Benzene Exposure and Hematopoietic Mortality: A Long-Term Epidemiologic Risk Assessment

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Background *Previous studies of a cohort of rubber hydrochloride workers indicated an association between benzene exposure and excess mortality from leukemia and multiple myeloma. To determine whether risks remain elevated with increasing time since plant shutdown, we extended follow-up from 1981 through 1996.*

Materials and Methods *We evaluated risk using standardized mortality ratios (SMR) and generalized Cox proportional hazards regression models.*

Results *Five new leukemia cases were observed in benzene-exposed white males, but the summary SMR for this group declined from 3.37 (95% CI = 1.54–6.41) to 2.56 (95% CI = 1.43–4.22). In regression models, cumulative exposure was significantly associated with elevated relative risks for leukemia mortality. Four new multiple myeloma deaths occurred, three of which were in workers judged to be unexposed.*

Conclusions *These findings reaffirm the leukemogenic effects of benzene exposure and suggest that excess risk diminishes with time.* Am. J. Ind. Med. 42:474–480, 2002. *Published 2002 Wiley-Liss, Inc.*†

KEY WORDS: benzene; rubber workers; leukemia; multiple myeloma; risk analysis; occupational health

INTRODUCTION

In 1986, the National Institute for Occupational Safety and Health (NIOSH) established the recommended exposure limit (REL) for benzene in the workplace at 0.1 part per million (ppm) [NIOSH, 1986]. In 1997, the American Conference of Governmental Industrial Hygienists (ACGIH) established a threshold limit value (TLV) of 0.5 ppm [ACGIH, 2000]. The only enforceable standard, the OSHA permissible exposure limit (PEL), has remained at 1 ppm since 1987 [Federal Register, 1987].

Each of these exposure standards is based at least in part on the mortality experience of a group of workers exposed to benzene while manufacturing rubber hydrochloride. This cohort has been periodically described by NIOSH [Infante et al., 1977; Rinsky et al., 1987, 1981]. Interest in this cohort has remained high since the previous update. Other researchers have performed independent analyses, varying statistical analyses, and sometimes proposing the use of other exposure estimates [Paustenbach et al., 1992; Crump, 1994, 1996; Paxton et al., 1994; Paxton, 1996; Finkelstein, 2000]. Regardless of which exposure estimates were used, the level of exposure to benzene has consistently shown a statistically significant relationship to leukemia mortality.

In order to assess whether this risk remains elevated with increasing time since plant shutdown, we continued to follow the cohort of rubber hydrochloride workers through December 31, 1996. The cohort has been followed an additional 15 years since our last follow-up date of December 31, 1981 [Rinsky et al., 1987], and now includes at least 20 years of follow-up since last exposure for every living cohort member.

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METHODS

Members of the cohort were employed at one of three rubber hydrochloride plants in two Ohio locations for at least 1 day between January 1, 1940 and December 31, 1976. Rubber hydrochloride operations at Location 1, St. Mary's, Ohio, began in 1939 and ceased in April 1976. At Location 2, Akron, Ohio, rubber hydrochloride production operations began in 1936 or 1937. Operations continued in ''plant 1'' of this facility until approximately 1949. In 1948, a second plant at Location 2, ''plant 2'' was constructed for rubber hydrochloride production; this plant became operational in mid-1949. Rubber hydrochloride production at this facility ceased in 1965.

We previously reported on only the 1,165 white males with at least 1 day of work in an exposed department between January 1, 1940 and December 31, 1965 [Rinsky et al., 1987], followed through December 31, 1981. In the current update, we included all 1,291 persons with at least 1 ppm-day of exposure between January 1, 1940 and April 31, 1976 in the SMR analysis, with no restrictions on race or gender. In addition, we modeled the exposure–disease relationship for all 1,845 non-salaried workers (1,291 exposed and 554 unexposed) who were alive as of January 1, 1950.

For the follow-up through 1981, vital status was ascertained using records from the Social Security Administration, the Ohio Bureau of Motor Vehicles, and a commercial tracing agency. Death certificates were obtained for all known deaths and coded by a certified nosologist using the rules of the International Classification of Disease (ICD) in effect at the time of death. To update vital status through 1996, we used records from the Social Security Administration and the National Death Index. The National Death Index provides coded causes of death. The additional deaths ascertained from this source were not sent for nosology coding.

The rubber hydrochloride operations have been previously described in detail [Rinsky et al., 1981, 1987]. Job-exposure matrices were created based on available air sampling data. Cumulative exposures (ppm-years) for each worker were derived from the matrices by summing daily exposure values using detailed work histories, as described in Rinsky et al. [1987], and dividing the result by 365.25.

Standardized Mortality Ratio (SMR)

All workers employed in an exposed area for at least 1 day after January 1, 1940 and still alive as of January 1, 1950 were included in the SMR analysis. We began to accumulate person-years at risk on January 1, 1950 to maintain consistency with previous reports by restricting analysis to deaths classified under the seventh or later revisions of the ICD. Underlying cause of death was used for all analyses. Person-years at risk of dying and the number of deaths observed were calculated beginning on January 1, 1950 or when the worker first accrued 1 ppm-day (1 full day of employment in an exposed area), whichever was later, and continued until December 31, 1996 or the date of death, whichever was first.

Person-years were stratified by increasing levels of cumulative exposure. For historical consistency, in the SMR analyses we maintained the strata used in our previous reports: 1 ppm-day to 39.99 ppm-years, 40–199.99 ppm-years, 200–399.99 ppm-years, and 400 or more ppm-years. These strata represent, respectively, a 40 year working-lifetime exposure to less than 1, 1–4.99, 5–9.99, and 10 or more ppm of benzene.

Standardized mortality ratios (SMRs) with 95% confidence intervals for all causes of death were calculated using NIOSH's PC-Life Table Analysis System (PC-LTAS), Version 1.0c [NIOSH, 1998]. PC-LTAS calculates expected numbers of deaths in a cohort by applying age (within 5 years), race, sex, and calendar time period (within 5 years) specific mortality rates from an external standard population to the corresponding person-years at risk in the cohort. US population death rates were used for comparison with death rates observed in the cohort. For leukemia, the NIOSH cause of death rate file for 1940–1999 (based on actual rates for 1940–1994 with rates for 1995–1999 duplicated from 1990 to 1994 actual rates) was used. For multiple myeloma and non-Hodgkins lymphoma, cause-specific rates of death are available only from 1960 onwards (before 1960, these causes were subsumed in the category ''other lymphatic and hematopoetic malignancies''). Therefore, for these outcomes, we began observation in 1960 and used the NIOSH cause of death file for 1960–1999 to obtain expected deaths.

Modeling

To evaluate the effects of benzene on risk of leukemia and multiple myeloma, as well as potential confounders and effect modifiers, we examined a generalized form of the Cox proportional hazards regression model. We used SAS (PROC PHREG, SAS Version 6.12) [SAS Institute, Inc, 1998] except when assessing linear models, which were examined using EpiCure version 2.0 [Hirosoft, 1993]. All workers employed for at least 1 day in the rubber hydrochloride departments after January 1, 1940 and alive as on January 1, 1950 were eligible for inclusion in the risk sets, regardless of exposure status. To be included in the risk set for a specific case, cohort members were required to have achieved at least the age at death of the case. Potential members of each risk set, exposed or unexposed, also had to have worked at least 1 day in a rubber hydrochloride department before reaching the age at which the case died. We terminated accumulation of exposure for each member of the risk set at the age of death of the case.

We examined several metrics for benzene exposure, as well as a number of covariates. Total benzene exposure was

estimated both by duration of exposure and by accumulated part-per-million years. We also examined benzene exposure as a dichotomous variable, where workers with cumulative exposure of at least 1 ppm-day were compared with their unexposed counterparts. To allow for an induction period between exposure and death, we applied various lag periods. For example, under a 5 year lag period, exposures accumulated by each member of the cohort during the 5 years prior to the age at which the case died are discounted. For leukemia, we used lag periods of 0, 2.5, 5, and 10 years in calculations of cumulative exposure and duration of exposure. For multiple myeloma, we applied lag periods of 10, 20, and 30 years.

In addition to these primary exposure metrics, we examined a number of potential confounders and effect modifiers. Race is known definitively only for deceased employees, but 99% of these were white, and from existing records, no non-white cases were identified. Therefore, we did not model race. We did examine the effect of gender. The rate at which cumulative exposure is received is thought to impact risk of disease for exposures such as ionizing radiation [Hill et al., 1984; Ullrich, 1984; Hornung and Meinhardt, 1987; ICRP, 1990]. We examined the impact of exposure rate (defined as cumulative exposure divided by duration of exposure) and peak exposure (defined as the highest exposure level experienced by each worker for any length of time).

RESULTS

Nine hundred and seventy-six members of the full 1,845-member cohort died between January 1, 1950 and December 31, 1996. This represents about 53% of all workers in the cohort. Similarly, ~53% of workers with at least 1 day in an exposed area had died (Table I). For the 1,291 exposed workers, person-years at risk of dying totaled 45,753. Ninety-seven percent of these person-years at risk were contributed by males.

In the 15 years since our last published update, the proportion of deaths has nearly doubled (Table II). As of December 31, 1996, about 94% of the living members of the cohort were at least 50 years old and 53% were age 70 or older. In addition, this follow-up period extends to 20 years the time since any living worker was last exposed at the plants, providing time for the emergence of latent disease.

Lifetable (SMR) Analysis

For all cohort members with at least 1 ppm-day of exposure, overall mortality during the years 1950–1996 was similar to that of the US population for that time period (Table III), with an SMR of 0.98 (95% CI = 0.90–1.05). Mortality from all malignant neoplasms was also as expected. However, deaths from lymphatic and hematopoetic neoplasms were elevated, with a combined SMR of 1.64 (95% CI = 1.06–2.42). The SMR for leukemia for the whole cohort was 2.47 (95% CI = 1.38–4.07) and for white males, 2.56 (95% CI = 1.43–4.22). There were 17 leukemia deaths in the cohort; however, two deaths, one male and one female, did not have the minimum 1 ppm-day of cumulative exposure required by the SMR analysis. Therefore, their deaths were not counted among the leukemia deaths, nor did they contribute to any expectation of death. The leukemia cases had widely varying times since first exposed (latency), with six of the 15 exposed deaths occurring at least 30 years after the worker's first exposure.

Among exposed white males, SMRs for leukemia were elevated for all exposure categories and increased with increasing exposure (Table IV).

Beginning observation in 1960, and using 1960–1999 rates for multiple myeloma, yielded an SMR of 2.04 (95% CI = 0.66–4.76) for men and women of all races and an SMR of 2.12 (95% CI = 0.69–4.96) for white males. Four cases of multiple myeloma have occurred in this cohort since the 1981 update, bringing the total to eight cases. Three of the four new cases occurred in unexposed persons who were not included in the SMR calculations. Of the five cases of multiple myeloma occurring in exposed workers in this cohort, four occurred in the lowest exposure category (1 ppm-day to 30.99 ppm-years of exposure), with the fifth case in the highest exposure category (> 400 ppm-years).

Information about each case of leukemia and multiple myeloma, including age at death, year of death, latency,

TABLE I. Cohort Demographics and Vital Status of Benzene-Exposed Workers

	Workers with at least 1 day worked in an exposed area			All workers, exposed and unexposed*		
	Alive	Deceased	Total	Alive	Deceased	Total
Male	593 (47.3%)	661 (52.7%)	1,254 (100%)	815 (47.4%)	906 (52.6%)	1,721 (100%)
Female	19 (51.4%)	18 (48.6%)	37 (100%)	54 (43.5%)	70 (56.5%)	124 (100%)
Total	612 (47.4%)	679 (52.6%)	1,291 (100%)	869 (47.1%)	976 (52.9%)	1,845 (100%)

*Includes all salaried employees employed in rubber hydrochloride departments, between January 1, 1940 and December 31, 1976 and alive as of January 1, 1950.

TABLE II. History of Cohort Follow-Up and Mortality Status

Study end year*	Follow-up through	Population	% Alive	% Deceased
1949	June 30, 1975	748 white males with at least 1 ppm-day exposure	75.9 (568)	24.1 (180)
1965	December 31, 1981	1,165 white males with at least 1 ppm-day	71.7 (835)	28.3 (330)
1976	December 31, 1996 (all workers)	1,845 workers, both genders, all races, alive as of January 1, 1950, exposed and unexposed	47.1 (869)	52.9 (976)
1976	December 31, 1996 (all exposed workers)	1,291 workers, both genders, all races, alive as of January 1, 1950, with at least 1 day worked in exposed area	47.4 (612)	52.6 (679)

*Study begin date is January 1, 1940 for each follow-up; end date is December 31 of the year indicated.

TABLE III. Observed and Expected Deaths* 1950–1996 in Rubber Hydrochloride Workers Exposed to at Least 1 ppm-day of Benzene

	Males and females, all races combined, n = 1,291			White males, n = 1,165		
Cause	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
All causes	679	695.33	0.98 (0.90–1.05)	656	663.46	0.99 (0.92–1.07)
All malignant neoplasms	171	166.25	1.03 (0.88–1.20)	167	159.80	1.05 (0.89–1.22)
Lymphatic and hematopoietic cancers combined	25	15.26	1.64 (1.06–2.42)	25	14.72	1.70 (1.10–2.51)
Leukemia	15	6.08	2.47 (1.38–4.07)	15	5.87	2.56 (1.43–4.22)
Multiple myeloma*	5	2.46	2.04 (0.66–4.76)	5	2.35	2.12 (0.69–4.96)
Non-Hodgkins lymphoma*	5	5.19	0.96 (0.31–2.25)	5	5.01	1.00 (0.32–2.33)

*Risk begins in 1950 and expected deaths are based on U.S. population rates 1950–1996 for all outcomes except multiple myeloma and non-Hodgkins Lymphoma (NHL). For multiple myeloma and NHL, risk begins in 1960, the first year separate rates are available. Expected deaths for these outcomes are based on 1960–1996 U.S. rates.

TABLE IV. SMRs for Leukemia in White Males Exposed to Benzene, by Exposure Category

Exposure category	1 ppm day–30.99 ppm-years	40–199.99 ppm-years	200–399.99 ppm-years	> 400 ppm-years
Observed	6	4	2	3
Expected	4.13	1.25	0.36	0.13
SMR (95% CI)	1.45 (0.53–3.31)	3.21 (0.86–8.89)	5.55 (0.62–24.08)	23.96 (4.82–78.51)

diagnosis, cause of death, cumulative exposure, and location and duration of employment, is given in Appendix A.

Cox Proportional Hazards Modeling

Leukemia

We examined the shape of the exposure–response function for cumulative exposure using exponential, linear, and power function (log of cumulative exposure) models (Fig. 1). We compared the results with stratified rate ratios. Due to the expansion of the cohort and the observation of an additional seven new cases since the last report, the exposure strata, selected to distribute the cases roughly equally in each interval, differed from those we used in the last report (and for the SMR in the current report). The linear and log-linear models produced nearly identical deviances (change in twice the log-likelihood from a saturated model). However, the linear model was closest to the rate ratios for intervals chosen. We examined alternative cutpoints which maintained an equitable distribution of cases over the strata and found that the linear model still provided the best fit, although all three models provide a very good fit to the data (Table V).

Figure 1 shows plots of the three models considered, compared to estimates of relative risk for each exposure interval.

With the linear model, the deviance for cumulative exposure became progressively greater as the lag was increased from 0–2.5, 5, and 10 years. Duration of exposure, which is often used as a proxy for cumulative exposure, showed an excess relative risk estimate of 39.2% per year of exposure ($P = 0.004$). The average exposure rate in ppm showed an excess risk of 7.6% per ppm of benzene ($P = 0.048$). Of these univariate analyses, the exposure metric best describing the relationship between benzene

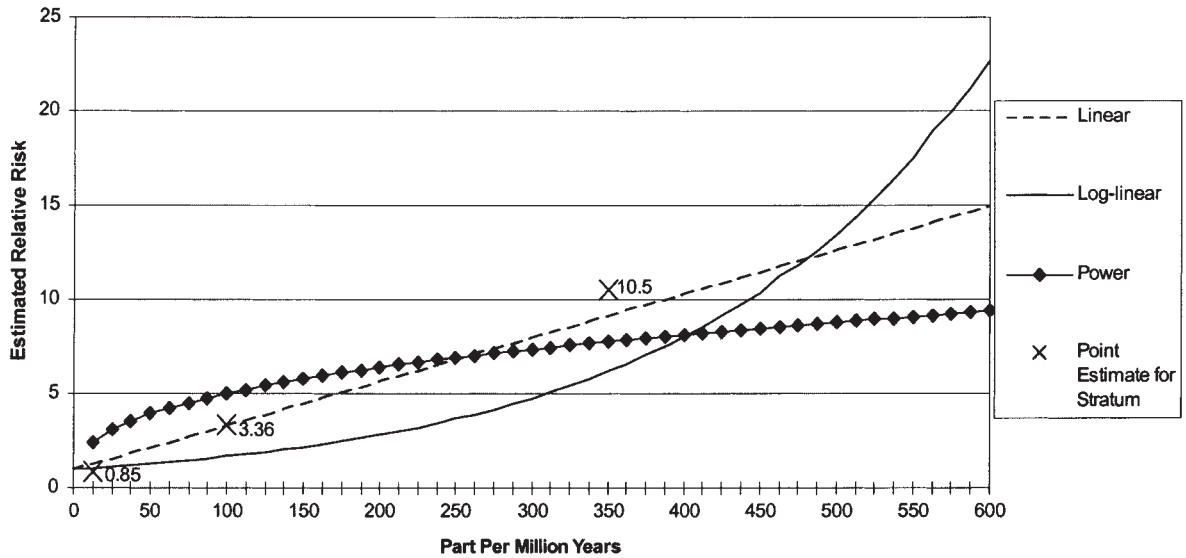

FIGURE 1. Benzene exposure (ppm-years) and estimated relative risk of leukemia using linear, log-linear, and power models.

exposure and leukemia mortality risk appears to be a linear function of cumulative exposure with no lag (Table VI).

Gender had no significant effect on the modeled relationship between cumulative exposure and disease. However, the number of female workers is so small that an effect would be difficult to detect.

Multiple Myeloma

We examined the relationship between benzene exposure and multiple myeloma using an exponential model. The regression analyses for multiple myeloma (Table VII) for the entire cohort showed a positive parameter estimate for cumulative exposure with a non-significantly elevated relative risk estimate of 1.003 per part-per-million year of exposure or 1.13 for a 40-year working lifetime at 1 ppm (95% CI = 0.95–1.34).

As minimum lag periods of 10, 20, and 30 years were imposed, parameter estimate decreased, becoming negative with the 20 year lag. Regardless of lag period, the model was unstable due to sparse data. No covariate attained statistical significance.

DISCUSSION

This update suggests that the relative risk of leukemia expressed as a single summary number has declined as this cohort has gained additional time since exposure. While six additional leukemia cases were found among exposed white males since the vital status ascertainment through 1981

TABLE V. Cox Proportional Hazards Models of Benzene Exposure and Leukemia Mortality Risk: Linear, Log-linear, and Power Models

Model (x = cumulative exposure)	Beta	Standard error	Deviance	Likelihood ratio χ^2	*P*-value
Linear: $(1 + \beta x)$	0.0233	0.0066	213.68	12.42	< 0.001
Log-linear: $\exp(\beta x)$	0.0052	0.0012	213.65	12.45	< 0.001
Power: $x^{\wedge}\beta$	0.3496	0.103	215.50	10.60	< 0.001

TABLE VI. Cox Proportional Hazards Models of Benzene Exposure and Leukemia Mortality Risk: Univariate Analyses of Comparison Sets Matched on Case Age at Death

Model: $\lambda_o(t)(1 + \beta x)$	Coefficient	Likelihood ratio χ^2	Excess relative risk	*P*-value
Cumulative exposure (ppm-years, no lag)	0.023	12.42	2.3% per ppm-year	< 0.001
Cumulative exposure (ppm-years lag, 2.5)	0.025	12.09	2.5% per ppm-year	< 0.001
Duration of exposure	0.392	8.20	39.2% per year	0.004
Exposure rate	0.076	3.92	7.6% per ppm	0.048

TABLE VII. Cox Proportional Hazards Models of the Relationship Between Benzene Exposure and Multiple Myeloma Mortality Risk

Model: $\lambda_o(t)\exp(\beta x)$	Coefficient	Standard error	Relative risk	*P*-value
Cumulative exposure—no lag	0.00301	0.00222	1.003 per ppm-year	0.1747
Cumulative exposure—10 year lag	0.001947	0.00283	1.002 per ppm-year	0.4919
Cumulative exposure—20 year lag	−0.002092	0.00638	0.998 per ppm-year	0.7429

[Rinsky et al., 1987], no new leukemia deaths occurred between 1992 and 1996. The standardized mortality ratio for white males declined from 3.37 (95% CI = 1.54–6.41) to 2.56 (95% CI = 1.43–4.22). However, while the risk of leukemia in this cohort has decreased with time, the summary SMR for the period 1950–1996 remains significantly elevated with more than 50% of the cohort deceased.

Rinsky [1989] previously suggested that the difference in the exposure distributions of the leukemia and multiple myeloma cases might be due to low cumulative exposure to benzene producing multiple myeloma, a relatively well-differentiated malignancy, while higher exposures lead to leukemia. They further speculated that the progressive reduction of benzene exposure levels over the decades might lead to more cases of multiple myeloma among workers with relatively low cumulative exposures. It is interesting to note that the parameter estimate for cumulative exposure becomes negative at longer latencies (20 years or more). While in the earlier studies, all multiple myeloma cases occurred among exposed workers, in this update, three new multiple myeloma deaths were observed among the unexposed, with only one new death among the exposed. This result suggest that: (a) the new cases may not be the result of benzene exposure or (b) exposure misclassification may have occurred. At any rate, the finding that the SMR for multiple myeloma continues to be elevated weighs against dismissing the possibility of a relationship between benzene exposure and multiple myeloma in this cohort.

We have followed this cohort since 1976. Consistently, we have seen significantly elevated risks for leukemia mortality, and elevated risks for multiple myeloma. The cohort is mature, with over 50% of members deceased by 1996. The summary SMR for the exposed-only cohort shows a greater than twofold elevation in leukemia mortality risk. Modeling shows a tenfold elevation in leukemia risk for workers exposed to more than 200 ppm-years.

For this cohort, the best estimate of relative risk from exposure to benzene at the OSHA PEL of 1 ppm-year over a 45 year working lifetime is 2.05. Over the same 45 year period, the risk is 1.53 at the ACGIH TLV of 0.5. At the NIOSH REL of 0.1, risk drops to 1.1. In the current update, we observed a fairly rapid decrease in excess relative risk after cessation of exposure, as well as a decline in risk estimates from previous updates. These observations highlight the advantages of reducing benzene exposure at the earliest possible opportunity.

APPENDIX A Deaths from Leukemia and Multiple Myeloma in the Rubber Hydrochloride Cohort

Year of death	Age at death	Latency (years since first exposed)	Cause of death (ICD code for cause of death, using ICD revision in effect at time of death)	Plant location	Duration of employment	Cumulative benzene exposure (ppm-yr)
a. Descriptions of deaths from leukemia						
1950	29	2	Chronic myelogenous leukemia (204.1)	1	1 month	0.10
1954	28	3.5	Myelogenous leukemia (204.1)	1	1.5 years	10.16
1957	57	15	Acute monocytic leukemia (204.2)	2	5 years	98.55
1958	36	17	Monocytic leukemia (204.2)	1	1.5 years	49.99
1958	60	13.5	Acute myelocitic leukemia (204.3)	2	11.5 years	259.50
1960	65	15.5	Acute myelogenous leukemia (204.3)	2	14 years	498.23
1961	62	22	Di Guglielmo's acute myelocytic leukemia (204.3)	2	13 years	478.45
1961	57	20	Acute granulocytic leukemia (204.3)	2	20 years	639.84
1974 (female)	82	Unexposed	Acute myeloid leukemia (205.0)	2	1.5 years	Unexposed
1979	67	37	Acute myeloblastic leukemia (205.0)	2	14 years	252.66
1984	67	17	Chronic myeloid leukemia (205.1)	2	7 years	10.27

(*Continued*)

APPENDIX A (*Continued*)

Year of death	Age at death	Latency (years since first exposed)	Cause of death (ICD code for cause of death, using ICD revision in effect at time of death)	Plant location	Duration of employment	Cumulative benzene exposure (ppm-yr)
1985	67	45	Acute lymphoid leukemia (204.0)	1	16 years	52.53
1985	67	27	Acute myeloid leukemia (205.0)	2	9.5 years	0.72
1986	80	Unexposed	Chronic myeloid leukemia (205.1)	2	3 days	Unexposed
1986	71	40	Leukemia—unspecified (208.9)	1	3 months	259.98
1987	81	38	Leukemia—unspecified (208.9)	1	4 months	0.79
1991	79	51	Myeloid leukemia—unspecified (205.9)	1	7 months	5.75
b. Descriptions of deaths from multiple myeloma (ICD-203)						
1963	52	22.5		1	4 days	0.11
1968	62	24.5		1	23 years	652.66
1980	69	25.5		1	1.5 years	19.50
1981	68	26.5		1	9 months	7.75
1989	68	38		1	1 month	0.10
1991	66	Unexposed		1	0.5 months	Unexposed
1993	78	Unexposed		2	4.5 years	Unexposed
1996	79	Unexposed		1	30 years	Unexposed

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