SHORT REPORT

Lung cancer mortality in arsenic-exposed workers from a cadmium recovery plant

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Background There is evidence that arsenic is a late-stage human lung carcinogen.

Aims To investigate lung cancer risks in a cohort of cadmium recovery workers in relation to period from ceasing exposure to arsenic.

Methods The mortality experience (1940–2001) of a cohort of 625 male workers from a US cadmium recovery plant was compared with expectations based on US national mortality rates.

Results There was a statistically significant (P < 0.05) negative trend in lung cancer standardized mortality ratios in relation to period from ceasing arsenic exposure.

Conclusions The findings are consistent with the hypothesis that arsenic is a late-stage human carcinogen.

Key words Arsenic; cadmium; cohort study; lung cancer.

Introduction

Taken together, two recent papers [1,2] concerning mortality in a cohort of workers from the UK Capper Pass tin smelter have provided important new evidence of lung cancer risks in relation to arsenic exposure. The findings that recent (late) exposures can be more important than exposures received in the distant past (i.e. that arsenic is a late-stage carcinogen) and that analyses of lifetime cumulative exposure can fail to identify a potent occupational carcinogen need to be assimilated by all occupational epidemiologists. As a consequence of these findings, there is now a need for a reanalysis of the other major studies on lung cancer risks in relation to arsenic exposure [3–5], as well as reanalysis of studies of nickel and cadmium exposures where arsenic may well be a major confounder [6–8]. The purpose of this report is to examine whether workers exposed to arsenic at a cadmium recovery plant had a pattern of lung cancer mortality that was consistent with exposure to a late-stage carcinogen.

Methods

The cohort identified by Stayner et al. [6] comprised 625 white male workers from a cadmium recovery facility located in the State of Colorado; these employees were employed for at least 6 months between 1 January 1940 and 31 December 1969. Detailed work histories were later extracted from extensive company time sheet records by researchers from the University of Birmingham [7,9]; the original work histories [6,10] collected by researchers from the US National Institute of Occupational Safety and Health (NIOSH) were found to be seriously in error.

Arsenic and cadmium were present in the bag-house flue dusts that made up the feed materials for the plant; arsenic exposures were limited to the initial plant processes that aimed to separate cadmium from the rest of the feed materials. For this analysis, the advice of company personnel was used to classify departments with arsenic exposure, namely, calcine, mixers and screeners, concentrated and dry dust, sampling, crushing, roasting, welders and burners and arsenic. A total of 469 employees had ever been employed in one of these departments. The remaining 156 employees had only ever been employed as a foreman or in one of the following departments: solution, pigment, tankhouse, retort, casting, weighing and packing, loading gang, lead, thallium, machine shop and maintenance. These remaining employees were considered to be unexposed to arsenic.

Earlier studies analysed mortality to the end of 1982 [6,7,11]. With the approval of the South Birmingham Research Ethics Committee, details of more recent deaths were sought from company pension records and from a web site containing the US Social Security Death Index (http://ssdi.rootsweb.com), searching for entries
separately by name and by social security number. Copies of death entries were then sought from State Vital Statistics Offices and underlying causes of death were coded to contemporaneous revisions of the International Classification of Disease (ICD). At the closing date of the survey (31 December 2001), 453 members of the cohort were known to have died (all ages); copies of death certificates were available for all but 26 (5.7%) of these deaths. A total of 22 employees were known to be alive on the study closing date by virtue of being in receipt of a company pension on that date, and a further 44 subjects were known to be alive because their deaths had occurred in later years. The remaining 106 study subjects (17%) were assumed to be alive on the study closing date.

Expected numbers of deaths were calculated from serial mortality rates for US white males applied to similarly defined arrays of person-years at risk (pyr) generated by the data. Workers entered the pyr at the end of the 6 months minimum period of employment, 1 July 1940 (or, in some analyses, the date last exposed to arsenic), whichever was the later date. They left the pyr on the closing date of the study or the date of death, whichever was the earlier date. Standardized mortality ratios (SMRs) were calculated as the ratio of observed deaths to expected deaths, expressed as a percentage (both numerator and denominator refer to underlying causes of death). These procedures were accomplished with the PERSONYEARS software [12]. Significance tests were two tailed and no contributions were made to observed or expected numbers past the age of 85. This censoring at 85 was applied for three reasons. Firstly, published mortality rates are only available for the open-ended age group 85 and the distribution of the cohort pyr by single years of age might be very different from that of the general population; secondly, the reliability of cause of death particulars is probably poorer at later ages and thirdly, any study subjects incorrectly classified as traced alive at the end of the study would have a disproportionate effect on the expected numbers for the open-ended age group.

**Results**

Observed and expected numbers of deaths from lung cancer and from all other causes are shown in Table 1 by period from leaving arsenic-exposed employment for the arsenic-exposed sub-cohort (n = 469). There is a statistically significant negative trend in the pattern of SMRs shown for lung cancer (chi square = 3.94, P < 0.05), with the highest SMR [SMR 300, observed (Obs) 6] shown for those workers with arsenic exposure in the preceding 10 years and unexceptional SMRs for those workers who had ceased arsenic exposure >30 years ago. There was no suggestion of a similar pattern being found for all causes other than lung cancer (chi square = 0.72, not significant). In addition, there was no overall excess of lung cancer in the 156 employees with no exposure to arsenic (not shown in Table) [Obs 6, expected (Exp) 8.5, SMR 71, 95% confidence interval 26–154], although there was also some suggestion (P = 0.06) of lung cancer SMRs in this latter group declining with period since leaving employment (≤9 years: Obs 2, SMR 198; 10–19 years: Obs 1, SMR 85; 20–29 years: Obs 2, SMR 113; ≥30 years: Obs 1, SMR 22).

**Discussion**

This study comprises a single test (do SMRs for lung cancer decline with period from ceasing arsenic exposure?) of a defined hypothesis (arsenic is a late-stage human lung

Table 1. Mortality from lung cancer and all other causes by period from leaving arsenic-exposed employment, US cadmium recovery plant workers (n = 469), 1940–2001

<table>
<thead>
<tr>
<th>Period from leaving arsenic-exposed employment (years)</th>
<th>Lung cancer&lt;sup&gt;a&lt;/sup&gt;</th>
<th>All other causes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs</td>
<td>Exp</td>
</tr>
<tr>
<td>&lt;9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6*</td>
<td>2.0</td>
</tr>
<tr>
<td>10–19</td>
<td>4</td>
<td>3.6</td>
</tr>
<tr>
<td>20–29</td>
<td>8</td>
<td>5.7</td>
</tr>
<tr>
<td>30–39</td>
<td>8</td>
<td>7.1</td>
</tr>
<tr>
<td>≥40</td>
<td>5</td>
<td>6.6</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>25.0</td>
</tr>
</tbody>
</table>

<sup>a</sup>P < 0.05, parenthesis indicates deficit. CI, confidence interval.

<sup>b</sup>Arsenic-exposed departments: calcine, mixing and screening, concentrated and dry dust, sampling, crushing, roasting, welders and burners, arsenic.

<sup>c</sup>ICD-9 162.

<sup>d</sup>Includes still employed.

<sup>e</sup>Includes 12 deaths for which cause of death was not available.
carcinogen). The findings are consistent with the hypothesis. The study, however, is limited by the relatively small number of lung cancer deaths available for analysis, by the fact that not all causes of death were established (although the expectation is that only a single lung cancer death was overlooked) and by the fact that a similar pattern was found in workers unexposed to arsenic (albeit this latter pattern was based on few observed deaths).

In 1993, a Working Group of the International Agency for Research on Cancer (IARC) published a monograph on the evaluation of carcinogenic risks to humans following exposure to cadmium and cadmium compounds [13]. The Working Group concluded that ‘There is sufficient evidence in humans for the carcinogenicity of cadmium and cadmium compounds’ and the overall evaluation was that ‘Cadmium and cadmium compounds are carcinogenic to humans (Group 1)’. The statistically significant positive trends of lung cancer risk with estimated cumulative cadmium exposure reported by NIOSH researchers in their analysis [6,10] of the cohort reported in the current paper were clearly key components of the sufficient evidence referred to in the IARC evaluation. In the intervening years, all other cohort studies that have similarly investigated the lung cancer/cadmium exposure hypothesis using individual quantitative estimates of cumulative cadmium exposure have failed to support the hypothesis [2,14–16]. It seems possible that the 1993 IARC Working Group did not recognize the potency of arsenic as a human lung carcinogen.

The calculation of SMRs by period since leaving employment (or ceasing exposure) is a simple way of identifying the possible presence of a late-stage carcinogen and is to be recommended for routine use.

Key points
- Arsenic trioxide appears to be a potent late-stage human carcinogen.
- The evidence that cadmium exposure has a discernible influence on lung cancer risks in humans is now inadequate.

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Conflicts of interest
None declared.

References