Predictions of mortality from mesothelioma

The update of predictions of mortality from pleural mesothelioma in the Netherlands provides welcome news that the peak number of mesothelioma deaths in men occurred up to 2010. 

G Berry
School of Public Health, University of Sydney, New South Wales, Australia; gerryb@health.usyd.edu.au

A W Musk
Sir Charles Gardiner Hospital, Nedlands, Western Australia

N H de Klerk
Department of Public Health, University of Western Australia

A Johnson, D H Yates
Dust Diseases Board [NSW] Research and Education Unit, Sydney University

References


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 personal 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 exposure 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 correlate 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 supportive of causality in the time series in epidemiological studies, which would appear implausible if the monitoring data were unrelated 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 the pattern of sufficient 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 are 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.
Mortality results for polyurethane manufacture understated

Sorahan and Nichols, 1 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. 2 We are concerned to correct this error, because the United Auto mobile, 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. 3

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 both 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. 4 We have observed SMRs for all-cause mortality as low as 60 in UAW vehicle assembly and stamping cohorts. 5 We suspect that these authors mentioned 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. 6 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 population, 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 closely related and commonly used substances, which are calculated to be sensitised and migrate into lower exposure strata greater than 10 years latency, itself a highly unusual observation. The confidence intervals overlap between strata, so while there is not a significant increase, there is no inverse latency response relation. In addition, much the largest portion of this long latency group must have come from two of the 11 plants (factories 3 and 4 in table 1) where exposures may have been different to those in the other nine facilities.

In summary, this study has a highly unusual and statistically significant increase in all cause mortality and respiratory disease mortality in the cohort as a whole, currently in both men and women. For women alone, and men and women combined, there was significantly increased mortality for lung cancer, and for both genders combined, pancreatic cancer. This is certainly "some evidence" for work related mortality, respiratory disease mortality, and cancer mortality in the exposure circumstance of polyurethane foam production. The nature of the cohort gave little prospect for observing an exposure response relation, if it were there.

We also note that, unlike all the other papers in this edition of the journal, these authors have neglected to acknowledge their funding source.

8 National Toxicology Program. TR-251: toxicology and carcinogenesis studies of commercial grade 2 (40% isocyanate/60% toluene diisocyanate) (CAS No. 2467-62-5) in F344/N rats and B6C3F1 mice (gavage studies). 1986.

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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 it is very unlikely that occupational exposures in any industry could have a discernable 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” diisocyanate 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 our sponsors (International Isocyanates Institute, Inc.) for not mentioning them; we had not noticed that the provision of such information had become commonplace in Occupational and Environmental Medicine.

T Sorahan, L Nichols
Institute of Occupational Health, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK; t.m.sorahan@bham.ac.uk

BOOK REVIEW

Chemical Weapons—Threat, Effects and Protection


Current concerns about terrorism have raised the spectre of chemical warfare. Coming at the end of a period of chemical weapon disarmament among many countries this is depressing. The mid 1990s incidents involving the release of the nerve agent sarin on the Tokyo subway have confirmed the reality of the threat: what can be made once can be made, and used, again. Because of this, toxicologists, pharmacologists, and physicians need to have access to texts that provide information in this area.

Such sources are few but this small, very well illustrated and up to date book is one of the best—especially as an introduction to the field. The Swedish Defence Research Agency (FOI) has a long and distinguished history in providing information on the chemical weapons field: this book confirms the unusual level of expertise that FOI can bring to bear in this area.

The book begins with an account of the history of chemical weapons. This is short but surprisingly detailed. An account of disarmament follows—again very interesting—and then a description of chemical weapons munitions is provided. This contains a lot of difficult to find information with details of how terrorists have used chemicals to kill and maim. Toxicologists will be most interested in the section dealing with individual chemical warfare agents. The choice of substances is unsurprising, but the descriptions of mechanisms and effects are first class and some useful graphs I had not seen before are included. The distinction between sarin and soman in terms of the mild effects–severe effects gap (expressed in terms of concentration)—much narrower in the case of soman than sarin—is something I have not seen elsewhere. The description of the clinical effects of exposure to mustard gas is accurate, though the authors might have stressed the prolonged photophobia and lacrimation, seen in some cases, more strongly. Therapy is well described, with H1-6 figuring as the oxime of choice in nerve agent poisoning. The authors do not mention pralidoxime salts and do not discuss obidoxime, though they show its formula. Availability of oximes is not discussed. This seems a weakness some readers may think that H1-6 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.

R L Maynard

INSTITUTE FOR RISK ASSESSMENT SCIENCES, URECHT UNIVERSITY, NETHERLANDS

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