NIOSH-00238092

Cancer Mortality among Workers with Benzene Exposure

Belinda Ireland, James J. Collins, Clarence F. Buckley,[1] and Susan G. *Riordan*

We updated a cohort mortality study of 4,172 workers at a chemical plant to examine cancer mortality among workers exposed to low levels of benzene. Overall mortality [standardized mortality ratio (SMR) = 1.0; 95% confidence interval (CI) = 0.9–1.1] and cancer mortality (SMR = 1.0; 95% CI = 0.8–1.3) rates were at expected levels for production workers with benzene exposure. We observed elevated, albeit imprecise, rates of leukemia (SMR = 2.3; 95% CI = 0.7–5.3) and multiple myeloma (SMR = 2.3; 95% CI = 0.7–9.4) in this group of workers. The leukemias and multiple myelomas occurred predominantly among workers 20 or more years after first exposure. The leukemias were not restricted to acute myelogenous subtypes, and they occurred predominantly among workers hired before 1950 at exposure levels lower than previously reported. Leukemia (SMR = 1.3; 95% CI = 0.6–2.4) and multiple myeloma (SMR = 1.2; 95% CI = 0.3–2.9) rates were at expected levels among maintenance workers with intermittent *high* exposure to benzene. These findings provide evidence on both sides of the debate about whether low benzene exposure increases the risk of multiple myeloma and all types of leukemia. (Epidemiology 1997;8:318–320)

Keywords: benzene, leukemia, multiple myeloma, exposure estimation, cohort study.

The International Agency for Research on Cancer[1] has concluded that a causal relation exists for benzene exposure and acute myeloid leukemias (AML), based on case reports[2,3] and a large epidemiology study of pliofilm workers with substantial benzene exposure.[4] Other studies and case reports have indicated that multiple myeloma, Hodgkin's lymphoma, and lung cancers may also be related to benzene exposure.[5–7] Nevertheless, studies of workers exposed to low benzene levels either have had null findings or have reported only slightly elevated rates of either AML or all leukemias.[8–11] We examined cancers of these sites in the present study to determine the effects of low benzene exposure. The plant that we studied was included in a previous industrywide benzene study, but, here, we broaden the year inclusion criterion, extend vital status follow-up, and employ a more extensive exposure evaluation.[11]

Subjects and Methods

We included all hourly male workers beginning employment between 1940 and 1977 at the Monsanto Company plant in Sauget, IL. Person-time accumulation began on hire date and ended at the earliest of: study termination date (December 31, 1991), the last day worked if lost to follow-up, or the date of death.

The study cohort comprised 4,172 men ascertained from work records and reports to the Internal Revenue Service. Follow-up was complete for 4,091 workers (98%): 1,821 (45%) were deceased, and 81 were lost to follow-up (2%). We obtained death certificates for all but 20 (1%) decedents. We included workers known to be deceased, but for whom we lacked a death certificate, in the all-cause mortality analysis.

Exposure Assessment

The benzene-using departments are: nitrobenzene, phenol, chlorobenzene, muriatic acid, and alkylbenzene production. Only the chlorobenzene and muriatic acid departments were still operational when the collection of exposure data began in 1980, so most exposures had to be estimated. We used information on process changes and the judgment of an industrial hygienist (C. F. B.) to estimate exposures.

We estimated continuous exposures as 8-hour time-weighted averages using the categories <1, 1–10, and 11–50 parts per million (ppm). We were unable to estimate potential for continuous benzene exposure for maintenance jobs. Since toxicologic data indicate that intermittent peak exposures may be important in leukemogenesis,[12] 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 jobs.

We cumulated individual daily exposure and divided the exposure categories into three groups: <12 ppm-

From the Monsanto Company, St. Louis, MO.

[1]Retired from the Monsanto Company.

Address correspondence to: James J. Collins, Monsanto Company, 800 N. Lindbergh Boulevard, St. Louis, MO 63167.

Submitted March 1, 1996; final version accepted December 4, 1996.

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months, 12–72 ppm-months, and >72 ppm-months. Cumulative exposures ranged from 0.12 ppm-month to 7,584 ppm-months, with a median of 36 ppm-months. Similarly, we cumulated the number of days with peaks into categories: no day over 100 ppm, <7 days, 7–40 days, and >40 days. The number of days with peak exposures greater than 100 ppm ranged from 1 to 2,590, with a median of 22 days.

Compared with workers of the pliofilm cohort,[1] cumulative benzene exposures in this study were low. Fifty per cent of the pliofilm cohort accumulated over 600 ppm-months of benzene exposure, compared with only 1% (16 workers) in our study.[1]

Statistical Analysis

We compared worker death races with rates for the population of Illinois. We calculated standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) using the Fisher exact method.[14,15] Study conduct followed the guidelines given by the Chemical Manufacturers Association.[16]

Results

Total mortality rates for unexposed production workers were higher than those for the Illinois population (SMR = 1.1; 95% CI = 1.0–1.2), largely from excesses of heart disease and lung cancer (Table 1). Exposed production workers had mortality rates similar to those of the Illinois population (SMR = 1.0; 95% CI = 0.9–1.1), and maintenance workers showed a slight mortality deficit (SMR = 0.9; 95% CI = 0.8–1.0). Elevated rates of central nervous system cancers and benign neoplasms were seen in all three study groups. The SMRs for leukemia were 2.3 (95% CI = 0.7–5.3) among production workers with benzene exposure, 1.3 (95% CI = 0.6–2.4) for maintenance workers with potential benzene exposure, and 1.1 (95% CI = 0.4–2.5) for production workers without benzene exposure. For multiple myeloma, the corresponding SMRs were 3.2 (95% CI = 0.7–9.4) for exposed production workers, 1.2 (95% CI = 0.3–2.9) for maintenance workers, and 0.5 (95% CI = 0.0–2.8) for unexposed production workers.

No increasing trend with benzene exposure existed for all deaths, all cancers, respiratory cancers, central nervous system cancers, or benign neoplasms among production workers. No death from Hodgkin's lymphoma or diseases of the blood or blood-forming organs occurred among exposed workers. The SMRs for all leukemias were 1.1 (95% CI = 0.4–2.6) in the nonexposed group and 2.5 (95% CI = 0.3–8.9) in the <12 ppm-months, 0.0 (95% CI = 0.0–5.4) in the 12–72 ppm-months, and 4.6 (95% CI = 0.9–13.4) in the ≥72 ppm-months categories. For acute nonlymphatic and chronic lymphoid leukemias, the SMRs were also elevated in the lowest and highest continuously exposed groups but were based on only 1 case each. The findings were similar when examined by peak exposure category (data not shown).

TABLE 1. Observed Deaths (OBS), Expected Deaths (EXP), SMRs, and 95% CIs for Selected Causes of Death by Cumulative Benzene Exposure Category

Cause of Death (ICD-8* Code)	Non-exposed	Production Workers OBS/EXP and SMR (95% CI) <12 ppm-month	12–72 ppm-month	≥72 ppm-month	Maintenance Workers OBS/EXP and SMR (95% CI)
All deaths (000–999)	643/523.0 1.2 (1.1–1.3)	111/96.5 1.2 (0.9–1.4)	81/79.0 1.0 (0.8–1.3)	11/7.5.5 1.1 (0.9–1.3)	905/953.95 0.9 (0.8–1.0)
All cancers (140–209)	157/135.8 1.2 (1.0–1.4)	21/25.0 0.8 (0.5–1.3)	15/20.5 0.7 (0.4–1.2)	28/19.1 1.5 (1.0–2.1)	242/226.54 1.1 (0.9–1.2)
Lung cancer (162)	62/46.57 1.3 (1.0–1.7)	11/8.77 1.3 (0.6–2.2)	6/7.28 0.8 (0.3–1.8)	9/6.61 1.4 (0.6–2.3)	108/77.29 1.4 (1.1–1.7)
Central nervous system cancer (191–192)	7/3.30 2.1 (0.9–4.4)	1/0.64 1.6 (0.0–8.7)	1/0.53 1.9 (0.0–10.5)	2/0.46 4.4 (0.5–15.8)	6/5.14 1.2 (0.4–2.5)
Hodgkin's disease (201)	0/1.11 0.0 (0.0–3.3)	0/0.22 0.0 (0.0–16.8)	0/0.17 0.0 (0.0–21.4)	0/0.13 0.0 (0.0–27.4)	2/1.72 1.2 (0.1–4.3)
Multiple myeloma (203)	1/1.97 0.5 (0.0–2.8)	0/0.37 0.0 (0.0–10.1)	2/0.29 6.8 (0.8–25.5)	1/0.27 3.7 (0.1–20.1)	4/3.48 1.2 (0.3–2.9)
Leukemia (204–207)	5/4.51 1.1 (0.4–2.6)	2/0.81 2.5 (0.3–8.9)	0/0.69 0.0 (0.0–5.4)	3/0.65 4.6 (0.9–13.4)	9/7.16 1.3 (0.6–2.4)
Chronic lymphatic (204.1)	1/1.01 1.0 (0.0–5.5)	1/0.17 5.9 (0.1–32.6)	0/0.15 0.0 (0.0–24.7)	1/0.15 6.7 (0.2–37.7)	1/1.56 0.6 (0.0–3.6)
Acute nonlymphatic (20.50, 206.0)	2/1.46 1.4 (0.2–5.0)	1/027 3.7 (0.1–20.6)	0/023 0.0 (0.0–44.1)	1/0.22 4.5 (0.1–25.3)	2/2.27 0.9 (0.1–3.2)
Diseases of blood/blood-forming organs (280–289)	2/1.46 1.4 (0.2–5.0)	0/0.25 0.0 (0.0–6.7)	0/0.21 0.0 (0.0–45.7)	0/0.19 0.0 (0.0–19.3)	0/2.37 0.0 (0.0–1.6)
Benign neoplasms (210–239)	3/1.20 2.5 (0.5–7.3)	3/0.23 13.0 (2.7–38.1)	0/0.19 0.0 (0.0–19.4)	1/0.17 5.7 (0.1–32.1)	6/2.01 3.0 (1.1–6.5)
All heart disease (390–398, 400.1, 400.9, 402,404 410–414, 420–429)	258/224.06 1.2 (1.0–1.3)	46/39.66 1.2 (0.8–1.5)	30/33.20 0.9 (0.6–1.3)	27/33.18 0.8 (0.5–1.2)	335/364.03 0.9 (0.8–1.0)
Death certificates not obtained	12	0	1	0	7
Persons at risk	1,814	666	378	164	2,182
Person-years	43,542	9,520	7,080	4,992	71,581

* ICD-8 = International Classification of Diseases, 8th revision.

SMRs for leukemia by year of hire for benzene-exposed production workers were 2.9 (95% CI = 0.8–7.4) for hire years 1940–1949, 1.6 (95% CI = 0.0–8.7) for hire years 1950–1959, and 0 (95% CI = 0.0–21.7) for hire years 1960–1977. The SMRs for interval from onset of exposure for these same workers were 0.0 (95% CI = 0.0–20.4) for <10 years, 2.9 (95% CI = 0.1–16.4) for 10–19 years, 0.0 (95% CI = 0.0–7.0) for 20–29 years, and 3.5 (95% CI = 0.9–8.9) for ≥30 years. Of the three multiple myelomas, one occurred among workers hired in 1940–1949 (SMR = 1.7; 95% CI = 0.0–9.2) and two among workers hired in 1950–1959 (SMR = 7.4; 95% CI = 0.9–26.8). Two multiple myelomas occurred 20–29 years after first exposure (SMR = 8.7; 95% CI = 1.1–31.4), and one occurred >30 years after first exposure (SMR = 1.7; 95% CI = 0.0–9.4).

Discussion

The evidence that benzene exposure causes AML is based on one large study with high benzene exposure. Several studies at lower exposure levels report negative findings or slightly elevated rates of AML or all leukemias and sometimes elevated cancer rates at other sites. Our study of workers with low benzene exposure found elevated but imprecise rates of leukemia and multiple myeloma among production workers 20 or more years after first exposure. The leukemias were not restricted to AML and occurred predominantly among workers hired before 1950 at lower exposure levels than previously reported. We observed no death from Hodgkin's lymphoma or diseases of the blood-forming organs. Maintenance workers with intermittent high exposure to benzene and workers exposed after 1949 had leukemia and multiple myeloma rates at expected levels. We also observed elevated rates of lung cancer, central nervous cancers, and benign neoplasms not associated with benzene exposure.

There are several limitations that we considered in evaluating these results. Exposure estimation was difficult for the 1940s and 1950s because little information was available. We assigned our highest exposures to jobs during that time, but exposures could have been much higher, given the greater potential for upset conditions. Four of the five leukemias occurred among production workers first exposed before 1950.

Death certificates are a poor source for obtaining leukemia diagnoses. Less than 70% of leukemia are recorded as such on the death certificate, and less than 75% of the leukemia recorded have the cell type correct.[17] Given the small number of leukemia deaths in our study, movement of a single death from chronic lymphocytic leukemia to AML would change our rates dramatically.

Arp and colleagues[18] have suggested that contaminants in coal tar-derived benzene may be responsible for lymphocytic leukemia deaths. Coal tar-derived benzene was used at the plant until the mid-1950s. Both lymphocytic leukemias occurred among workers exposed before 1950.

There is debate about whether low benzene exposure increases the risk of multiple myeloma and all types of leukemia, or just AML.[19,20] Our study provides some support for both sides of the debate. Our findings are limited by imprecision, the potential for exposure underestimation, and the inconsistency of leukemia and multiple myeloma rates between production and maintenance workers. The findings on leukemia subtypes may be further limited by confounding exposure to coal tar-derived benzene.

Acknowledgments

We acknowledge the valuable contributions of data management from Diane Bowens, death certificate coding from Carole Penn and Carolyn Watkins, mortality follow-up from Phyllis Korte, plant support from industrial hygienists Tom Blank and Janet Noble, and from Pat Schaeffer. We also thank John Acquavella, Elizabeth Delzell, Harvey Checkoway, and Gerard Swaen for their helpful comments on the manuscript.

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