

Carcinogenicity

Ethylene oxide and cancer

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Is the evidence for its carcinogenicity conclusive?

For decades, ethylene oxide (ETO) has attracted considerable research interest as a direct alkylating agent and likely human carcinogen. Nevertheless, the epidemiological findings from occupationally exposed populations have not been convincingly strong and consistent to permit Working Groups of the International Agency for Research on Cancer (IARC) to conclude, in the terminology used, that there is *sufficient* rather than *limited evidence* that exposure to ETO causes cancer in humans. In 1994, ETO was nevertheless upgraded in the overall evaluation from group 2A to group 1—that is, from being *probably carcinogenic to humans* to be a *human carcinogen* as based on supporting evidence from other data relevant to the evaluation of carcinogenicity and its mechanisms. Normally a group 1 classification requires *sufficient evidence* for a carcinogenic effect in humans.

In view of the exceptionable IARC evaluation from 1994, the present follow up and extended mortality analyses from 1987 to 1998 of a large US cohort of 18 235 ethylene oxide exposed workers is a most important epidemiological contribution by Steenland *et al* in this issue.¹ However, the analyses show no clear excess mortality from cancer in comparison to expected numbers derived from the general population, except for bone cancer as represented by six cases only. The so called healthy worker effect that usually appears when the mortality experience of a worker cohort is compared to that of the general population comes through also in this study, and the mortality in both sexes from all causes was 90% of the expected, somewhat lower for women than for men. Usually coronary heart disease is thought of as responsible for a

substantial part of the healthy worker effect, but less so in the present follow up where it was relatively but marginally higher than the overall mortality—that is, 92% as the average and even above the expected for men. The healthy worker effect phenomenon is usually thought of as having less impact on cancer mortality, but one may wonder about a masking effect of this kind, namely if the workers with exposure to ETO through some sort of selection would have had a particularly healthy lifestyle with a favourable cancer outcome compared to the general population.

The fact that this cohort has about the same cancer mortality experience as the general population could certainly be interpreted as suggesting a downgrading of ETO in the IARC classification, especially in view of the several such re-evaluations that have recently been made for other compounds.² However, the investigators went further and undertook also exposure-response analyses within the cohort and thereby indicted a carcinogenic effect for haematopoietic cancers (particularly non-Hodgkin's lymphoma, myeloma, lymphocytic leukaemia), even if limited to males and with little contribution from the now added follow up from 1987. There was also some evidence for increased breast cancer mortality.

Different approaches were taken for evaluating the exposure-response relationships—that is, with regard to lag time requirements and by using the log of the measure of exposure in terms of ppm-years. In dealing with an exposure that is most likely to be harmful, it is clearly necessary to go into further analyses than just the traditional SMR estimations when these suggest no evidence of effect. A problem is,

however, to know how to deal with the timing of the exposure and how to best create a measure of exposure that is biologically relevant.

The authors report that models using duration of exposure, peak exposure, and average exposure did not predict haematopoietic cancer as well as models using cumulative exposure, which lends support to the common use of time integrated exposure measures (in this study ppm-years) in cancer epidemiology. The combination of a lag requirement and the use of the log of the time integrated exposure may have given particular weight to the exposure that occurred in some time window in relation to the point in time of the manifestation of the disease. Some further evaluations and comparisons of various large scale cohorts of the aspects of how to best deal with the measures of exposure could very well be worthwhile.

A final question, and speculation, could be what the IARC Working Group on ETO would have said if the present study had been available at the time—that is, would the conclusion have been *sufficient evidence* of a carcinogenic effect in humans or would the Group have stuck to *limited evidence* in this respect. Even if there was no clear excess (except for the bone tumours) in comparison the general population, the results of the further internal exposure-response analyses would have supported an “epidemiological upgrading”, probably not convincing all members of the Working Group, however.

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