LEUKEMIA RISKS IN RELATION TO BENZENE EXPOSURES: AN EXAMINATION OF THE DATA

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Introduction

The central issues in current discussions about the relation between benzene exposures and the risks of leukemia are not whether there may be a causal link but rather under what circumstances of exposure and for what types of leukemia might such a link operate. This chapter will focus on the first of these two questions. The studies available to address the quantitative aspects of risk are few in number, small in size, and subject to varying interpretations. They are reviewed here from the point of view that an attempt to construct a quantitative risk pattern on the basis of these studies may help to identify questions of importance for further resolution of this issue. Four studies have reported risks in relation to some measure of benzene exposure, as ppm in air in the workplace, the units on which most of the discussion and debate has centered (Figure 1). These studies were published between 1974 and 1983 (Aksoy, Erdem and Dincol 1974; Infante, Rinsky, Wagoner et al. 1977; Ott, Townsend, Fishbeck et al. 1978; Tsai, Wen, Weiss et al 1983). Comprehensive discussion of each study is not possible here, but for each study the risks, exposures, and some general comments will be presented.

Aksoy and colleagues

In December, 1974, Aksoy and colleagues at the Section of Hematology of the Istanbul Medical School reported an analysis of their clinical experience with leukemia cases among shoe-workers exposed chronically to benzene (Aksoy, Erdem and Dincol 1974). Over a seven year period they had identified twenty six cases which they attributed to an underlying population of 28,500 such workers. A calculation was described the result of which the authors took as evidence of a "marked and statistically significant increase" in the incidence

of leukemia among such workers over that of the general population. They claimed to have provided "cogent evidence for the clinical impression of leukemogenic effects of benzene in man." Their conclusion was based on a ratio of 13 per 100,000 events observed to 6 per 100,000 expected, or 2.17. However, attentive reading of both their report and the source cited for the expected value indicates some problems with this calculation. The observed cases were incident cases of preleukemia and acute leukemia in Istanbul hospitals from 1967-1973. The expected number was based on a report of leukemia deaths in twenty-four countries in 1965 (Gunz 1970). No adjustment was made for age differences between the populations compared, incidence was compared with mortality, and no evidence was provided to suggest that the leukemia rates for Turkey resembled those of the twenty-four countries. These and other issues (such as those raised by Matanoski in an earlier presentation in this symposium) dictate some caution in evaluating the risk estimate presented by these investigators.

More crucial to the immediate discussion is the information on exposures to benzene related to this estimate of risk. The 1974 report just cited identified all twenty-six cases and their source population as shoe workers, exposed to benzene as a solvent, said to be present in 9 to 88 percent of the composition of the adhesives in use (Aksoy, Dincol, Akgun et al. 1971; Aksoy, Erdem and Dincol 1974). The authors stated, "The working conditions in the industry are not good; their shops are usually small, not hygienic, and poorly ventilated; the concentration of benzene was found to reach a maximum of 210-650 parts per million when adhesives containing benzene were in use." In six additional reports, variously citing these cases and others, other information is given to suggest benzene concentrations of 150-650 ppm, as

exposures occurring for eight hours or more daily, for a mean duration of 6.7 years, among these cases (Aksoy 1980; Aksoy 1977; Aksoy, Dincol, Akgun et al. 1971; Aksoy, Dincol, Erdem et al. 1972; Aksoy and Erdem 1978; Aksoy, Erdem and Dincol 1976). Benzene concentrations ranging from 15-30 ppm were reported outside working hours (Aksoy, Dincol, Akgun et al. 1971).

These reports do not indicate which locations were monitored or how many, how they were selected, when the reported measurements were obtained in relation to the detection of cases of leukemia, or precisely what the exposures were in terms of eight hour Time-Weighted Averages (TWA). They do not, with few exceptions, provide estimates of exposure specific to individuals. However, they do suggest that in a large occupational group exposed for several years at levels commonly reaching into the hundreds of ppm, an excessive rate of leukemia occurrence was observed. This excess risk of leukemia in the late 1960s and early 1970s was considered to have abated by 1975, the apparent decline being attributed to substitution of other material for benzene beginning in 1969 (Aksoy 1980).

Infante and colleagues

In July, 1977, Infante and colleagues, of the U.S. National Institute for Occupational Safety and Health, reported the results of a study of a cluster of 7 leukemia cases and a population of 748 pliofilm workers, at two localities in Ohio, all of whom were judged to have had "direct exposure to benzene" in the period 1940-1949 (Infante, Rinsky, Wagoner et al. 1977a). Two overall estimates of leukemia risk were presented, one being an SMR of 474 when pliofilm workers and fibrous-glass workers were compared, with seven deaths observed versus 1.5 expected. When white US males were the comparison group, the SMR was 506. An SMR specific for myelogenous and monocytic leukemia of

1004 was presented later in the report, challenged in subsequent published correspondence, and revised to 857 (Infante, Rinsky, Wagoner et al. 1977a; Infante, Rinsky, Wagoner et al. 1977b; Tabershaw and Lamm 1977). A still later analysis, restricted to workers with greater than five years of exposure, resulted in an SMR of 2100.

Regardless of which risk estimate one considers, the levels of benzene exposure which may have been experienced by these workers are of particular interest. The available reports give differing impressions. The authors of the original report described the process of pliofilm production during which benzene exposure could occur and cited monitoring data for one of the two localities (Infante, Rinsky, Wagoner et al. 1977a). Levels from 0 to 10 or 15 ppm had been described in a 1946 document which was cited, although the authors made the less specific claim that "employees' benzene exposure was generally below the recommended limit in effect at the time of each survey." A chronological table of these recommended limits was then presented which ranged from a maximum allowable concentration of 100 ppm in 1941 to an eight hour TWA of 10 ppm in 1971. However, the 10 ppm standard was not in effect until eight years after the death of the last of their seven cases, as indicated in a later report (Rinsky, Young and Smith 1981).

In that later report, Rinsky and others provided very extensive detail as to the available exposure information. They emphasized the conclusion, based on this study, that "benzene is a human carcinogen at a range of exposures not greatly above the current legal standard," which, at the time of that report, was an eight hour TWA of 10 ppm (Rinsky, Young and Smith 1981). However, that same report gave contrary information on individual exposure estimates for the leukemia cases, with five of seven having 35 or 40 ppm eight hour TWA

exposures, one having "probably less than 100 ppm," and one, among those employed prior to any ventilation of the work area, having no quantitation provided. In a still later report, White, Infante and Chu (1982) stated: "The average benzene exposure over the period of 1937 to 1954...was 83 ppm. Over the period 1937-1975, the average benzene exposure was 50 ppm". Since, according to Rinsky and others, the great preponderance of the potential exposure period among the seven cases occurred in the 1937-1954 interval, the figure of 83 ppm appears to be the more relevant of the two (Rinsky, Young and Smith 1981). The basis for these estimates is unclear, however, since no monitoring data were available, according to the Rinsky report, for the location where five of the seven workers were employed, until a date after all but the last case had discontinued employment there (Rinsky, Young and Smith 1981).

Some additional information can be gleaned from the reports, as follows. Limited benzene monitoring data were available for one location well within the actual exposure period of interest (Rinsky, Young and Smith 1981). The authors estimated the personal benzene exposure histories for six of the seven cases but indicated a lack of information both on the earliest years of exposure, for all but one case, and on possible benzene exposures additional to those involved in the pliofilm process, for four of the seven cases. The reported values could therefore be interpreted as possible underestimates of the actual exposures of these workers. Use of respiratory protective equipment by workers at some times and locations was mentioned, but not in reference to any of the leukemia cases themselves. For the six or seven cases, exposures apparently occurred prior to any workplace ventilation, such conditions perhaps accounting for 50 percent of the cumulative exposure period among these workers. No

attempt at characterization of personal exposures among other members of the study population was reported. Notably, also, the last of these seven deaths occurred in 1961 (Rinsky, Young and Smith 1981).

Ott and colleagues

In 1978, Ott and Colleagues, from the Dow Chemical Company, reported on mortality among workers occupationally exposed to benzene (Ott, Townsend, Fishbeck et al. 1978). Of 594 such workers, 335 had been exposed prior to 1950, the three work areas involved having been operated from 1920, 1935, and 1936, respectively. In the analysis most specific for benzene exposures, the occurrence of one death coded as leukemia was related to 0.9 cases expected on the basis of US white male mortality over the corresponding calendar period, which would yield a relative risk of 1.11. In a larger group with substantial other exposures, 53 additional subjects added 0.1 expected cases of leukemia and one observed leukemia death, which would yield a relative risk of 2. A third death was necessarily excluded from these calculations since it had not been recorded as due to leukemia as the underlying cause on the death certificate.

Benzene exposure levels, by work area, were reported as eight hour TWA values from 1944 at the earliest, in one area, to 1952-1953 in the other two areas. The eight hour TWA values over the period of study were estimated from varying numbers of samples, at specified locations. The minimum and maximum values of these estimates were 0.1 and 35.5 ppm, respectively. For the individual cases, the work histories permitted estimates of eighteen months of potential exposure below 2 ppm eight hour TWA, for one case, and two years of potential exposure at 2-9 ppm, in addition to other chemical exposures, for the other case.

The workplace monitoring data for the mid-1940s and early 1950s, when these workers were exposed, were limited, but the corresponding estimated 8-hour TWAs were in the 9-35.5 ppm range. Multiple occupations, and multiple exposures while employed by Dow, occurred for the first and second of these two cases, respectively. An incidence estimate was also given, in a single sentence in the discussion section of the Ott report. However, there is a difficulty with this calculation, in that the expected number of cases excluded lymphocytic and monocytic cell types, while the cell types were not known for all three of the cases included. For one case, death was ascribed to 'leukemia' and not further specified; a later statement gives the impression of myelocytic leukemia, type not specified. Accordingly, the expected value may have been underestimated, the ratio of observed to expected therefore overestimated, and the impression of a statistically significant excess was incorrect. The sensitivity of all risk estimates from this study to the addition or subtraction of a single case is to be noted, although the expected numbers of deaths are only slightly below those of the Infante study (Infante, Rinsky, Wagoner et al. 1977).

Tsai and colleagues

In 1983, Tsai and colleagues, of the Gulf Oil Corporation, reported on a study of workers in benzene areas of a refinery (Tsai, Wen, Weiss et al. 1983). The study cohort included all male workers ever employed in the principal petrochemical units of a single refinery from late 1952 through 1957. From mortality data for US males, 0.42 deaths from leukemia were expected among the 454 workers studied. No case of leukemia was observed, so that the SMR was 0. It was noted as well that no still-living employee had developed leukemia, as of 1979, but the methods of ascertainment were not stated.

Monitoring data were judged to be inadequate prior to 1973, but personal sampling data, based on a total of 1394 samples taken from 1973-1982, indicated benzene concentrations from below 0.1 ppm (43 percent of samples) to 25 ppm or above (1 percent of samples). These values were not adjusted to eight hour TWAs. The duration of exposure was on average 8.0 years for white and 4.5 years for non-white workers, with one-half of the cohort working in benzene areas prior to 1965 and 80% so employed for at least one year.

The size of the study population provided for only a very small expectation of leukemia deaths. The fact that exposures were reported as single sample values rather than 8-hour TWAs suggests that potential exposure levels were well below those in the Dow study, at least in the period for which data were available. Qualitative information on the nature of the benzene exposures of these workers was not provided.

Conclusions

The data on benzene concentrations in these studies are valuable, though far short of the ideal, as a guide to arraying the reported leukemia risks in relation to potential exposures. Differences in data quality, manner of reporting, and other aspects not addressed here, limit the comparability of these studies. Further, the term "environmental data" and not "exposure data" should perhaps be used, since actual individual exposures can only, at best, be inferred.

The qualitative information on the work environments represented by these studies, when available, is also valuable in further characterizing the nature of the potential exposures, as to general hygienic features, chronology of process changes, and so on. More detailed and more consistent reporting of such information, as in the Rinsky (Rinsky, Young and Smith 1981) report, would be useful.

It has been implied that existing data demonstrate significant risks of leukemia for workers near the current exposure standard of 10 ppm eight hour TWA (Rinsky, Young and Smith 1981). The strongest evidence from these studies is that excessive risks are related to exposures at levels in the hundreds, eighties, or fifties of ppm, for several years; the conflicting impressions about the pliofilm workers' exposures, perhaps in the 35-40 ppm range plus other, unquantified exposures, should be resolved. In any case, these observations are not consistent with the contention that the 10 ppm level has been demonstrated to relate to significant excess risk. If valid, this contention could be of great importance for the health and safety of potentially exposed workers. Resolution of this issue would be aided most by further epidemiologic studies which addressed, among others, the following questions:

-- Can the observations among the Ohio pliofilm workers be replicated elsewhere, thus possibly adding to the weight of evidence from only seven cases of leukemia concerning long-term exposures in the 25-100 ppm range?

-- Can actual excess risks of leukemia at or near a 10 ppm eight hour TWA exposure level be demonstrated? If so, under what conditions of exposure? If not, can such risks reasonably be excluded at this or higher exposure levels but below those described for the affected pliofilm workers?

-- What is the distribution, and what are the conditions, of benzene exposure levels in the workplace today? To what extent do the hazards shown in two of these four historical studies persist?

If there were, as claimed, some two million potentially exposed workers as recently as 1977 (Infante, Rinsky, Wagoner et al. 1977a), and presumably many more in the more remote past in the U.S. alone, studies of greater size and of

at least the quality of those reported to date should be feasible. Such studies could add importantly to the limited data presently available on the quantitative relations between benzene exposures and the risks of leukemia. Observations on specific types of leukemia would be of greatest value. The implications of these questions for public health practice, for regulatory policy, and for the extensive litigation in progress and in prospect would seem to lend some urgency to establishing a firmer basis for the answers.

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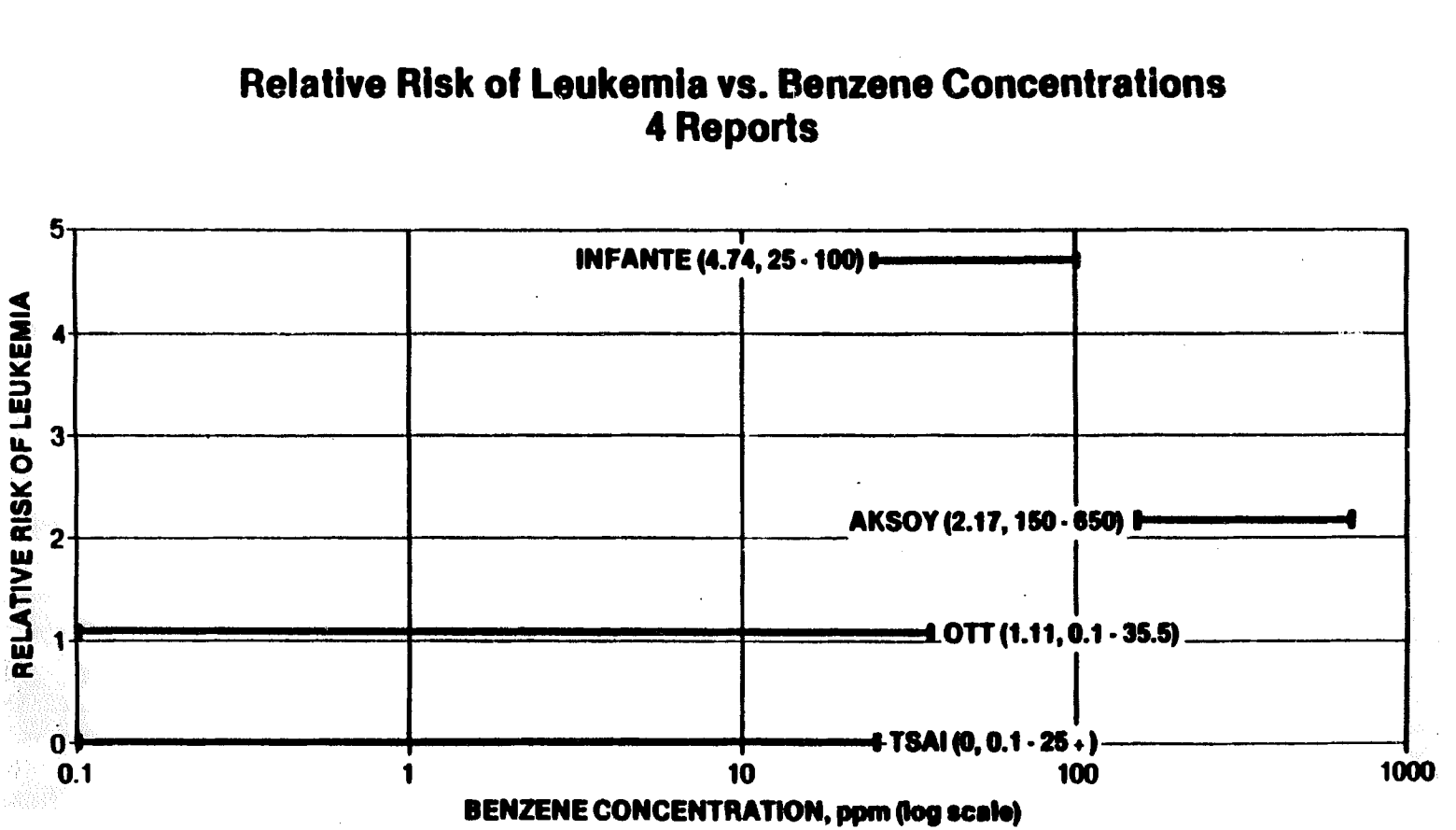
Relative Risk of Leukemia vs. Benzene Concentrations
4 Reports
RELATIVE RISK OF LEUKEMIA
5
4
3
2
1
0
INFANTE (4.74, 25 - 100)
AKSOY (2.17, 150 - 650)
LOTT (1.11, 0.1 - 35.5)
TSAI (0, 0.1 - 25+)
0.1
1
10
100
1000
BENZENE CONCENTRATION, ppm (log scale)

Figure 1

EPIDEMIOLOGY AND HEALTH RISK ASSESSMENT

PROCEEDINGS OF A SYMPOSIUM

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