CORRESPONDENCE

An epidemiological study of workers potentially exposed to ethylene oxide

Sir,—We were surprised to see the recent publication by Wong and Trent (1993;50:308–16) of a mortality study of 18 728 workers exposed to ethylene oxide. Wong and Trent have analysed the data from the study originally conducted by ourselves at the National Institute for Occupational Safety and Health (NIOSH) in collaboration with the National Cancer Institute (NCI). Wong and Trent did their study based on the personnel records that we microfilmed and sent to them at the request of the companies studied. They have included 18 728 workers instead of our 18 254 (for reasons we do not understand), and they also have one additional year of follow up. Nowhere in their article do Wong and Trent cite our work,1 which was published fully a year before their article was accepted for publication (Wong was a reviewer of our work before its acceptance). Nor do they make clear that we initiated and designed the original study, that we collected the data at the 14 study plants (after visiting 35), that Wong was hired by the industry involved as a consultant, and that he was provided with the data we collected as a way of conducting an independent audit of our selection of the exposed from among all plant employees. Wong and the companies involved then decided to go further and conduct their own analysis of the data. Much of this background to the study has been described.2

For Wong and Trent to state that "we studied by far the largest cohort of workers exposed to ethylene oxide to date" without explaining this background is a misrepresentation of who actually did this study.

Wong and Trent’s results are similar to ours, as might be expected (both analyses are straightforward life table analyses), although their interpretation tends to downplay the carcinogenic risk of ethylene oxide. Despite general agreement, there are some problems with their analyses, primarily due to the fact that they did not code detailed work histories. For example, their analyses by latency (time since first exposure) are invalid, as they did not code dates of first exposure. This may account for some inconsistencies between our findings of positive trends for all cancers and haematopoietic cancer with latency and their failure to find such a trend.

We believe that the reanalyses of data, for the purpose of using new analytical techniques or for meta-analysis, is often worthwhile and NIOSH has often made its data available for these purposes. We strongly object, however, to Wong and Trent having conducted an essentially duplicate analysis without citing the prior analysis or fully explaining the origins of the data. We do not know the policy of your journal regarding this issue, but we suspect that you were unaware of our prior analysis.

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1 Steenland K, Stayner L, Greife A, et al. Mortality among workers exposed to ethylene oxide. N Engl J Med 1991;324:1402–7.
2 Steenland K, Stayner L, Greife A. Assessing the feasibility of retrospective cohort studies. Am J Ind Med 1987;12:419–30.

Authors’ reply

Sir,—To respond to the comments raised by Steenland and Stayner, an understanding of the background of our study1 and the NIOSH study2 is necessary. In the mid-1980s, the National Institute for Occupational Safety and Health (NIOSH) approached the Health Industry Manufacturers Association (HIMA) for access to its member companies’ data. Specifically, NIOSH was interested in conducting a cohort mortality study of workers exposed to ethylene oxide. One of us (OW) acted as HIMA’s consulting epidemiologist to assist both HIMA and NIOSH in identifying the appropriate data for the study. The initial agreement between HIMA and NIOSH was that NIOSH would provide all the necessary data for HIMA or its consultant to audit and verify NIOSH’s data and analysis. In particular, such data would include coded work history information and death certificates obtained by NIOSH. After NIOSH had completed microfilming employment records at the participating companies, NIOSH recanted its earlier agreement of providing all the necessary data to HIMA for an audit and verification.

In 1988, HIMA awarded us a contract to conduct an independent study of employees of its member companies who were exposed to ethylene oxide. For demographic and work history information, HIMA member companies provided us with more than 44 000 employment records. These records included not only the NIOSH microfilms but also additional records not microfilmed by NIOSH (microfiche, hard copies, and computer tapes). For exposure classification, we relied primarily on the walk through surveys conducted by NIOSH industrial hygienists at facilities of HIMA member companies. Data collected at these surveys included information provided by HIMA member companies, such as process histories, industrial hygiene data, job descriptions, discussions with company industrial hygienists, etc. In anticipation of future comparisons between our study and the NIOSH study, we used the same cohort definition of a minimum of 90 days of exposure. In reviewing the NIOSH microfilms, we discovered illegible records, inconsistent dates, and gaps in employment histories. It was necessary for us to contact individual companies to resolve these discrepancies. We then coded and computerised all the employment records. Our review of these records identified a cohort of 18 728 employees.

We sent the data to the Social Security Administration (SSA) for vital status determination. To supplement the SSA follow up, we also sent the data to the National Death Index (NDI) and member companies for determination of vital status. We also checked our cohort against the SSA Death Master File (DMF). For those identified to have died, we obtained death certificates. We completed our study and presented the results to HIMA in late 1990 and a final report was submitted to HIMA in 1991. Our 1992 paper is a shortened version of this report. We did not consider it necessary nor appropriate to include the above lengthy discussion of the background of the two studies in our publication. In retrospect, however, we regret the oversight of not citing the NIOSH study.
The statement by Steenland and Stayner that we have analysed the data from the study conducted by NIOSH is a gross exaggeration. Our study was based on employment records microfilmed by NIOSH, additional employment records from member companies (microfiche, hard copies, and computer tapes), vital status information from various sources (SSA, NDI, DMF, member companies), and death certificates from state health departments. All these data sources were equally important in our study, and we have properly identified and acknowledged every source in our paper.

The discrepancy in cohort size between our study1 and the NIOSH study2 is most likely the result of additional information we obtained from the participating companies. As stated earlier, the NIOSH microfilms contained both illegible and incomplete work history information. It was necessary for us to obtain additional information from member companies to resolve these data gaps. To our knowledge, NIOSH had never gone back to the member companies for additional information.

Steenland and Stayner criticised our study for lack of detailed exposure information. Although we recognised the value of valid exposure data in epidemiological studies, that is not to say that a study is better simply because it has some exposure estimates, valid or otherwise. One of us (OW) participated in some of the walk through surveys and in reviewing the NIOSH exposure classification. Although much resources (from both NIOSH and HIMA member companies) were spent on historical exposure estimates, the validity of the estimates provided by the NIOSH model is questionable. Several member companies have expressed their concerns regarding the inaccuracy of such estimates. For example, at one facility, the NIOSH model predicted that the exposure for a steriliser/operator in 1977 was 19.3 ppm, but industrial hygiene measurements based on 17 samples indicated that the actual exposure was 45.2 ppm. We are strongly of the opinion that the NIOSH exposure estimates were inaccurate and would have been a major source of misclassification if they were incorporated in the analysis.

As we stated in our paper,1 average duration of exposure was only about one year shorter than average duration of employment. Thus duration of employment was a close surrogate measure for exposure. We defined latency as time since first employment. NIOSH defined latency as time since first exposure. The difference was minor. The statement by Steenland and Stayner that we failed to observe a "trend" for all haematopoietic cancer by latency was inaccurate. Our data did show an "upward trend" for all haematopoietic cancer. As this broad International Classification of Disease (ICD) category consists of several heterogeneous diseases, however, we attached little interpretation to it. It would be far more meaningful to examine the individual cancer categories within this broad category. Such analyses were done. In particular, as noted in our paper, as there was a significant increase of non-Hodgkin's lymphoma in men, we performed a latency analysis of non-Hodgkin's lymphoma for men, and no trend was detected.

Similar to our results, NIOSH's analyses also failed to show any trend by latency for more specific individual disease categories.

The statement by Steenland and Stayner characterising our study as "an essentially duplicate analysis" of the data is inaccurate. Data sources aside, we have presented far more analyses than the NIOSH paper. To start with, we presented standardised mortality ratios (SMRs) for 50 causes of death in most analyses, whereas a much smaller number of causes of death was presented by NIOSH (most tables in the NIOSH's paper had only 10 causes of death). Furthermore, as previously pointed out by one of us (OW), the category "non-Hodgkin's lymphoma" used in the NIOSH study (ICD 202) was incorrect. In the 8th ICD, non-Hodgkin's lymphoma consists of both codes 200 and 202. Our analysis of non-Hodgkin's lymphoma was based on the proper ICD categories. Finally, we also provided analyses for all four major histological cell types of leukaemia.1 NIOSH did not analyse leukaemia data by cell type.

Steenland and Stayner accused us of "downplaying" the carcinogenic risk of ethylene oxide. It should be pointed out that nowhere in their own paper did Steenland and Stayner conclude that their data had shown a carcinogenic effect of ethylene oxide. In fact, even though Steenland and Stayner found that "overall there was no significant increase in mortality from any cause in the study cohort," they concluded that, because of the small sample size, "our (NIOSH's) findings are therefore not conclusive." Thus with regard to whether ethylene oxide is carcinogenic to humans, the only conclusion that NIOSH could offer was no conclusion.

NIOSH's conclusion of their study being not conclusive begs the question why NIOSH conducted the study in the first place. As stated in the letter by Steenland and Stayner, a feasibility study was conducted by NIOSH before the actual mortality study. Based on the results of the feasibility study, NIOSH estimated that the mortality study would have adequate statistical power (80% at α = 0.05) to detect a risk ratio as small as 2.0 for all haematopoietic cancer and 2.7 for leukaemia. Our calculation indicated that the NIOSH study actually had adequate power to detect risk ratios as small as 1.47 and 1.79 for all haematopoietic cancers and leukaemia, respectively. Thus the actual power of the NIOSH mortality study was much higher than what was anticipated based on the NIOSH feasibility study. We can only assume that the NIOSH mortality study was given a "go ahead" only after a careful consideration of the anticipated statistical power.

1 Wong O, Trent LS. An epidemiological study of workers potentially exposed to ethylene oxide. Br J Ind Med 1992;50:308-16.
2 Steenland K, Stayner L, Greife A, et al. Mortality among workers exposed to ethylene oxide. N Engl J Med 1991;324:1402-7.
3 Wong O. Mortality among workers exposed to ethylene oxide. N Engl J Med 1991;325:1254.

Neuropsychological performance and solvent exposure among car body repair shop workers

Sir,—In the article by Daniell et al (1993;50:368-77) reference is made to NIOSH Method 1500 as applied to methyl ethyl ketone. Methyl ethyl ketone is unstable on coconut shell charcoal: this finding led to the development of Method 2500 (2-butanone), dated 15 February 1984.1 The compound has never been