CORRESPONDENCE

Re: Extended Follow-up of a Cohort of British Chemical Workers Exposed to Formaldehyde

Recently, Coggon et al. presented data from an extended follow-up of a cohort of British chemical workers exposed to formaldehyde (1). In 1984, Donald Acheson and Martin Gardner initiated the mortality study and circulated a prepublication draft of their report (2) to a peer group of epidemiologists and invited them to discuss it at the Medical Research Council’s Environmental Epidemiology Unit in Southampton. During the discussion, the important question was raised as to the most suitable population to use for comparison.

Although it may seem obvious to compare the rates derived from the group under investigation with those obtained from the local population for cancer mortality and morbidity studies, members of the audience queried whether it was appropriate for this study (2). By then, members of the audience were aware of a number of studies in which a comparison using local rates had been erroneous. One type of error arose in the study of mortality in a group of workers at a factory where antimony smelting took place (3). The study reported an excess of lung cancer deaths when national rates were used for comparison, which persisted when regional rates were used. A “shadow” study comparing the rate of cancer mortality among the study group with the rates derived from an even more restricted geographical unit effectively eradicated this excess (unpublished data) because the overlap between the study and the control populations was so great that, in effect, the subjects were being compared with themselves, and in consequence no excess mortality was to be expected.

Another complication in interpretation arises when most workers in the catchment area have been exposed to the same permutations and combinations of carcinogenic agents, such as when, for historic or economic reasons, noxious industries are juxtaposed. By comparing the standardized lung cancer rate by age and sex of the study group with the local rates, the magnitude of the cancer excess calculated will be an underestimate of the true risk.

For the epidemiologist studying the burden of common tumors such as bronchial carcinoma in a working-class population, there is often a need to use imperfect historic data, which were neither collected nor preserved for retrieval and analysis, and an awareness that there might be important confounding factors to consider and adjust for. Consequently, the epidemiologist has the option of making comparisons with national rates adjusted for social class. Coggon and his colleagues might care to discuss the merits of their comparing the study group with local geographic variations rather than social class–adjusted national rates.

Exposures that led to an excess mortality of less than 2% (for example, in the case of ionizing radiation) were once considered acceptable. With such institutions as the Royal Society categorizing “acceptability” of risk as an excess mortality of less than 1 in 100 000, researchers and epidemiologists should declare when the ability to detect such levels with confidence for bronchial carcinoma is beyond the limits of methodology. Although such frankness would permit the calculation with confidence of epidemiologic studies to workforces or their representatives and on the research ethics committees to whom study proposals are made, it is important that individuals involved in formulating public health policy be informed of the limitations of study population sizes and methodologies to measure such low-order risks. Coggon et al. (1) concluded that further follow-up of industrial cohorts, particularly those with relatively high levels of exposure to formaldehyde, may help resolve the outstanding uncertainties. What industry population size did they have in mind that would permit the calculation with confidence of the orders of risk at the exposure levels experienced occupationally and domestically?

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REFERENCES


NOTE

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As Dr. Greenberg points out, the optimal choice of reference rates in occupational cohort studies is not always straightforward. The advantage of comparison with data for the general population is that these data are often readily available and statistically stable. Bias may occur, however, if a substantial proportion of the reference population is materially exposed to the agent or agents under study or if they differ importantly in their exposure to other risk factors for the disease.

In our study, we calculated expected numbers of deaths for lung cancer from national rates, both with and without adjustment for local differences in mortality. Neither method is ideal. On the one hand, comparisons with the national population are potentially more prone to confounding by differences in smoking habits and in exposure to outdoor air pollutants. On the other hand, the local populations whose mortality was used to adjust expected numbers will have included proportionately more cohort members and therefore a higher percentage of individuals with exposure to formaldehyde. This proportion was still relatively small, however, and we therefore give greater weight to the locally adjusted analysis, although as we indicated, there remains a possibility of residual confounding.

Greenberg also raises the possibility of carcinogenic exposures in other industries near our study factories, a point that has been made by others (1). The potential for confounding would then depend on the extent to which cohort members had at some time worked in the industries concerned. If this were common, the case for a locally adjusted
comparison would be even stronger. If it were rare, a national comparison might have advantages.

Adjusting for social class would be another way of addressing nonoccupational confounders. However, we preferred geographical adjustment because place of residence seemed likely to provide a better proxy for relevant confounders (smoking and outdoor air pollution) and had been used in both previous analyses of the cohort (2,3).

The acceptability of risk entails value judgments that will differ from person to person and according to the nature of the hazard and the perceived benefits that accompany the risk. We agree that no epidemiologic study can directly exclude an excess lifetime risk of one in 100,000, except for an extremely rare disease. Nevertheless, epidemiology does contribute usefully to risk assessment, even when such low risks are of concern. An absence of detectably elevated risk in an adequately powered study of heavily exposed workers can provide strong reassurance that any risks from much lower exposures in the general environment will be negligible. Also, when exposure limits are set on the basis of toxicologic data, there will inevitably be uncertainties associated with the extrapolation from animals to man. It is therefore important to check, if possible, that epidemiologic data do not indicate a higher risk than would be predicted from animal model data.

In the case of formaldehyde, the available epidemiology is broadly reassuring, but additional data from cohorts such as ours could give greater reassurance or, alternatively, might lead to the identification of a hazard that is at present unclear.

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REFERENCES