Cancer risks in a UK benzene exposed cohort

Sorahan and colleagues recently published the results of a cohort mortality and morbidity study of workers purportedly exposed to benzene in the UK. Despite inherent problems with their data analyses, the authors nevertheless concluded that “the study does not support claims that exposure to benzene affects risks for lymphohaematopoietic malignancies other than ANLL.” In my opinion, the discrepancies and flawed analyses preclude this study from being used to make any health determination for workers exposed to benzene.

Lock of information on cancer deaths among cohort members

The authors admit to evidence of “under-ascertainment,” or non-identification, of cancer registrations. This is an understate-ment. Indeed, with the exception of cancer of the lip (observed versus 0.2 expected), the highest risk of cancer achieving statistical significance was “cancers of uncertain origin” (SMR = 140, based on 68 cancer deaths, \( p < 0.001 \)). Their morbidity analysis also suffers from “under-ascertainment” for specific types of cancer experienced by these workers as the authors state that an estimated 60 cancer registrations remained untraced.

Closer scrutiny of their data also reveals an even greater problem with “under-ascertainment” of cancer deaths during the 1968–74 follow up period—the period of death for those cohort members who likely experienced the highest benzene exposure levels. For the 1968–74 follow up period, I estimate that 51% (46 of 91) of the cancer deaths had no information provided on their specific type of cancer. My analysis is as follows: the data in table 2 of the Sorahan et al report indicate that 761 cancer deaths occurred during the entire follow up period of 1968–2002. In the text, the report states that 670 cancer deaths occurred during the period 1968–74. Therefore, 91 (761 – 670) cancer deaths had to have occurred during the 1968–74 and 2001–2002 follow up periods. Of these 91 cancer deaths, the number with undetermined type can be calculated as follows: for the period 1975–2000, “there were 102 deaths for which no cancer registration had been received”. Of these, the Office of National Statistics (ONS) produced cancer registrations for 80, leaving 22 cancer deaths for the period 1975–2000 as unspecified. Since 68 cancer deaths could not be specified for the entire follow up period of 1968–2002, 46 (68 – 22) of the cancer deaths that had no information on type of cancer had to have occurred between 1968–74 and 2001–2002. (Sorahan and colleagues state that they made no attempt to search for cancer registrations for the cancer deaths that are known to have occurred during these follow up periods, but do not explain the rationale for this decision.) If one assumes that cancer registrations have improved over time, most of the under-ascertainment in cancer registration is likely to have occurred in the earlier period of follow up, that is, 1968–74. Because there was an under-ascertainment of cancer registrations of up to 51% (46/91) for the 1968–74 period, the study cannot accurately calculate any reliable cancer risk from exposure to benzene during this period. Given the rarity of haematopoietic neoplasms, the identification of only a few among the estimated 46 unspecified cancer deaths for this period could produce highly significant results.

Lack of information on benzene exposure

Information on benzene exposure was provided for only 130 of the 233 (56%) establishments that contributed cohort members to the study, and this information was limited to the “average” benzene exposure at the facilities in 1966–67. Given that the cohort included workers exposed to benzene in the 1940s and that it was followed to 2002 for mortality, and to 2001 for morbidity, the average exposure level for a “facility” based on the 1966–67 period has little meaning in terms of benzene exposure to the cohort members. Further, the authors state “others might only be exposed for a few hours each week; such information was not available to the study”. Therefore, the exposure recrea-tion is dubious at best given (i) the paucity of exposure information and (ii) the lengthy intervening time period between initial exposure to benzene and the attempted exposure determination. The inclusion of individuals in the benzene cohort who were not exposed to benzene compromises the identification of the cohort and dilutes estimates of relative risk of diseases related to benzene exposure.

Lack of analysis by latency period

The authors present data by period of death, but they do not present information by latency. Such an analysis may provide useful information on more complete ascertainment of cancer deaths as acute leukaemia appears to have a relatively shorter average latency period than B-cell cancers such as chronic lymphatic leukaemia, multiple myelo-ma, and some non-Hodgkin’s lymphomas (NHL), all of which have been associated with benzene exposure, or benzene containing solvents.** For example, data from the Haynes et al study indicate that the risk of ANLL/MDS was more significantly associated with recent benzene exposure, whereas NHL was associated with more distant exposure prior to diagnosis. While the numbers are small in the Sorahan et al study, the earliest period of follow up for which data are presented suggests that risk for acute non-lymphocytic leukaemia (ANLL) is higher in the earlier 1968–75 period (SMR = 265) based on three deaths, than from the more distant follow up period of 1976–2002 (SMR = 169) based on 11 deaths. Unfortunately, this issue cannot be more fully explored because of the limitations in ascertainment of specific cancer deaths.

Lack of statistically significant excess of mortality from ANLL

The authors erroneously state that their data “show a statistically significant excess of ANLL.” In fact, an increased risk for ANLL only achieves statistical significance when two deaths from acute unspecified leukaemia (AUL) are included as deaths from ANLL. The authors inclusion of the AULs along with the true ANLL deaths in the category “acute leukaemia deaths” would result in 14 observed versus 8.48 expected (SMR = 165), which also is not statistically significant. The results of their morbidity analysis as well do not show a significant excess of ANLL among the benzene cohort members.

In summary, there are inherent data limitations in the Sorahan et al study: (i) “under-ascertainment” of cancer deaths; (ii) unverifiable benzene exposure for individual cohort members; (iii) inadequate attention to analysis by latency; and (iv) improper categorisation of ANLL. As a result, the study provides little information on which to evaluate health risks from occupational exposure to benzene.

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References


Authors’ reply

Dr Infante has estimated incorrectly from our recent paper that of the 68 deaths (expected 48.5) attributed to “secondary and unspecified neoplasms”, 46 occurred in the early period of follow up (1968–74). In fact there was no such early preponderance (Obs 2, Exp 2.6, SMR 77, 95% CI 9 to 277). The miscalculation apparently arose from his assumption that a death from carcinomatosis implied the lack of a record in the national cancer registration system, whereas such records existed for no fewer than 65 of the 68 deaths, including 22 with more informative diagnoses (of which nine were lung cancer or mesothelioma). In our view, these two diseases probably account for most of the excess mortality shown for unspecified cancer.
As stated in our paper, further tabulations of SMRs for acute non-lymphocytic leukaemia (ANLL) (for example, by period of hire, interval from hire) were carried out, but no clear trends were found although the numbers of deaths were small. Reasons for the selection of conditions under the heading of ANLL were supplied in the introduction to our paper and we recommend the classification to others. Dr Infante appears not to want to use our study findings for “any health determination”. But for this large cohort of UK workers exposed to benzene in many different industries in the 1940s, 1950s, and 1960s, the health determination seems fairly clear cut: benzene caused an excess of ANLL that was small in absolute terms.

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