Scand J Work Environ Health 1983;9(1):1-8

<https://doi.org/10.5271/sjweh.2448>

Issue date: Feb 1983

Individual susceptibility to inhaled particles. A methodological essay.

by [Liddell D](#), [Miller K](#)

This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/6344199

This work is licensed under a [Creative Commons Attribution 4.0 International License](https://creativecommons.org/licenses/by/4.0/).

Individual susceptibility to inhaled particles

A methodological essay

by Douglas Liddell, PhD,¹ Klara Miller, PhD²

LIDDELL D, MILLER K. Individual susceptibility to inhaled particles: A methodological essay. *Scand j work environ health* 9 (1983) 1–8. Many workers severely exposed to inhaled particles have remained unaffected – what has protected them? Some workers have been affected despite mild exposure – what has rendered them vulnerable? There has been little progress in answering even the first question, and there can be no guarantee that factors rendering the lightly exposed vulnerable are the converse of those protecting the heavily exposed. An answer to the second question would be useful, say, for screening. But it requires study at the low end of the exposure scale, and there are many variables, probably intricately related, to be taken into account. A case/referent design might seem an obvious approach, but in its classical form it incurs essential and perhaps insurmountable difficulties. A longitudinal epidemiologic study would have to be very large, very complex, and very long in duration. Animal experiments also would have to be large and complex, probably embracing most of the animals' life span, but even so they could not take all relevant variables into account. It is recognized that the present paper has emphasized many difficulties and may thus appear negative in approach. Furthermore, although a compromise epidemiologic design is put forward, it is speculative.

Key terms: animal experiments, asbestos, coal mine dust, conditional analysis, epidemiologic design, HLA, low exposure, protection, quartz, vulnerability.

In the earliest description of asbestosis, by Dr Montague Murray in 1906, it was reported that, not only the proband, but all nine of his colleagues in the carding room where he started work had died at about the age of 30 years (14); no thought of differences in individual susceptibility arose. The classic report, in 1930, on effects of asbestos dust on the lungs, by Merewether & Price (31), revealed: "the outstanding importance of length of employment . . . and the negligible effects of age, on the production of fibrosis [p 11];" "a much longer average period of employ-

ment of the cases of fibrosis in the group in the least dusty process as compared with the other [equally dusty] groups [p 14]"; and that among those employed at least 20 years in the dustier processes the prevalence of fibrosis was 84.6 % (p 14, table 7). Despite this last figure, the prevalence in the complete sample was only 26.2 %, ie, 95 cases of fibrosis among the 363 persons radiographed. However the fact that nearly three-quarters of the subjects did not have radiological signs of fibrosis appeared to be explained completely by short employment or work in less dusty processes. Indeed the only questions raised on host susceptibility concerned age and sex, and both were discounted by Merewether & Price (31). As the prevalence of other fibroses could be higher – for instance in a chest radiographic survey of the 235 men working in an Ontarian gold mine in 1925, 122 (or 51.9 %) were found to have definite

¹ Department of Epidemiology and Health and Institute of Occupational Health and Safety, McGill University, Montréal, Canada.

² Immunotoxicology and Inhalation Department, British Industrial Biological Research Association, Carshalton, Surrey, England.

Reprint requests to: Prof D Liddell, McGill University, 3775 University Street, Montréal, Québec, Canada H3A 2B4.

silicosis (with or without tubercular complication) or suspected silicosis, less than half being truly negative (33) – the clear priority was dust suppression (31).

After the introduction of the Asbestos Regulations of 1931 in the United Kingdom, great improvements in occupational hygiene have been made which have been maintained in most occupational settings worldwide, especially since the 1950s. Far from being an almost inevitable outcome of long exposure to certain inhaled particles, disease has become comparatively rare, and for many years issues of individual susceptibility have been a major concern. Although there has been little progress in elucidating these issues, interest remains high, as evidenced by their discussion at four important recent conferences on the ill effects of inhaled particles and fibers: in Johannesburg (asbestos, 1977) (13); in Lyon (mineral fibers, 1979) (44); in Cardiff (inhaled particles generally, 1980) (47); and in Montreal (asbestos, 1982). It is not without interest that the 1982 meeting, in Chicago, of the American College of Epidemiology, warmly supported the suggestion by Dr Bernard Greenberg that the future of epidemiology (generally) might be mainly concerned with the elucidation of the variation in host susceptibility factors.

In our various capacities, we have been consulted at most stages, from initial design to manuscript review, of studies of these issues in relation to inhaled particles. These experiences have suggested to us the need for the current review; in it we make many statements that may appear self-evident but which we feel are required, because frequently full attention has not been paid to the principles enunciated.

Objectives for studies of variations in susceptibility

Objectives for studies of variations in susceptibility may concern either “protection” – from the effects of severe exposure – or “vulnerability” – despite scanty exposure. Until recently, the phenomenon of interest has been that, even among those with a working lifetime’s exposure to dust concentrations worse by several orders of magnitude than could be tol-

erated in the last quarter of the twentieth century, a substantial portion of workers remained unaffected. One example is the 188 male miners and millers in the city of Thetford Mines, who were 60–69 years of age and had been occupationally exposed for at least 40 years to chrysotile fiber concentrations averaging over 60 times the current British control limit. All 188 were still fit enough to be at work, and only 52 % had radiological signs of asbestos-related respiratory abnormality (25). The question arises as to what factors *protected* the 188 “survivors” and, among them, the 48 % without radiological abnormality. On the other hand an unusually high proportion (over 5 %) of the Canadian workers who assembled crocidolite gas mask filters for only a short period of time have so far succumbed to the otherwise extremely rare tumor mesothelioma (28), and the natural question is what factors played a role in the *vulnerability* of this minority to the development of tumors. A similar point has been made by Selikoff & Lee (42), but for all these examples the different biological mechanisms must be borne in mind. However, in any particular disease process, it remains essential to distinguish between protection and vulnerability, as discussed by Liddell and co-workers (22), ie, between no sign of disease despite massive exposure and definite disease associated with minimal exposure. It should be borne in mind that the reverse phenomena are not of great interest; in other words it is no surprise that disease should be overt in those whose lungs have been grossly insulted nor that pathological response is rare in the lightly exposed. Nor is there any guarantee that any protective factors revealed in the heavily exposed would be the converse of vulnerability factors in the lightly exposed.

For many years it has been possible to identify persons severely exposed occupationally to inhaled particles who yet fail to manifest signs or symptoms. Investigation of these subjects, and contrast with those similarly exposed but frankly diseased, has been the approach taken so far in studies of susceptibility (in the general sense). The mechanisms of protection are not without interest, but the concern now should be with vulnerability, particularly if the result could provide a potential

means of screening out those whom it would be unwise to employ.

For the present-day screening of individual workers it becomes essential to investigate at the comparatively low end of the exposure scale. There remain differences in approach which depend on the agent and how it acts, as illustrated by the following examples. *Coal mine dust*: progressive massive fibrosis very seldom attacks those not already showing at least category 2 of small rounded opacities in the International Labour Office's (ILO's) classification of radiographs of the pneumoconioses; furthermore only those few miners and examiners with the larger radiographic opacities (categories B and C) of progressive massive fibrosis have shortened expectations of life (8, 17, 19, 30). Therefore screening might be acceptable at early manifestation of coal workers' pneumoconiosis – which is thought not to progress after exposure has ceased – in the expectation that category 2 of small opacities (and hence life-threatening progressive massive fibrosis) could be prevented. *Asbestos*: so little is known of the effect of withdrawal from asbestos exposure, despite the work of the Becklake and Rubino groups (4, 37), that effective screening could only be on the grounds of factors measurable before any disease manifestation. *Quartz*: again screening would have to precede even preliminary diagnosis because fibrosis due to the inhalation of quartz dust is thought to be progressive (48).

Investigation of the effects of mild exposure is a comparatively new concept. To date the most valuable epidemiologic studies have been those including both severe and slight exposures and so have allowed an examination of exposure-response relationships (29), or those in which concentrations have been generally severe (41). However none of these studies were designed for, and so have not allowed, the elucidation of protective factors, let alone the clarification of factors related to vulnerability. As for animal experiments, they have, traditionally, been concerned with excessive exposures in order to achieve adequate response well within the life span of the species. (Indeed artificial routes of administration of particulate

matter have often been used to accelerate findings. Such an experiment may however be misleading in any circumstances; intrapleural injection of a fiber that could not have penetrated deeply into the human lung, or would soon have been eliminated and would not in any case have led to biological effects in the human pleura, might well produce animal effects unheard of in man.) Because of such excessive doses, the insults to the lungs, pleura, or peritoneum have been so massive that, by the end of the experimental period, all (or nearly all) animals were adversely affected, and thus it has not even been possible to investigate the question of protection.

A practical problem in screening is illustrated by the asbestos-smoking interaction in lung cancer. This interaction is very probably greater than additive (29, 39), but, in today's social climate, it would not be considered acceptable to deny employment involving asbestos exposure to smokers. The enhanced risk of asbestos-related disease in the presence of any specific factor would have to be truly enormous before screening action could be taken.

Clearly, the search for a means of occupational screening is daunting in the extreme. Nevertheless, because, as already described, interest in host factors still exists, it seems desirable to explore further some of the problems in studying them. Particular attention will be paid to differential vulnerability to low exposure to inhaled particles.

Measurements

Outcome

It will have become clear that, to achieve the last-stated aim, the response of interest must be not mortality (because it would be an extremely rare response to low exposure) but specific morbidity, or even minor biological effects. In man great difficulties arise because the signs and symptoms of occupational lung diseases (depressed lung function, cough, dyspnea, wheezing, etc) are not pathognomic. (This is of course true of most other pathological conditions.) It applies even to radiographic signs, which are generally considered the most specific to pneumoconiosis, as

the ILO classifications of radiographs of the pneumoconioses have warned for many years, and still do (18).

Another frequently asked question concerns the period, which is usually long (15–50 years, perhaps, in man), between first exposure to inhaled particles and even the earliest manifestation of disease. One aim of vulnerability studies might be to identify subjects in whom this “lag period” is comparatively short and to discover whether such shortening is due solely to normal biological variation or can be explained by other factors. Another complication is the possibility that the lag period depends on the level and pattern of exposure, as has been suggested for asbestosis (31) and for mortality from asbestos-induced lung cancer (40), although for the latter there is some evidence to the contrary (24).

Exposure

With many particles and fibers, only a tiny proportion of what is inhaled is retained in the lung for long periods. Asbestos retention rates appear to depend on whether exposure has been to chrysotile or to amphibole and on the dimensions of the fibers; long-term retention rates of specific fibers (measured post-mortem) are known to be highly variable (36). Rates also differ with *inert particulate matter*, and they probably vary with the form of inhaled particles. On the other hand *quartz* – because of its cytotoxic properties – is more or less permanently retained in the respiratory system (21). Furthermore, it is likely that, for any specific dust, the proportions that penetrate and are eliminated from the human lung are highly variable, perhaps affected by infection, smoking, etc. Even if such variation is small, it could lead to large differences in fibrogenic or carcinogenic potential (12). At first thought, it seems that amphibole, because of its low solubility, might be less affected by this argument, but even were amphibole fibers not only to have fairly uniform penetration but were also retained indefinitely in most subjects, fundamental changes in the fibers themselves (9) could lead to even greater variability.

The degree of variation from each source may well differ considerably between

subjects, and such differences are not so far measurable in man, although they may be among the most important factors being searched for.

Another problem is whether exposure has been relatively constant, highly variable but more or less continuous, or intermittent, perhaps with exposure-free intervals of many years. Despite considerable past investigation, there is little evidence indicating what constitutes a reliable *model* of dose-response; accumulated exposure has been found to be an acceptable surrogate for dose in certain circumstances and has certainly illuminated discussion of the “usual” exposure-response relationships (5, 27, 29). However, even for this purpose, it is not entirely plausible on biological grounds, and it seems unlikely to be appropriate in the present context. Thus it would be important to evaluate the “profile” of each subject’s exposure.

Additional potential susceptibility factors

Studies of genetic factors in man, in relation to asbestos, coal mine dust, or other inhaled mineral particles, have not yet shown convincing associations with an increased frequency of specific major histocompatibility complex antigens, now generally termed HLA (11, 43, 45). This failure may perhaps be due to the paucity of evidence so far accumulated (6), but even where the association between HLA and disease is the strongest known, ie, in ankylosing spondylitis, 10 % of Caucasian patients lack the diagnostic antigen B27. This finding indicates that one or more genes other than B27 – possibly one not even linked to HLA – may also be involved (10). Indeed recent experimental evidence suggests that there may well exist a whole class of genetic determinants, not linked to HLA, that also control recognition of foreign substances (35). Moreover very few persons positive for B27 develop ankylosing spondylitis; the specificity is only about 8 %. How then could such an association – and we cannot expect a stronger one – be used for purposes of screening for employment? Thus genetic testing for vulnerability to any inhaled particulate matter is presently of restricted value.

Immunologic considerations of a rather different nature include which inhaled mineral dusts are accompanied by altered immunoregulatory mechanisms. Such alterations have been demonstrated with asbestos in both animals and man (15, 20, 32), but it is not known whether they are of genetic origin. Another possibility is familial weakness to all forms of respiratory disease, although such weakness has usually been associated with a component of hypersensitivity or atopy (38).

Further factors – some true host factors, others exposure-modified – which cannot be ignored include effort, minute ventilation, and mode of breathing. Although discounted 50 years ago under certain severe and specific conditions (31), even age at first exposure and sex have to be borne in mind. For example Peto (34) claims that the former is perhaps the most important risk factor for the development of asbestos-related mesothelioma.

Copathogens and interrelationships

Other pathogens, for instance, smoking, will probably also be involved, and other environmental coagents – as yet unidentified – have been postulated to be of major importance (2). The interrelationships between many of the variables mentioned in the various preceding paragraphs are, in our view, likely to be intricate, particularly correlations between behavioral and environmental factors. The corollary is that a positive finding from a study which did not embrace all the variables of potential interest may not have revealed the most important factors.

Study design

Epidemiologic aspects

There are three basic strategies for analytical epidemiology, ie, cross-sectional, case-referent and cohort, but the inherent disadvantages of cross-sectional surveys effectively rule them out in the present context (26). Walker has pointed out another possibility, ie, that data from cases only are satisfactory under certain circumstances, the proviso being that ex-

posure and vulnerability factors are not correlated (46). This proviso does not seem to apply generally, and so this approach is not followed in the present paper.

A *case-referent design* appears attractive at first sight. For this purpose, a case would have to be defined as a person showing at least some signs or symptoms of disease *due* to inhaled particles despite a *known* low level of exposure to such particles. Practically there are great difficulties over both the words emphasized in the previous sentence. These include the nonpathognomic nature of signs and symptoms. In addition the immediate reaction of most physicians to the presentation of a case (as just defined) is that the exposure cannot have been as low as reported; either there has been unrecorded exposure (for many possible reasons, such as temporary failure of control measures or exposure of a non-occupational nature) or, where personal samplers have been in use, the samplers have not been worn continuously or have malfunctioned. Becklake also refers to the possibility of “greater-than-average susceptibility” of the individual, but only in the clinical setting (3). A referent would be a subject free of signs or symptoms associated with disease related to inhaled particles although having had at least the same degree of exposure (unless exposure is unrelated to all other factors, which seems to us very unlikely). Despite difficulties over precise definitions, it should be comparatively easy to obtain agreement as to subjects who could be treated as referents. However, great care would have to be taken that the exposure of the referents was not so great that the issues of protection and vulnerability were confused.

Because cases are going to be rare, particularly in the future, a case-referent design might appear to be the only feasible approach. However it has effectively to be ruled out in its traditional form – where exposure would be assessed historically *after* the selection of cases and referents – because by definition some *advance* knowledge of exposure would be required in order to make the selection. Although it might be possible to incorporate the approach into a cohort study (see the following discussion), the result would be, in effect, only a means of analysis

(1, 27). In addition, if other factors have not been assessed throughout the period of follow-up, there would remain the "cart/horse" issue (16), ie, which factors present in cases but not in referents have contributed to the development of the disease and which are consequences of it.

Any effective *longitudinal* (or *cohort*) study would have to be very large because of the implication inherent in modern conditions of a low incidence of any response. In theory an "ideal" study might be devised. It would be longitudinal, following workers from their first employment, measuring each subject's exposure and all the other uninherited factors affecting him, each at frequent intervals (ie, effectively continuously), until such time as response is revealed. Clearly this procedure is quite infeasible; apart from the unconscionable effort, there is also the problem of labor turnover, particularly in early stages of employment and among the young – who might otherwise be the most suitable subjects because of having been uncontaminated by other agents.

Some longitudinal compromise might be considered. This compromise would also involve a fairly full preemployment examination for all men, but inclusion into the study group would occur only after the worst of initial turnover is past, ie, after say five years. Thereafter there would be a need for regular examinations, including immunologic tests, etc, although the interval between examinations might be perhaps two years. Personal samplers would still have to be worn continuously, but might be particularly long-running to reduce the measurement load. Work study would also be required of all subjects at frequent intervals.

A *rather different approach* would be to make a selection for study of "affected" and "unaffected" workers completely without regard to exposure, ie, abandoning the preceding definitions. This is of case-referent nature and so suffers from the problems of this basic design. However, it is not only simple in concept but also flexible, for example, in allowing matching (if deemed desirable) by such factors as age at study and sex. The unavoidable complication comes in the analysis, which would clearly have to be carried out *conditional upon exposure*. In other words, in

the discrimination between the affected and the unaffected, the exposure variables would have to be entered first. Given that the model of "exposure-response" is appropriate, it is possible, even likely, that the exposure variables would turn out to be the best discriminants; once they had been entered, the conditioned analysis – ie, *further* discrimination between the affected and unaffected in terms of the factors of real interest – could be insensitive (23). With an inappropriate model, however, discrimination in terms of unsatisfactory exposure variables might be so impaired that other factors could appear to be important artefactually. With a good model, the findings concerning vulnerability, even if essentially negative, could still be of real importance; with a bad model, the supposed positive findings could be misleading.

Animal experiments

Much of what we have written applies *mutatis mutandis* to the design of animal experimentation in this field. In particular the study of vulnerability to low exposure would require extremely large samples to provide a sufficient number of responders ("vulnerables") – despite low exposure – to justify their comparison with the remainder. An important consideration is that the animals would have to be closely monitored for long periods to insure that any response was not due to extraneous factors such as opportunistic infection (7). Certain of the discussed factors – activity patterns, mouth versus nose exposure, human host-susceptibility factors, etc – would be virtually impossible to examine in animal experiments. Whatever other factors might be investigated experimentally, there would remain the essential difficulty of extrapolating from animal experience to man.

These difficulties do not deny the role of animal experimentation in the investigation of human biological effects of inhaled particles, but the relevance of such studies lies primarily in biological and toxicological *mechanisms* – such as altered host reactions induced by alveolar macrophages subsequent to phagocytosis of the mineral dust – in the development of the disease.

Concluding remarks

There are two distinct objectives in studies of human "susceptibility" to disease induced by inhaled particles. The first is to discover what factors protect against disease in the situation of severe exposure; the second is to determine what factors are associated with vulnerability when exposure is slight. The first objective could probably have been achieved in the past but, because severe exposure should no longer exist, would be difficult to meet nowadays. The second could not, in our view, lead to positive action (eg, screening) unless tests were discovered with a specificity much higher than that presently observed.

However, as the second objective is potentially one of great practical relevance, we emphasize the following problems: (i) the need to examine the low end of the exposure scale, (ii) the very large number of possible factors that cannot be ignored, (iii) the difficulty of animal experimentation with exposures low enough to be relevant to today's problems, so that responders would be a tiny proportion, (iv) the essential, and probably insurmountable, difficulties of the "obvious" design (ie, a traditional case-referent study), and (v) the great expense of any longitudinal epidemiologic study large enough and long enough in duration to have acceptable power.

Perhaps the most promising possibility of progress lies in epidemiologic studies in which affected and unaffected workers are chosen without regard to exposure but are compared for susceptibility factors only after differences in exposure have been taken into account. Indeed should it turn out that, despite the caveats in this paper, "protection" and "vulnerability" were complementary after all (in which case the same variables would discriminate all along the exposure scale), this design, although imperfect, might be the only simple way of discovering that fact.

Acknowledgments

We thank many colleagues, especially MR Becklake, JC McDonald, R Oseasohn and DC Thomas, for help in improving earlier drafts. The views we express are

our own and must not be taken to commit any other individual or any organization.

References

1. Acheson ED. Comment on the evolving case-control study. In: Ibrahim MA, ed. *The case-control study: Consensus and controversy*. J chronic dis 32 (1979) 28–29.
2. Bazas T, Bazas B, Kitas D, Gilson JC, McDonald JC. Pleural calcification in North-West Greece. Lancet 2 (1981) 254.
3. Becklake MR. Asbestos-related diseases of the lung and other organs: Their epidemiology and implications for clinical practice. Am rev respir dis 114 (1976) 187–227.
4. Becklake MR, Liddell FDK, Manfreda J, McDonald JC. Radiological changes after withdrawal from asbestos exposure. Br j ind med 36 (1979) 23–28.
5. Berry G. Dose-response in case-control studies. J epidemiol community health 34 (1980) 217–222.
6. Bodmer WF. The HLA system and disease: The Oliver Sharpey Lecture 1979. J r coll physicians london 14 (1980) 43–50.
7. Burrell R. Immunological reflections on asbestos. Environ health perspect 9 (1974) 297–298.
8. Cochrane AL, Haley TJL, Moore F, Hole D. The mortality of men in the Rhondda Fach, 1950–1970. Br j ind med 36 (1979) 15–22.
9. Crawford D, Miller K. Structure and structural changes in crocidolite asbestos associated with biological systems. Micron 12 (1981) 25–28.
10. Dick HM, Sturrock RD, Goel GK, Henderson N, Camesi B, Rooney PJ, Dick WC, Buchanan WW. The association between HL-A antigens, ankylosing spondylitis and sacro-iliitis. Tissue antigens 5 (1975) 26–32.
11. Evans CC, Lewinsohn HC, Evans JM. Frequency of HLA antigens in asbestos workers with and without pulmonary fibrosis. Br med j 1 (1977) 603–605.
12. Gibbs GW. Susceptibility to the asbestos-related diseases. In: Glen HW, ed. *Proceedings of asbestos symposium, Johannesburg, 3–7 October 1977*. National Institute for Metallurgy, Randburg, South Africa 1978, p 114.
13. Glen HW, ed. *Proceedings of asbestos symposium, Johannesburg, 3–7 October 1977*. National Institute for Metallurgy, Randburg, South Africa 1978.
14. Harries PG. The effects and control of diseases associated with exposure to asbestos in Devonport dockyard. Institute of Naval Medicine, Gosport 1971, p 11. (Report CRWP 1/71).
15. Haslam PL, Lukoszek A, Merchant JA, Turner-Warwick M. Lymphocyte responses to phytohaemagglutinin in patients with asbestosis and pleural mesothelioma. Clin exp immunol 31 (1978) 178–188.
16. Hill AB. *A short textbook of medical statistics*. Hodder and Stoughton, London 1977, pp 285–296.

17. International Labour Office. Third international conference of experts on pneumoconiosis (Sydney, 1950). Geneva 1953.
18. International Labour Office. Guidelines for the use of ILO international classification of radiographs of pneumoconioses. Revised edition 1980. Geneva 1980, p 3. (Occup safety & health ser no 22 (rev 80)).
19. Jacobsen M. Dust exposure, lung diseases, and coalminers' mortality. Doctoral dissertation. University of Edinburgh, Edinburgh 1976.
20. Kagan E, Solomon A, Cochrane JC, Kuba P, Rochs PH, Webster I. Immunological studies of patients with asbestosis: II Studies of circulating lymphoid cell numbers and humoral immunity. *Clin exp immunol* 28 (1977) 268-275.
21. Klempman S, Miller K. The *in vivo* effects of quartz on rat thoracic lymph nodes. *Br j exp pathol* 58 (1977) 557-564.
22. Liddell D, Eyssen G, Thomas D, McDonald C. Radiological changes over 20 years in relation to chrysotile exposure in Quebec. In: Walton WH, ed. *Inhaled particles IV*. Pergamon, Oxford 1977, pp 799-813.
23. Liddell FDK. Multivariate response in more than one sample. *Statistician* 26 (1977) 1-15.
24. Liddell FDK. Latent periods in lung cancer mortality in relation to asbestos dose and smoking. In: Wagner JC, ed. *Biological effects of mineral fibres*. International Agency for Research on Cancer, Lyon 1980, pp 661-665. (Scientific publication 30).
25. Liddell FDK, Gibbs GW, McDonald JC. Radiological changes and fibre exposure in chrysotile workers aged 60-69 years at Thetford Mines. *Ann occup hyd* 26 (1982) 889-898.
26. Liddell FDK, McDonald JC. Survey design and analysis. In: McDonald JC, ed. *Recent advances in occupational health*. Churchill Livingstone, Edinburgh 1981, pp 95-105.
27. Liddell FDK, McDonald JC, Thomas DC. Methods of cohort analysis: Appraisal by application to asbestos mining. *J r stat soc A* 140 (1977) 469-491.
28. McDonald AD, McDonald JC. Mesothelioma after crocidolite exposure during gas mask manufacture. *Environ res* 17 (1978) 340-346.
29. McDonald JC, Liddell FDK, Gibbs GW, Eyssen G, McDonald AD. Dust exposure and mortality in chrysotile mining, 1910-75. *Br j ind med* 37 (1980) 11-24.
30. McLintock JS, Rae S, Jacobsen M. The attack rate of progressive massive fibrosis in British coalminers. In: Walton WH, ed. *Inhaled particles III*. Unwin, Old Woking 1971, pp 933-952.
31. Merewether ERA, Price CW. Report on effects of asbestos dust on the lungs and dust suppression in the asbestos industry. His Majesty's Stationery Office, London 1930.
32. Miller K, Weintraub Z, Kagan E. Manifestations of cellular immunity in the rat after prolonged asbestos inhalation. I Physical interactions between alveolar macrophages and splenic lymphocytes. *J immunol* 123 (1979) 1029-1038.
33. Paterson JF. Silicosis in hard-rock miners in Ontario. Ontario Department of Mines, Toronto 1959 (Bulletin 158).
34. Peto J. The incidence of pleural mesothelioma in chrysotile asbestos textile workers. In: Wagner JC, ed. *Biological effects of mineral fibres*. International Agency for Research on Cancer, Lyon 1980, pp 703-711. (Scientific publication 30).
35. Rosenstreich DL. Genetics of resistance to infection. *Nature* 285 (1980) 436-437.
36. Rowlands N, Gibbs GW, McDonald AD. Asbestos fibres in the lungs of chrysotile miners and millers - A preliminary report. *Ann occup hyg* 26 (1982) 411-415.
37. Rubino GF, Newhouse ML, Murray R, Scansetti G, Piolatto G, Aresini G. Radiologic changes after cessation of exposure among chrysotile asbestos miners in Italy. *Ann ny acad sci* 330 (1979) 157-161.
38. Salvaggio JE. Immunological mechanisms in pulmonary diseases. *Clin allergy* 9 (1979) 659-668.
39. Saracci R. Asbestos and lung cancer: An analysis of the epidemiological evidence on the asbestos-smoking interaction. *Int j cancer* 20 (1977) 323-331.
40. Seidman H, Selikoff IJ, Hammond EC. Short-term asbestos work exposure and long-term observation. *Ann ny acad sci* 330 (1979) 61-89.
41. Selikoff IJ, Hammond EC, Seidman H. Mortality experience of insulation workers in the United States and Canada, 1943-1976. *Ann ny acad sci* 330 (1979) 91-116.
42. Selikoff IJ, Lee DHK. *Asbestos and disease*. Academic Press, New York, NY 1978, p 279.
43. Turner-Warwick M. HL-A and asbestos-related lung disease. *Br j dis chest* 71 (1977) 219-220.
44. Wagner JC, ed. *Biological effects of mineral fibres*. International Agency for Research on Cancer, Lyon 1980. (Scientific publication 30).
45. Wagner M. Preliminary report on immunological studies of persons exposed to asbestos. In: Glen HW, ed. *Proceedings of asbestos symposium, Johannesburg, 3-7 October 1977*. Institute of Metallurgy, Randburg, South Africa 1978, pp 113-114.
46. Walker AM. The use of case series data for risk assessment. In: Prentice R, Whittemore AS, ed. *Environmental epidemiology: Risk assessment*. Proceedings of 8th SIAM Institute for Mathematics in Society Research Application Conference, Alta, UT, June 1982. Society for Industrial and Applied Mathematics, Philadelphia (in press).
47. Walton WH, ed. *Inhaled particles V*. *Ann occup hyg* 26 (1982) 954 p.
48. Ziskind M, Jones RN, Weill H. Silicosis. *Am rev respir dis* 113 (1976) 643-665.

Received for publication: 24 June 1982