative exposure or dose for the defined period of time (t_1 , t_2). The

duration of the sampling period is often a limitation in that personal samples are rarely run for more than four or eight hour periods and static samples may run for one to five days. This limits the possibility of detecting periods of high and low exposure which may have a seasonal or maintenance cycle.

The concentration of fibres in lung tissue is often referred to as lung burden. This is not considered to be a reliable measure of dose as there are differences in tissue fibre concentrations between lung lobes, lung parenchyma, subpleural and parenchymal areas, and even between immediately adjacent sites. Also, fibres are cleared, redistributed, and also possibly dissolved at varying rates so that the measured tissue burden does not represent a time integral of all fibres that at a given time have been present in that tissue. The participants agreed that lung burden measurements, although variable, do show correlation with the risk of disease and provide a marker for individual lung burden in the absence of measurements of environmental exposure although they are not a substitute for them.

No simple measure of dose exists and at present periodic environmental monitoring of the airborne exposures on a person or site specific basis are used to estimate cumulative exposure. This is usually measured directly or converted into an index of exposure based on the measurement of fibres $> 5 \mu\text{m}$ long with aspect ratio $\geq 3:1$ as determined by phase contrast microscopy (PCM).¹⁵ Further information such as the complete distribution of fibre sizes (length by diameter) in the airborne dust or samples for experimental purposes, together with fibre mineralogy, surface chemistry, and durability may be essential for more specific dose determination. Surface characteristics, in conjunction with measures of durability, are areas of potential further investigation.

ASSESSING PAST EXPOSURE

Whereas future measurements are important, risk estimates must be based on past measurements. To obtain information on historical exposure, several methods are at our disposal.¹⁶

(1) Reconstitution of historical exposure scenarios can give quantitative information on type and level of past exposure.

(2) Exposure assessment can be based on *algorithms* for ranking past exposure on an absolute scale from plant area job specific information; *statistical models* with the fit used for extrapolation of incomplete exposure measurements; and *deterministic models*, which include the physics of dust generation and exposure.

All these methods are promising and should be further developed. A view was expressed that a job exposure matrix approach would not work for low exposed cohorts.

(3) Lung tissues from necropsies. Lung tissue analysis¹⁷ is affected by many methodological and technical aspects. Some improvements were proposed including: *reference levels* against which to judge a possible exposure should be established by the same laboratory using the same method. This notion implies that no generally applicable background lung burdens can be established at present; *interlaboratory comparisons* to establish background tissue levels, which do not exist at present; *more uniform reporting* of the many fibres other than asbestos (rutile, diatoms, aluminium silicates, gypsum) which account for about half of the lung burden in the general population. *Population based* necropsy studies are feasible and deserve consideration in countries having compulsory autopsy.

MICROSCOPY MEASUREMENTS

Whereas the comparatively large fibre diameter and the isotropic nature of common MMMFs (for example, glass wool, rock wool, and slag wool) allow evaluation by optical microscopy, asbestos and other mineral fibres in the non-occupational environment must be evaluated by analytical electron microscopy. Analytical transmission electron microscopy (ATEM) can be used to reliably identify and size the smallest mineral fibres. Analytical scanning electron microscopy (ASEM) can be used to count and obtain some identification, based on chemistry, of fibres visible by phase contrast optical microscopy, but has serious limitations for analysing fine fibres or those with low atomic weight elements such as sodium.¹⁸

The data available for background airborne asbestos and MMMF exposures in buildings³ suggests that in terms of fibres $> 5 \mu\text{m}$ long, analytical sensitivities for individual samples of the order of 0.0001 to 0.00001 f/ml are required to attempt statistically meaningful estimates of occupant exposures. Due to the presence of non-asbestos materials most electron microscopical methods cannot exceed loadings of 41/mm² of exposed filter area requiring that at least 2.5 mm² of filter area be examined to achieve an analytical sensitivity of 0.0001 f/ml. This amount of effort, although possible, is expensive and the use of multiple samples to better characterise the building, which, when combined, give the target analytical sensitivity, is the preferred sampling strategy.

CONCENTRATIONS OF FIBRES IN BUILDINGS

Average airborne concentrations of fibres $> 5 \mu\text{m}$ long in the occupied spaces of buildings without significant damage are of the order of 0.0001 f/ml for MMMF and asbestos. Personal exposures will be significantly higher for maintenance workers who regularly disturb asbestos materials. The effect of such disturbances on the cumulative exposure of building occupants, taken as a whole, is unlikely to contribute significantly given the limited temporal

and spatial extent of most maintenance activities in occupied rooms.

Rational approaches for determining exposure standards (P Brochard)

Three state of the art papers were presented. These were *review of methods of mathematical extrapolation for risk assessment* by G Thomas, *use of experimental and epidemiologic data in establishing maximal exposure values in the general environment (indoor, outdoor)* by J Hughes, and *research and regulation of asbestos and mineral fibres in Japan* by T Higashi and M Kido.

Risk control policy is based on the equilibrium between the possible health consequences of using a chemical substance and the technical, social, and economic implications of it being controlled or banned. The quest for this equilibrium is at the origin of the evolution of concepts: toxicologists have added to the concept of "zero risk", defined for acute effects, the concept of "acceptable risk" particularly regarding long term chronic or carcinogenic effects.¹⁹ Adherence to this concept allows definition of exposure limits that might be considered to represent negligible impact—that is, minimal risk.²⁰

Toxicologists use two approaches to propose exposure standards: (1) the safety factor approach; (2) quantitative risk assessment.²¹

(1) The safety factor approach consists of weighting the no observable adverse effect level (NOAEL) by a coefficient called safety factor, enabling the determination of an acceptable exposure level in humans taking into account the need to protect high risk segments of the human population.²² This implies the existence of a threshold defined as the *subtoxic dose* which is not of sufficient magnitude to elicit a subsequent *observable response*.²³ Also, as far as cancer is concerned, the very notion of a threshold is debatable.²⁴ In these conditions the principle of application of a safety factor can be questioned: while a threshold can be observed at the level of a population, its determination at an individual level has not yet been shown²³; this is due to heterogeneous individual susceptibility. The US EPA has adopted the safety factor approach in its safety assessment of systemic effects other than cancer and gene mutations. It defines a reference dose as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime".²⁵

(2) Mathematical models have been largely developed for use in the quantitative risk assessment approach, especially concerning carcinogens. Most of the models have been developed from the levels of exposure found in experimental models and extrapolated to the low exposures in humans. Some

of them integrate both the problems of interspecies variations and the possibility of a dose-effect relation with or without a threshold. The interest of biologically based models²⁶ for extrapolation purposes was emphasised.

In the quite exceptional case of asbestos, as in that of ionising radiations, available data provided models for related cancer. For lung cancer, Hughes and Weill²⁷ used the relation $O-E = E(b/100)x$, where O is the number of cancers observed, E the cancers expected, b the variable slope in function of the cohort studied, and x the cumulative dose in f/ml × year. For mesothelioma they derived the equation: $I_{(t)} = Kc[t^{3.2} - (t-d)^{3.2}]$, where I is the incidence, c the average concentration in f/ml, t the latency in relation to the start of exposure, d the duration of exposure and K a variable coefficient depending on the cohort, from the equation initially proposed by Peto *et al.*²⁸ Despite the fact that coefficients b and K vary according to the industrial process and therefore the fibre type, the results of the computed risk assessment fit reasonably with the available data concerning occupationally exposed workers.²⁷ These models may overestimate the values at low doses by ignoring the notion of "effective threshold" proposed by Browne^{29,30} and illustrated by the increase in the latent period over the expected life span when reducing the dose. All major United States regulation agencies have adopted this methodology as a policy choice for making decisions on the consequences to public health of potential carcinogenic agents. They have, however, made a series of conservative assumptions (the worst-case plausible path of risk estimation), which can grossly overestimate health risk. This has been the object of passionate debates between the conservative protection of public health point of view and the realistic point of view taking into account the social and economic consequences of overly stringent and costly regulation.³¹

Finally, an even more complex problem is that of new fibres where a carcinogenic effect has been shown with experimental animals (usually at high doses) and where epidemiological data are not available. On what basis should we propose the exposure standards for humans?

Identification and assessment of cofactors (J Bignon)

What is covered by the term cofactor? Is it another carcinogen that strengthens the carcinogenic potential of fibres or is it a non-carcinogenic facilitating agent? Is it a host factor that increases the susceptibility of exposed subjects?

Although there were very few non-smokers in cohorts of asbestos workers, it has been shown that tobacco smoking increases the risk of lung cancer in relation to asbestos exposure.³²⁻³⁴ It is not known if

this is a synergistic effect of two carcinogens, benzo-a-pyrene in tobacco smoke and asbestos fibres, or if tobacco smoke works as a facilitating factor. An in vitro study has shown that tobacco smoke facilitates the penetration of asbestos fibres into bronchial epithelial cells in culture.³⁵ Elsewhere other carcinogens carried or absorbed by fibres, such as metals (particularly Fe²⁺) and chemicals might work in synergy with fibres. This hypothesis needs to be confirmed by more studies.

A second group of facilitating factors might be non-fibrous particles that are usually associated with fibres. Indeed, it has recently been shown in animal inhalation studies that such non-fibrous dusts increased the carcinogenic potential of fibres,³⁶ this putative factor has not been sufficiently assessed in animal or in human studies. The mechanisms involved in this synergistic effect are not known, but might be related to an overloading of the lung clearance systems. Also, other factors such as diet, particularly vegetable consumption, may be important, but to date have not been sufficiently investigated.³⁷

The host factors relate to the genetic or immunological susceptibility, neither aspect having been sufficiently explored. In future, we should focus on (1) family clusters of mesothelioma and childhood mesothelioma, (2) immunological responses at the alveolar and pleural levels before and during the initiation of lung cancer and mesothelioma to assess the effect of different doses and fibre types.

Methodology needed for collaborative epidemiology (D Hémon)

Three state of the art papers were presented. These were *objective exposure assessment* by T Schneider, *reconstitution of past exposures* by B Fallentin, and *the French experience of a mesothelioma register and review of other European experiences* by P Brochard.

Epidemiology has been successful in describing exposure-response relations in identifying sources of variability of occurrence of disease and in detecting hazardous environmental conditions that can be the target of preventive actions.^{38,39} This has led to a number of specific and basic requirements some of which are listed:

The *outcome* of concern should be precisely defined at several levels—namely, asbestos related diseases, lung fibrosis, lung cancer, or mesothelioma; intermediate effect (for example, fibrogenesis) reflecting high exposure and/or predicting more severe disease occurrence (pleural plaques); and direct exposure related effects (for example asbestos lung burden).

The *exposure* of concern should also be precisely defined—namely, type (type of asbestos fibre, distribution of lengths and diameters); level (in the environment and/or target organ); and duration (and age at exposure, time distribution, latency, age at risk).

The *base population* to which results seen in a sample can be generalised may be occupationally or geographically defined, and restricted (or not) to that considered to be at high risk because of age, sex, life-style and/or other environmental or constitutional conditions.

The choice of *study design* (cohort, case-control, cross sectional, case control within cohort) has strong consequences on the exposure-outcome associations that can be investigated with precision and power, the biases that can be controlled, and the type and quality of information that can be gathered.

Selection bias is a major problem in epidemiological investigations as movements in and out of a population as well as social correlates on participation in surveys can be closely related to health state.

Ascertainment of health state based on death certificates, register data, hospital records.

Ascertainment of exposure by subjective methods to reconstitute past environmental exposures, and/or by objective methods such as environmental measurements and biological clues of exposure or burden.

Confounders and effect modifiers may dilute or enlarge associations artificially.

The *power* of a study has also proved to be a major problem particularly concerning the interpretation of negative results.

Statistical analysis of data has also shown the great increase in power that results from the detailed definition and quantification of exposure and other parameters of interest.

“Weak associations epidemiology” is concerned with the problem of detecting and describing effects that in magnitude may be within the margin of variations of biases and random fluctuations. Thus the epidemiological community of scientists must identify and study problems that can be considered by epidemiological methods; (direct epidemiological evaluation of some exposure-risk associations, identification and validation of early lesions that are predictive of higher future risks, identification of particular segments of the population that are at higher risk to a given exposure, analysis of disease heterogeneity). This can only be achieved by active collaboration between investigators from a wide range of specialties.

Tools for pooling data and for pooling knowledge (A-J Valleron)

Two state of the art papers were presented. These were *meta-analysis in epidemiology* by D Costagliola and *the Delphi methods* by M Guiguet.

The number of subjects necessary to evaluate the potential risks of cancer associated with low exposures is so large that it can seldom be attained in any single study. Let us take the extreme example of the epidemiology of lung cancer associated with environmental low doses, Hughes and Weill²⁷ have

estimated the number of lung cancers attributable to six years of exposure to asbestos in schools. Without exposure 32 000 subjects are expected to die from lung cancer from a population of one million. Among a similar cohort exposed to 0.001 f/ml of mixed fibres, 0.6 additional lung cancers are expected. The relative risk is therefore 1.000019. This is an *expected* relative risk obtained from mathematical extrapolations. A prospective study aimed at showing with *facts* that *actually* the *observed* risk is as high as 1.000019 would require⁴⁰ two groups of 2 654 billion subjects ($\alpha = \beta = 0.05$). Therefore such risks can only be evaluated by mathematical modelling and the use of sensitivity analysis is crucial. Shifting to "low" exposures at work a well designed cohort study, based on data from the same paper of Hughes and Weill, would require two groups of 5 000 subjects to show that the relative risk of lung cancer is 1.05 for subjects exposed during 20 years at 0.5 f/ml, as would be expected from model projections. This implies collaborative works or meta-analysis.

Surprisingly some individual studies based on small numbers of subjects have led to figures of increased risk of cancer in subjects exposed to very low doses of asbestos. The two rational explanations are that the actual risk at such low doses is much higher than the one predicted from extrapolation models, or that the studies were wrong because of a bias in the measurement of the dose, or of the effect. Also, there could be a publication bias—that is, among numerous small studies, only those that led to "significant" results were published.

To obtain answers on risk assessment for exposures at work, it may be tempting to pool the results obtained from individual surveys to obtain sufficient statistical power. This is usually referred to as a meta-analytic approach. Only one meta-analysis study had been done in the field of epidemiology of gastrointestinal cancer associated with asbestos,⁴¹ whereas this approach has been used in several instances in studies of passive smoking in which one is faced with comparable methodological difficulties of risk assessment. Use of meta-analysis implies fulfilling two conditions, one avoiding publication bias by establishing a registry of all studies, two assessing that each of the constituting studies meet given quality criteria. Meta-analysis on its own may well not bring new knowledge but the procedure for systematically and critically examining studies according to a set of well defined rules might be valuable and informative, as noted by Dr Saracci.

As there are such great difficulties in directly assessing risk of cancer, alternative methods might be considered. Delphi methods, which rely on a panel of experts who try in an interactive, anonymous process to provide consensus values for unknown parameters of interest, were suggested as a possible help to assess what is a reasonable value for an acceptable risk.

Professor McDonald expressed the opinion that methodologically it remains more important to concentrate firstly on well established statistical methods to separate duration from intensity, to see whether the linear hypothesis is correct, and secondly on the incidence of indicator diseases, such as mesothelioma, in large populations.

Conclusions (A-J Valleron, J Bignon)

The following key conclusions were reached:

CONCERNING THE ESTIMATION OF RISKS

Although there are deficiencies and uncertainties associated with the dose-response relations between exposure to asbestos fibres and lung cancer and mesothelioma, extrapolation from the occupational derived dose response relations to indoor or outdoor low dose levels, such as might be encountered in buildings, suggests that public health risks are below those that can reasonably be measured. The question remains unanswered as to the possible risk associated with exposures below a measurable level, and the risk for custodians and maintenance workers who can at times be exposed to peak doses.

The data for man made mineral fibres are even less well defined than for asbestos. The order of magnitude of risk of lung cancer attributable to association with slag and rock wools remains controversial. Exposures to glass wool and to continuous filament glass fibres have not been associated with increased risk of lung cancer. Special attention must be directed towards protecting workers from exposure to long thin durable fibres such as some ceramic fibres, which have been shown to produce cancers in experimental animals by inhalation. The concept of biopersistence of natural and man made fibres needs further research, which will be the theme of the workshop on *biopersistence of respirable synthetic fibres and minerals* to be held 7–9 September 1992 at IARC in Lyon.⁴²

CONCERNING THE EXPERIMENTAL TECHNIQUES

Animal models offer the same limitations as epidemiological studies for assessing risks at low exposure. The parameters that must be taken into account to produce valid tests of fibres in experimental animals have been established and with refinements in defining of surface properties and biopersistence, there is a body of opinion that valid *in vitro*, *in vivo*, and short term animal models do exist that can be applied to rapidly test the potential of fibres of various dimensions to increase cancer risks. The advantages and limitations of various methods of measuring exposure by tissue analysis and by electron microscopical methods in quantifying airborne fibre concentrations are now reasonably well known. The future demands closer interaction between laboratories with increasing uniformity and attention

to the measurement and reporting of parameters designed to improve the knowledge of exposure and of mechanisms of disease causation and risk prediction.

CONCERNING THE EPIDEMIOLOGICAL METHODOLOGY

Because of the necessity of huge sample sizes, multicentre studies are essential to provide valid information on the possible effects in humans of low level exposures to natural and man made fibres. The development of alternative biostatistical methods and the improvement of the quality of existing mathematical and statistical approaches must be encouraged.

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Requests for reprints to: A-J Valleron, B₃E—Faculté de Médecine Saint Antoine, 27 rue Chaligny, 75571 Paris Cedex 12, France.

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Examples of common forms of references are:

- 1 International Steering Committee of Medical Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1979;1:532-5.
- 2 Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosino-phil chemotactic factor of anaphylaxis during cold challenge. *N Engl J Med* 1976;294:687-90.
- 3 Weinstein L, Swartz MN. Pathogenic properties of invading micro-organisms. In: Sodeman WA Jr, Sodeman WA, eds. *Pathologic physiology: mechanisms of disease*. Philadelphia: W B Saunders, 1974:457-72.