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Benzene and Leukemia: An Epidemiologic Risk Assessment

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To assess quantitatively the association between benzene and leukemia, we evaluated the rate of mortality experienced by a cohort occupationally exposed to benzene. Using data from historical air sampling surveys, we estimated the daily benzene exposure for each member of the cohort. The expected number of leukemia deaths was calculated and compared to the actual number of leukemia deaths that occurred. The overall standardized mortality ratio (SMR) for leukemia was 337. Person-years at risk within the cohort were stratified by increasing levels of cumulative benzene exposure. The resulting SMRs increased from 109 to 322 to 1186 and to 6637 with respective increases in cumulative benzene exposure from less than 40 ppm-years to 40–199, 200–399, and greater than 400. The shape of the exposure-response relation was examined with a case-control analysis. Another analysis was performed to take into account an induction period for leukemia. All of the analyses demonstrated that a strongly positive exposure-response relationship exists between benzene and leukemia. Previous attempts to quantify this cohort's risk of developing leukemia were based on surrogates of exposure, such as duration of employment. Using actual air sampling data to estimate individual exposures represents a marked improvement over these previous attempts and emphasizes the importance of conducting industrial hygiene surveys and maintaining historical exposure records.

The etiologic association between benzene and leukemia has been firmly established by clinical observations, epidemiologic studies, and by carcinogenesis bioassays (*1–14*). However, largely because of the 1980 Supreme Court decision requiring OSHA to demonstrate "significant risk of material health impairment" at a given level of benzene exposure, the setting of an exposure standard became dependent upon estimates of the exposure-response relationship. The efficacy of such a risk assessment based on epidemiologic observation is conditional on the validity of the estimates of exposure for the population under study.

In 1987, NIOSH published the results of a risk assessment of benzene and leukemia based on a cohort of rubber workers occupationally exposed to benzene during the manufacturing of rubber hydrochloride (*15*). This same cohort had been studied earlier and the resulting qualitative causal association between benzene and leukemia reported. Although the experiences of other benzene-exposed populations has been studied, this cohort was unique by virtue of its combination of size, the relative purity of exposure, and the exceptional record system that existed chronicling the changes in measured area benzene concentrations over 35 years of operations. This record system allowed the reconstruction of a benzene exposure history profile not dependent on perception or recall specific for each individual worker in the cohort. It is this exposure profile that gives this study the advantage in defining the exposure-response relationship.

The concept behind the development of the NIOSH benzene risk assessment was straightforward; if the daily amount of exposure to benzene an individual received at their job could be estimated then the individual's cumulative amount of exposure could be calculated for any time in their past. Person-years at-risk could then be stratified by actual cumulative exposure, and relative risk could be calculated for each category of increasing exposure. This would be a major improvement over previous attempts at quantitating the exposure-response relationship that had been used in previous analyses of this cohort. These previous attempts used surrogates of exposure, such as duration of employment, which were inherently less accurate because they failed to take into account different intensities of exposure resulting from differences between jobs, changes in production levels and engineering improvements over time.

Development of an exposure matrix was central to the process of determining the personal exposure history of an individual worker. The exposure matrix had to take into account the individual's specific job as well as the time period in which that job was being performed. For every individual in the cohort a personnel folder existed that very accurately chronicled their job history by list-

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ing the department code, a job title, and the date that specific job operations began and ended. The rubber hydrochloride department under study operated at two different geographical locations. Unusually complete and extensive historical industrial hygiene measurements for one of these locations were available from a number of sources including company records, Ohio Department of Health records, Ohio Industrial Commission records, from a survey conducted by the University of North Carolina, and finally from a survey conducted by NIOSH in the course of studying this cohort. These historical industrial hygiene data were primarily area samples rather than personal samples. The exposure matrix was composed by grouping actual jobs into exposure classes based on the areas in which the job was performed.

Ten exposure classes were eventually defined. For each year from 1939 to 1976, the annual mean of the measured benzene concentrations was tabulated into the appropriate exposure class by year cell in the matrix. In years where no historical environmental data existed, interpolation was made between the values for the years where such measurements did exist or, in those years where there was no earlier (or later) measurement, the most proximate value was projected back (or forward). Industrial hygiene measurements were sparse at the second location but the processes and job assignments were essentially identical. Benzene exposure levels measured at the first location were assumed as naturally occurring simulations of exposure levels in corresponding areas at the second location. The completed exposure matrix provided a reference to estimate the daily exposure experienced by each individual in the cohort.

The rate of leukemia mortality experienced by this cohort was determined by using the NIOSH Life-Table Analysis System to generate expected numbers of cause-specific deaths, within 5-year age and 5-year calendar time periods (*16*). These calculations were based on United States white male death rates specific for the same 5-year age and calendar time periods, applied to the number of person-years at-risk of dying. Person-years were further stratified by cumulative benzene exposure and by 5-year latency periods (interval since initial exposure). To determine cumulative benzene exposure, an individual's daily benzene exposure was obtained from the appropriate cell in the exposure-class/year matrix. Exposures were then accumulated by summation of the daily values over a individual's entire working career. The cohort was divided into four categories of exposure. These exposure strata were 1 ppm day to 39 part per million years (ppm-years), 40 to 199 ppm-years, 200 to 399 ppm-years, and more than 400 ppm-years. These boundaries correspond to the cumulative exposure that would result from average annual exposures to less than 1, 1 to 5, 5 to 10, and 10 or more parts per million benzene, respectively, accumulated over a 40-year working lifetime. Observed numbers of deaths for each cause were divided by the expected to obtain cause-specific standardized mortality ratios (SMRs).

Additionally, to identify the functional form of the exposure-response relationship, a matched case-control analysis was performed using conditional logistic regression. Ten controls were matched to each leukemia death by year of birth and year first employed. These controls were selected from among those cohort members still alive at the time of death of the corresponding case. Because the case-control analysis uses an internal control (as opposed to the U.S. general population used as the referent group in the SMR analysis), it has the additional benefit of controlling for other exposures as well as any additional background exposure to benzene that may have been present.

A statistically significant increase in deaths from all lymphatic and hematopoietic neoplasms was observed. (There were 15 observed deaths versus 6.6 expected, SMR = 227.) This increase was due mainly to excess numbers of deaths from leukemia (9 observed versus 2.7 expected, SMR = 337, CI = 154–641) and from multiple myeloma (4 observed versus 1 expected, SMR = 409, CI = 110–1047). SMRs for leukemia, over the four exposure strata demonstrated a marked, progressive increase with increasing exposure to benzene (SMRs = 109, 322, 1186, and 6637). No apparent pattern was evident for these deaths with regard to latency, which ranged from under 5 to over 30 years.

SMRs for multiple myeloma, over the four original exposure strata, did not increase with increasing exposure. Three of the four myeloma cases had less than 40 ppm-years exposure (based upon our assumptions of dose), and all four occurred after 20 years of latency. All four of these deaths were from the same location.

Using the case-control analysis, we determined that the equation best describing the odds ratio for leukemia in relation to cumulative exposure to benzene was

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

(CI = 0.0028–0.0224, $\chi^2 = 6.4$, $p = 0.011$). To take into account an induction period for leukemia, benzene exposures occurring within the 5-year period prior to the death of a case were eliminated from the calculated cumulative exposure. The odds ratios increased slightly as did the statistical significance of the observation.

The major findings of this analysis were: *a)* that a strongly positive exposure-response relationship exists between benzene and leukemia; *b)* that, based upon the model, this relationship extends downward to mean annual exposure levels of less than 1 ppm, cumulated over a 40-year working lifetime; and *c)* that there also exists in the population studied a statistically significant excess of deaths from multiple myeloma.

Because the environmental data used in this risk assessment were collected for reasons other than to support epidemiologic study, they are not complete. Measured environmental levels did not exist for all years and had to be constructed from extant data. In some cases this meant allowing a single measured exposure to serve for a number of years. Episodes of high exposure because of such temporary circumstances as spills and process upsets were probably overlooked by the industrial hygiene surveys. In addition, percutaneous absorption of benzene,

a route of exposure that has been shown to be of potential importance, was not examined. Nevertheless, the existing environmental data are unusually comprehensive in comparison to those typically available for retrospective cohort studies. They permit a reasonable estimate of cumulative benzene exposure during rubber hydrochloride production for each member of this study population. If the environmental data are in error, we believe they likely err by overestimating actual average exposures, for two reasons. First, the majority of the measurements were taken by industrial hygienists looking for trouble spots within the process rather than trying to document typical personal exposures. Second, the economic viability of the rubber hydrochloride manufacturing process depended upon efficient recovery of costly solvent; indeed, much of the process was dedicated toward this end. Continuous high-level contamination by benzene of a large ventilated area would not have been economically acceptable.

Periodically we intend to update this analysis by following up on the mortality experience of the cohort. Subsequent to these analyses presented we learned of the occurrence of another leukemia death among the cohort. Ten additional controls were chosen and the case-control analysis was repeated. This resulted in slightly lower odds ratio but increased the statistical significance of the relationship. The data from this additional case serves as additional corroborating evidence.

Multiple myeloma, which was the cause of death in four members of this cohort, has been observed previously in persons exposed to benzene (*17*). In addition, several recent toxicologic studies have demonstrated lymphoid malignancies in both rats and mice exposed to benzene (*18–21*). It is of interest that three of the four deaths from multiple myeloma that were observed in this cohort occurred among the group with the lowest cumulative exposure to benzene (< 40 ppm-years), and that all four required exceptionally long latency periods for hematologic malignancies (> 20 years). These two observations raise the possibility that low cumulative exposures to benzene may produce a relatively well-differentiated malignancy such as multiple myeloma, whereas higher exposures lead to leukemia. In this construct, it is conceivable that the progressive reduction of exposures to benzene, which has been achieved over the last several decades, may lead to a situation in which multiple myeloma will in the future become manifest in a large population of workers with relatively low cumulative exposures to benzene. The present observations must, however, be interpreted cautiously in absence of further corroborations.

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