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 lymphoepitheliomatosi cancer among workers in the Pliofilm cohort. 1,2 In spite of a series of analyses of this population, 3-6 no previous analyses have provided specific risk estimates for acute myeloid leukaemia (AML) although the cohort has been widely viewed as providing 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 196), 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 390).

Specificity was proposed by Hill some years ago as one of several considerations in evaluating causality, 7 but even then with strong caveats: “We must not, however, overemphasise the importance of the character ‘specificity’” (page 297). Subsequent experience and evolution of epidemiological methods has led to virtual abandonment of this as a useful criterion for causality 8 except insofar as it suggests a pattern of bias in self-reported 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 integrat ed the results from the two reports (table). 9,10 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 diminish the apparent association between benzene exposure and leukaemia. Wong’s assertion that these standardised mortality ratios are specific and meaningful is therefore an oversimplification.

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 largely unfounded. The results are statistically non-significant, and the exposure was related to deaths from other causes.” 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 myeloblastoid leukemia, 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.

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.” 1,2 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 that 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 occupational medicine: “I do not wish to emphasise the importance of specificity.” 9 What Savitz and Andrews have omitted from their citation is the example given by Hill: “we also know a case of Hill.” 10 Savitz and Andrews comment 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 the medical profession. Therefore, Savitz’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 based 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, they believed that the statistical analysis on the ground that “the number of non-AML cases in aggregate (admittedly, a heterogeneous group) is sufficient to analyse.” Mere sufficiency of cases does not provide scientific support for any statistical analysis which totally disregards our current understanding of the underlying biological mechanisms is meaningless.

Wong 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 largely unfounded. The results are statistically non-significant, and the exposure was related to deaths from other causes.” 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 myeloblastoid leukemia, 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 investigations 10 and other

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>3.30 (1.79-5.80)</td>
</tr>
<tr>
<td>AML</td>
<td>6</td>
<td>1.19</td>
<td>5.03 (1.64-10.97)</td>
</tr>
<tr>
<td>Non-AML</td>
<td>8</td>
<td>2.70</td>
<td>2.96 (1.25-5.84)</td>
</tr>
</tbody>
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