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 lymphomatoepoietic cancers among workers in the Pliofilm cohort. In spite of a series of analyses of this population,1,2 no previous analyses have provided specific risk estimates for acute myeloid leukaemia (AML) although the cohort has been followed for 24 years.2,3 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,” 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.”2 (page 301)

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 teristic” (page 297). Subsequent experience and evolution of epidemiological methods has led to virtual abandonment of this as a useful criterion for causality except insofar as it suggests a pattern of bias that is self-report ed exposure data or incomplete follow up. 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 scrutinised the data from the two reports (table).1,3 These data indicate that the association is stronger for AML than for total leukaemia, but the differences in association for AML and total leukaemia are modest. Also, movement of a single case from AML to another cell type would considerably diminish our impression of just two 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 cohort 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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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.”1 Firstly, the actual specificity of the 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. 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 in leukaemia. We could emphasise the importance of specificity.2 What Savitz and Andrews have omitted from their citation is the example given by Hill: “The finding that 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 medical practice. Therefore, this 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 a considered 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.

Frankly, 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 [the Pliofilm 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 myeloid to lymphoid, 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 investigations4-6 and other

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

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<th>Cause of death</th>
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<th>Expected deaths</th>
<th>SMR (95% CI)</th>
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<td>14</td>
<td>3:89</td>
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