CORRESPONDENCE

Risk of myelogenous leukaemia and multiple myeloma in workers exposed to benzene

Editor—The recent report by Wong presents valuable new analyses concerning benzene and lymphoepithelioepithelioma cancers among workers in the Pliofilm cohort.1 In spite of a series of analyses of this population,2-4 no previous analyses have provided specific risk estimates for acute myeloid leukaemia (AML) although the cohort has been widely viewed as a potential evidence most pertinent to that outcome. The effort to examine patterns associated with leukaemia subtypes is clearly worthwhile, for the reasons presented by Wong.

However, we would like to challenge two aspects of this report: (a) the claim that “Specificity is one of the major criteria for causation” (page 297) and (b) the assertion that “by lumping all cell types into a single category, the misconception that benzene can increase the risk of other cell types of leukaemia may be created.” (page 309).

Specificity was proposed by Hill some years ago as one of several considerations in evaluating causality, but even then with strong caveats: “We must not, however, overemphasise the importance of the characteristic of specificity.” (page 297).

Subsequent experience and evolution of epidemiological methods has led to virtual abandonment of this as a useful criterion for causality5 except insofar as it suggests a pattern of risk in self-report ed exposure data or incomplete follow up for disease. Given the established multiplicity of consequences of ionising radiation, tobacco smoke, asbestos, oral contraceptives, physical activity, and fruit and vegetable consumption, for example, it is actually rather difficult to identify any biologically active exposure that is specific in its consequences.

With inferences from the Pliofilm cohort pertaining to leukaemias other than AML, Wong correctly asserts that the numbers of cases of individual cell types are so small as to preclude meaningful analysis, but the number of total non-AML cases (admittedly, a heterogeneous group) is sufficient to analyse. To examine whether the association between benzene exposure and total leukaemia observed previously in this cohort is driven by AML cases, we reanalyzed the results from the two reports (table).3 5 These data indicate that the association is stronger for AML than for total leukaemia, but the differences in association for AML, non-AML, and total leukaemia are modest. Also, movement of a single case from AML to another cell type would considerably disturb any interpretation of the magnitude of risk of total cases would obliterate it, which serves as a reminder of just how imprecise these standardised mortality ratios are. Wong emphasises the distinction in dose-response patterns found for AML v total leukaemia, but the numbers of cases available from this study preclude making such subtle distinctions. Given these results, the claim that they point specifically towards AML as the only type of leukaemia associated with benzene exposure in this cohort is unwarranted.

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Results for AML, non-AML, and total leukaemia in Pliofilm cohort study

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Observed deaths</th>
<th>Expected deaths</th>
<th>SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total leukaemia</td>
<td>14</td>
<td>3-89</td>
<td>3-60 (1-97-6-04)</td>
</tr>
<tr>
<td>AML</td>
<td>6</td>
<td>1-19</td>
<td>5-03 (1-84-10-97)</td>
</tr>
<tr>
<td>Non-AML</td>
<td>8</td>
<td>2-70</td>
<td>2-96 (1-25-5-84)</td>
</tr>
</tbody>
</table>

Author’s reply—Savitz and Andrews raised two points about my recent paper “Risk of acute myeloid leukaemia and multiple myeloma in workers exposed to benzene.”6

Firstly, they questioned whether specificity of disease should be included as a criterion for causation analysis. Secondly, they argued that the data from the Pliofilm cohort indicated exposure to benzene could result in an increased risk of leukaemia cell types as well as acute myeloid leukaemia (AML).

With regard to the first point, Savitz and Andrews might have misunderstood what “specificity” means. Specificity of disease refers to being “distinct,” and does not imply “non-multiplicity” or “exclusiveness.” In my paper, I did not claim that benzene can cause AML, therefore benzene cannot cause other types of leukaemia or other diseases. Certainly we know that, given sufficient exposure, benzene can cause both AML and aplastic anaemia. In the Pliofilm cohort, AML and aplastic anaemia are specific (or distinct) diseases. Therefore, specificity does not contradict multiplicity, as long as the diseases involved are specific and meaningful diagnostic entities.

To support their first point, Savitz and Andrews cited a statement in Hill’s 1965 paper on causation: “If benzene is a cause of leukaemia, there is no reason why occupational exposure to nickel can cause lung as well as nasal cancer” (page 297). Again, both lung and nasal cancers are specific diagnostic entities recognised by the medical profession. This Hill’s paper was hardly an endorsement for the practice of combining heterogeneous disease categories for statistical analysis.

Most importantly, specificity of disease is not a statistical issue, but should be scrutinised on the biology of the disease. It makes little sense to lump different diseases into a single category for causation analysis. Before any statistical analysis, one must review and validate an analysis. Any statistical analysis which totally disregards our current understanding of the underlying biological mechanisms is meaningless, as non-AML is not a recognised diagnostic entity. Although Savitz and Andrews themselves admitted that such a category was heterogeneous, the majority of the data in my paper does not support their view. If Savitz and Andrews endorses combining heterogeneous leukaemia cell types for analysis.

With regard to the second point, Savitz and Andrews provided a risk estimate for AML. Such an estimate is meaningless, as non-AML is not a recognised diagnostic entity. Although Savitz and Andrews themselves admitted that such a category was heterogeneous, the majority of the data in my paper does not support their view. If Savitz and Andrews endorses combining heterogeneous leukaemia cell types for analysis.

Finally, Savitz and Andrews concluded: “the claim that these results (results which I provided in my paper) point specifically toward AML as the only type of leukaemia associated with benzene exposure in this cohort is unwarranted.” I did not claim in my paper that the data from the Pliofilm cohort showed that benzene did not cause other types of leukaemia besides AML. I simply stated the following: “For cell types other than AML, the Pliofilm study does not provide sufficient cases for any meaningful analysis. The specific cell type with the second largest number of cases in the Pliofilm study was myelodysplasia, consisting of only two deaths. One of the two deaths from CML was employed at the plant for one month in 1948, and died two years later in 1950 at the age of 29. His cumulative exposure was 0-10 ppm-years. Clearly this case could not have been associated with exposure at the plant.” Therefore, the Pliofilm study offers little useful information on the relation between benzene exposure and leukaemia cell types other than AML.

The evidence for the lack of an association between benzene and other leukaemia cell types comes from recent laboratory investigations7-8 and other
vivo thereby increasing investigations of myeloid progenitor cells, thereby increasing the number of cells at risk of developing leukaemia. Furthermore, this effect is selective for myeloid cells only. Similarly, epidemiological cohort and case-control studies based on analyses of specific leukaemia cell types did not detect any increased risk of other leukaemia cell types in people exposed to benzene. None of the evidence from these laboratory or epidemiological investigations was considered by Savitz and Andrews.

In my paper I provided an account of why different leukaemia cell line types were combined for analysis in some epidemiological studies in the past and why such an analysis would not be appropriate or meaningful given recent developments in laboratory research on the subject. In particular, I showed that ignoring the heterogeneity of leukaemia cell types would underestimate the risk of AML at high concentrations of benzene exposure. Although benzene exposures are uncommon in developed countries, in some parts of Asia and Eastern Europe they have not been totally eliminated. Advocating an analysis which ignores the underlying biological mechanisms of the disease on one hand and underestimates the risk of occupational exposure on the other is a disservice to the workers.

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Comment on EQM Testmate OP cholinesterase kit

Editor—we read with interest the report by London et al, on the EQM Testmate OP cholinesterase kit. We have previously reported good reproducibility of repeated measurements of haemoglobin and erythrocyte cholinesterase with this kit under field conditions. The Pearson correlation coefficient for duplicate measurements on the 23 samples in that study was 0.93 (in a range of 0.31-0.98). The correlation between duplicate erythrocyte cholinesterase measurements conducted recently on 20 blood samples, with a production model of the field kit, was 0.98 (Amway 2, unpublished data). In epidemiological studies, the kit has been found to be sensitive to subtle differences in cholinesterase activity based on exposure.

We do not offer an explanation for the poor performance of the kit, in the study of London et al, under conditions apparently similar to those under which our evaluation showed good repeatability. However, we recently have found that the temperature adjustment of cholinesterase activity by the kit can be a source of significant error. In one experiment, we measured haemoglobin and erythrocyte cholinesterase activity according to the manufacturer's specifications, at different ambient temperatures, on blood from the same unexposed person. A sample of blood was drawn in heparin the night before testing and stored at 4°C overnight (in six separate aliquots). Each aliquot was defrosted 30 minutes before testing. Figures 1 and 2 suggest that the temperature adjustment by the kit is not accurate, as measured activity on the same sample varied considerably with temperature both for plasma and for erythrocyte cholinesterase.

In another experiment, we examined the rate of thermal equilibration of the kit by moving a Testmate kit from a cool room, where the kit's internal thermometer and an independent external thermometer read 8°C, to a room where the external thermometer read 40°C. The internal thermometer of the kit (the basis for the colorimeter's temperature adjustment) registered only 30°C after 120 minutes at ambient temperature of 40°C. Moving the kit from an air-conditioned vehicle to a non-airconditioned field site has been, in our experience, a common scenario. Such rapid changes in temperature immediately before measuring cholinesterase would result in considerable error.

Although we have found repeated cholinesterase measurement to be highly reliable, in contrast to the experience of London et al, we think that variable temperatures under field conditions result in significant error in the accuracy of cholinesterase measurement by the kit. This problem might be solved if the manufacturer were to provide accurate temperature adjustment factors, and if they were to measure directly the temperature of the reagent solution, rather than the temperature of the colorimeter.

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NOTICES


The Department of Epidemiology and Public Health, and Department of Air Quality, University of Wageningen, The Netherlands, in collaboration with The Netherlands Institute for Health Sciences (NIHES) have organised this course. The course is divided in plenary morning sessions and parallel afternoon sessions. The parallel sessions include two modules: module 1: environmental epidemiology; module