Lymphohaematopoietic cancer mortality among workers with benzene exposure

J J Collins, B Ireland, C F Buckley, D Shepperly

Occup Environ Med 2003;60:676–679

Exposure to high levels of benzene increases the risk of acute non-lymphocytic leukaemias (ANL). Some studies indicate that multiple myeloma, Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, chronic myeloid leukaemia, and various myelodysplastic syndromes may also be related to benzene exposure. Studies of workers exposed to low benzene levels have been null or reported only slightly increased rates of ANL or all leukaemias. The dose rate of benzene, or the exposure concentration received over time, appears important for assessing cancer risk in experimental systems. Specifically, some argue that a critical concentration must be present before cancer risk is increased. Most previous studies of benzene workers have used cumulative exposure independent of concentration to assess risk. We examine lymphohaematopoietic cancers in the present study to determine the effects of low cumulative benzene exposure and short term exposure peaks. The plant that we studied was included in a previous industry wide benzene study. The cancer rates of the workers at this plant have been reported previously, but we extend the number of peak exposures greater than 100 ppm to benzene is a better predictor of risk than cumulative exposure. We found no trends by peak exposures for any of the cancers. However, when peak exposures over 100 ppm for 40 or more days were considered, the observed number of all leukaemias (SMR = 2.7, 95% CI 0.8 to 6.4), ANL (SMR = 4.1, 95% CI 0.5 to 14.9), and multiple myeloma (SMR = 4.0, 95% CI 0.8 to 11.7) were greater than expected. While the observed number of deaths is small in this study, the number of peak exposures greater than 100 ppm to benzene is a better predictor of risk than cumulative exposure. The dose rate of benzene and a threshold for exposure response may be important factors for evaluating lymphohaematopoietic risk.

Subjects and methods
We included all hourly workers beginning employment between 1940 and 1977 at the Solutia plant, previously Monsanto, in Sauget, Illinois. Person time accumulation began on hire date and ended at the earliest of study termination date (31 December 1997), the last day worked if lost to follow up, or the date of death. The study cohort included 4172 men and 975 women. Exposures for maintenance jobs since exposure to benzene is intermittent and highly variable. We also estimated the number of days for which a 15 minute exposure excursion in excess of 100 ppm was likely. We estimated potential for peak exposures for all job types.

We cumulated individual daily exposure and divided the exposure categories into three groups used in the previous study: less than 1 ppm-year, 1–6 ppm-years, and greater than 6 ppm-years. Cumulative exposures ranged from 0.1 ppm-years to 632 ppm-years with a median of 3 ppm-years. Similarly, we cumulated the number of days with peaks into categories used in the previous study: no day over 100 ppm, less than 7 days, 7–40 days, and more than 40 days. The number of days with peak exposures greater than 100 ppm ranged from 1 to 2590 with a median of 22 days. Most job types in the plant had no potential for peak exposures over 100 ppm.

We compared worker death rates with rates for the population of Illinois. We calculated standardised mortality ratios (SMRs) and 95% confidence intervals (CI) using the Fisher exact test. See end of article for factors for evaluating lymphohaematopoietic risk.

Abbreviations: ANL, acute non-lymphocytic leukaemia; CI, confidence interval; SMR, standardised mortality ratio
RESULTS
Table 1 presents SMRs for workers in cumulative benzene exposure categories for selected causes of death. Total mortality SMRs for the no exposure category is 1.0 (95% CI 1.0 to 1.1), for <1 ppm-years is 0.9 (95% CI 0.8 to 1.1), for 1–6 ppm-years is 1.1 (95% CI 1.0 to 1.2), and for >6 ppm-years is 1.0 (95% CI 0.9 to 1.1). The all cancer SMRs range from 0.9 (95% CI 0.8 to 1.2) in 1 ppm-years category to 1.3 (95% CI 1.1 to 1.5) in the >6 ppm-years exposure category. SMRs greater than one for central nervous system cancers and lung cancer were seen among exposed and unexposed workers. The SMRs for all leukaemias were 1.0 (95% CI 0.5 to 1.8) for no exposure, 0.7 (95% CI 0.1 to 2.5) for <1 ppm-years, 1.4 (95% CI 0.4 to 3.6) for 1–6 ppm-years, and 1.7 (95% CI 0.6 to 3.8) for the >6 ppm-years. ANL SMRs show a similar trend by exposure category, but chronic lymphatic leukaemia does not. The SMRs for multiple myeloma increase with cumulative exposure category, but neither Hodgkin’s disease nor non-Hodgkin’s lymphoma shows a similar trend.

Table 2 presents SMRs for workers in short term peak benzene exposure categories. No increasing trend with peak benzene exposures is present for any of the causes of death examined. However, SMRs in the >40 days with peak exposures over 100 ppm are 4.0 (95% CI 0.8 to 11.7) for multiple myeloma, 2.7 (95% CI 0.8 to 6.4) for all leukaemias, 4.1 (95% CI 0.5 to 14.9) for acute non-lymphatic leukaemia, 1.6 (95% CI 0.4 to 3.6) for multiple myeloma, 2.7 (95% CI 0.8 to 6.4) for all leukaemias, 4.1 (95% CI 0.5 to 14.9) for acute non-lymphatic leukaemia, and 1.6 (95% CI 1.1 to 2.3) for lung cancer. While not shown in either table, no deaths from anaemia (ICD-8, 280–289) were found among benzene exposed workers.

Of the 22 leukaemia deaths, 15 occurred among workers with benzene exposure (12 with cumulative exposure, four with cumulative and peak exposure, and three with only peak exposure). The SMR for all cumulative exposed workers is 1.3 (95% CI 0.7 to 2.3) and the SMR for all peak exposed workers is 1.8 (95% CI 0.7 to 3.6). SMRs for leukaemia by year of hire for all benzene exposed workers were 0.9 (95% CI 0.4 to 1.7) for hire year 1940–49, 1.6 (95% CI 0.4 to 4.1) for hire year 1950–59, and 3.2 (95% CI 0.8 to 11.7) for hire year 1960–77. The SMRs for interval from onset of exposure for exposed workers were 1.3 (95% CI 0.0 to 7.0) for <10 years, 2.2 (95% CI 0.5 to 6.5) for 10–19 years, and 1.1 (95% CI 0.6 to 1.9) for 20+. Ten of the 13 deaths from multiple myeloma occurred among workers with benzene exposure (eight with cumulative exposure, two with cumulative and peak exposure, and two with only peak exposure). Six occurred among workers hired in 1940–49 (SMR = 1.3, 95% CI 0.5 to 2.9), three among workers hired in 1950–59 (SMR = 2.8, 95% CI 0.6 to 8.0), and one among workers hired 1960 or later (SMR = 2.7, 95% CI 0.1 to 13.1). All 10 deaths from multiple myeloma occurred 20 or more years after first exposure (SMR = 1.8, 95% CI 0.9 to 3.3).

DISCUSSION
Unlike the Pliofilm worker study, we found little evidence of increasing leukaemia or ANL risk with increasing cumulative exposure to benzene.2,3 However, there were more leukaemias (5 observed, 1.8 expected) and more ANL (3 observed, 0.8 expected) than expected when peak exposures over 100 ppm for 40 or more days were considered. There was little or no increased risk in any of the lower exposure categories for these cancers. The Pliofilm worker study also found an increased risk of multiple myeloma among benzene workers, but this increased risk was not related to cumulative exposure. We also observed increased rates of multiple myeloma among our benzene workers and there is an indication of increasing risk with increasing cumulative exposure. However, we also observed increased rates of multiple myeloma among workers...
Table 2

<table>
<thead>
<tr>
<th>Cause of death (ICD-8 code)</th>
<th>&lt;7</th>
<th>7–40</th>
<th>&gt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td>All deaths (000–999)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMR (95% CI) OBS/EXP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cancer (140–209)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMR (95% CI) OBS/EXP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukaemia (204–207)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign neoplasms of brain, eye and CNS (224, 225, 238, 743.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths certificates not obtained</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persons at risk</td>
<td>4417</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>129000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There is continuing debate about whether low benzene exposure increases risk of multiple myeloma and all types of leukemia, or just ANL. Our study found increased rates of ANL and multiple myeloma at benzene concentrations greater than 100 ppm. High and intermittent benzene exposure was related to the highest risk. Our findings were limited by imprecision, and the potential for exposure and disease misclassification. Nevertheless, the dose rate appeared important for evaluating lymphohaematopoietic cancer risk in our study.

ACKNOWLEDGEMENTS

Solutia supported this study. We acknowledge the valuable contributions of data management from Diane Bowens, programming support
Mortality among benzene workers

from Susan Riordan, death certificate coding from Carole Penn and Carolyn Watkins, mortality follow up from Phyllis Korte, and the plant support from industrial hygienists Tom Blank and Janet Noble, and from Pat Schaeffer.

---------------

Authors' affiliations
J J Collins, D Shepperly, Solutia, 575 Maryville Centre Drive, St Louis, MO 63141, USA
B Ireland, St Louis University
C F Buckley, Retired from Monsanto

REFERENCES
Lymphohaematopoietic cancer mortality among workers with benzene exposure

J J Collins, B Ireland, C F Buckley and D Shepperly

Occup Environ Med 2003 60: 676-679
doi: 10.1136/oem.60.9.676

Updated information and services can be found at:
http://oem.bmj.com/content/60/9/676

These include:

References
This article cites 28 articles, 7 of which you can access for free at:
http://oem.bmj.com/content/60/9/676#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Other exposures (1023)
Solvents (39)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/