# BENZENE AND LEUKEMIA

## An Epidemiologic Risk Assessment

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**Abstract** To assess quantitatively the association between benzene exposure and leukemia, we examined the mortality rate of a cohort with occupational exposure to benzene. Cumulative exposure for each cohort member was estimated from historical air-sampling data and, when no sampling data existed, from interpolation on the basis of existing data. The overall standardized mortality ratio (a measure of relative risk multiplied by 100) for leukemia was 337 (95 percent confidence interval, 154 to 641), and that for multiple myeloma was 409 (95 percent confidence interval, 110 to 1047). With stratification according to levels of cumulative exposure, the standardized mortality ratios for leukemia increased from 109 to 322, 1186, and 6637 with increases in cumulative benzene exposure from less than 40 parts per million–years (ppm-years), to 40 to 199, 200 to 399, and 400 or more, respectively. A cumulative benzene exposure of 400 ppm-years is equivalent to a mean annual exposure of 10 ppm over a 40-year working lifetime; 10 ppm is the currently enforceable standard in the United States for occupational exposure to benzene. To examine the shape of the exposure–response relation, we performed a conditional logistic-regression analysis, in which 10 controls were matched to each cohort member with leukemia. From this model, it can be calculated that protection from benzene-induced leukemia would increase exponentially with any reduction in the permissible exposure limit. (N Engl J Med 1987; 316:1044-50.)

AN etiologic association between benzene and leukemia was suggested by a series of case reports beginning more than 50 years ago.[1-6] Those clinical observations were corroborated subsequently by epidemiologic studies[5,7-11] and, more recently, by carcinogenesis bioassays.[12-15] Benzene is now generally considered by national and international scientific bodies to be a human carcinogen.[16-18]

To reduce the risk of leukemia in industrial workers exposed to airborne benzene, the U.S. Occupational Safety and Health Administration (OSHA) promulgated in 1978 an occupational-exposure standard that reduced the permissible workplace concentrations of benzene 10-fold,[19] from the previously acceptable eight-hour time-weighted average of 10 ppm in air to a new eight-hour time-weighted average of 1 ppm. This action was based on the qualitative demonstration of the carcinogenicity of benzene in case reports and epidemiologic studies.[20]

In 1980, in a decision of profound importance for governmental risk assessment,[21] the U.S. Supreme Court invalidated the OSHA benzene standard of 1 ppm.[22] The Court stated that OSHA had failed to provide "substantial evidence" of the need for regulation, in that it had not demonstrated a "significant risk of material health impairment" at the previous level of 10 ppm. Since that decision, epidemiologic research on benzene has moved from qualitative evaluation of carcinogenicity to quantitative assessment of the dose–response relation between benzene and leukemia. At least three quantitative assessments have recently been published.[17,18,23] In each, the amount of benzene exposure has been found to correlate positively with the risk of death from leukemia. All three analyses, however, were based on estimates of group exposure rather than on estimates of the exposure of individual workers. The resultant risk estimates were therefore subject to wide variances.

To reduce the uncertainties of those assessments, we have reexamined the mortality experience of a cohort of rubber workers with previously documented exposure to benzene. This cohort is the largest to be studied in a risk assessment, and it offers the most extensive historical record of exposures to airborne benzene. Since our previous evaluation of the mortality rate of this cohort,[10] the life-table analysis system of the National Institute for Occupational Safety and Health (NIOSH) has been modified to allow incorporation of data on individual exposures[24]; previously, only the duration of employment could be used as a surrogate for exposure. Also, an additional 6.5 years of observation had elapsed since the previous evaluation, allowing us to update this analysis to 1982. We report here on the relation in this cohort between occupational exposure to benzene and death from leukemia.

### BACKGROUND

This study was based on the experience of workers at three plants at two locations in Ohio that manufactured a natural rubber film (rubber hydrochloride). The details of the process have been described previously.[10] In brief, natural rubber was dissolved in benzene and spread on a conveyor. The benzene was then evaporated and recovered, and the resultant thin film was stripped from the conveyor, rolled, and milled according to specifications. Rubber hydrochloride was manufactured at Location 1 from 1939 until April 1976. Production at Location 2 was carried out in two separate plants. At the first, it began as a research and development project; commercial production then began in 1936 or 1937 and continued until 1949, when the second plant began operation. This operation continued until 1965. Operations at all

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three plants were essentially identical. Although hydrochloric acid, soda ash, natural rubber, and small amounts of plasticizers were used, benzene was the only chemical in the rubber hydrochloride plants that could reasonably be associated with hematologic toxicity. The rubber hydrochloride plants were located within larger industrial facilities. Employees were likely during their working careers to have worked in areas of these facilities where materials other than rubber hydrochloride were produced.

Industrial-hygiene records describing past atmospheric concentrations of benzene at the plants were available from the Industrial Commission of Ohio, the Ohio Department of Health, the University of North Carolina, NIOSH, and company records. These records have been described previously.[10,20] Because most of the measurements in these records were made not to support an epidemiologic study but rather to identify problems with compliance, there are gaps in the data. These gaps were filled by estimating exposures (see Methods). Nonetheless, the data represent an unusually complete record of past exposures for a retrospective cohort study covering this period. They indicate that as knowledge of the toxicity of benzene increased and recommended exposure levels were revised downward, the company kept pace with those revisions. Thus, for the most part, employees' eight-hour time-weighted average exposures to airborne benzene were within the limits of the standard in effect at any given time. As is characteristic of industrial processes, however, there were occasional excursions above these limits. A detailed description of those excursions in relation to individual exposures has been presented previously.[10,20]

## Methods

### Estimation of Past Exposures

Detailed job histories for each employee were obtained from company personnel records. Each employee's record was reviewed to identify the department symbol that indicated work in a rubber hydrochloride plant at either location. Each unique rubber hydrochloride job title (described in a short narrative on the personnel record) was assigned a numerical code. Job codes and employment dates were then abstracted for each employee who had worked in a rubber hydrochloride department. Because of the large number of job codes in the record system (resulting from numerous variations in job titles), codes were fitted to broader categories, referred to as "exposure classes," which could be associated with specific manufacturing areas. In general, exposure classes represented areas in which industrial-hygiene data had been collected. In some instances, job titles did not readily fit into a single area; in such situations, hybrid exposure classes were developed.

A job-exposure matrix, which tabulated exposure-class codes by year, was constructed for each of the two locations. For Location 1, actual results from past industrial-hygiene measurements[10] were entered in their respective cells in this matrix. Cells for which no data were available were completed by interpolation between available previous and subsequent values. When interpolation could not be performed because no measured value existed for an exposure class in the first or last year of the study, the nearest measured value for that exposure class was projected forward or backward. Industrial-hygiene measurements obtained at Location 2 were applied to the matrix in similar fashion. Processes and job assignments were essentially identical at both locations, so benzene exposure levels measured at Location 1 were assumed to be naturally occurring simulations of exposure levels in corresponding areas at Location 2, when actual exposure measurements did not exist.

### Population

All nonsalaried white men employed in a rubber hydrochloride department for at least one day between January 1, 1940, and December 31, 1965, were eligible for the study. Men whose initial exposure occurred after December 31, 1965, were excluded, because 1965 was the year in which production of rubber hydrochloride ceased at Location 2. Very few men were first hired at Location 1 after 1965.

Vital status was ascertained for the cohort through December 31, 1981. Follow-up for vital status was accomplished primarily through the Social Security Administration, but also through the Ohio Bureau of Motor Vehicles and a commercial agency specializing in locating people. Cohort members who were not traced were considered to be alive as of the study's ending date. Death certificates for all the known deaths were obtained and coded by a qualified nosologist according to the rules of the *International Classification of Diseases, Adapted for Use in the United States,* that were in effect at the time of death. Each code was then converted to one of 89 "death categories" for use in the NIOSH life-table analysis system.

### Analytical Methods

The NIOSH life-table analysis system[24] was used to generate expected numbers of cause-specific deaths, within five-year age and five-year calendar periods. These calculations were based on death rates for U.S. white males specific for the same five-year age and calendar periods, applied to the number of person-years at risk of dying. Person-years were further stratified according to cumulative benzene exposure and five-year latency periods (intervals since the initial exposure). To determine cumulative benzene exposure, a person's daily benzene exposure was obtained from the appropriate cell in the exposure class–year matrix. These daily values were then summed for a man's entire working career.

The accumulation of observed deaths and of person-years at risk of dying began on January 1, 1950, or on the first day on which his cumulative personal exposure to benzene reached 1.0 ppm-day (one day of employment in an exposed department), whichever occurred later. Observation ceased on December 31, 1981, or on the date of death — whichever occurred earlier.

The person-years in the cohort were divided into four categories of exposure. These exposure strata were 1 ppm-day to 40 ppm-years, 40 to 199.99 ppm-years, 200 to 399.99 ppm-years, and more than 400 ppm-years. These boundaries correspond to the cumulative exposures that would result from average annual exposures to less than 1, 1 to 4.99, 5 to 9.99, and 10 or more ppm of benzene, respectively, accumulated over a 40-year working lifetime.

To obtain cause-specific standardized mortality ratios, the observed numbers of deaths from each cause were divided by the expected numbers and multiplied by 100. Ninety-five percent confidence intervals were calculated for each cause of death examined.[25] In addition, a matched case–control analysis was performed with use of conditional logistic regression. This analysis was intended to (1) evaluate the exposure terms that govern the relation between the risk of death from leukemia and exposure to benzene, (2) evaluate the effect of potential confounders and effect modifiers on this relation, and (3) identify the functional form of the exposure–response relation.

The exposure terms evaluated were cumulative exposure, duration of exposure, and rate of exposure (cumulative exposure divided by duration of exposure). Ten controls were matched to each cohort member who died of leukemia for the year of birth and the year first employed. As suggested by Thomas,[26] these controls were selected from among the cohort members still alive at the time of death of the corresponding case.

Because it is generally believed that some latency period subsequent to an initial exposure is required for leukemia to develop, a separate analysis that "lagged" exposures was also performed. Within each matched set, all benzene exposures within the five-year

Table 1. Observed and Expected Deaths from All Causes, All Malignant Neoplasms, and Lymphatic and Hematopoietic Cancers in Rubber Workers Exposed to Benzene.

| Cause of Death | No. of Deaths | | Standardized Mortality Ratio (95% C.I.)* |
|---|---|---|---|
| | Observed | Expected | |
| All causes | 330 | 331.6 | 99 (89–111) |
| All malignant neoplasms | 69 | 66.8 | 103 (80–130) |
| Lymphatic and hematopoietic cancers | 15 | 6.6 | 227 (127–376) |
| Leukemia | 9 | 2.7 | 337 (154–641) |
| Multiple myeloma | 4 | 1.0 | 409 (110–1047) |

*C.I. denotes confidence interval.

period before the death of the case were ignored in calculating each person's cumulative total.

## Results

### Cohort Analysis

A total of 1165 white men with at least 1 ppm-day of cumulative exposure to benzene through December 31, 1965, were included in the cohort. They contributed 31,612 person-years at risk. On December 31, 1981, a total of 819 (70.3 percent) were alive, 330 (28.3 percent) were dead, and 16 (1.4 percent) were lost to follow-up. Those lost to follow-up were considered to be alive as of the study's ending date.

Neither the mortality from all causes of death combined (330 observed vs. 331.6 expected) nor the mortality from all malignant neoplasms combined (69 observed vs. 66.8 expected) was above the expected rate (Table 1). There was, however, a statistically significant increase in deaths from all lymphatic and hematopoietic neoplasms (15 observed vs. 6.6 expected; standardized mortality ratio, 227; 95 percent confidence interval, 127 to 376). This increase was due mainly to excess numbers of deaths from leukemia (9 observed vs. 2.7 expected; standardized mortality ratio, 337; 95 percent confidence interval, 154 to 641) and from multiple myeloma (4 observed vs. 1 expected; standardized mortality ratio, 409; 95 percent confidence interval, 110 to 1047).

Standardized mortality ratios for leukemia, over the four exposure strata (1 ppm-day to 39.99 ppm-years, 40 to 199.99 ppm-years, 200 to 399.99 ppm-years, and more than 400 ppm-years) demonstrated a marked, progressive increase with increasing cumulative exposure to benzene (standardized mortality ratios were 109, 322, 1186, and 6637, respectively) (Table 2). No apparent pattern was evident for these deaths with regard to latency, which ranged from under 5 to over 30 years; however, seven of the nine persons with leukemia had less than 20 years of latency.

Because this observation was based on only nine deaths from leukemia, there was the possibility that this strongly positive trend in leukemia-associated mortality might be an artifact produced by our choice of boundaries for the exposure categories. To examine this possibility, we arbitrarily changed the sizes of the categories, first by halving the original ranges to 0 through 19, 20 through 99, 100 through 199, and 200 or more ppm-years, and then by doubling the original ranges to 0 through 79, 80 through 399, and 400 or more ppm-years. The resultant standardized mortality ratios continued in both instances to show a strongly positive trend of increasing risk with increasing exposure. (Standardized mortality ratios for exposure ranges $\times$ ½ = 134, 277, 0 deaths, and 2338; ratios for exposure ranges $\times$ 2 = 141, 609, and 6833.) These findings are evidence of the robustness of the observed association.

Standardized mortality ratios for multiple myeloma over the four original exposure strata did not increase with increasing exposure (Table 3). Three of the four men who died of myeloma had less than 40 ppm-years of exposure (on the basis of our assumptions of dose), and all four deaths occurred after 20 years of latency. All four were from Location 1. Case descriptions of the deaths due to leukemia and multiple myeloma are given in Table 4.

### Case–Control Analysis

Examination of data from the case–control analysis indicated that the mean cumulative exposure was higher for cases than for controls (254 vs. 50 ppm-years). Also, the average duration of exposure was longer for the cases (8.7 vs. 2.6 years). Finally, there was a difference in rates of exposure between cases

Table 2. Observed and Expected Deaths from Leukemia in 1165 White Men with at Least One Day of Exposure to Benzene from January 1, 1940, through December 31, 1965, According to Cumulative Exposure and Years of Latency.

| Latency (yr) | Exposure (ppm-yr) | | | | |
|---|---|---|---|---|---|
| | 0.001–40 | 40–200 | 200–400 | >400 | total* |
| | *observed/expected deaths* | | | | |
| <5 | 2/0.10 | 0/0.02 | — | — | 2/0.12 |
| 5–10 | 0/0.16 | 0/0.05 | 0/0.01 | — | 0/0.22 |
| 10–15 | 0/0.22 | 1/0.07 | 1/0.02 | 0/0.00 | 2/0.31 |
| 15–20 | 0/0.27 | 1/0.09 | 1/0.03 | 2/0.01 | 3/0.39 |
| 20–25 | 0/0.32 | 0/0.10 | 0/0.03 | 1/0.01 | 1/0.46 |
| 25–30 | 0/0.37 | 0/0.12 | 0/0.04 | 0/0.01 | 0/0.54 |
| >30 | 0/0.40 | 0/0.16 | 1/0.04 | 0/0.01 | 1/0.62 |
| Total* | 2/1.83 | 2/0.62 | 2/0.17 | 3/0.04 | 9/2.66 |
| Standardized mortality ratio | 109 | 322 | 1186 | 6637 | 337 |
| Confidence interval | 12–394 | 36–1165 | 133–4285 | 1334–19,393 | 154–641 |

*The numbers of expected deaths have been rounded.

Table 3. Observed and Expected Deaths from Multiple Myeloma in 1165 White Men with at Least One Day of Exposure to Benzene from January 1, 1940, through December 31, 1965, According to Cumulative Exposure and Years of Latency.

| Latency (yr) | Exposure (ppm-yr) | | | | |
|---|---|---|---|---|---|
| | 0.001–40 | 40–200 | 200–400 | >400 | total |
| | *observed/expected deaths* | | | | |
| <5 | 0/0.02 | 0/0.01 | | | 0/0.02 |
| 5–10 | 0/0.04 | 0/0.01 | 0/0.00 | | 0/0.05 |
| 10–15 | 0/0.07 | 0/0.02 | 0/0.01 | 0/0.00 | 0/0.10 |
| 15–20 | 0/0.09 | 0/0.03 | 0/0.01 | 0/0.00 | 0/0.14 |
| 20–25 | 1/0.12 | 0/0.04 | 0/0.01 | 1/0.00 | 2/0.18 |
| 25–30 | 2/0.15 | 0/0.05 | 0/0.02 | 0/0.00 | 2/0.22 |
| >30 | 0/0.17 | 0/0.07 | 0/0.02 | 0/0.01 | 0/0.27 |
| Total | 3/0.65 | 0/0.24 | 0/0.07 | 1/0.02 | 4/0.98 |
| Standardized mortality ratio | 458 | * | * | 5347 | 398 |
| Confidence interval | 92–1339 | | | 70–29,753 | 110–1047 |

*No deaths were observed with these exposure levels.

and controls, with cases averaging approximately 24 ppm of benzene per day, as compared with approximately 16.5 ppm per day for controls.

To evaluate the exposure terms that govern the exposure–response relation between benzene and leukemia and to assess potential confounders and effect modifiers, we analyzed the case–control data using conditional logistic regression.[27] This analysis produces odds ratios of the general form

$$OR = \exp(B_1X_1 + \cdots + B_nX_n),$$

where $X_i$ represents exposure variables, potential confounders, or effect modifiers, and $B_i$ coefficients to be estimated. Odds ratios calculated by this technique are expressed relative to that of an unexposed worker, in which $X_i$ is considered to be 0.

We examined several models to identify one that would adequately explain the risk of death from leukemia with the minimal number of terms. In our first examination, we considered three exposure variables separately — cumulative exposure, duration of exposure, and average exposure rate — and we fitted three separate models, one for each of these variables. In these three models, cumulative exposure (ppm-years) was found to be the strongest single predictor of death from leukemia ($\beta = 0.0126$; 95 percent confidence interval, 0.0028 to 0.0224; chi-square = 6.4; $P = 0.011$). Then, for a more complex examination of the same three intercorrelated exposure variables, we constructed another model in which all three were entered simultaneously. In this model, only cumulative exposure was found to contribute materially to the risk of death from leukemia, although it is not possible with only nine cases to establish cumulative exposure as the unqualified best expression. Interactions among cumulative exposure, duration, and rate of exposure were also examined.

Table 4. Descriptions of Deaths from Leukemia and Multiple Myeloma in 13 Workers Exposed to Benzene.

| Case No. | Age at Death | Year of Death | Latency* (yr) | Cause of Death† | Corroborating Medical Reports | Plant Location; Duration of Employment | Cumulative Benzene Exposure (ppm-yr) |
|---|---|---|---|---|---|---|---|
| 1 | 36 | 1958 | 17 | Monocytic leukemia (204) | None available | Location 1; 1½ yr | 49.99 |
| 2 | 29 | 1950 | 2 | Chronic myelogenous leukemia (204) | Hospital, autopsy, tissue slides | Location 1; 1 mo | 0.10 |
| 3 | 60 | 1958 | 13½ | Acute myelocytic leukemia (204) | Hospital, hematologist | Location 2; 11½ yr | 259.50 |
| 4 | 65 | 1960 | 15½ | Acute myelogenous leukemia (204) | Hematologist, hospital, tissue slides | Location 2; 14 yr | 498.23 |
| 5 | 62 | 1961 | 22 | Di Guglielmo's acute myelocytic leukemia (204) | Hospital, physician | Location 2; 13 yr | 478.45 |
| 6 | 57 | 1961 | 20 | Acute granulocytic leukemia (204) | Hospital, tissue slides, autopsy | Location 2; 20 yr | 639.84 |
| 7 | 57 | 1957 | 15 | Acute monocytic leukemia (204) | Tissue slides | Location 2; 5 yr | 98.55 |
| 8 | 28 | 1954 | 3½ | Myelogenous leukemia (204) | None available | Location 1; 1½ yr | 10.16 |
| 9 | 67 | 1979 | 37 | Acute myeloblastic leukemia (204) | None available | Location 2; 14 yr | 252.66 |
| 10 | 69 | 1980 | 25½ | Multiple myeloma (203) | None available | Location 1; 1½ yr | 19.50 |
| 11 | 52 | 1963 | 22½ | Multiple myeloma (203) | Hospital | Location 1; 4 days | 0.11 |
| 12 | 62 | 1968 | 24½ | Plasma-cell sarcoma (203) | Hospital | Location 1; 23 yr | 652.66 |
| 13 | 68 | 1981 | 26½ | Multiple myeloma (203) | None available | Location 1; 9 mo | 7.75 |

*Latency was defined as the length of time (in years) from the date of first exposure until death.
†In parentheses is the *International Classification of Diseases* code as determined by a nosologist from information on the death certificate.

None of those interaction terms were found to contribute significantly to the model in predicting the risk of death from leukemia.

The shape of the exposure–response function was then evaluated with use of several models. First, since the distribution of cumulative exposures was highly skewed, we examined a logarithmic transformation of cumulative exposures. The results of this analysis indicated that the fit for this model (chi-square = 4.86; P = 0.027) was less adequate than that determined above for the untransformed measure (chi-square = 6.4; P = 0.011). Then, to investigate the possibility of a more general form of curvature, we added a quadratic term for cumulative exposure. This maneuver did not significantly improve the fit of the model, however (P = 0.91). From these findings, we determined that the untransformed model provided the best representation of the exposure–response relation. With this model, the equation best describing the odds ratio for leukemia in relation to cumulative exposure to benzene was determined to be

$$OR = \exp(0.0126 \times \text{ppm-years}).$$

The exposure–effect curve defined by this equation was plotted (Fig. 1). Ninety-five percent confidence intervals were calculated for cumulative lifetime exposures to benzene ranging from 0 to 400 ppm-years. From this equation, the average cumulative exposure of the cases and controls (69 ppm-years) was found to produce an odds ratio relative to the unexposed workers of 2.4 (95 percent confidence interval, 1.2 to 4.7). To ensure that the odds ratios for the matched sets of cases and controls were homogeneous (a prerequisite for the above analyses), interactions between cumulative exposure and the matching variables (year of birth and year of first exposure) were introduced into the model. Neither of these interactions was found to be significant.

To take into account an induction period for leukemia, benzene exposures occurring within the five-year period before the death of a case were eliminated from the calculated cumulative exposure of each man in a matched set. We then reexamined the effect of cumulative exposure. The odds ratios increased slightly ($\beta = 0.0169$), as did the statistical significance of the observation (chi-square = 6.7; P = 0.010).

## Discussion

The principal findings of this analysis are that (1) there is a strongly positive exposure–response relation between benzene and leukemia; (2) on the basis of our model, this relation can be projected downward to mean annual exposure levels of less than 1 ppm cumulated over a 40-year working lifetime; and (3) in the population studied, there was also a statistically significant excess of deaths from multiple myeloma.

The environmental data used in this risk assessment are admittedly incomplete. Measured environmental levels of benzene did not exist for all jobs in all years. Gaps had to be filled by interpolation from existing data. This interpolation was performed according to preestablished rules and without knowledge of a person's disease outcome. In some cases this procedure required that we allow a single measured exposure to serve as an index of exposure for a number of years. Episodes of high exposure due to such temporary circumstances as spills and process upsets were probably overlooked by the

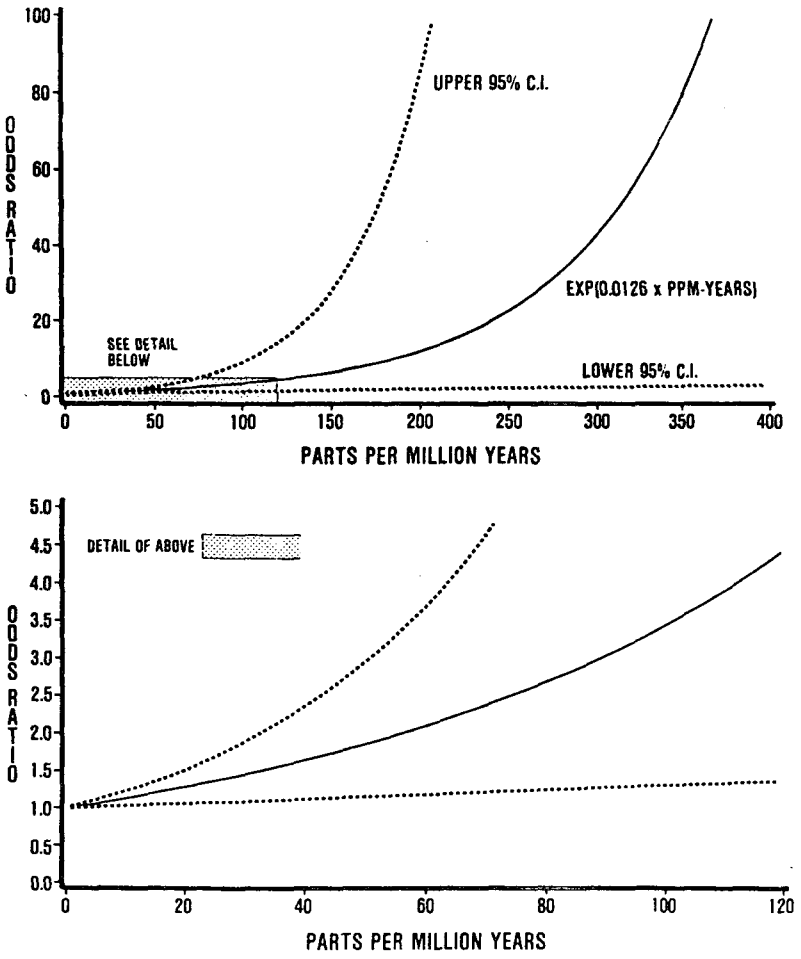


Figure 1. The Risk of Leukemia in Relation to Cumulative Exposure to Benzene.
The lower panel shows an enlarged detail of the lower left-hand section of the upper graph.

industrial-hygiene surveys and are therefore not reflected in our calculations of exposure. Percutaneous absorption of benzene, a route of exposure that has recently been shown to be of potential importance, was not examined.[28] Nevertheless, the existing environmental data are unusually comprehensive in comparison to those typically available for retrospective epidemiologic studies. They permit a reasonable estimate of cumulative benzene exposure during rubber hydrochloride production for each member of this study population. Examination of these exposure data led us to conclude that employees' historical eight-hour time-weighted average exposures to airborne benzene had generally not exceeded the limits in effect at any given time.

If the environmental data are in error, we believe they probably err in overestimating actual average exposures, inasmuch as the majority of measurements were taken by industrial hygienists looking for trouble spots within the process rather than trying to document typical occupational exposures. There were strong economic incentives in the rubber hydrochloride manufacturing process to recover the costly benzene efficiently; indeed, much of the process was dedicated to that end. Continuous contamination of the work area by benzene at the average levels of exposure assigned in this study would not have been economically acceptable.

The 95 percent confidence interval becomes extremely wide in the higher dose ranges considered (Fig. 1). This is primarily a function of there being only nine deaths from leukemia in the series. However, both the categorical and the conditional logistic regression analyses indicated exponential increases in relative risk with increasing cumulative exposure to benzene. Therefore, although the exact estimate of relative risk at higher dose levels lies within a wide range of estimates, it follows nevertheless that an exponential decrease in risk will result from any lowering of exposure levels.

The credibility of an association such as that observed here increases if it remains evident after imposition of a lag period reflecting induction latency. In this instance, a lag period was imposed by discounting for all persons in the matched sets all benzene exposures that had occurred in the five years before the death of the cohort member. After that maneuver, not only did the association between benzene exposure and death from leukemia remain evident, but it actually increased slightly in strength.

After performing these analyses, we learned of another death from leukemia in the cohort, of a 68-year-old man who died in 1984 (after our vital-status follow-up date of December 31, 1981). The cause of death recorded on the death certificate was "medullary failure due to myelocytic leukemia due to myeloproliferative disease, systemic mast cell disease." This man had worked in exposed jobs at Location 2 for about 3½ years, between August 1952 and May 1957. His estimated cumulative benzene exposure was 90.56 ppm-years. Thirty-four years had elapsed between his first exposure and his death. Because the vital status was not determined for members of the cohort beyond 1981, inclusion of this case in the series is not entirely consistent with the selection criteria, which called for controls to be selected from among cohort members still alive at the time of the death of the case. Therefore, these additional data are not included in our estimates of risk but serve as corroborating evidence.

Multiple myeloma, the cause of death in four members of this cohort, has been observed previously in persons exposed to benzene, although also in small numbers.[29] In addition, several recent toxicologic studies have demonstrated lymphoid cancers in both rats and mice exposed to benzene.[13-15] It is of interest that three of the four deaths from multiple myeloma that were observed in this cohort occurred in the group with the lowest cumulative exposure to benzene (<40 ppm-years), and that all four persons who died had exceptionally long latency periods for hematologic cancers (>20 years). These two observations raise the possibility that relatively low cumulative exposures to benzene may produce a relatively well-differentiated cancer such as multiple myeloma, whereas higher exposures may lead to leukemia.

In conclusion, the results of this risk assessment indicate that an exponential decrease in the risk of death from leukemia could be achieved by lowering occupational exposure to benzene. According to the model derived in this study, a worker occupationally exposed to benzene at an average exposure level of 10 ppm for 40 years would have an increased risk of death from leukemia of 154.5 (95 percent confidence interval, 3.1 to 7785). If the average exposure were lowered to 1 ppm, that excess risk would decrease to 1.7 (95 percent confidence interval, 1.1 to 2.5). At 0.1 ppm, the risk would be virtually equivalent to the background risk (odds ratio, 1.05; confidence interval, 1.01 to 1.09).

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