

# Exhibit 236

ORIGINAL ARTICLE

# Lymphatic and Hematopoietic Cancers Among Benzene-Exposed Workers

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**Objective:** High benzene exposure is related to acute nonlymphocytic leukemia. Recently, myelodysplastic syndrome has been observed at low benzene exposure levels. **Methods:** We updated a mortality study of workers with benzene exposure examining acute nonlymphocytic leukemia and myelodysplastic syndrome. We calculated standardized mortality ratios with 95% confidence intervals and examined latency and trends for cumulative exposure levels. **Results:** All leukemias (standardized mortality ratio = 1.21; 95% confidence interval = 0.74 to 1.97) and acute non-lymphocytic leukemia (standardized mortality ratio = 1.04; 95% confidence interval = 0.34 to 2.44) were at expected levels. We observed one death from myelodysplastic syndrome (standardized mortality ratio = 6.48; 95% confidence interval = 0.17 to 38.15). We observed no trend for cumulative exposure levels. **Conclusions:** Our results for all leukemias are consistent with a small increase in risk observed in the lower-exposed subgroups of the Pliofilm study; however, our results are also consistent with no increased risk especially for acute nonlymphocytic leukemia.

Exposure to high benzene levels has been related to hematotoxicity and increased risk of acute nonlymphocytic leukemia.<sup>1,2</sup> The Pliofilm rubber worker study has been seminal in helping to set exposure standards for benzene including the US Environmental Protection Agency's cancer potency factor, the Occupational Safety and Health Administration's permissible exposure limit, and the American Conference of Governmental Industrial Hygienists' proposed threshold limit values.<sup>2</sup> Other leukemias and lymphoid neoplasms have also been reported to be associated with benzene exposures in some studies.<sup>1</sup> Currently, the International Agency for Research on Cancer classifies benzene as carcinogenic to humans on the basis of sufficient evidence of acute nonlymphocytic leukemia.<sup>1</sup> Recently, myelodysplastic syndrome (MDS) has been observed in an epidemiology study at relatively low benzene exposure levels.<sup>3</sup> Myelodysplastic syndrome is a disease of the blood-forming tissue in the bone marrow and sometimes precedes acute nonlymphocytic leukemia. Myelodysplastic syndrome has been reported to be associated with benzene exposure.<sup>4,5</sup> Given the recent findings for MDS at relatively low benzene exposures, we updated a previous mortality study of workers with benzene exposure at a Dow Chemical plant in Midland, Michigan.<sup>6</sup>

## MATERIALS AND METHODS

The earlier study done at the Midland, Michigan, site examined the leukemia risk among 2266 benzene workers.<sup>6-8</sup> In the earlier study, the vital status of workers was followed from January 1, 1940,

to December 31, 1996.<sup>6</sup> We extended the follow-up an additional 13 years to December 31, 2009.

We used the exposure assessment for benzene developed for the previous study.<sup>6,7</sup> Benzene was a raw material used in chlorobenzene and alkyl benzene production areas, and was also used in the ethyl cellulose production area as a solvent. Industrial hygiene measurements available in these departments since 1944 until their close in the late 1970s were used to estimate job-specific exposures over time, as shown in Table 1.<sup>7,9</sup> Generally, exposures were highest in the earliest years of operation and in the ethyl cellulose department. Employee work history information was mapped to department and job exposure levels to obtain individual average daily benzene exposure and cumulative estimates. Five exposure categories were derived from the data in Table 1: less than 1 ppm (average 0.5 ppm), 1 to 2 ppm (average 1.5 ppm), 2 to 9 ppm (average 5 ppm), 10 to 24 ppm (average 15 ppm), 25 ppm or more (average 30 ppm).

Because several diseases such as leukemia subtypes, non-Hodgkin lymphoma, and Hodgkin lymphoma were not recognized in early International Classification of Diseases (ICD) revisions, the risk was calculated for only those years when the relevant cause of death appeared as a distinguishable code in the ICD. Myelodysplastic syndrome was first introduced as a diagnostic category in the mid-1970s by the French-American-British Cooperative Group of hematologists.<sup>10</sup> Myelodysplastic syndrome was coded as a disease of the blood and blood-forming organs in the 9<sup>th</sup> Revision of the ICD (238.7), but was reclassified as a neoplasm in the 10<sup>th</sup> Revision of the ICD (D46).<sup>11</sup> The ICD-10 was used for death certificate coding since 1999 in the United States.

The mortality experience of 2266 workers exposed to benzene was investigated using a retrospective cohort design. The Occupational Cohort Mortality Analysis Program was used to calculate cause-specific standardized mortality ratios (SMRs) for the study group.<sup>12</sup> To evaluate precision of the SMR estimates, 95% confidence intervals (95% CI) were calculated. The age-/race-/sex-/year-/cause-specific mortality rates for the United States were used for comparison and for adjustment for differences in distributions of these factors. Analyses were done with and without a 15-year and a 30-year latency intervals, assuming that an exposure-related cancer or other disease might not be manifest until after the latency interval.<sup>6</sup> Exposure-response relationships were evaluated using a categorical analysis for the SMRs by defining three cumulative exposure categories chosen to approximate terciles of the total number of cancer deaths. We also examined death certificates with lymphatic and hematopoietic cancers as an underlying cause of death to determine whether MDS was listed as a contributing cause on the death certificate.

## RESULTS

Table 2 compares vital status follow-up for this study with the original study. The update added 12,481 person-years (94,892 – 82,411) and 536 additional deaths (1,590 to 1,054). No workers were lost to follow-up in our extended study compared with 0.6% (13 of the 2266) in the previous study. The average duration of exposure to benzene was 4.9 years (range, 30 days to 44.7 years),

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**TABLE 1.** Summary of Measurements of Benzene Levels in the Study Production Areas, 1944 to 1973

Job Categories	Survey Years	Number of Personal Samples per Job	Range of Samples, ppm	Estimated TWA, ppm
Chlorobenzene				
Job not specified	1944–1948	43*	0.0–259	15.0
Jobs in initial chlorination and distillation	1964	2–5	2.0–3.9	0.5–2.8
Other Jobs	1964	1–7	0.0–2.1	0.1–1.0
Jobs in initial chlorination and distillation	1973	18–24	1.0–6.2	4.6–6.2
Other jobs	1973	3–39	1.0–42.0	0.1–4.6
Alkyl benzene				
Alkylation operators	1953	5–25	0.0–100.0	9.0–11.0
Alkylation operators	1965	2–36	0.0–56.0	1.0–7.3
Mechanics	1965	3–4	0.0–250.0	1.0–10.0
Other jobs	1965	2–39	0.0–56.0	1.0–5.3
Alkylation operators	1971–1972	30–135	0.0–283.0	0.3–13.0
Mechanics	1971–1972	30–94	0.0–283.0	1.3–14.7
Other jobs	1971–1972	30–135	0.0–74.0	0.6–5.3
Ethyl cellulose				
Manufacturing jobs	1952	13–25	0.0 to >100	17.0–35.3
Fabrication area	1953	9	10–937	35.0
Technician in laboratory	1961	4	105–210	15.0
Manufacturing jobs	1965	4–24	0.2–575	5.0–17.0
Fabrication area	1965	†	0.0 to >100	11.0–32.0
Manufacturing jobs	1973	25–38	0.1–321.0	3.8–4.0
Technician in laboratory	1974	29	0.7–184	4.0

\*These 43 samples are area samples.  
†Area sample of continuous monitoring with infra-red analyzers.  
TWA, Time-weighted eight-hour average exposure.

**TABLE 2.** Descriptive Statistics of the Dow Chemical Study Population From the Previous Study and the Current Follow-Up

Description	Bloemen et al <sup>6</sup>	This Study
Study size, <i>n</i>		
Total workers	2,266	2,266
Total person-years	82,411	94,892
Vital status follow-up, <i>n</i> (%)	<b>December 31, 1996</b>	<b>December 31, 2009</b>
Alive	1,212 (53.5)	676 (29.8)
Dead	1,054 (46.5)	1,590 (70.2)
With death certificates	Not reported	1,575
Without death certificates	Not reported	15
Lost to follow-up or censored	13 (0.6)	0* (0.0)

\*Follow-up for decedents was censored at the date of death.

and the average cumulative exposure was 35.1 ppm-years (range, 0.5 to 499.5 ppm-years).

Table 3 presents SMRs and 95% CIs for all workers and for the subset with 30 or more years since the first exposure to benzene compared with the US population. The 15-year latency interval (data not shown) was very similar to the total study population. For both groups, all deaths and all cancers combined were less than expected. For cancers of the lymphatic and hematopoietic tissue among all workers, there were more observed cancers than expected for all leukemias (SMR = 1.21; 95% CI = 0.74 to 1.97), total myeloid

leukemia (SMR = 1.25; 95% CI = 0.54 to 2.47), acute myeloid leukemia (SMR = 1.11; 95% CI = 0.35 to 2.58), acute nonlymphocytic leukemia (SMR = 1.04; 95% CI = 0.34 to 2.44), and all other leukemias (SMR = 1.38; 95% CI = 0.45 to 3.21). We observed an SMR of 6.48 (95% CI = 0.17 to 38.15) for MDS on the basis of one death. This death occurred in the 30-year or more latency period. We also observed an SMR of 4.46 (95% CI = 1.22 to 11.43) for mesothelioma and SMRs of 0.78 (95% CI = 0.64 to 0.96) for cerebrovascular disease, 0.80 (95% CI = 0.73 to 0.87) for all heart disease, and 0.85 (95% CI = 0.71 to 1.00) for nonmalignant

**TABLE 3.** Standardized Mortality Ratios, 95% Confidence Intervals, and Observed Deaths for Selected Causes of Death for All Workers and Workers With 30 or More Years Since the First Benzene Exposure

Cause of Death (ICD 10 <sup>th</sup> Revision Codes)*	Total Study Population SMR (95% CI) [Obs]	> 30 yrs Latency SMR (95% CI) [Obs]
All causes (A00–Y89)	0.93 (0.88–0.97) [1,590]†	0.82 (0.77–0.87) [1,181]†
All cancers (C00–C97)	0.97 (0.88–1.07) [411]	0.95 (0.85–1.07) [306]
Buccal cavity and pharynx (C00–C14)	0.79 (0.32–1.62) [7]	0.87 (0.28–2.02) [5]
Digestive organs and peritoneum (C15–C26, C48)	0.84 (0.68–1.04) [88]	0.81 (0.62–1.03) [62]
Respiratory system (C30–C39)	1.03 (0.88–1.22) [150]	1.00 (0.82–1.21) [110]
Bronchus, trachea, and lung (C33–C34)	1.05 (0.89–1.24) [146]	1.02 (0.84–1.23) [108]
Mesothelioma (C45)‡	4.46 (1.22–11.43) [4]†	3.47 (0.72–10.14) [3]
Prostate (C61)	0.90 (0.63–1.25) [36]	0.89 (0.60–1.26) [31]
Kidney (C64–C65)	0.78 (0.34–1.55) [8]	0.80 (0.29–1.74) [6]
Bladder and other urinary (C66–C68)	0.84 (0.42–1.51) [11]	1.04 (0.52–1.86) [11]
Malignant melanoma (C43)	1.16 (0.46–2.38) [7]	0.95 (0.26–2.42) [4]
Central nervous system (C70–72)	1.01 (0.48–1.86) [10]	1.14 (0.46–2.35) [7]
Thyroid gland and other endocrine glands (C73–C75)	1.62 (0.20–5.87) [2]	1.25 (0.03–6.93) [1]
All lymphatic and hematopoietic tissue (C81–C96)	1.01 (0.73–1.36) [42]	1.07 (0.74–1.51) [33]
Hodgkin disease (C81)§	0.90 (0.11–3.26) [2]	1.32 (0.03–7.36) [1]
Non-Hodgkin lymphoma (C82, C83.0–C83.8, C84, C85.1–C85.9)§	0.97 (0.54–1.60) [15]	1.02 (0.53–1.78) [12]
Leukemia (C91–C95)	1.21 (0.74–1.97) [20]	1.23 (0.69–2.02) [15]
Total lymphoid leukemia (C91)	0.93 (0.25–2.39) [4]	0.82 (0.17–2.40) [3]
Total myeloid leukemia (C92)	1.25 (0.54–2.47) [8]	1.35 (0.54–2.77) [7]
Acute myeloid leukemia (C92.0)	1.11 (0.36–2.58) [5]	1.07 (0.29–2.74) [4]
Acute nonlymphatic leukemia (C92.0, C93.0, C94.0)	1.04 (0.34–2.44) [5]	1.02 (0.28–2.60) [4]
All other leukemia (C93–C95)	1.38 (0.45–3.21) [5]	1.29 (0.35–3.31) [4]
All other lymphopoietic tissue (C88, C90, C96)§	0.67 (0.22–1.57) [5]	0.83 (0.27–1.95) [5]
All other malignant neoplasms (C44, C46–C47, C76–79, C80, C97)	1.27 (0.91–1.73) [40]	1.14 (0.76–1.65) [28]
Myelodysplasia (D46)‡	6.48 (0.17–38.15) [1]	6.88 (0.17–38.32) [1]
Cerebrovascular disease (I60–I69)	0.78 (0.64–0.96) [98]†	0.79 (0.63–0.97) [85]†
All heart disease (I00–I02, I05–I09, I11, I13–I14, I20–I28, I30–I52)	0.80 (0.73–0.87) [564]†	0.67 (0.60–0.73) [393]†
Non-malignant respiratory disease (J00–J99)	0.85 (0.71–1.00) [135]	0.82 (0.68–0.99) [117]†
All external causes of death (V01–Y89)	1.04 (0.81–1.30) [74]	0.71 (0.49–0.99) [33]
Unknown causes	15	2
Number of persons at risk	2,266	1,851
Person-years	94,892	34,216

\*Deaths were coded to the ICD revision in force at the time of death.

†Statistically significant at 5% level.

‡Disease classifications not introduced until the 10<sup>th</sup> Revision of the ICD.

§Disease classifications not introduced until the 6<sup>th</sup> Revision of the ICD.

||Disease classifications not introduced until the 8<sup>th</sup> Revision of the ICD.

CI, confidence intervals; ICD, International Classification of Diseases; Obs, observed death; SMR, standardized mortality ratio.

respiratory disease. In the subgroup with 30 or more years of latency, similar SMRs were observed. One possible exception was seen for all external causes of death, with an SMR of 1.04 (95% CI = 0.81 to 1.30) for total population, but an SMR of 0.71 (95% CI = 0.49 to 0.99) among workers with 30 or more years of latency.

We examined exposure–response trends for cancers of interest for the three cumulative exposure categories, as shown in Table 4. There were no statistically significant linear trends for any dis-

ease category. Nevertheless, there were imprecise trends with exposure levels for all leukemias ( $P = 0.15$ ) and total myeloid leukemias ( $P = 0.24$ ). The highest SMRs for these causes were seen at the highest exposure category: 1.72 (95% CI = 0.86 to 3.17) for leukemia and 1.93 (95% CI = 0.53 to 4.94) for total myeloid leukemia. Only one MDS case was seen, occurring in the highest cumulative exposure category (SMR = 25.05; 95% CI = 0.63 to 139.58). We did not find any MDS as a contributing cause of death for any of the 42 lymphatic and hematopoietic cancers.

**TABLE 4.** Observed Deaths, Standardized Mortality Ratios, 95% Confidence Intervals for Selected Causes of Death by Cumulative Exposure to Benzene With Linear Trend Test and Test for Group Heterogeneity

Disease	Cumulative Exposure, ppm-yr			P Value for Trend	P Value for Homogeneity
	0–3.9 SMR (95% CI) [Obs]	4.0–24.9 SMR (95% CI) [Obs]	25 + SMR (95% CI) [Obs]		
Hodgkin disease	0.0 (0.0–5.28) [0]	2.63 (0.32–9.51) [2]	0.0 (0.0–4.85) [0]	0.35	0.15
Non-Hodgkin lymphoma	1.23 (0.45–2.69) [6]	1.10 (0.41–2.40) [6]	0.58 (0.12–1.69) [3]	0.26	0.53
Leukemia	0.60 (0.12–1.76) [3]	1.23 (0.49–2.53) [7]	1.72 (0.86–3.17) [10]	0.15	0.25
Total lymphoid leukemia	0.78 (0.02–4.36) [1]	0.68 (0.02–3.78) [1]	1.31 (0.16–4.72) [2]	0.53	0.81
Total myeloid leukemia	0.0 (0.0–1.79) [0]	1.78 (0.48–4.54) [4]	1.93 (0.53–4.94) [4]	0.24	0.15
Acute myeloid leukemia	0.0 (0.02.50) [0]	1.87 (0.39–5.47) [3]	1.39 (0.17–5.03) [2]	0.88	0.81
Acute nonlymphocytic leukemia	0.0 (0.0–2.38) [0]	1.77 (0.37–5.18) [3]	1.30 (0.16–4.69) [2]	0.60	0.27
All other leukemia	0.90 (0.02–5.05) [1]	1.58 (0.19–5.70) [2]	1.58 (0.19–5.71) [2]	0.80	0.89
All other lymphatic tissue	0.0 (0.0–1.61) [0]	1.15 (0.24–3.37) [2]	0.77 (0.09–2.77) [2]	0.72	0.29
Myelodysplasia	0.0 (0.0–72.29) [0]	0.0 (0.0–64.58) [0]	25.05 (0.63–139.58) [1]	0.11	0.29

CI, confidence intervals; Obs, observed death; SMR, standardized mortality ratio.

## DISCUSSION

This is the third update of the mortality levels of these benzene workers. With the extended observation period, we have found very similar rates of lymphatic and hematopoietic cancers compared with the three previous studies of these workers. Our results for all leukemias combined are consistent with a small elevation in risk observed in the lower-exposed subgroups of the Pliofilm study; however, our results are also consistent with there being no significant increased risk especially for acute nonlymphocytic leukemia.<sup>13</sup> We also observed one death from MDS.

A limitation of this study is the reliance on death certificates for examining cancers of the hematopoietic and lymphatic system because misclassification sometimes occurs for such causes.<sup>14</sup> Moreover, because many of these cancers and MDS as well are treatable and often survivable, they might not appear on death certificates. Thus, it has been argued that there may be little value in studies of MDS or acute lymphocytic leukemia based solely on death certificates.<sup>3</sup> There is also evidence that MDS is underreported and underdiagnosed.<sup>11,15</sup> Some cases can be relatively mild, and many affected individuals may not undergo hematological evaluation necessary for diagnosis.<sup>15</sup> Leukemias are also thought to be underreported on death certificates.<sup>14</sup> Nevertheless, our workers are provided periodic workplace examinations owing to their benzene exposure and are provided medical insurance. Thus, it is likely they receive more complete and earlier disease work-up while they are employed than the general population, making diagnosis of leukemias and MDS more accurate than for the US population overall. Another limitation of this study is because acute nonlymphocytic leukemia and MDS are relatively rare causes of death, even a relatively large number of exposed workers may exhibit too few deaths to thoroughly examine trends.

The strengths of this study are the extensive benzene exposure monitoring that allowed us to estimate exposure levels with some degree of confidence for the jobs back through time, and the completeness of our work history information of the entire study population. This study benefited from long and complete follow-up. This update has approximately doubled the number of cancers from the last update to provide more precise risk estimates.

The mean benzene exposure in this study was 35.1 ppm-years. Thus, our workers had lower exposures than Pliofilm workers<sup>16</sup> but higher exposures than petroleum workers.<sup>3</sup> In the most recent update of the Pliofilm worker study, the SMR for all leukemia was 2.47

(95% CI = 1.38 to 4.07).<sup>13</sup> Nevertheless, the SMRs were highest in the first 5 years since the last exposure, indicating that risk may decline rapidly after exposure ceases.<sup>17</sup> We did not observe a decline in leukemia rates between this study and the three previous studies of these workers, and there was no change in the leukemia risk when latency was considered. Thus, consideration of latency did not influence the risk estimates in this study. In addition, the SMRs in this study for the lymphohematopoietic cancers were consistent with there being no increased risk in each study of these workers.

Myelodysplastic syndrome is a group of heterogeneous hematopoietic stem-cell disorders that lead to peripheral cytopenias. Up to 30% of MDS cases progress to acute myelogenous leukemia.<sup>11,15</sup> We observed one death from MDS in this study in the highest exposure category after a long latency period. The high exposure for this case is consistent with a study in Shanghai that found increased rates of MDS at exposure levels greater than 20 ppm.<sup>18,19</sup> Nevertheless, a recent study of petroleum workers found increased rates of MDS at lower exposure levels.<sup>3</sup> It should be noted that these workers also experienced concomitant exposure to other petroleum-related chemicals. Nevertheless, the finding is consistent with another study in which acute myelogenous leukemia and MDS are associated with several different exposure metrics, some indicating low exposures.<sup>5</sup> Without additional research, it is difficult to conclude that low or high benzene exposures increased the risk of MDS.

Our results for all leukemias are consistent with a small increase in risk observed in the lower-exposed subgroups of the Pliofilm study; however, our results are also consistent with no increased risk especially for acute nonlymphocytic leukemia. We did find one death from MDS in the highest exposure category in this study. Although some previous studies associate benzene exposure to increased risk for MDS, the level of benzene exposure that may be associated with this finding is still an open issue. Although current benzene exposures are much lower than the historical levels reported in this study, continued workplace vigilance on this chemical is prudent.

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