Risk assessment of leukaemia and occupational exposure to benzene

Sir,—Swaen and Meijers (1989;46:826–830) have proposed a risk assessment of leukaemia based on three negative epidemiological studies of workers exposed to low concentrations of benzene.1,2 The risk assessment departs from the upper 95% confidence limit (SMR) that was assumed to be 100, based on 79 cases of leukaemia observed in these three studies. Exposure to benzene was assumed to have been 5 ppm for ten years.

Three questions come to mind: (1) Were all workers in the three cohorts exposed to benzene? (2) What was the actual level of exposure to benzene? (3) Was there any indication of a healthy worker effect, which could question the validity of the assertion that these studies were really negative?

From the quoted reports, the answer to the first question seems to be a rather clear no. In the study among petroleum industry workers by Thorpe,1 the author himself considers that less than 30% of the cohort had been exposed to benzene. The study by Rushton and Alderson2 was conducted among workers in the United Kingdom oil industry, "including some exposed to benzene", to quote the paper. It gave no indication about what proportion of the workers actually was exposed, but given the type of industry studied, it seems reasonable to guess that it was not most of them. The study by Parkes et al4 was conducted in the rubber industry, where exposure to benzene is restricted to some specific job categories.4 Again, there is no information in the paper to allow a reliable estimate of the proportion of those exposed but it is likely, given the wide range of occupational groups lumped together, that many were unexposed. It is apparent that one cannot assume that all workers were exposed to benzene in these studies. Even if those who were exposed did not show an excess incidence of leukaemia, the number of cases among the exposed was much less than 79, and consequently, the confidence limits of the SMR that were calculated underestimate the uncertainty by an unknown margin.

No reliable estimate of the true exposure to benzene seems possible from the published reports. The paper by Thorpe1 mentions some measurements for the exposed workers, which were mainly in the 1–4 ppm range. The other two papers supply no data on exposure at all. With such scant information, it is questionable whether one should attempt a quantitative risk assessment at all. A large uncertainty exists, which the authors do not adequately consider.

When comparing industry workers with the general population, the potential bias caused by the healthy worker effect should always be considered. Thorpe1 actually reported SMRs of 121 among the exposed workers, and 60 among the unexposed workers. Because of the small numbers of cases of leukaemia, neither was significantly different from 100, but a simple comparison of these numbers suggests both a healthy worker effect and a two fold difference in risk between exposed and unexposed personnel. A recent study reported in this journal1 has also suggested a healthy worker effect for leukaemia among male chemical workers unexposed to benzene. Swaen and Meijers do not discuss this potential bias, and it seems that at least suggestive evidence exists that (some of) the studies they selected were not that "negative" at all.

A small point concerns an error in the calculation of the SMR confidence limits. The limits should be 80–125 rather than 89–112; the authors have forgotten to take the 1.96 factor in their formula into account; this error changes the numerical outcome of their exercise considerably.

It would seem that the studies used in the risk assessment do not really permit an acceptable quantitative estimate of the risk of leukaemia associated with low level exposure to benzene. It is definitely valuable to use negative epidemiological studies in risk assessments, but we should make sure that the studies we cite are sufficiently informative for the purpose.

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The authors' reply:
The first point raised by Brunekreef is whether or not all the workers in the three negative studies were exposed to benzene. It is clear, as stated in our paper, that not all the cohort members were exposed to benzene and it would have been better to base the risk assessment on those subjects who did experience exposure. Other reports exist, however, of epidemiological studies of workers exposed to low concentrations of benzene in which no excess mortality from leukaemia has been found. Other studies of oil refinery workers generally are negative. Studies of coke plant byproduct workers do not show excess mortality for leukaemia, although it is certain that exposure to benzene was present.23 Studies in the American rubber industry provided evidence for a risk for lymphatic leukaemia after exposure to solvent, which contrasts with the generally accepted view that benzene only induces leukaemia of the non-lymphatic type.

It would require an extensive review of publications to identify all the cohort studies of workers who had also experienced co-exposure to benzene. In the chemical industry where exposure to benzene can be present and was definitely present in the past, occupational physicians are aware of the potential health risks, but case reports on benzene related cases of leukaemia in the industry are rare. The negative studies taken as a basis for risk assessment of low concentrations of benzene may not be flawless, but they represent a larger body of non-systematic information that points to a non-existing risk for leukaemia after
exposure to low concentrations of benzene.

Another issue raised by Brumkeeff is the possibility of a healthy worker effect. In the three studies combined, 79 deaths from leukaemia were found vs 83 expected. Thus there does seem to be a small healthy worker effect. To avoid bias from this, we did not work with the SMR of 95 (the actually observed SMR), but preferred to base the extrapolation on the SMR of 100. This, of course, makes the extrapolation more conservative. The SMR of 95 has an 95% upper value of 118. Furthermore, it must be clear that using a two sided confidence interval makes the extrapolation more conservative as it coincides with a one-sided interval of 97.5%.

The extrapolation based on the three negative studies was merely intended as an example and not as the only basis on which the risk evaluation was made. The purpose was to show that even after treating the negative studies with great uncertainty, they lead to a lower estimation of the risks than the positive studies of highly exposed workers.


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