BENZENE AND LEUKEMIA

An Epidemiologic Risk Assessment

ROBERT A. RINSKY, M.S., ALEXANDER B. SMITH, M.D., M.S., RICHARD HORNUNG, DR.P.H., THOMAS G. FILLOON, B.S., RONALD J. YOUNG, M.S., ANDREA H. OKUN, M.S., AND PHILIP J. LANDRIGAN, M.D., M.Sc.

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[3,7-11] 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 (OSH.4) promulgated in 1978 an occupational-exposure standard that reduced the permissible workplace concentrations of benzene IO-fold.[19] from the previouslv acceptable eight-hour rime-weighted average of 10 ppm in air to a new eight-hour time-weighted averaee of I 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 carcinogenicitv 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 positivelv 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 Safetv and Health (NIOSH) has been modified to allow incorporation of data on individual exposures[24]; previously, onlv 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 analvsis to 1982. We report here an the relation in this cohort between occupational exposure to benzene and death from leukemia.

BACKGROUND

This studv was based on the experience of workers at three plants at two locations in Ohio that manufactured a natural rubber film (rubber hvdrochloride). The details of the process have been described previouslv.[10] In brief. natural rubber was dissolved in benzene and spread on a convevor. 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 I 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

From the National Institute fa Occupanonal Safety and Health. Centers fa Disease Control. Division of Surveillance. Hazard Evaluations. and Field Studies. Cincinnati. OH 45226. where reprint requests should be addressed to Mr Rinsky