

Benzene Exposure and Multiple Myeloma

A Detailed Meta-analysis of Benzene Cohort Studies

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ABSTRACT: Case reports and epidemiological studies of workers exposed to benzene have demonstrated associations with a number of lymphohematopoietic diseases, but the association with multiple myeloma (MM) has been less apparent. Data from all of the “benzene cohort studies” conducted to date have been selected and evaluated for inclusion in a meta-analysis. The analysis demonstrates a significant excess in the relative risk (RR) of MM in relation to benzene exposure. Pooling the data from seven cohort studies, a meta-analysis yields a statistically significant weighted RR estimate of 2.13 (95% CI = 1.31–3.46). In the analysis of cohort data, an understanding of the cohort follow-up period in relation to benzene exposure and RR of MM is important. Exposure-related RRs of disease decline after the median latency periods are exceeded, particularly when exposure has terminated decades earlier. The positive epidemiological evidence for benzene as a cause of MM is supported by biological plausibility for such an effect from benzene exposure. Studies of refinery workers are difficult to interpret in relation to benzene exposure and risk of MM, but are limited in the study design and analysis. Nonetheless, they provide some support for an association between refinery work and MM.

KEYWORDS: benzene; myeloma; leukemia; cancer risk; occupational; follow-up period; petrochemicals

INTRODUCTION

Multiple myeloma (MM) is a neoplasm of plasma cells that are derived from B-lymphocytes located primarily in the bone marrow. For the past 40 years,

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a secular increase in the incidence of MM is apparent in many industrialized countries. In the United States, the current death rate is about twice as high in men as compared to women and about twice as high in blacks as compared to whites. Case reports and epidemiological studies of workers exposed to benzene have demonstrated associations with a number of diseases of the lymphohematopoietic system, including aplastic anemia, various cytopenias, myelofibrosis, myelodysplastic syndrome, leukemia, and non-Hodgkin's lymphoma (NHL), but the association between benzene exposure and MM as demonstrated among cohorts of benzene-exposed workers has been less apparent. The suspicion of an association between benzene exposure and MM was first raised in case reports by Torres *et al.*¹ in 1970. Subsequently, Aksoy *et al.*² added four more cases of benzene-associated MM to the literature. An association was further supported in 1983 by DeCoufle *et al.*³ who identified two cases of MM in a cohort of only 259 benzene-exposed chemical workers. In 1987, the update of mortality among Pliofilm workers by Rinsky *et al.*⁴ provided much stronger evidence of a link between benzene exposure and MM. Since that time, elevated risks of MM have been identified in other benzene cohorts,⁵⁻⁸ and investigators have reported a dose-response for MM in relation to cumulative dose, or in relation to the number of peak benzene exposures experienced by the cohort.⁷ On the other hand, several studies of benzene cohorts have reported no elevated risk for MM.⁹⁻¹¹ The Sorahan *et al.* study,¹¹ however, has been criticized for significant under-ascertainment of cancer deaths.¹²

Epidemiological studies have demonstrated an elevated risk of MM associated with painting, or with paints containing organic solvents,¹³⁻²⁰ many of which have been contaminated with benzene, while other studies of painters have shown no association with an elevated risk of MM.^{21,22} Chemical workers also have demonstrated an elevated risk of death from MM.²³

Some studies of refinery workers have provided data indicating an elevated risk of MM,²⁴⁻²⁹ while others have not.³⁰⁻³² Interpretation of the findings from the study of cohorts of petroleum refinery workers, however, is sometimes limited by the difficulty in determining benzene exposure to cohort members on a retrospective basis in the absence of exposure monitoring data, particularly when extrapolating exposures 30 or more years back in time. Mis-classification of benzene exposure among these workforces, however, will dilute the findings of cohort studies and usually bias results of dose-response analyses toward the null hypothesis of no association.

Another difficulty in identifying an association epidemiologically, particularly within the benzene cohort studies, *per se*, arises from the low mortality rate of MM in the general population, e.g., 3×10^{-5} and the fact that most benzene-exposed cohorts have been small. In addition, investigators have sometimes combined MM with other forms of lymphoma in their analyses. As a result, information from these studies related specifically to benzene and MM is sparse.

THE COHORT FOLLOW-UP PERIOD USED TO ESTIMATE THE RELATIVE RISK OF DISEASE SHOULD CONSIDER THE MEDIAN LATENCY PERIOD FOR THE DISEASE OF ETIOLOGICAL INTEREST

The follow-up periods of several of the benzene cohorts have been extended over time. Several reports reflecting these different periods of follow-up for the benzene cohorts have been published. As a result, the same cohort indicates different estimates in the relative risk (RR) of the diseases of interest depending upon the follow-up period. Silver *et al.*³³ state that a longer follow-up period is generally thought to result in a more precise estimate of RR for the exposed population, but that the effect of follow-up time, *per se*, on risk has not been given much attention. They expressed concern that summary estimates of risk may not be generalized to the same cohort, or to other cohorts followed for different lengths of time.

As an occupational cohort is followed over time, one should expect a rise and then a fall in the RR of disease related to the exposure associated with the disease. Silver *et al.*³³ cite several examples of exposure and disease where upon cessation of exposure, the RR of disease rises and then declines, e.g., atomic bomb survivors and RR of leukemia, uranium miners and RR of lung cancer, and asbestos exposure and RR of lung cancer. The discontinuation of cigarette smoking is also known to result in a decline over time in the RR of lung cancer. It is unlikely that one would determine the RR of lung cancer in relation to cigarette smoking by following a cohort of ex-smokers until their death and then base the estimate of RR on the final follow-up period. Likewise, it may be inappropriate to determine the risk of disease related to occupational exposures based on the final follow-up of an occupational cohort that may have received its last exposure decades earlier.

This raises the question, "which follow-up period should be selected for a qualitative estimate of the RR of disease?" In general, the period of follow-up which includes the median latency period for the disease of interest should be included, but the estimate of RR often declines when follow-up extends much beyond this period. Subsequent to this period, one should expect to observe a decline in the RR of the disease. A few of the factors responsible for the observation of this decline in disease risk over time are mentioned. First, for a "stop exposure cohort," e.g., one in which the cohort members are no longer exposed, the mortality experience of the cohort being followed in successive years of follow-up will reflect health risks related to successively lower exposures. Second, for a cohort that has new members added as the follow-up period is extended, risk of disease related to the exposure of interest also should decline, because newer cohort members, in general, will have been employed in more recent time periods when occupational exposures were lower. Third, it is likely that those more susceptible to disease risk related

to the toxic exposure may die at relatively shorter latency periods than those less susceptible. Thus, the surviving cohort members as a group, may be less susceptible than the overall cohort, and therefore demonstrate a lower RR of disease in relation to the exposure. Therefore, if an occupational exposure response relationship exists, one should expect a decline in exposure to be accompanied by a decline in the RR of disease.

In the study of refinery workers in the United States, a fourth phenomenon is at play in relation to a reduction of RR of disease as new follow-up periods are added. Many of the jobs that entail high-level exposure to hydrocarbons have been performed over the past 20–30 years by contract employees. These employees are not included in the cohort study analyses of plant employees, because they do not work directly for the refinery. As a result, more recently hired refinery cohorts are comprised of workers, who in general have experienced lower exposures as compared to those hired in earlier times, even in situations where atmospheric exposure levels may have remained the same. For this reason alone, one should expect to see a decline in the risk of diseases related to refinery employment as cohorts are followed over time.

As a result of the interplay of these factors, RR estimates based on successive follow-up periods should be expected to result in successively lower estimates of RR of disease, and particularly for follow-up periods that extend beyond the median latency period for the disease being evaluated.

METHODOLOGY FOR DETERMINING SELECTION OF BENZENE COHORTS FOR ANALYSIS

In order to determine the extent to which benzene may be a cause of MM, the data from all of the “benzene cohort studies” conducted to date have been evaluated for inclusion in the analysis. These studies were chosen for evaluation with the assumption that the cohort members were selected on the basis of a determination that they were actually exposed to benzene. This is in contrast to the information available from the study of refinery workers. With the latter group of cohorts, it is difficult to determine which cohort members may have been exposed to measurable levels of benzene, when these exposures occurred, and their degree of benzene exposure. Thus, eight cohort studies of workers exposed to benzene were identified from the literature. These studies are listed in TABLE 1. In some cases, the cohorts have been updated several times and additional cohort members have been added over the years of follow-up. The strengths and weaknesses of individual studies have been evaluated and the basis for inclusion or exclusion of data from the studies is explained. The overall estimate for the RR of MM is then calculated.

TABLE 1. Options for selecting observed and expected deaths from multiple myeloma identified in the benzene cohort studies as published to date by author and year of publication

Multiple myeloma					
Cohort	Authors	Year	Obs	Exp	SMR
1	DeCoufle <i>et al.</i>	1983	1	0.23	4.35
2	Rinsky <i>et al.</i>	1987	4	0.98	4.09
	Rinsky <i>et al.</i>	2002	5*	2.46*	2.04*
3	Wong	1987	2	0.56	3.57
			3*	0.10*	30.00*
4	Fu <i>et al.</i> (Florence)	1996	3	1.04	2.88
5	Yin <i>et al.</i> [†]	1996	1	2.50	0.40
6	Ireland <i>et al.</i>	1997	3*	0.93*	3.23*
	Collins <i>et al.</i>	2003	8	4.20	1.90
7	Bloemen <i>et al.</i>	2004	3	4.16	0.72
8	Sorahan <i>et al.</i> [‡]	2005	6	9.50	0.63

Obs=observed; Exp = expected.

*Alternate data points considered, but rejected for use in analysis.

[†]Calculated as RR using disease rates in non-benzene-exposed industrial workers.

[‡]Not selected because of evidence of significant under-ascertainment of cancer deaths.¹²

REVIEW OF STUDIES AND ESTIMATE OF RELATIVE RISK OF MYELOMA AMONG BENZENE COHORT STUDIES

In a small cohort study of white male chemical workers exposed to benzene, DeCoufle *et al.*³ observed two “cases” of MM and one “death” from MM, e.g., one of the MM cases died from acute nonlymphocytic leukemia (ANLL) following treatment with radiotherapy and chemotherapy for MM. The authors did not calculate an expected number of deaths for MM alone, but rather estimated an expected number of 0.23 deaths for causes MM, polycythemia vera, and other neoplasms of the lymphoid tissue combined (ICD 8th Revision codes 202, 203, and 208). Thus, one can estimate that DeCoufle observed one “death” from MM versus 0.23 expected, standardized mortality ratio (SMR) = 4.35 [95% confidence interval (CI) = 0.1–24.2].

The update of the NIOSH Pliofilm study of benzene-exposed workers by Rinsky *et al.*⁴ demonstrates a statistically significant excess of death from MM. Four deaths from MM were observed versus 0.98 expected, SMR = 4.09 (95% CI 1.10–10.47). The workers who died from MM all had a latency period of more than 20 years (ranging from 22 to 27 years). The median latency period was 25 years since initial exposure to benzene.

Rinsky *et al.*,³⁴ however, have provided more recent analyses for MM and leukemia among the Pliofilm cohort members. In the follow-up through December 31, 1996, there is now a total of five MM deaths and 2.35 expected among white males for an RR of 2.12. When the authors included white women,

TABLE 2. Effect of follow-up time on risk estimates for leukemia and myeloma in the NIOSH Pliofilm study of white males

Causes of death	All causes		Leukemia		Myeloma	
	Obs	SMR	Obs	SMR	Obs	SMR
	Authors					
Infante <i>et al.</i> ³⁵ 1950–1975 follow-up <i>N</i> = 748	140	0.75*†	7	5.60*	2	NE
Rinsky <i>et al.</i> ^{‡56} 1950–1975 follow-up <i>N</i> = 1006 (+258)	229	1.06	8	4.68*	2	NE
Rinsky <i>et al.</i> ⁴ 1950–1981 follow-up <i>N</i> = 1165 (+159)	330	0.99	9	3.37*	4	4.09*
Rinsky <i>et al.</i> ³⁴ 1950–1996 follow-up <i>N</i> = 1165	656	0.99	15	2.56*	5	2.12

Cohort first exposed 1936, last exposed 1976. NE = expected not estimated; *N* = number in cohort; Obs = observed.

**P* < 0.05.

†Follow-up only 75% completed.

‡Includes addition of workers first exposed > 1950, "group 2."

†Additions to cohort during updated follow-up.

who were newly added to the cohort, the observed remained at five MM deaths, but the expected increased to 2.45, SMR = 2.04 (95% CI = 0.66–4.76).

The Rinsky *et al.*³⁴ update of the NIOSH Pliofilm benzene cohort is accompanied by another analysis by Silver *et al.*³³ This paper states that the RR for MM (and leukemia) in relation to benzene exposure rises and then declines with successive years of follow-up of the benzene cohort, whose last exposure occurred in 1976. The RRs for leukemia and MM by follow-up period are shown in TABLE 2. The data demonstrate a decline in the SMR for leukemia from 5.60 in the original report³⁵ to 2.56 in the last published follow-up, and a decline in the SMR for MM from 4.09 in the Rinsky 1987 publication to 2.12 in the most recent follow-up. As a possible interpretation for the fall in the RR of these diseases among the Pliofilm benzene cohort members over time, Silver *et al.*³³ offer two explanations. First, the 1996 cohort follow-up period resulted in 20 years passing between the last benzene exposure to the cohort and the end of the follow-up. Since the follow-up period in the most recent publication is likely to be well beyond the median latency period for benzene to induce leukemia in general (they acknowledge that different types of leukemia may have different median latencies, but the majority in this cohort were ANLL), following up the cohort over such a long period of time results

in less expression of the disease and hence a lower RR. Second, they argue that workers, who were the most susceptible to leukemia from benzene, succumb relatively earlier to the disease, leaving a less susceptible population at risk for the majority of the follow-up period. Silver *et al.*³³ state that summary estimates are misleading and that time-specific estimates must be provided, or one may underestimate the risk to the exposed workers. Although the authors did not address MM in as much detail as they did for leukemia, the same phenomena is apparent.

As a result of reviewing the two above-mentioned papers by the NIOSH investigators, preference was given to the data on benzene exposure and RR of MM from the follow-up that was completed in 1981 by Rinsky *et al.*⁴ This follow-up period was selected for the following reasons: (a) from the NIOSH Pliofilm cohort study, 25 years appears to be the median latency period for benzene exposure and death from MM as shown in the Rinsky *et al.* 1987 paper; therefore, one might expect the RR to begin to decline shortly after this period of time; and (b) benzene exposure to the cohort began in 1936 and ended in 1976—a 40-year maximum exposure period; therefore, 1956 is the most likely mid-point year of the exposure period. The addition of 25 years (estimated median latency for benzene exposure and MM in the study) to the 1956 mid-point cohort exposure year leads to 1981 as the follow-up year that might provide the most sensitive period for evaluating the RR of MM among cohort members. Based on the findings and discussion by Silver *et al.*,³³ one might also justify using data from the 1981 follow-up to estimate risk from MM and leukemia, because risk for both of these diseases declines after this period in the published studies.

In the benzene cohort study by Wong,⁸ using the U.S. general population for comparison of mortality, the author only presented results for observed and expected deaths from MM for the group intermittently exposed to benzene. He observed two deaths from MM versus 0.56 expected (SMR = 3.57; 95% CI = 0.43–12.90). For the overall cohort continuously exposed to benzene, he observed three deaths from MM versus none in a comparison group comprised of workers at the same facilities not exposed to benzene. Wong³⁶ considered the internal comparison group the most appropriate in his study. Therefore, one could select the RR of 3.57 or a risk of 30 (3 versus 0.1 by arbitrarily assigning 0.1 to the expected for the internal comparison group). An SMR of 3.57 for MM was selected as the most conservative estimate of MM risk for this cohort.

Fu *et al.*⁵ studied mortality among two cohorts of shoe manufacturers; one from three English towns and the other from Florence, Italy. The authors stated “the exposure information necessary to calculate time-related variables was not available for the English shoe workers” and “. . . only job title as indicated in the 1939 census was collected, and dates of employment were not available.” They further indicated that “it is unclear how much exposure to benzene occurred among workers in the British shoe and boot industry. . . documentation on the

specific solvents to which the workers in this study were exposed are not available” (p. 395). They considered 2.5% of the cohort having been highly exposed to “solvents,” though they lacked information on the content of the solvents.

The authors stated that the Florence shoe workers began to use benzene in the early 1950s. They estimated that 70% of the glue consisted of benzene before 1960. By the end of 1963, however, a national law required that the benzene content of glues be limited to 2%. Exposure concentrations were not available, but the authors stated that atmospheric benzene exposures in the Pavia shoe industry ranged from 25 to 600 ppm. They further estimated that 26% of the cohort was highly exposed to “solvents.” Since it is not known whether the English cohort was exposed to solvents containing benzene, data from the Florence cohort only were included in the analyses. The observed risks for leukemia and MM among these two cohorts are consistent with the view that there was little, or no use of benzene among the English shoeworkers, but that benzene was used by the Florence cohort members. For the Italian cohort, the SMRs for leukemia and MM were 214 (eight deaths observed) and 288 (three deaths observed), respectively. For the English cohort, the SMRs for leukemia and MM were 89 (16 deaths observed) and 104 (eight deaths observed), respectively.

The most recent update of the study of Chinese workers exposed to benzene by Yin *et al.*⁹ does not indicate any excess of MM. There was one observed case of MM versus 2.50 expected based on comparison to rates among non-benzene-exposed workers, (RR = 0.40, 95% CI = 0.1–10.7). These data were used in the analyses. MM has a much less frequent occurrence in the Chinese population as compared to Western populations and the authors noted that this factor resulted in little statistical power to assess its risk as indicated by the wide confidence interval surrounding the estimate of risk.

Ireland *et al.*⁶ evaluated mortality in a small cohort of benzene-exposed workers at the Monsanto Company in Sauget, Illinois. For MM among benzene-exposed production workers, three deaths were observed versus 0.93 expected (SMR = 3.23, 95% CI 0.7–9.4) For workers who had achieved 20+ years since first benzene exposure (latency), there were three deaths observed from MM versus 0.82 expected deaths (SMR = 3.66, 95% CI = 0.75–10.7). For workers who had estimated cumulative benzene exposure of between 1 ppm-year and >6 ppm-years, there were three observed deaths versus 0.56 expected (SMR = 5.36, 95% CI = 1.1–15.7).

The Ireland *et al.*⁶ benzene cohort was followed up for 7 more years with the addition of 245 workers by Collins *et al.*⁷ Overall, they observed eight MM deaths versus 4.2 expected (SMR = 1.9, 95% CI = 0.8–3.8). For those cohort members with estimated benzene exposures between 1 ppm-year and >6 ppm-years, there were six MM deaths versus 2.8 expected (SMR = 2.14, 95% CI = 0.8–4.67). The authors noted that 10 of 13 deaths from MM occurred among workers exposed to benzene (eight with known cumulative

TABLE 3. Cohort mortality study of hourly workers, who began employment at Monsanto Company in Sauget, Illinois between 1940–1977

	Myeloma		Leukemia (ANLL)	
	Obs	SMR	Obs	SMR
Ireland <i>et al.</i> ⁶ 1940–1991 follow-up <i>N</i> = 4172	3	3.23	2	2.78
Collins <i>et al.</i> ⁷ 1940–1997 follow-up <i>N</i> = 4417 (+245)	8	1.90	5	2.17

Myeloma by cumulative benzene dose (ppm-years)							
Nonexposed		< 1ppm-year		1–6 ppm-years		>6 ppm-years	
Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR
5	1.1	2	1.4	2	1.5	4	2.6

Myeloma by no. of days with peak exposures >100*							
None		<7		7–40		>40	
Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR
9	1.2	0	0.0	1	1.7	3	4.0

Collection of benzene exposure data began at 1980, cohort median cumulative benzene exposure = 3 ppm-year. Obs = observed.

*15-min exposure period.

+Additions to cohort during updated follow-up.

exposure) and they all achieved 20 or more years of latency, SMR = 1.80 (95% CI = 0.9–3.3).

The effect of follow-up time on the RR of MM and leukemia in the Monsanto cohort can be seen from the data in TABLE 3. Results from the two follow-up periods indicate that the SMR for ANLL was lowered from 2.78 (two deaths) to 2.17 (five deaths). The SMR for MM declined from 3.23 (three deaths) to 1.90 (eight deaths) between the follow-up periods. Therefore, the cohort shows a reduction in risk of MM and leukemia as the follow-up period is extended. The most recent overall results by Collins *et al.*⁷ were included in the estimate of MM risk in the meta-analysis. This was done based on the following information. The cohort of Monsanto employees was followed up from 1940 to 1997, a 57-year period. The authors stated that all of the benzene-exposed MM deaths occurred more than 20 years after the initial exposure and one death is known to have occurred more than 30 years after the initial exposure, but they did not provide information on latency for specific cases. Therefore, a 25-year latency period was assumed based on this information along with the

information provided in the NIOSH study. Since the mid-point exposure year for the cohort would be 1969 and the median latency for MM was assumed to be 25 years, a follow-up around the time of 1994, or a short time later may provide the most full expression of RR for MM among the cohort members. The earlier follow-up of the cohort was to 1991 and the latter was to 1997. Since 1994 is midway between these, and the latency might actually be longer than the assumed 25 years, the results based on the 1997 follow-up period were selected.

Though not a part of the overall benzene cohort analysis, Collins *et al.*⁷ also evaluated lymphohematopoietic cancer by cumulative and peak benzene exposure. The authors concluded that they found increasing risk with cumulative benzene exposure and MM. They stated, "For MM, the SMRs were 1.1 (95% CI 0.3–2.5) in the nonexposed group, 1.4 (95% CI 0.2–5.1) in the <1 ppm-years, 1.5 (95% CI 0.2–5.4) in the 1–6 ppm-years, and 2.6 (95% CI 0.7–6.7) in the >6 ppm-year group" (p. 676). However, when peak exposures over 100 ppm for 40 or more days were considered, the SMR for MM was 4.0 (95% CI 0.8–11.7). The authors stated that a high number of peak exposures to benzene is a better predictor of risk than cumulative exposure (for MM and leukemia) and concluded that dose–rate of benzene exposure may be an important factor for evaluating benzene exposure and lymphohematopoietic cancers.

Ott *et al.*³⁷ followed up 594 workers employed at the Dow Chemical facility in Midland, Michigan from 1940 to 1973. These workers were exposed to benzene prior to 1940. Bond *et al.*³⁸ included an additional 362 cohort members for a total of 956 and extended the follow-up of the cohort till 1982. Bloemen *et al.*¹⁰ combined the Midland, Michigan cohort previously studied by Ott *et al.*³⁷ and by Bond *et al.*³⁸ with a new group of 1310 workers characterized as having been employed in chlorobenzol area jobs with the lowest benzene exposures in unidentified Dow facilities in the United States. Cohort follow-up was extended till 1996. In the latter study, analyses were not presented separately for the previously studied Dow Midland facility cohort members and for the cohort additions from other facilities. As a result, it is not possible to determine the effect of follow-up time on risk estimates for MM and leukemia for the original Dow Midland cohort. The benzene exposures for the entire cohort¹⁰ were terminated by 1978 as ethylcellulose production was discontinued in 1977, while the chlorobenzol and alkyl benzene operations ceased in 1978.

The results from the follow-up of the Dow chemical workers are shown in TABLE 4. In the most recent publication, Bloemen *et al.*¹⁰ observed three deaths from MM versus 4.17 expected, the SMR = 0.72 (95% CI = 0.15–2.10). In the previous publication by Bond *et al.*,³⁸ one MM death had been observed, but an expected number of deaths was not provided. For death from ANLL among cohort members, there were four observed versus 3.6 expected, SMR = 1.11. Yet, in the previous two follow-up analyses of the Midland portion of the

TABLE 4. Results of Dow Midland benzene cohort mortality study by authors and follow-up period

Authors	Causes of death							
	All causes		ANLL			Myeloma		
	Obs	SMR	Obs	Exp	SMR	Obs	Exp	SMR
Ott <i>et al.</i> ³⁷ 1940–1973 follow-up <i>N</i> = 594	102	0.80*	3	0.80	3.75 [†]	0	NE	—
Bond <i>et al.</i> ³⁸ 1940–1982 follow-up <i>N</i> = 956 (+362)	225	0.84*	4	0.90	4.44*	1	NE	—
Bloemen <i>et al.</i> ¹⁰ 1940–1996 follow-up <i>N</i> = 2266 (+1310) [‡]	972	0.90*	4	3.60	1.11	3	4.17	0.72
Within last follow-up period (1983–1996)			0	2.70	—	2	???	???

Benzene exposures to the cohort ceased in 1977 and 1978. NE = no expected provided; Obs = observed; Exp = expected.

* $P < 0.05$.

+Additions to cohort during updated follow-up.

[†]SIR was 3 “cases” versus 0.8 expected based on Third National Cancer Survey incidence data.

[‡]Number of very low benzene-exposed cohort members added from facilities other than Midland.

??? = not calculated.

cohort, the results for ANLL demonstrated a statistically significant excess. Ott *et al.*³⁷ reported a standardized incidence ratio (SIR) of 3.75 and Bond *et al.*³⁸ reported an SMR of 4.44. As shown in TABLE 4, within the new follow-up period of 1983–1996, no additional deaths from ANLL were observed, while 2.7 deaths from this cause were expected. Exposures to the cohort began prior to 1940 and by the end of the most recent follow-up period, 19 years have elapsed since the last exposure for those who remained on the job until the operations ceased in 1977–1978. Since the cohort selection began with those employed in 1938 and all benzene exposures were terminated by 1978, and assuming a 25-year median latency period for MM, the most sensitive follow-up period may have been around 1983. Therefore, the Bond *et al.*³⁸ study which followed the cohort through 1982 may have provided the best estimate of MM risk among the cohort members. For this follow-up, one death from MM was observed and an expected was not provided. Therefore, the study results based upon the Bloemen *et al.*¹⁰ follow-up to 1996 were included in the meta-analysis as shown in TABLE 5.

Sorahan *et al.*¹¹ recently published the results of a cohort mortality and morbidity study of workers exposed to benzene in the United Kingdom. The

authors observed a slight deficit for MM (SMR = 0.63, 95% CI = 0.2–1.4). The risk for total leukemia was slightly elevated (SMR = 1.37, 95% CI = 0.86–2.07) as was the risk for AML (SMR = 1.82, 95% CI = 0.94–3.18). In the study, the highest risk of cancer achieving statistical significance was “cancers of uncertain origin,” SMR = 140, based on 68 cancer deaths, $P < 0.001$. Because of significant under-ascertainment of cancer deaths that occurred among the cohort members,¹² it is difficult to include this study in the analysis for MM. Furthermore, among cohort members who died in the earliest period of follow-up, e.g., 1968–1974, cancer registrations were missing for an estimated 50% (46/91) of the cancer deaths. As such, they likely represent deaths that occurred among cohort members who were exposed during earlier periods of employment, when benzene exposures were relatively higher. Since MM and other lymphohematopoietic cancer deaths are so rare, the identification of only a few additional deaths from these causes can make a significant difference in the estimate of RR. Other limitations of the study also have been noted.¹² Because of these limitations, the study results were not included in the meta-analyses.

SUMMARY OF DATA FROM THE BENZENE COHORT STUDIES IN RELATION TO RISK OF MYELOMA

The evaluation of the study design, methodology and data from the eight

TABLE 5. Summary of estimates of relative risk of myeloma identified in benzene cohort studies selected for inclusion in analysis by author and year of publication

Estimates of risk of multiple myeloma					
Authors	Year	Obs	Exp	SMR	95% CI
DeCoulfle <i>et al.</i>	1983	1	0.23	4.35	(0.1–24.2)
Rinsky <i>et al.</i>	1987	4	0.98	4.09	(1.1–10.5)
Wong	1987	2	0.56	3.57	(0.4–12.9)
Fu <i>et al.</i> (Florence)	1996	3	1.04	2.88	(0.6–8.4)
Yin <i>et al.</i> [†]	1996	1	2.50	0.40	(0.1–10.7)
Collins <i>et al.</i>	2003	8	4.20	1.90	(0.8–3.8)
Bloemen <i>et al.</i>	2004	3	4.16	0.72	(0.2–2.1)
All studies combined					
Overall pooled added numbers		22	13.67	1.61	(1.01–2.44)
Weighted (Poisson) RR*				2.13	(1.31–3.46)

Obs = observed; Exp = expected.

[†]Yin *et al.* calculated relative risks based on incidence rates (the others used SMRs) increasing the estimated standard errors.

*For the weighted estimate, all individual study weights were derived from standard errors calculated assuming a Poisson distribution (<http://home.clara.net/sisa/smr.htm>). Pooled weighted ln RR and RR estimates and confidence limits were derived using standard methods for meta-analysis, fixed effects model (χ^2 test of homogeneity, $P > 0.05$).^{39,40}

benzene cohort studies published to date resulted in the use of data from seven of the studies upon which to base an estimate of the RR of MM, as shown in TABLE 5. Using the overall pooled numbers, there are 22 observed MM deaths and 13.67 expected, SMR = 1.61 (95% CI = 1.01–2.44). For the weighted estimate, all individual study weights were derived from standard errors calculated assuming a Poisson distribution (<http://home.clara.net/sisa/smr.htm>). Pooled weighted In RR and RR estimates and confidence limits were derived using standard methods for meta-analysis, fixed effects model (χ^2 test of homogeneity, $P > 0.05$).^{39,40} The pooled weighted estimate of MM risks is shown in TABLE 5, RR = 2.13 (95% CI = 1.31–3.46). Of the studies included in the estimate, the RR of MM for five studies ranged from 1.90 to 4.35. In two of the studies, the RR for MM was 0.40 and 0.72. In one of these studies,¹⁰ benzene exposure had terminated 20 years prior to the last year of follow-up, and was based on a follow-up period that was 13 years beyond the estimated most sensitive follow-up year to observe an elevation in the risk of MM in the study. This factor may have had some influence on the estimate of MM risk observed in the study.

BIOLOGICAL PLAUSIBILITY OF BENZENE AS A CAUSE OF MULTIPLE MYELOMA

In addition to the evaluation provided above, there is a biologically plausible basis for establishing benzene as a cause of myeloma^{3,4,41}: (a) MM is a tumor of plasma cells within the bone marrow, which are derived from B-lymphocytes; (b) the bone marrow is a target organ for benzene toxicity causing aplastic anemia, various cytopenias (including depression of B-lymphocytes,⁴² myelofibrosis, myelodysplastic syndrome, and leukemia; (c) benzene is associated with an increased risk of chromosomal damage to circulating lymphocytes^{43–45}; (d) and, more recently to DNA damage to B-lymphocytes specifically⁴⁶; (e) workers exposed to benzene also have demonstrated an elevated risk of chronic lymphocytic leukemia,^{27,30,47} which is also a cancer of B cell lineage. Thus, benzene has shown very specific toxicity and genetic alteration not only to the target organ, the bone marrow, but also to the specific cells within the bone marrow from which plasma cells are derived, e.g., the B-lymphocytes.

The findings in humans are consistent with the results of the National Toxicology Program study of benzene in experimental animals.⁴⁸ This study demonstrated that benzene induced solid tumors at multiple sites in both rats and mice. The study also demonstrated a highly significant dose–response for lymphoma in male and female mice exposed to benzene.⁴⁸ Cronkite *et al.*⁴⁹ also have demonstrated the induction of lymphomas in mice exposed to benzene by inhalation. Therefore, at least six lines of evidence support the epidemiological finding that benzene exposure is associated with a significantly elevated risk of myeloma.

DOES EVIDENCE FROM TWO LARGE COHORT STUDIES OF REFINERY WORKERS SUPPORT OR DETRACT FROM THE EVIDENCE PROVIDED BY BENZENE COHORT STUDIES?

Although the purpose of the evaluation was to determine whether or not the benzene cohort studies provided evidence of an association between benzene exposure and myeloma, results from two of the largest cohort studies of petroleum refinery workers were also reviewed. This was done in order to put the findings of these studies into perspective in relation to those of the benzene cohort studies.

Australian Health Watch Study

The Australian Institute of Petroleum periodically publishes the results of its medical surveillance program referred to as Health Watch. Employees must have 5 years of employment to enter the program which was initiated in 1980. After termination of employment, the members of the cohort can choose to stay in the program or opt out. Between 1992 and 2004, six reports that represent the findings of morbidity and mortality among these workers have been reviewed.^{24–27,30,31} The findings for the incidence and mortality of myeloma are presented in TABLE 6 and the results for leukemia incidence are shown in TABLE 7. In the overall analysis for myeloma, the SIR ranges from a high of 1.9 in the 10th Report²⁵ to 1.7 in the 11th Report.²⁶ Myeloma mortality ranges from an SMR of 2.6 in the 9th Report²⁴ to 1.7 in the 11th Report. As shown in TABLE 6, for the entire study population in the 11th Report, 15 cases of MM were observed, SIR = 1.7 (95% CI 0.9–2.8). Among workers employed in terminal work, a significant excess of myeloma was demonstrated, 10 cases of MM were observed, SIR = 2.50 (95% CI = 1.2–4.6). Among refinery workers, the risk of MM was essentially identical to the expected, SIR = 1.08 (95% CI = 0.4–2.8). The significant elevation in MM risk among terminal workers is noteworthy because as shown in TABLE 7, the highest RR of leukemia was also observed among terminal workers (16 observed versus 8.8 expected, SIR = 1.82, 95% CI = 1.04–2.95).²⁶ Gray *et al.*²⁷ concluded that the significantly elevated leukemia risk identified among terminal workers in the 11th Report “is probably explained by the historically higher exposures in terminals rather than any other site characteristic” (p. xiv). It is not clear from the study why this same comment could not be made in relation to the significant excess of MM that was identified among terminal workers. In the journal publication of this study,³¹ the authors do not include the results for the analysis of MM among terminal workers. The reason for the omission of the results of this analysis in the journal publication is not provided.

In additional analyses of the Australian petroleum refinery workers, Gray *et al.*²⁷ were able to demonstrate a dose–response for benzene exposure and

TABLE 6. Health Watch: The Australian Institute of Petroleum Health Surveillance Program (began in 1980)

		Myeloma					
		Incidence			Mortality		
		Obs	SIR	(95% CI)	Obs	SMR	(95% CI)
Ref. 24	9th Report (1992)	6	1.8	(0.7–3.9)	6	2.6	(1.0–5.7)
Ref. 25	10th Report (1998)	13	1.9	(1.0–3.3)	8	1.6	(0.7–3.2)
Ref. 26	11th Report (2000)	15	1.7	(0.9–2.8)	11*	1.7	(0.9–3.1)
	Terminals	10	2.5	(1.2–4.6)			
	Refinery	4	1.08	(0.4–2.8)			
Ref. 31	Gun <i>et al.</i>	15	1.7	(0.96–2.84)	8*	1.6	(0.7–3.2)

Obs = observed.

*Difference in number of deaths is likely explained by Gun *et al.* following the cohort to the end of 1996, while the 11th Report followed the cohort to the end of 1998; no analysis was presented for terminal workers in Gun *et al.*

leukemia, but not for benzene exposure and MM. However, the dose–response analysis for benzene exposure and MM contained only six cases of MM spread over three dose groupings—far too small a number upon which to draw any meaningful conclusions about the lack of a dose–response. (Nine of the 15 MM cases in the study were used to set the RR to 1.0 for comparison.)

Wong and Raabe Meta-analysis of Myeloma Risk among Refinery Workers

Wong and Raabe³² have evaluated mortality from MM through meta-analyses of petroleum-exposed cohorts. This study did not demonstrate an

TABLE 7. Health Watch: The Australian Institute of Petroleum Health Surveillance Program (began in 1980)

		Leukemia incidence		
		Obs	SIR	(95% CI)
11th Report ²⁶	Terminals	16	1.8	(1.04–2.95)
	Refinery	11	1.3	(0.67–2.39)
	All workplaces	30*	1.5	(1.02–2.15)
Gun <i>et al.</i> ³¹	All workplaces	27*	1.4	(0.91–2.02)

Obs = observed.

*Difference in number of cases is likely explained by Gun *et al.* using a shorter follow-up period. See footnote to Table 6.

elevation in risk for MM. For workers employed at U.S. refineries, the myeloma SMR = 0.97 (95% CI = 0.81–1.17). With data combined for workers employed in the United States, the United Kingdom, Canada, and Australia, the myeloma SMR = 0.95 (95% CI = 0.83–1.07). The authors concluded that petroleum workers are not at an increased risk of myeloma as a result of their exposure to benzene, benzene-containing liquids, or other petroleum products in their work environment. These conclusions, however, must be placed in perspective related to other causes of death among those included in the meta-analysis. Somewhat surprisingly, the authors do not provide information on the SMRs for the category “all causes of death,” nor for the category “all cancer deaths.” Therefore, it is not possible to evaluate the impact of the “healthy worker effect” (HWE) on the findings related to MM. Evaluation of the HWE in the study is particularly relevant because of the previously published findings regarding the U.S. gasoline distribution workers, who were also included in the Wong and Raabe meta-analysis for MM.³²

For example, the Wong *et al.*⁵⁰ study of U.S. petroleum distribution workers contributed over 18,000 cohort members to the Wong and Raabe³² meta-analyses for MM. For those who were considered land-based terminal workers, their overall mortality rate was only 50% of the expected based on death rates for the U.S. standard population. The overall mortality rate for marine workers was 77% of the standard population rates. Enterline⁵¹ suggested that these findings may be due to selection bias in the Wong *et al.* study of gasoline distribution workers.⁵⁰ Concern about the methodology used in the study was also expressed by Infante⁵² during the evaluation of the Wong *et al.* study.⁵⁰

Further suspicion about selection bias in the Wong and Raabe studies of refinery workers^{32,53,54} is provided by differences in the numbers of cohort members being followed up during identical time periods of follow-up, and also by different numbers of cohort members being followed up when the authors conducted meta-analyses for MM,³² leukemia,⁵³ and NHL,⁵⁴ as presented in separate publications.

In terms of exposure to benzene among the cohorts evaluated by Wong and Raabe,^{32,53,54} the authors provide little credible information. In the myeloma study, Wong and Raabe³² state that the benzene component in the gasoline is highly correlated with total hydrocarbon (THC) exposure. Their source for this opinion is Smith *et al.*⁵⁵ Yet, Smith *et al.*⁵⁵ stated that THC was a reasonable surrogate for one or more of the major hydrocarbon components in the vapor mixture of gasoline based on sampling data after 1969, but that “benzene was an exception to this because the benzene content of gasoline has varied over time as a result of changes in gasoline blending practices by the refineries” (p. 14). Since Wong was a co-author of the THC exposure assessment study,⁵⁵ one would surmise that he might have known about the limitations of using gasoline as a surrogate for benzene exposure in MM study.³² The use of a constant proportion of benzene in the THC vapor, as done by Wong and Raabe,³² will result in mis-classification of benzene exposure.

In summary, the significant increase in MM incidence among terminal workers in the Health Watch cohort study²⁶ provides some evidence of an association between benzene exposure and MM. The Wong and Raabe meta-analysis of refinery workers³² cohorts shows no association between refinery work exposures and RR of MM, but the analyses suffer from limitations in data presentation, benzene exposure mis-classification, and potential selection bias. As a result, they do not allow for any meaningful interpretation regarding benzene exposure and RR of MM. Nor do the findings detract from the evidence that benzene exposure is a cause of MM, as supported by the current meta-analysis of data from the benzene cohort studies in conjunction with other findings related to the toxicity of benzene on B-lymphocytes and lymphoma in experimental animals.

CONCLUSIONS

A meta-analysis of data from all well-conducted benzene cohort studies demonstrates a statistically significant elevation in the risk of death from MM.

Consideration of cohort follow-up period in relation to median latency period for the disease being evaluated is important in determining the RR of disease.

The positive epidemiological evidence for benzene and myeloma is supported by other study results related to the biological plausibility for such an effect from benzene exposure.

Cohort studies of refinery workers are difficult to interpret in relation to benzene exposure and risk of MM, because of limitations in exposure assessment, study design, and analysis. Yet, one large study of petroleum refinery workers provides suggestive additional evidence of an association between benzene exposure and myeloma.

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