LETTERS

PostScript

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Predictions of mortality from mesothelioma

The update of predictions of mortality from pleural mesothelioma in the Netherlands provides welcome news that the peak number and the total during 2000–28 are now predicted to be only a little more than half of the figures predicted only four years earlier. This marked change in prediction has occurred because the known decrease in asbestos use after 1984 and a ban in 1993 were taken into account in the modelling, and there were five extra years of data (1994–98).

Since most mesotheliomas are caused by asbestos the pattern of use during different periods of time has a marked influence on the risk in cohorts whose working lives covered different periods. The marked effect of the discontinuation of crocidolite importation by 1970 into the United Kingdom on the amount of crocidolite found in the lungs of men born in 1943 or later, who developed a mesothelioma between 1990 and 1996 when aged 36–52 years, was clear when compared with the lung contents of mesotheliomas in 1976 and 1977. The average amount of crocidolite in the lungs of the men with mesothelioma in 1990–96 was about a tenth of that in the lungs of the 1976–77 cases. This difference was a consequence of the shorter period of exposure and the longer time since exposure during which elimination of fibres occurred in the absence of new exposure.

The importance of the effect of elimination is illustrated by results from former workers at the Wittenoom crocidolite mine and mill in Western Australia. Exposure of this group ceased in 1966 when the mine and mill were closed. Based on an analysis of the number of deaths with mesothelioma in men to the end of 1986, predictions were made of the number occurring up to 2020. The model of the mesothelioma deaths rate used was that the rate increased with a power of time since exposure, moderated by a factor representing elimination of crocidolite fibres over time since exposure. Rates of elimination from zero to 15% per year were considered. Assuming no elimination, which was the usual model used at that time, predicted mortality from mesotheliomas by 2020 was less than twice as high.

Personal exposure assessment in the epidemiology of air pollutants

In commenting on our paper published recently in *Occupational and Environmental Medicine*, Kromhout and van Tongeren admonish us for paying insufficient attention to the earlier literature on occupational pollutant exposures. While no doubt an element of their criticism is justified, we feel that the exposure situation for the general public is sufficiently different that it should not be assumed that findings in the occupational environment can necessarily be extrapolated to environmental exposures of the general public. A large component of the non-occupational exposure arises from diffuse sources and may therefore be very spatially homogeneous at locations such as people’s homes which are often relatively remote from outdoor pollution sources.

There has been some controversy in the literature regarding the extent to which measurements at fixed central urban background monitoring locations can reflect the exposures of large urban populations who spend much of their time indoors at locations relatively remote from the monitoring station. It has been typical to find that for an individual, daily personal exposures correlated with concentrations at the monitoring station, while if data are pooled from many individuals, the exposures appear to be uncorrelated with ambient air data. This finding suggests that the diffuse background as represented by the central urban monitor does account for a substantial proportion of variance in the exposure of an individual, and this conclusion is supported by the lack of a strong association between personal exposure and ambient air concentrations in epidemiological studies, which would appear implausible if the monitoring data were uncorrelated to human exposures. The finding of our paper that microenvironment measurements do, in general, well represent individual personal exposures in that microenvironment (except for the personal cloud of PM10) is far from self-evident from much of the earlier literature and is a useful addition to knowledge.

The fact that cigarette smokers were outliers in the regression analysis shows not unexpectedly that they generate strong local concentration gradients and would therefore need to be treated differently in any modelling of personal exposures. In the absence of such local sources of pollution, our study supports the concept that suficient microenvironment measurement data available, it would be perfectly feasible to model personal exposures with some degree of reliability. Kromhout and van Tongeren advocate the use of personal exposure measurements in environmental epidemiological studies. In doing so, they fail to acknowledge the magnitude of such studies. For example, in the large North American cohort studies, 8111 subjects were recruited in the Harvard Six Cities Study and over one million in the American Cancer Society Study. Were it possible to reconstruct the exposure environments of those individuals, even in a rather general way from time activity diaries, a considerable refinement would have been achieved. Even in panel studies, which typically recruit a far smaller number of individuals, the subjects are frequently drawn from susceptible groups and therefore not willing to be encumbered with troublesome and heavy sampling equipment. It must be remembered that concentrations in environmental samples are typically orders of magnitude lower than in occupational samples, therefore requiring higher flow rates.

References

Mortality results for polyurethane manufacture understated

Sorahan and Nichols, writing in this journal, incorrectly understated the strength of evidence for work related increased mortality among their cohort of production workers in the UK flexible polyurethane foam industry. Their study actually found “some” evidence for a work related increase in all-cause mortality, respiratory disease mortality, and lung cancer mortality in this exposure circumstance, especially taking into account the healthy worker effect. We are concerned to correct this error, because the United Automobile, Aerospace and Agricultural Implement Workers of America (UAW) represents substantial numbers of workers exposed to this process, and the UK data provide the first evidence of a mortality hazard in this industry, in contrast to two previous, perhaps weaker studies.

The authors observed an all-cause standardised mortality ratio (SMR) among men of 107 (101 to 113), and a respiratory disease SMR of 120 (101 to 141). Increased mortality of similar magnitude from these causes was observed among the smaller number of women, and the SMRs for both genders combined were significantly increased. Raised SMRs for all-cause and respiratory disease mortality are hardly ever seen in occupational cohorts except for foundry and asbestos workers. Typically, the SMR for all-cause mortality is about 80 and the SMR for most cancer causes about 90 in the absence of exposure to a carcinogen at the site. We have observed SMRs for all-cause mortality as low as 60 in UAW vehicle assembly and stamping cohorts. We are sure that these authors noted a deficit for all-causes in the abstract of their previous study of this cohort, but make no mention of the excess in the present paper. For lung cancer, the authors noted a significant SMR of 181 (126 to 251) for lung cancer among women. They discount this partly because the SMR of 107 (90 to 227) among men was only slightly increased compared to the general public, without also noting that the combined SMR was 117 (101 to 136) and statistically significantly increased. The authors also fail to mention that the SMRs for pancreatic cancer were increased to a similar degree in both genders, and the combined SMR was 147 (102 to 212) and significantly increased. We believe that consistency in direction of effect is more important than statistical significance, especially in view of the healthy worker effect bias against seeing an effect if it were there.

These findings apply to an exposure circumstance with several suspect agents. The isocyanates are a group of mixtures and are non-malignant respiratory disease. Therefore, the increase in mortality from this cause is of distinct interest. In addition, pancreatic cancer has been associated with exposure to isocyanates, based on gavage studies of tolune diisocyanate. In our experience, the most substantial exposure with carcinogenic risk in foam moulding is methylene chloride, although brominated and chlorinated alcohol flame retardants, and formaldehyde are usually present in foam moulding operations. Catalyst amines may also be absorbed through the skin in physiologically significant amounts. These multiple exposures, often in different parts of the process, including off-gassing from stored foam, undermine the ability to see an effect of isocyanates alone.

We now turn to the exposure response portion of the study. Health related termination of exposure has previously been noted as an obstacle to finding an exposure response effect based on duration. Those with highest exposure to isocyanates would be expected to be sensitised and migrate into lower exposure jobs; in any event, there were only 19 of 1652 deceased workers with more than five years in higher exposed jobs, no lung cancer victims, and only two respiratory disease victims. In our view, the absence of an exposure response relation in a cohort with such a small higher exposed group detracts little from our concern for occupational cause of an observed excess. More damaging to the evidence of occupational causation is the absence of a monotonically increasing trend with latency from first exposure: The general trend of increased risk in exposure strata greater than 10 years latency, clearly significant for all-cause mortality, is not seen in those with greater than 30 years latency. However, we note that the all-cause and respiratory disease SMRs are at unity or above for this long latency strata, itself a highly unusual observation.

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Authors’ reply

Constructive informed criticism of occupational epidemiological studies from Trades Union representatives is to be welcomed, even though on this occasion the criticisms are levelled at ourselves. However, we are not convinced that it is fair to say that we made no mention of the excess SMR for all causes mortality when the second sentence of the results section stated: “In males, there were significantly increased SMRs for all causes (Obs 1298, SMR 107, p < 0.05) ...” It is fair to say that we did not attach very much importance to this slightly increased SMR. We remain convinced that is it is very unlikely that occupational exposures in any industry could have a discernible influence on all-cause mortality without obvious major effects on cause specific mortality being apparent. The finding of an all-cause SMR of 105 in the sub-cohort of male workers with any period of toluene diisocyanate (TDI) exposed employment is consistent with such a conviction. It should also be remembered that, in the UK at least, socioeconomic status has a major influence on all-cause mortality for reasons other than occupational exposure.

We also remain convinced that the excess SMR for female lung cancer is not due to isocyanate exposure because none of the female lung cancer cases had any period of isocyanate exposed employment. Dr Mirer suggests that occupational exposures other than TDI should be considered, and the usefulness and completeness of the study could be improved if it were possible to carry out a retrospective quantitative exposure assessment for all exposures of interest and for each of the 4612 unique factory/department/job entries in the study job dictionary. While we mentioned in our original discussion section that all the available human studies are “low” exposure studies, the particular limitation that only a little more than 1% of all deaths in our study occurred in subjects with five years or more of “higher” isocyanate exposure could also have usefully been mentioned.

We have never wished to suggest that the current UK update is the last word on the topic of possible long term health risks associated with the manufacture of flexible polyurethane foam. It is likely that an update of the epidemiological study of Swedish flexible polyurethane foam industry workers will be published in 2003, and it will be important to compare the Swedish findings with the recent UK findings. Finally, we apologise to compare the Swedish findings with the epidemiological study of Swedish flex-polyurethane foam. It is likely that an update topic of possible long term health risks current UK update is the last word on the usefulness and completeness of the study could be improved if it were possible to carry out a retrospective quantitative exposure assessment for all exposures of interest and for each of the 4612 unique factory/department/job entries in the study job dictionary. While we mentioned in our original discussion section that all the available human studies are “low” exposure studies, the particular limitation that only a little more than 1% of all deaths in our study occurred in subjects with five years or more of “higher” isocyanate exposure could also have usefully been mentioned.

In conclusion, this is the best short and well illustrated account of chemical weapons I have seen. The authors have sensibly stayed away from too much detail and controversy, but anybody following their advice will handle an incident involving chemical weapons in a safe and competent way. This is an excellent book that should be in every toxicologist’s library.

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Further information

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exonex is not discussed. This seems a weakness as some readers may think that HI-6 is readily available: it is not.

Further sections deal with decontamination and protection: suits and respirators are described. Managing an incident is described and the authors sensibly build their recommendations on how chemical incidents that do not involve chemical warfare agents should be managed. Detection systems are described. Detector paper, as well as complex instruments, is described and this is helpful: detector paper may have an important role to play in rapid checking of chemicals spilled on the ground. A nice device for detecting nerve agents is described: the Detection Ticket 90 system. The book concludes with a short glossary and a carefully chosen bibliography.

In conclusion, this is the best short and well illustrated account of chemical weapons I have seen. The authors have sensibly stayed away from too much detail and controversy, but anybody following their advice will handle an incident involving chemical weapons in a safe and competent way. This is an excellent book that should be in every toxicologist’s library.