plants to cover bales of rags before shipment. A possible asbestos related cancer risk may also exist in other non-asbestos occupational setting previously thought to present little risk to workers.1

Hilt also raises the intriguing question of asbestos disease risk among "maintenance workers." Lilis and her co-authors studied chemical industry maintenance workers2 and she has recently co-authored a study of maintenance personnel employed by the New York City Board of Education.3 This study was conducted to evaluate the health status of those employees considered by the Board potentially to have had occupational exposure to asbestos materials. Of 115 workers examined, 23\% had x ray abnormalities consistent with exposure to asbestos. A significant burden of asbestosis was found to exist among this group even when individuals with previous shipyard exposure were excluded (26\%).

The United States Environmental Protection Agency estimates that about 30 000 school buildings across the United States contain friable asbestos. These materials may pose an important risk to the health of a large workforce of maintenance personnel previously thought not to be at risk. As suggested by Hilt's study, continued surveillance of such groups will provide the important information necessary to define clearly the risk of developing non-malignant and malignant asbestos diseases due to indirect asbestos exposure.

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References


Investigating dose response relations on occupational mortality studies

SIR,—Swaen and Volovics in this journal (1987;44:642–4) and Whittemore in the American Journal of Industrial Medicine have independently discussed an approach to the calculation of dose response relations in occupational mortality studies that looks at the problem of determining risk when employment and observation times overlap. These authors have pointed out that risk among workers with longer employment times may be underestimated, compared with workers with briefer employment, if all of the person-years of observation used to calculate SMRs are attributed to the longest employment category. To avoid an artefactual flattening of the dose response relation, they propose a method by which person-years of observation are left behind in exposure categories pertaining to shorter periods of employment as a worker continues in employment and subsequently moves into categories of longer employment. Distributing person-years in this manner is an improvement over the method that attributes person-years to the highest exposure category, but invalid inferences may still be drawn for those diseases such as lung cancer and mesothelioma in asbestos workers in which the risk of disease varies with the length of time from first exposure.

Implicit in the calculation of the SMR is the assumption that the risk among any subgroup of workers is a constant multiple of the underlying risk in the comparison population. If this assumption does not hold the SMR is uninformative as a summary measure. Whittemore cites an extreme example in which an occupational exposure increases the death rate among men but decreases it among women. An overall SMR for both sexes combined is uninformative here and sex specific SMRs are required. In the case of many occupational exposures the annual risk of disease is not constant, but varies with the period from first exposure. Asbestos associated lung cancer, for example, does not usually become apparent until 15 or more years from first exposure whereas the incidence of mesothelioma increases with the third or fourth power of time from first exposure. In situations such as these a worker's risk, relative to that in the reference population, varies with time and the multiplicative assumption underlying the SMR is violated unless latency specific comparisons are made.

What is the effect of applying the proposed method of leaving behind person-years as workers move into longer employment categories? By logical necessity, the person-years left behind will be of shorter "latency" than the years contributed to longer employment categories, and the "average latency" will tend to increase from one exposure grouping to the next. If
risk varies with latency this difference in average latencies will force the SMRs in the shorter employment categories to be lower than those in the longer employment categories because the person-years in these shorter categories are diluted by the relatively lower risk person-years left behind by those workers moving on the the higher categories. The result is an artefactual steep dose response relation.\(^2\)

This conclusion is nicely illustrated with some data, shown in the table from a study of lung cancer risk among Ontario gold miners.\(^3\) The data are stratified according to an exposure variable, years in exposure weighted by an estimate of dustiness, and “latency,” the time since first exposure to dust. It is clear from the table that there is no increase in lung cancer risk until at least 20 years after first exposure. In addition, within each latency period there appears to be little variation in risk, an observation that is confirmed by a statistical test of homogeneity\(^4\) which indicates no significant differences among the SMRs in each latency group. Nevertheless, the data in column A, which are the totals for each exposure stratum, suggest a trend of increasing risk with increasing exposure, an impression which is confirmed by a Poisson regression analysis\(^5\) which fits a linear trend term \((p < 0.051)\). Column B in the table presents the data restricted to 20 or more years from first exposure. Two SMRs are changed from column A; the SMRs in the two lowest exposure strata are both increased as a result of elimination of the dilution effect of the low risk years before 20 years latency. Although the SMRs in the highest exposure categories appear to be somewhat larger than those of the lowest exposure categories, the strong impression of a dose response relation has disappeared. Poisson regression analysis indicates that the linear trend term is no longer significant \((p = 0.20)\) and that there is no significant variation about the mean SMR of 148.

It may be concluded that the time dependency of risk is an important factor that must be given consideration when dose response relations are examined. Trends must be examined within latency strata such that the multiplicative risk assumption of the SMR is satisfied. If the risk varies with time and a summary statistic is desired a weighted average such as is calculated to account for the effect of age or calendar period, might be computed.

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**References**


Dr Swaen and Volovics reply:

We agree with the comments made on our short article which considered only one particular issue in the analysis of occupational cohort studies when the epidemiologist intends to investigate dose response relations. Of course the concept of latency should be incorporated into the analysis and it should not be taken for granted that cause specific SMRs are a constant multiple of the underlying risk in the comparison group for each dose latency specific group.

Since the manifestation of the carcinogenic process, which the epidemiologist attempts to investigate by means of a cohort study, is strongly related to time, background incidence, occurrence of other carcinogens, and changes in exposure concentrations, this process becomes complicated. The more so because our understanding of the human carcinogenic process is limited.
Clearly the routinely performed crude person-time analyses are incapable of providing enough insight to unravel the part played by each factor separately in the aetiological process.

A better understanding of the carcinogenic process can lead to a refinement of the propositions used to justify the construction of analytical models that may be applied to the data. Among latency, other issues to be considered are: diminution of risk after termination of exposure, bioaccumulation of dose, existence of threshold levels due to dose dependent metabolism breakdown of DNA repair mechanisms, and the possible existence of a limited pool of susceptible subjects.

If we knew with certainty that only a small percentage of a cohort (say < 1%) was susceptible to the carcinogenic potency of a certain chemical this notion would have a major impact on the model to be applied to the data.1

Another issue that should be kept in mind in the analysis of dose response relations and not mentioned in our article is the often encountered steep decrease in exposure concentrations over time. Occupational exposure to vinyl chloride, for instance, has been estimated to have decreased over time from 1000 ppm between 1945 and 1955 to 300 and 400 ppm from 1966 to 1972 and even to concentrations smaller than 5 ppm after 1973.2 Evidently handling dose defined as duration of employment in the case of occupational exposure to vinyl chloride may be a gross oversimplification and may lead to an unrealistic analysis of the dose response relation.

It will be a long time before epidemiologists can formulate and test models encompassing all these issues.

References

Book reviews


In these proceedings of the 9th international meeting on N-nitroso compounds held in Baden, Austria, in September 1986 there are well over 100 separate contributions, divided into nine major groups: molecular and biochemical mechanisms, metabolism, reaction with macromolecules, methods for detection, biological effects, endogenous formation, laboratory studies on formation, measurement of exposure, tobacco and betel-quid carcinogenesis, and clinical and epidemiological studies. For someone not directly involved experimentally, the papers may appear formidable in their diversity and detail and the difficult problem of providing a link or thread to enable the outsider to understand the underlying importance of the various contributions has been approached by means of a five page overview.

Nitrosamines are often formed by reactions of amines and inorganic nitrite. Much interest in this reaction has been because of nitrites in food and tobacco. N-nitrosodiethanolamine can be formed by this type of reaction and has been found in metal working fluids. N-nitrosopiperazine can apparently be formed in vivo from piperazine. From papers presented at the symposium, occupational exposure to these nitrosamines does occur and is detectable using urinary monitoring. Nitrosamines are also used as an important tool for understanding cancer mechanisms, thus there is plenty of interest to the industrial toxicologist.

The book will be read by those who participated in the symposium or have a specific interest. One of the annoying features of the text, however, was the absence of proper citation of the references. Consequently, tracing back interesting work is impossible without a detailed knowledge of relevant reports and much of the usefulness of the work to the more general reader is lost. Because of this and the inevitable "bittyness" of the articles I do not think that the more general reader will find this book useful.

PAUL ILLING


The original edition of this book was published in 1982. It was based on the contributions to a conference. The present edition has been updated and expanded. There are 38 contributions and the individual contributions are usually short and inevitably there are repetitions. It provides, however, a comprehensive review of the occupational dermatoses. As the articles are still based on the lecture format, most contain lengthy tabulations, patch test batteries, the ingredients of acrylic cement, wood products chemical list, to mention only a few.

One of the longest chapters is on the problems associated with the production and processing of