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Reviews and Commentary

BENZENE AND LEUKEMIA

A REVIEW OF THE LITERATURE AND A RISK ASSESSMENT[1]

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The major purpose of this paper is to review the evidence, primarily epidemiologic, pertaining to the relation between benzene and leukemia. Benzene is widely considered to be a leukemogen for human beings, but its potency is uncertain. Since low-level exposures to benzene characterize many occupational settings, it is important to determine to what extent, if at all, low exposures increase leukemia risk. Moreover, as we write, the US Occupational Safety and Health Administration is attempting to reduce workplace exposures from an eight hour time-weighted average level of 10 parts per million (ppm) to 1 ppm. This paper also includes an evaluation and critique of various risk assessments of benzene and leukemia. These risk assessment; were done for policymaking and were developed to predict the leukemogenic effect of benzene exposures in the vicinity of the present occupational standard of 10 ppm.

Abbreviations: CI, confidence interval; ppm, parts per million; RR, relative risk.

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BACKGROUND

In 1981, a Working Croup of the International Agency for Research on Cancer concluded Ilint there was sufficient evi-Jence that benzene is carcinogenic to humans (1). Specifically, they concluded that exposure to benzene muy damage the hematopoietic system and that evidence from epidemiologic studies establishes a causal relation between benzene and acute myelocytic leukemia. In the same report, it was noted that the evidence linking benzene with cancer other than acute myelocytic leukemia was inadequate. Benzene is included on the list of carcinogens published by the Secretary of the US Department of Heaith and Human Services (2) and is designated as a suspect carcinogen by the American Confcrcnce of Governmental Industrial Hygienists (3).

The present Occupational Safety and Health Administration regulation for exposure to benzene was established in 1971 and revised in 1974 (4). The regulation limits exposure to an eight-hour time-weighted average of 10 ppm with a ceiling concentration of 25 ppm over a 10-minute period and a peak concentration not lo exceed 50 ppm for more than 10 minutes.

This regulation was established because benzene was known to be a bone marrow depressant and because of its acute toxicity; benzene was not generally recognized as a carcinogen at that time. Indeed. in 1974. the National Institute for Occupational Safety and Health noted that. although case reports, chromosomal srudies. and several epidemiologic studies suggested a link between benzene and leukemia. the evidence was not sufficient to conclude that it was a carcinogen (5). However, in 1976, the National Institute for Occupational Safety and Health recommended that benzene be regulated as a carcinogen because of new epidemiologic evidence (6). In that year, the Occupational Safety and Health Administration issued an emergency temporary standard for occupational exposure to benzene which stipulated an eight-hour time-weighted average of 1 pprn with a ceiling level of 5 ppm for any 15-minute period. This became the Occupational Safety and Health Administration standard in 1978 (7). However, a number of organizations representing industrial concerns obtained an injunction *against* the new standard. In 1980, the Supreme Court struck the 1 ppm standard, stating in essence that the Occupational Safety and Health Administration had not demonstrated that the 10 ppm standard was unsafe (8). Thus. a controversy remains about the reasonable exposure limit in occupational settings and especially about the leukemogenic effect of low-level exposures.

SCIENTIFIC EVIDENCE

The potential adverse health effects of benzene have been evaluated in experimental studies of animals, in investigations of chromosomes, and in epidemiologic studies of workers exposed to benzene. Here, we emphasize the epidemiologic studies because they have provided both the qualitative and the quantitative estimates of the leukemogenic effect of benzene on which risk assessments and regulations largely have been based. Nevertheless. a brief summary of the results of animal studies and of chromosomal studies is pertinent, since these have also contributed to the evaluation of the leukemogenicity of benzene.

Animal studies

The carcinogenicity of benzene has been assessed experimentally in rats and mice using several exposure methods, such as skin application. inhalation, intragastric, and subcutaneous administration (11. The International Agency for Research on Cancer reviewed these and other studies of animals in 1982 and concluded that 'there is limited evidence that benzene is carcinogenic in experimental animals" (1). Additional studies now have been reported, and they strengthen the hypothesis that benzene is an animal carcinogen which acts on several organ systems (9–12). However, this work has limitations which affect its relevance to the evaluation of the relation between benzene and leukemia in human beings. None of tne experimental work provides an adequate animal model for benzene-induced myelocytic leukemia. Although the studies have demonstrated the induction of nonmalignant hematologic disorders by benzene, the carcinogenic effects are confined largely to nonhematologic tissues. In rats and mice, for example, benzene appears to be strongly related to the Occurrence of carcinoma of the zymbal gland, a structure with no human analog. An additional limitation of the animal studies is the lack of data on the potential carcinogenicity of benzene exposures below 100 ppm.

Chromosome studies

Despite several studies. benzene has not been found to be a genotoxic (DNA-reactive) agent (13). However, it causes chromosome breaks and other chromosomal changes in animals, and it has been suggested that an excess of chromosomal aberrations occurs among human beings exposed to benzene (1.11). Studies of workers with benzene-induced blood disorders have consistently shown an increased prevalence of chromosomal aberrations in so-

matic cells. However, studies of workers who had low (<25 ppm) benzene exposures or who had no overt signs of chronic benzene poisonine have been inconsistent with respect to cytogenetic findings. In addition, many of these studies are quite small, and most have methodological deficiencies, including inadequate assessment of average or cumulative benzene exposure, failure to adjust for age differences between groups, and no dose-response evaluations. Moreover, there are no data that establish a relation between chromosomal aberrations and the subsequent development of leukemia or other disease.

Epidemiologic studies

Eleven epidemiologic studies have evaluated the association between benzene and leukemia (14-28). These studies were preceded by many case reports of leukemia patients with industrial benzene exposure and by descriptions of series of leukemia cases associated with benzene exposure, two of which have been updated by Aksoy (29) in Turkey and by Vigliani (30) in Italy.

Aksoy (29) studied 51 leukemia cases, identified in 1967–1983, among men occupationally exposed to benzene in Istanbul, Turkey, and he estimated that from 1967 to 1975 the crude incidence rate of leukemia was 13 per 100,000 person-years among shoe workers, compared with six per 100,000 person-years among men in the general population. However, the validity of these estimates and the meaningfulness of the comparison of the leukemia rates of shoe workers with those of the general population are doubtful because ascertainment of leukemia cases was incomplete and was not conducted in the same manner for the two groups.

Vigliani (30) in Italy reported 11 leukemia cases that occurred between 1942 and 1974 in Milan and 13 cases that occurred between 1959 and 1974 in Pavia among workers in shoe and rotogravure factories. Benzene exposures were thought to have ranged from 26 to 600 ppm for workers handling glues in shoe factories and from 200 to 400 ppm for workers in the rotogravure plants. Vigliani estimated that the incidence rate of acute leukemia among workers heavily exposed to benzene was 20 times higher than that of the general population, but this estimate is not adequately documented.

The epidemiologic studies of benzene and leukemia are summarized in table 1. They are reviewed briefly below.

In a hospital-based case-control study in France, Girard and Revol (14) evaluated the association between benzene and leukemia and other hematologic diseases. The cases were hematology service patients, of whom 140 had acute leucosis (also referred to as acute leukemia in the study report), 61 had chronic lymphocytic leukemia, and 56 had myeloid leukemia. There were also 124 controls hospitalized for nonhematologic conditions. Exposure to benzene and toluene was determined by questioning subjects about chemicals which they had used during the 10-year period preceding the hospitalization. Relative risks for benzene or toluene were 3.3 (95 per cent confidence interval (CI) = 1.2–8.9) for acute leucosis/leukemia, 4.1 (1.4–12) for chronic lymphocytic leukemia, and 1.8 (0.5–6.6) for myeloid leukemia. This study suggests a strong positive relation between most forms of leukemia and benzene or toluene. However, it does not distinguish between benzene and toluene, and it provides no estimate of dose-response.

Ishimaru et al. (15) conducted a study of 303 leukemia cases and 303 controls in Nagasaki and Hiroshima, Japan. The study evaluated occupational exposures to benzene and to medical x-rays; potential exposure was determined on the basis of subjects' occupations. The relative risk of leukemia was 2.5 (95 per cent CI = 1.3–5.0) for persons with occupations involving potential benzene or medical x-ray exposure compared with those with no such exposures.

The main limitation of this study is its use of occupation as a surrogate for benzene exposure. Each occupation classified as in-

TABLE 1

Summary of epidemiologic studies of benzene exposure and leukemia

Study location and year of publication (reference number)	Study design and observation period	No. and type of subjects	Exposure measure	SMR* or RR† for leukemia (95% confidence interval)
France, 1970 (14)	Case-control 1966–1969	257 leukemia cases; 124 hospital controls	Occupational or household exposure to solutions containing benzene or toluene	RR = 3.3 (1.2–8.9) (acute leukemia) RR = 4.1 (1.4–12) (chronic lymphocytic leukemia) RR = 1.8 (0.5–6.6) (myelocytic leukemia)
Japan, 1971 (15)	Case-control, 1945–1967	303 adult leukemia cases; 303 controls	Employment in an occupation involving potential exposure to benzene or x-rays	RR = 2.5 (1.3–5.0)
Europe, 1974 (16)	Retrospective follow-up 1962–1971	38,000‡ employees of oil company affiliates. Referent: general population	Employment involving potential exposure to >1% benzene for >5 years	SMR = 121 (37–205)
United States, 1977 and 1981 (17, 18)	Retrospective follow-up 1950–1975	1,006 rubber hydrochloride (Pliofilm) workers. Referent: 1) general population; 2) 1,447 fibrous glass workers; 3) 398 nonbenzene-exposed rubber hydrochloride workers	Employment involving exposure to benzene for at least 1 day during 1940–1959, duration of employment	SMR = 560 (225–1,154) (first exposed in 1940–1949, general population referent) SMR = 2,100 (706–5,073) (exposed for >5 years, general population referent)
United States, 1996 (19)	Retrospective follow-up 1950–1965	1,165 rubber hydrochloride (Pliofilm) workers. Referent: general population	Employment involving benzene exposure for at least 1 day during 1940–1965; cumulative benzene exposure (ppm-years)	SMR = 337 (154–641) (overall cohort) SMR = 109 (12–394) (0.001–39.99 ppm-years) SMR = 322 (36–1,165) (40.0–199.99 ppm-years) SMR = 1,186 (133–4,285) (200.0–399.99 ppm-years) SMR = 6,637 (1,334–19,393) (≥400.0 ppm-years)
United States, 1996 (20)	Retrospective follow-up 1940–1975	594 benzene workers. Referent: general population	Cumulative benzene exposure (ppm-months)	SMR = 200 (24–722) (leukemia mortality) RR = 3.6 (myelocytic leukemia)

ited States, 1978 (20)	Retrospect[illegible] follow-up, 1940–197[illegible]	[illegible] benzene workers Referent: general population	Cumulative benz[illegible] exposure (ppm-months)
[illegible]ited States, 1986 (21)	Retrospective follow-up, 1940–1982	956 benzene workers. Referent: general population	Cumulative benzene [illegible]posure (ppm-months)
O[illegible]sted Co., MN, 1980 (22)	Case-control, 1965–1974	138 adult leukemia cases; 276 controls	Medic[illegible] in[illegible] to[illegible] benz[illegible] ne exposu[illegible]
U[illegible]ed Kingdom, 1981 (23)	Case-control, 1960–1974	Oil refinery workers; 36 cases; 216 controls	Employment involvi[illegible] to[illegible] reduce[illegible] high benzene exposure
U[illegible]ed States, 1983 (24)	Retrospective follow-up, 1960–1977	259 chemical workers. Referent: general population	Employment during 1[illegible]7–1970 at a p[illegible] that has used large am[illegible]nts of benzen[illegible]
Un[illegible]ed States, 1983 (25)	Retrospective follow-up, 1946–1977	4,602 chemical workers. Referent: 1) general population; 2) 3,074 chemical workers with no occupational benzene exposure	Exposed to benzene for [illegible]6 months, co[illegible] uous vs. intermittent e[illegible]posure; cumula[illegible] exposure (ppm-months); duration of e[illegible] sure and time since firs[illegible] exposure
Uni[illegible]ed States, 1983 (26)	Retrospective follow-up, 1952–1978	454 oil refinery workers. Referent: 1) general population; 2) 10% sample of nonbenzene-exposed refinery workers	Employment in benzen[illegible]-related prod[illegible] tion units; duration [illegible] benzene-rela[illegible] work
United States, 1983 (27)	Case-control, 1964–1973	Rubber manufacturing workers: 15 lymphocytic leukemia cases; 30 controls	Primary benzene exposu[illegible] employment jobs involving direct use of benzene
			Secondary benzene expo[illegible]re employme[illegible] in work areas where benz[illegible]ne was used[illegible] no direct use in job
United States, 1984 (28)	Case-control, 1964–1973	11 lymphocytic leukemia cases; 1,350 controls	Employment in work areas where benz[illegible] was used

* SMR, standardized mortality ratio.
† RR, relative risk.
‡ Total, exposed and unexposed. Number of workers exposed and unexposed not stated

volving potential benzene exposure may have included workers with no exposure to benzene, as well as workers with exposure to chemicals other than benzene. In addition. the relative risks were not reported separately for benzene and medical x-ray exposures, and no attempt was made to quantify leukemia risk according to intensity or duration of benzene exposure.

Thorpe (16) investigated leukemia incidence and mortality among 38.000 active workers and annuitants at eight European affiliates of a large oil company. The observation period was from 1962 to 1971. Employees were classified either as having been exposed to benzene (potential exposure for at least five years to refinery streams or petroleum products containing at least 1 per cent benzene) or not (no or only occasional benzene exposure). The ascertainment both of benzene exposure and of leukemia occurrence was conducted separately by each of the affiliates. The expected number of leukemia deaths was derived from the general population mortality rates of the countries in which the affiliates were located. For workers potentially exposed LO benzene, the standardized mortality ratio was 121 (95 per cent CI = 37-205), whereas the standardized mortality ratio was 80 for the unexposed.

This study has a number of limitations. Ascertainment of leukemia cases and documentation of exposure were inadequate. In addition. the report indicates that there was considerable uncertainty about the age structure of the overall cohort. For these reasons, the validity of the reported standardized mortality ratios is questionable. The standardized mortality ratio of 121 for leukemia among potentially exposed workers in unremarkable. However, the study is neither persuasively positive nor negative because of the lnck of an analysis of leukemia mortality by induction period, the unexplained deticit of deaths from leukemia among the unexposed and the lack of documentation of the methods used to identify leukemia deaths and to determine benzene exposure.

In 1977. Infante et al. (17) reported the preliminary findings of a retrospective follow-up study of 1,006 workers employed in the manufacture of rubber hydrochloride (trade name, Pliofilm) at three plants in two Ohio locations. Rinsky et al. (18) presented additional results from this study in 1981. XI1 workers with at least one day of exposure to benzene during 1940 through 1959 were included, although most of the results pertained to the 748 men who were first exposed between 1940 and 1949. These men were followed through mid-1975. The investigators used historical benzene exposure monitoring data to describe exposun conditions at the two locations. Although these data were sparse, especially for location 2, the investigators believed that exposure tended to be below the recommended limits.

The mortality experience of the benzene-exposed workers was compared with that of US white men, unexposed rubber hydrochloride workers at the study plants (n = 398), and white male fibrous glass workers in Ohio in = 1,447). The standardized mortality ratio for leukemia among the 748 men who were first exposed between 1940 and 1949, compared with that of the general population, was 560 (95 per cent CI = 225-1,154), based on seven observed deaths. Using the fibrous glass workers as the referent. the standardized mortality ratio was 473. There were no deaths from leukemia among the unexposed rubber hydrochloride workers: the expected number was not reported but was probably small.

Five of the seven leukemia deaths occurred among men with five or more years of benzene exposure (standardized mortality ratio = 2,100). All of the leukemias were of the myelocytic (acute, 4; chronic, 1) or monocytic (acute. 1; unspecified, 1) cell type. Among men wiio had first been exposed to benzene between 1950 and 1959. there was one death from myelogenous leukemra compared with 0.5 expected.

Rinsky et al. (19) have recently updated this investigation. The updated study includes 1,165 men who had been exposed to benzene for at least one day during 1940–1965 and extends follow-up through 1981.

The update also uses a jnh-exposure linkage procedure to estimate the cumulative benzene exposure of the men in the study. The leukemia standardized mortality ratio for the overall cohort compared with the general population was 337, based on nine observed and 27 expected leukemia deaths. The findings of the updated study are discussed further in the next section.

The study of rubber hydrochloride workers is the strongest evidence available that benzene is associated with myelocytic leukemia. Even so, the estimate of the standardized mortality ratio for benzene-exposed workers is imprecise. Moreover, the study contains little relevant data on the exposure levels associated with excess leukemia mortality. Five of the seven leukemia deaths occurred at location 2, for which measurements on benzene levels were particularly sparse. Furthermore, location 2 was the site of several manufacturing operations. including tire manufacturing, in addition to rubber hydrochloride production, It is likely that four of the five men with leukemia at location 2 had started working there before 1940, and one had started in 1944. Benzene has been used as a solvent in tire manufacturing therefore. many of the study members from location 2 may have been exposed to benzene in departments other than rubber hydrochloride. and their actual exposure levels may have been underestimated.

Ott et al. (20) conducted a retrospective follow-up study of 594 Dow Chemical Company employees occupationally exposed to benzene in the prnduction of alkyl benzene. chlorobenzene, and ethyl cellulose. Men employed in these operations from 1938 to 1970 were identified and followed-up through 1973. The study was updated to include an additional 362 exposed employees, and follow-up was extended through the end of 1982 (21). Cumulative exposure to hentene was estimated for each cohort member. The expected numbers of leukemia deaths were derived from leukemia mortality rates of ail US white men.

Four leukemia deaths occurred among benzene-exposed workers, whereas 2.1 were expected. Another deceased worker hnd myelomonocytic leukemia, hut. this wns not certified as the underlying cause of death and was not included in *the* mortality analysis. The four leukemias were of the myelocytic cell type. Ott et al. estimated an incidence rate ratio of 4.4 (95 per cent CI = 1.2-11) for myelocytic leukemia for benzene-exposed workers relative *to* the general population.

The average cumulative exposure of cohort members can be estimated from data presented in the updated report. Among a total of 242 expected deaths from all causes, the cumulative exposure category was 0-499 (midpoint,250) ppm-months for 151 of the expected deaths, 500-999 (midpoint, 750) ppm-months for 35, and 1,000+ (say 1,250) ppm-months for 56. Thus, the average cumulative exposure of cohort members is estimated as 554 ppm-months, or about 46 ppm-years. The cumulative benzene exposures were lower than this for three of five of the leukemia cases.

The mnjot limitations of this study are its small size and thus its imprecise estimate of the effect of benzene on the occurrence of leukemia. The observation that the cumulative benzene exposure of three of the five leukemia cases probably was below the average cumulative exposure of the entire cohort has several possible implications: there may be a threshold effect of benzene among susceptibles; the leukemias may not have been caused by benzene: or the benzene exposure estimates may have been incorrect.

Linos et al. (22) evaluated the relation hetween leukemia and benzene in a case-control study of 138 leukemia cases and 276 controls. Any mention of a history of exposure to benzene listed in the medical recnrds was the sole criterion of benzene exposure. The relative risk was 3.3 (95 per cent CI = 0.6-28), based on four exposed cases and three exposed controls. Three of the exposed cases had chronic lymphocytic leukemia. This studv is largely uninformative because of the limited information on henzene exposures and because of its small size.

Rushton and Alderson (23) conducted a case-control study of leukemia within a large cohort of workers at eight oil refineries in the United Kingdom. An earlier retrospective follow-up study of these workers (31) had reported a standardized mortality ratio for leukemia of 94. The case-control study included 36 leukemia deaths which occurred among men employed between 1950 and 1975 and 216 controls who had worked at the refineries during the same period. Measurements of workplace benzene levels were not available. However, study subjects were classified as having been exposed to low, medium, or high leveis of benzene based upon their work histories. The relative risk for medium or high exposure compared with low exposure was 2.0 (95 per cent CI = 1.0–4.0). The relative risk was not higher among men with high exposure compared with medium exposure, and, furthermore, relative risk did not appear to be related to length of service at the refineries. The relative risks for the various types of leukemia were not presented.

The results of this study are supportive of a leukemogenic effect of benzene-or other solvents used in conjunction with benzene. However, the informativeness of the study is limited by the lack of data on exposure leveis and by the absence of any analyses by duration of *exposure* or by induction period.

Decouflé et al. (24) evaluated the mortality experience of 259 men employed between 1947 and 1960 at a chemical manufacturing plant. Large amounts of benzene had been used at the plant, but no measurements of benzene levels were available. Employees had also worked with other chemicals. These men were followed from 1960 through 1977. There were three deaths from leukemia compared with 0.44 expected (standardized mortality ratio = 682; 95 per cent CI = 141–1,992). The cell types of the three leukemias were chronic lymphocytic, acute monocytic, and acute myelomonocytic.

Wong (25) conducted a retrospective follow-up study of 4,602 male chemical workers at seven plants. The study group included men who had been exposed to benzene for at least six months between 1946 and 1977. Jobs were classified as involving intermittent or continuous benzene exposure. For workers with continuous exposure. cumulative exposure to benzene (ppm-months) was calculated by using length of employment and the estimated eight-hour time-weighted average for each job. Using the distribution of workers according to a cumulative ppm-months benzene measure presented by Wong, the average exposure of continuously exposed workers is estimated to be about 366 ppm-months (about 30 ppm-years). This corresponds to a time-weighted average of about 3 ppm, since the average duration of exposure was 10 *years*. The mortality rates of exposed workers were compared with those of US men and with those of an internal comparison group comprised of 3,074 men who had worked at the same or at nearby chemical plants but who were not exposed to benzene.

For the overall group of exposed workers. there was a slight excess of leukemia deaths compared with US men (seven deaths, standardized mortality ratio = 117; 95 per cent CI = 47–242). Four of these leukemias were of the lymphocytic cell type, two were myelocytic (both chronic), and one was unspecified. Among unexposed workers, these were no leukemias, whereas 3.4 were expected (two-tailed p value = 0.07). The standardized mortality ratio for all causes was similar for the exposed workers (standardized mortality ratio = 87) and unexposed workers (standardized mortality ratio = 75).

Six of the leukemia deaths among exposed workers occurred among men with continuous exposure (standardized mortality ratio = 135; 95 per cent CI = 50–295). However. for these workers, there was no consistent trend in the standardized mortality ratio for leukemia over categories of either duration of exposure or cumulative exposure, although the latter test for trend, using the nonexposed internal comparison

group, yielded a one-tailed p value of 0.01. The standardized mortality ratio increased with years since first exposure from a value of 0 for under 10 years to 182 (four leukemia deaths) for at least 20 years. For men with cumulative benzene exposure of at least 60 ppm-years, the leukemia standardized mortality ratio was 276 based on three deaths.

This study contains some evidence of a positive relation between benzene and leukemia. However, the overall standardized mortality ratio of 117 for leukemia is not statistically significant and the slight excess could be due to confounding by exposure to other chemicals. Moreover, the study is too small to provide an adequate assessment of dose-response. Because unexposed workers had a deficit of leukemia deaths, no confidence can be placed in statistical tests of trend which include the unexposed group. The fact that none of the leukemia deaths among the benzene-exposed workers was acute myelocytic leukemia further detracts from a causal interpretation of the study results.

Tsai et al. (26) reported the mortality experience of 454 men who had been employed at an oil refinery between 1952 and 1978 and who had worked in benzene-related production units. Review of industrial hygiene data for 1973–1982 indicated that the median exposure level in these units was about 0.5 ppm. Comparison groups consisted of the general US male population and a 10 per cent sample of nonbenzene-exposed workers at the same refinery (n = 823). There were no leukemia deaths among the workers exposed to benzene. The expected numbers, based on general population rates, were 0.42 for all exposed workers and 0.29 for workers employed for at least one year in a benzene-related unit. There were five deaths from leukemia and lymphatic cancer among unexposed workers, but no data were presented on the expected numbers of deaths. Although this study found no excess of leukemia, its small size and the relatively small proportion (36 per cent) of the cohort with an adequate follow-up period preclude any firm conclusion about the risk of leukemia associated with the low levels of benzene described.

Several case-control studies of leukemia and solvent exposures have been conducted within the rubber industry (27, 28, 32.33). Three of these studies were besed on the same series of cases from one rubber company (27, 28, 32). A fourth study included this series plus additional cases from three other companies (33). Each study reported a positive association between lymphocytic leukemia and solvents. This association was present in only one of the four rubber companies, and it was not found for other leukemia cell types.

Two of the studies evaluated the relation between lymphocytic leukemia and exposure to specific solvents, including benzene (27, 28). In the study by Arp et al. (27), exposure to benzene and to other solvents was determined by linking subjects' work histories with historical information on specific solvents used in various work areas and processes. Subjects were classified as having "primary" benzene exposure if they had worked in areas where benzene was used and if their jobs entailed direct handling of benzene or benzene-containing solutions. Subjects were considered to have "secondary" exposure if they had worked in areas where benzene was used but did not have jobs involving direct contact. Quantitative levels of benzene exposure were not estimated. The relative risk of lymphocytic leukemia was 4.5 for workers with primary benzene exposure and 1.5 for workers with secondary exposure. Estimated relative risks for exposure to solvents other than benzene were nearly identical to those for benzene. 4.5 for primary exposure and 1.6 for secondary exposure.

Checkoway et al. (28) studied 11 of the lymphocytic leukemia cases included in the study by Arp et al. and 1,350 controls. Benzene exposure was determined on the basis of employment in work areas where benzene was used: no distinction was made between primary and secondary benzene exposures. The relative risk of lymphocytic leukemia was 2.5 for workers with benzene

exposure. Elevated relative risks were found for workers exposed to a number of other solvents, including acetone, carbon disulfide, carbon tetrachloride, ethylacetate, and hexane.

These studies do not provide persuasive evidence of a causal relation between benzene and lymphocytic leukemia among rubber workers. The confidence intervals of the relative risk estimates are wide, reflecting the imprecision of these estimates. and they include the null value of 1.0. Moreover. it is evident that these rubber workers were exposed to solvents other than benzene and some of these *are* associated with a relative risk of leukernin that is at least as large as that for benzene. Because exposure classification was not mutually exclusive with regard to solvents, it is possible that the observed association between benzene and lymphocytic leukemia is due. not to benzene, but to other solvents whose use is correlated with the use of benzene.

In addition to the studies described above, investigations of large groups of rubber workers (32, 34–42), newspaper web pressmen (43), and refinery workers (16, 31, 44–55) evaluated leukemia mortality or incidence, and some have found excesses (32, 34-37, 41, 43, 46, 48–51, 53, 54). Workers in thue industries are exposed to solvents other than benzene and to other chemicals as well. Several authors have noted that because of this, leukemia excess~!hmong rubber and refinery workers should not be attributed solely to benzene.

In the aggregate, the epidemiologic evidence suggests a link between benzene and leukemia. However, this evidence is not conclusive because it comes primarily from the single relatively small study by Rinsky ut al. (19). The other epidemiologic data provide, at best, weak evidence of a causal association between benzene and leukemia. No study rules out the possibility that observed associations between benzene and leukemia are attributable, at least in part, to confounding by solvents other than benzene. As others have pointed out (28), this possibility has nut been explored adequately in the rubber industry, an observation which also applies to the petrochemical industry and to other industries in which there is widespread exposure to many solvents. Also, because the major pertinent studies have been small. little confidence can be placed in available quantitative estimates of the magnitude of any association: Measures of benzene exposure levels for relevant time periods are extremely sparse in all of the studies. Therefore, considerable doubt remains about the leukemogenic effect of benzene at specific exposure levels and especially at low leveis.

Risk assessments

The expression "risk assessment" describes the final step in a long process. The process usually begins with an effort, often based solely on experimental findings in animals, to describe a dose-response relation between a carcinogen and a cancer. This phase of the process usually involves extrapolation from observed, usually high, dose levels to hypothetical, usually low. dose levels. The process then continues by the making of a generalization to man on the basis of the results in animals. This generalization involves a number of assumptions to equate both the manner of dosing and the manner of responding of animals and man. These assumptions are usually not subject to evaluation.

In other instance:, the process of risk assessment does not employ findings from animals but rather uses epidemiologic findings on human beings. in such instances, the difficulties of the animal to man generalization cue irrelevant. Nonetheless, the process may still lead to results of dubious validity. There are two common reasons for this: 1) the available data are sparse and 2) the people studied experienced quite high exposures so that some extrapolation is necessary to predict effects at lower doses.

Efforts to describe a risk assessment for benzene and leukemia are in the second category. There are little meaningful animal data. Data for human beings are few and relate to uncertain, but probably rather

high, exposure levels. Thus, efforts to describe the extent of small increases in leukemia risk as a consequence of low-level exposure to benzene must lead to imprecise results.

The benzene-leukemia risk assessments have used 'linear" and 'exponential" models to relate benzene exposures to leukemia. However, the use of such mathematical models obscures the fact that the data are too sparse to provide an adequate description of the shape of the dose-response curve. Essentially, the results of most of the benzene-leukemia risk assessments can be well approximated by assuming that the leukemia "effect" is directly proportional to the dose. usually measured as lifetime cumulative exposure. For example. if 15 years of exposure to 10 ppm (150 ppm-years) of benzene is associated with a twofold excess of leukemia deaths, then it is assumed that 30 years of exposure to 10 ppm (300 ppm-years) of benzene would cause a fourfold excess. This linear model is generally considered "conservative" in that it probably overestimates the leukemogenic effects at low doses. It must be borne in mind, however, that the validity of a linear model in the benzene-leukemia risk assessments is not established.

The concept of a "threshold" is meaningful for the benzene-leukemia risk assessments and relates directly to the issue of what constitutes a meaningful measure of benzene exposure. Moat of the benzene-leukemia risk assessments are based on cumulative benzene exposures: these are obtained hy multiplying years of exposure by the average ambient benzene levels. Thus. exposure to 1 ppm benzene for 10 years is considered as the equivalent to exposure to 10 pprn henzene for one year. This method of obtaining a summary exposure measure is used frequently in carcinogen risk assessments. the motivation being its simpiicity. Nonetheless. it mav not be particularly meaningful. The human hody metabolizes and excretes with no apparent harm low levels of toxic substances thnr are harmful at higher levels. This mav be true of henzene. That is. there may be a level of benzene exposure below which no leukemogenic effect occurs. Thus, a lifetime of exposure to benzene at 1 ppm may entail no increased leukemia risk, although a nonthreshold linear model using a cumulative exposure measure might entail an appreciable excess risk. A related problem is that of peak exposures. No adequate provision is made in the risk assessments for the possibly high, perhaps very high, benzene levels that may be uniquely harmful. These intermittently high exposures *are* of special concern with respect to the Pliofilm cohort, a group upon which most risk assessments are largely based. There *is* evidence that these workers were occasionally exposed to benzene levels high enough to require hospitalization for aplastic anemia (56). Thus, it is plausible that the excess leukemia mortality observed among the Pliofilm cohort was due to transient high exposures.

We do not suggest that carcinogen risk assessments are never useful. However, in the present situation of a risk assessment for benzene and leukemia. there are special problems. There are few human studies relevant to an evaluation of the relation between henzene and leukemia. and thnse that exist are small. Thus, estimates of the leukemogenic effect of benzene are imprecise. An even more serious limitation in that the levels of henzene to which the workers in these cohorts were exposed are essentially unknown. These particular limitations must be considered in the context of the more general limitations of carcinogen risk assessment.. A reasonable argument couid be made that the data pertaining to benzene and leukemia are inadequate for the purposes of a meaningful risk assessment. Nonetheless. such risk assessments have been and probably will continue to be done.

Five benzene-leukemia risk assessments are reviewed below. An attempt is made to refine and to extend the findings of some of them. We also present our own risk assessment. However. we emphasize that by dning so we do not endorse the validity of a benzene-leukemia risk assessment re-

sult. We wish only to consider the various assumptions of these risk assessments and to evaluate the extent to which their results agree or differ.

The White et al. *risk assessment*

One risk assessment has been made by White et al. (57) of the Office of Carcinogen Identification and Classification, US Occupational Safety and Health Administration. These investigators used the so-called one-hit, non-threshold model. Although this is an exponential mathematical model, it is essentially linear in the range of benzene exposures considered. For clarity, the results are approximated below by us with a simple linear model. The original model and our approximation produce almost identical results.

This risk assessment is based upon the results of two retrospective follow-up studies: the study of rubber hydrochloride workers originally reported by Infante et al. (17) and later updated by Rinsky et al. (18) (hereafter termed the Pliofilm study) and the first report of the study of Dow chemical workers by Ott et al. (20). White et al. considered other epidemiologic studies of benzene and leukemia inadequate for the purpose of a risk assessment.

Using the assumptions of White et al. regarding the findings of the Pliotilm study, the excess risk of death from leukemia (P_d) resulting from a specified benzene exposure is approximated by the following equation:

$$P_d = P_w\left(\frac{\text{SMR} - 100}{100}\right)\left(\frac{d_e}{d}\right),$$

where P_w = risk of death from leukemia for a white man from age 20 through 84 years with no occupational exposure to benzene (P_w = 7/1,000 according to White et al.); SMR = the standardized mortality ratio—the mortality rate of leukemia among workers exposed to benzene divided by the rate among men in the general population and multiplied by 100 (a standardized mortality ratio of 2,100 was used by White et al.); d = the average cumulative benzene exposure sustained by members of the Pliofilm cohort expressed in ppm-years (415–1,500 ppm-years according to White et al.); and d_e = the cumulative benzene exposure (expressed in ppm-years) for which an estimate of the excess leukemia mortality is desired.

Thus, for example, if 1,000 men were exposed in the workplace for 30 years to 10 ppm of benzene (300 ppm-years per man), this modified version of the White et al. risk assessment predicts that between 28 and 101 of the exposed men will die from benzene-induced leukemia. This is as compared with a baseline of seven deaths among unexposed men. Throughout the remainder of this paper we will use an exposure level of 300 ppm-years to compare the results of the various risk assessments.

The standardized mortality ratio of 2,100 was obtained from the observation of five leukemia deaths compared with 0.23 expected among men who had been employed for five or more years. White et al. excluded workers with fewer than five years of employment because the elevated leukemia risk was observed largely among the long-term employees. This is a prejudicial justification for excluding the short-term employee~*A.more defensible basis for their exclusion is that over half of these men had been employed for less than one year, and therefore had little benzene exposure. Nonetheless. White et al. do apply their risk assessment method to exposure durations as short as one year. It is inappropriate to derive a modei excluding the experience of those with short exposure durations and, yet, to apply it to this very same situation.

The ambient benzene levels experienced by the Pliofilm workers were considered to be equal to the then current recommended standards. This assumption is controversial. Infante et al. (58) maintain that this assumption overestimates the actual benzene exposures (and, hence, that their risk assessment underestimates excess leukemia mortality). Others (59, 60) believe that the actual benzene exposures were consid

erably higher than the recommended standards. A point of agreement is that the actual henzene exposures sustained by members of the Pliofilm cohort are unknown. as Infante et al. (58) recognize. This uncertainty about the benzene leveis is the major limitation of a risk assessment based on the Pliofilm cohort. White et al. obtained a lower bound for the average benzene exposure (415 ppm-years) by multiplying the average recommended standards for 1937 through 1954 (83 ppm) by five years, the minimum employment duration. The upper bound for the average benzene exposure (1,500 ppm-year) was obtained by multiplying the average recommended standard for 1937 through 1975 (50 ppm) by the maximum length of employment, 30 years. These bounds cover a broad range of henzene exposures and neither is likely to accurately describe the benzene exposure ofa typical worker. It is unclear why White et al. did not estimate individual cumulative benzene exposures by multiplying each year of employment of each subject by the standard prevailing in that year and then summing these exposure years. This failure is a major shortcoming of their risk assessment. However. this problem was corrected in a more recent risk assessment based on these data (see below).

White et al. also did a risk assessment based upon the results of the first report of the Dow study. This risk assessment yielded results similar to those obtained from the Pliofilm data. As mentioned earlier, the men in the Dow cohort probably were exposed to considerably lower levels of benzene (cumulative exposure of about 345 ppm-years) than were the men in the Pliofilm cohort. Although there were two leukemia deaths observed. compared with one expected in the Dow study. White et al. did not use the resulting standardized mortality ratio of 200: rather. a relative incidence rate of 3.75 is used. This relative incidence rate is based upon the occurrence of three myelocytic leukemia cases among the cohort compared with 0.8 expected. It is emphasized that this risk assessment is based on only three leukemia cases and so is very imprecise.

The International Agency for Research on Cancer *risk assessment*

The International Agency for Research on Cancer (1) also has estimated that benzene levels similar to those experienced by men in the Pliofilm cohort are likely to cause an excess of 140-170 leukemia deaths per 1,000 men exposed for a working lifetime. The estimate of 140 excess leukemia deaths was obtained by considering that those men who had been employed for at least five years had experienced a 20-€old excess in leukemia mortality and that the risk that a man will die from leukemia in the absence of benzene exposure is about seven per 1,000. The same assumptions were made by White et al. (57). The International Agency for Research on Cancer considered this estimate a lower bound for the risk associated with a working lifetime (45 years) at similar levels. However, it can be inferred from table 11 of Rinsky et al. (18) that the average duration of employment among men who had worked for at. least five years was about 11 yean. Presumably. 45, as opposed to 11, years of exposure at such benzene levels would cause about a fourfold higher excess. The figure of 170 was obtained by considering that the overall excess in the Pliofilm cohort. was 460 per cent (i.e., the rate of leukemia among the cohort was 5.6 times that of the general population ratel and that the average duration of employment of *leukemia cases* was 8.5 years. The authors then assumed that chis overall excess would increase "smoothly" (presumably, linearly) from zero just after initial exposure to about 2,400 per cent after 45 years (i.e., 460 × 45/8.5). The resulting ape-specific excesses were then applied to the age-specific leukemia rates. and the figure of 170 excess cases nf leukemia per 1,000 men was ohtained.

In our opinion, their second risk assessment is wrong. The problem is evident in their statement that "the overall relative

risk of 5.6 in the Rinsky study derives from leukaemia cases who had an average of 8.5 years of exposure." A relative risk does not derive from leukemia cases: it is obtained from the comparative mortality experience of exposed and unexposed persons. The authors should have used the average employment duration of the entire cohort (3.2 years, our estimate baaed upon information in Rinsky et al. (18)) rather than that of the leukemia cases. Thus, the estimate of the excess aiter 45 years of exposure would be about 6,500 per cent (i.e., 460 × 45/3.2) rather than 2,400 per cent. If this correction is made. the result would be about three times as high.

The authors judged that the Pliotilm cohort members had been exposed to between 10 and 100 ppm of benzene. They state that 'assuming exposure was at the upper end of the range, then it is reasonable to postulate that a working lifetime exposure to 100 ppm of benzene would be likely to result in 140–170 case3 of leukemia per 1,000 exposed workers." However. it is unlikely that these men were exposed constantly to as much as 100 ppm benzene, and it is certainly true that they were not exposed for as long as 45 yean. Thus, this statement is not justified by the results of the Pliotilm study. According to the White et al. risk assessment (57), 45 years of exposure to 100 ppm benzene would produce between about 420 and 1,500 excess leukemia deaths per 1,000 men. Because of the problems discussed above, little confidence can be placed in the risk assessment done by the International Agency for Research on Cancer, and their methodology is not applied to an exposure situation of 300 ppm-years.

The Carcinogen *Assessment Croup risk assessment*

The Carcinogen Assessment Croup of the US Environmental Protection Agency (61) has also done a benzene-leukemia risk assessment. The Group attempted to estimate the number of excess leukemia deaths in the general population attributable to exposure to benzene ai an air pollutant. However, their methodology can be applied to an occupational setting.

The Group's risk assessment was based upon the results of the Pliotilm study (17, 18), the Dow study (20), and Aksoy's study (29). For the Pliotilm study, they used an overall standardized mortality ratio of 720, based upon nine observed leukemia cases compared with 1.25 expected. The nine observed cases include two that were "known to exist" but were not mentioned on the death certificate. Since the expected number of deaths is based only upon information on death certificates, the inclusion of these *two* extra cases yields a spuriously high standardized mortality ratio. This group assumed that the Pliofilm cohort members had been exposed to between about 24 and 40 ppm of benzene. However, they erroneously assumed that these men had been employed for 25 to 35 years, whereas their actual period of employment was considerably shorter. If their risk assessment is appiied to a workplace exposure of 300 ppm-years, an estimate of about 15 excess leukemia deaths per 1,000 men is obtained. However, because of the errors discussed above, no confidence can be placed in this estimate.

The Carcinogen Assessment Croup also based a risk assessment on the results of the Dow study. In doing so, they this time correctly estimated the duration of employment of the cohort. Applying their risk assessment to 300 pprn-years of benzene yields an excess of 47 myelocytic leukemia deaths per 1,000 men so exposed. This result is similar to that obtained by White et al. (57). The Group also attempted to use the results of the study by Aksoy (29) in a risk assessment. However, it is difficult to interpret the result because of the many limitations of Aksoy's study and we therefore do not consider this risk assessment meaningful.

The Rinsky et ai. risk assessment

This risk assessment is based upon the update of the Pliotilm cohort (19) and is an improvement over that done by White et

al. (57) insofar as a cumulative measure of benzene exposure was obtained for each cohort member.

Rinsky et al. (19) report standardized mortality ratios according to four levels of cumulative benzene exposure (less than 40 ppm-years, 40–200 ppm-years, 200–400 ppm-years. and greater than 400 ppm-years). The corresponding number of leukemia deaths and the standardized mortality ratios (which have been divided by 100 so that they can be compared with the odds ratios presented below) are 2 and 1.1; 2 and 3.2; 2 and 11.9; and 3 and 66, respectively. Thus, there is a strong positive relation between cumulative benzene exposure and leukemia mortality in this study.

These investigators. however, did not use the results of the cohort study to do the risk assessment, but, instead, did a nested case-control study (10 matched controls per case) and used conditional logistic regression to derive an exposure-response relation between cumulative benzene exposure and leukemia mortality. Based upon their risk assessment. they would predict that 300 ppm-years of benzene exposure would result in an odds ratio (a relative mortality rate) of about 44, which we calculate would yield about 250 excess lifetime leukemia deaths among 1,000 men exposed to 10 ppm for 30 years beginning at age 20 years.

In our opinion. their risk assessment should have derived from the results of the cohort study rather than from those of the case-control study. Presumably, an estimate of cumulative benzene exposure was available for all cohort members. Thus. the need to restrict the analysis *to* a subset of the subjects is unclear. More importantly, if their model is applied to the data obtained in the cohort study. the estimated odds ratios for the four categories of cumulative benzene exposure presented above (using midpoints of exposure categories and 480 ppm-years for the highest. open-ended category) are 1.3, 4.5, 43.8 and 423, respectively. Although the interpretation of an odds ratio is not strictly comparable to that of a standardized mortality ratio. they are both a measure of the relative rate of disease among the exposed compared with the unexposed and therefore should be similar. It is apparent that the Rinsky et al. model overestimates the observed standardized mortality ratios in the upper two exposure categories, especially in the highest. As an alternative risk assessment based on these data, we fitted a Poisson regression model using the four reported standardized mortality ratios and the midpoint of their four cumulative exposure categories (62). Our predicted standardized mortality ratios are 1.2, 2.8, 13.6, and 65, respectively. Our model provides a considerably better fit. to the observed standardized mortality ratios than does the model of Rinsky et al. Our predicted number of excess leukemia deaths for 1,000 men exposed to 10 ppm benzene for 30 years beginning at age 20 years based upon the Poisson regression model is 82.

The Crump and Allen risk assessment

Crump and Allen (63) also have done a benzene-leukemia risk assessment. Their risk assessment is based upon the results of the Pliofilm cohort, the Dow cohort, and Wong's study of chemical workers.

These investigators used two types of linear models for their risk assessment. The first, the absolute risk model, assumes that the number of excess leukemia deaths attributable to a specific amount of benzene exposure is constant at every age (an additive excess). The second, a relative risk model, assumes that the increase in leukemia mortality at any age for a given level of benzene exposure is directly proportional to the baseline age-specific leukemia mortality rate (a multiplicative excess). They also considered three measures of benzene dose: 1) lifetime cumulative exposure. 2) a weighted cumulative exposure which considers recent benzene exposures as most relevant (exposures sustained between 2.5 and seven years before follow-up) and provides progressively less weight to exposures sustained in the more distant past, and 3) a window exposure method which essen-

tially ignores all benzene exposures sustained more than 15 years in the past. Their relative risk model used in conjunction with lifetime cumulative exposure yielded the highest risks. Since the other risk assessments discussed above used a relative risk model with lifetime cumulative exposure as a measure of benzene dose, we report here only these results from Crump and Allen's report. However, it is emphasized that their risk assessment result based upon the absolute risk model used in conjunction with the window exposure method yielded results about one-eighth as high as those reported here. This observation demonstrates that risk assessment results will vary widely depending upon the choice of the model and the measurement of benzene dose.

Crump and Allen estimated that 40 years of exposure beginning at age 20 years to 10 pprn benzene would cause 88 excess leukemia deaths per 1,000 men so exposed. By simple linear interpolation, we estimate that their risk assessment method applied for 30 years to 10 ppm (beginning at age 20 years) would yieid about 68 excess leukemia deaths.

These investigators also did a risk assessment based solely on the Pliofilm cohort using n relative risk model with a lifetime cumulative dose. They did their own analysis of the Pliofilm cohort and were able to include additional years of follow-up. They report eight observed leukemia deaths versus about 3.0 expected, yielding a standardized mortality ratio of 268. Their risk assessment result based upon the Pliofilm cohort is 63 excess leukemia deaths per 1,000 men exposed to 400 ppm-years of benzene, or about 48 for 300 ppm-years. They also did a risk assessment based solely on Wong's study. From these data. they calculate that exposure to 10 ppm benzene beginning at age 20 years and continuing for 40 years would cause 121 excess leukemia deaths per 1,000 exposed men (or about 94 for 300 ppm-years). However, they point out that this excess is due largely to a deficit of leukemia mortality among the unexposed and therefore place little confidence in it.

Some of the discrepancy between the risk assessment results on the Pliofilm cohort reported by Rinsky et al. and Crump and Allen apparently results from disagreement between them as to the levels of benzene to which these men were exposed. Crump and Allen's estimates of the benzene exposures are generally higher (and therefore their risk assessment results are lower) than those of Rinsky et al., especially for exposures sustained between 1940 and 1948. However, Crump and Allen calculated that if their exposure estimates are decreased to levels more comparable with those of Rinsky, their risk assessment results would increase by about only 25 per cent.

Our risk assessment

We have used the method suggested by Enterline (64) for our risk assessment. An estimate of lifetime excess leukemia deaths attributable to benzene is obtained by dividing the difference between the observed and expected number of leukemia deaths by the total number of expected deaths (ail causes) in the cohort. The underlying assumption of this method is that the proportional excess leukemia mortality observed during the follow-up period will continue until all cohort members have died. If a cohort is followed until most of its members are deceased, the method will be accurate. On the other hand, if a cohort has been followed for only a small fraction of its life expectancy, this risk assessment method must extrapoiate the proportional excess to future deaths and hence the result is likeiy to be less valid and less precise.

In the latest report of the Pliofilm study (19), 6.34 excess leukemia deaths were observed among the cohort (observed = 9, expected = 2.66). The total number of expected deaths was 331.6. Therefore, the number of excess leukemia deaths per 1,000 exposed men is estimated as

$$1{,}000 \times (6.34/331.6) \text{ or } 19.$$

To apply the method to an exposure situa-

tion of 300 ppm-years, the benzene exposures experienced by the Pliofilm workers must be considered and. furthermore. it is assumed that excess leukemia mortality is directly proportional to cumulative benzene dose. It can he inferred from table 2 of their report that the average cumulative benzene exposure among members of the Pliofilm cohort was about 69 ppm-years. The excess number of leukemia deaths resulting from 300 ppm-years is then estimated as:

(6.34/331.6)

x (300 ppm-years/69 ppm-years)

= 83 per 1,000.

We also applied Enterline's method to the Pliofilm cohort for follow-up through 1975 (18) so that the result could be compared wit 11 that of White ct. al. (57). The observed number of leukemia deaths as of that time was seven versus an expectation of 1.25. The total number of expected deaths was 161.3. We assumed, as did White et al.. that these men had been exposed to between 50 and 83 ppm benzene (say, 66 ppm). The average duration of employment for the entire Pliofilm cohort was about 3.2 years. The result is an excess of about 51 leukemia deaths per 1,000 men exposed to 300 ppm-years benzene. This result agrees reasonably well with that obtained by White et al. for long-term workers only. It should be mentioned that the cumulative benzene exposure level assumed by White et al. in their risk assessment and the level considered by us in this risk assessment are appreciably higher than the level of 69 ppm-years presented in the latest report of the Pliofilm cohort (19).

Enterline's risk assessment method also can be appiied to the latest report of the Dnw cohort in which there were four leukemia deaths observed versus 2.1 expected (21). These men had an average cumulative benzene exposure of about 46 ppm-years and the total number of expected deaths was 268.6. Thus. it is estimated that 300 ppm-years of benzene exposure would result in

(1.9/268.6)

× (300 ppm-years/46 ppm-years)

= 46 per 1,000 excess leukemia deaths.

The retrospective follow-up study of refinery workers hy Tsai et. d. (26) included estimates of benzene exposures. These workers were typically exposed to less than 1 ppm of benzene (median. 0.5 ppm). The average duration of employment was about seven years, resulting in an average cumulative benzene exposure of about 3.5 ppm-years. If these refinery workers were subjected to the same benzene-induced leukemin mortality as were the Pliofilm workers, their overall standardized mortality ratio would be about 112. Therefore, the observation that there was no leukemia death observed compared with 0.42 expected does not contradict the results of the above risk assessments. Tsai's study is simply too small and the benzene exposures too low for it to contribute to the benzene-leukemia risk assessment.

The study by Wong (25) of chemical workers also contains estimates of benzene exposures. There were 3,536 men "continuously' exposed to benzene in this study. Their average cumulative benzene exposure was about 30 ppm-years. There were six observed leukemia deaths compared with 4.4 expected (standardized mortality ratio = 1351 and the total number of expected deaths was 613. Therefore, the number of excess leukemia deaths resulting from exposure to 300 ppm-years is estimated as:

(1.57/613)

x (300 ppm-years/30 ppm-years)

= 26 per 1,000.

The result does not agree well with that of Crump and Allen (63). The discrepancy is in part related to the observation that there is no consistent dose-response relation between leukemia mortality and the cumulative benzene dose in Wong's study and in part to the deficit of leukemia among the

unexposed in this study. For these reasons, we believe that Wong's study is not as informative to a risk assessment as are the Pliotilm and Dow studies.

Summary of risk assessments

Five risk assessments for benzene-induced leukemia have been reviewed. Table 2 presents a summary of the results of four of the risk assessments based on the Pliofilm and Dow cohorts, along with our own estimates. Some of these investigators did not directly calculate the estimates displayed in table 2, but we extended their methodology to this particular exposure situation.

Our own risk assessment results, those of Crump and Allen (63), and those of White et al. (57) agree fairly well.' The Carcinogen Assessment Group estimate is too low for the Pliofilm study because of an error regarding the duration of employment of this cohort. as discussed. Their risk assessment result based upon the Dow study, however, agrees well with the other results. Given the different methodologies and assumptions applied by the various risk assessment authors. the results, with the exception of that of Rinsky et al. (19), are reasonably consistent.

The result reached by Rinsky et al. is considerably higher than the others. It is difficult to understand why and, unfortunately, we cannot directly attempt to replicate their case-control results. However. we did do two risk assessments based on the results of the cohort study from which their case-control study derives. Our result using Poisson regression is 82 excess leukemia deaths per 1,000 men exposed to 300 ppm-years. while our result based upon Enterline's method is 83. Since the Rinsky et al. result does not agree with the others. including two independent risk assessments (ours and that of Crump and Allen) based upon the same cohort. we believe their result is too high.

An interpretation of these risk assessment results is that the Pliofilm study indicates an appreciable excess leukemia rink attributable to benzene and that, the other studies provide some support, or at least do not contradict this. However, it must be borne in mind that the other studies were either very small or suffered serious methodological problems. so that, despite the observation that they *seem to* support the results of a risk assessment based upon the Pliofilm study, little confidence can be placed in them.

TABLE 2

Numbers of lifetime excess leukemia deaths per 1,000 workers exposed to 10 ppm benzene for 30 years, as estimated by various risk assessments

Risk assessment (authors, ref. no.)	Study from which risk assessments derive: Pliofilm cohort (Follow-up through: 1965)		Dow cohort (Follow-up through: 1969)	
White et al. (57)	30-104* (Midpoint, 67)	(Not done)	32-93† (Midpoint, 62)	(Not done)
Carcinogen Assessment Group (61)	15	(Not done)	17‡	(Not done)
Rinsky et al. (19)	(Not done)	250	(Not done)	(Not done)
Crump and Allen (63)	(Not done)	18	68§	(Not done)
Present study	51	83	17	86

* Based on cohort members with five or more years of employment.

† Leukemia cell types other than lymphocytic or monocytic.

‡ Myelocytic leukemia only.

§ Based on the Pliofilm cohort, the Dow cohort, and Wong's study.

TABLE 3

Summary of epidemiologic studies from which the risk assessment results presented here are derived

Study (ref. no.)	Leukemia deaths		Total expected deaths	Cumulative benzene exposure (in ppm-years)
	Observed	Expected		
Pliofilm study (19)	9	2.7	332	69
Dow study (21)	4	2.1	269	46
Tsai et al. (26)	0	0.12	59	1
Wong et al. (25)	6	4.1	613	30
Total	19	9.6	1,273	42*

* A weighted average according to the expected number of deaths in each study.

The results of the epidemiologic studies which we considered in our benzene-leukemia risk assessment are displayed in table 3. The overall standardized mortality ratio from these four studies is 198. A weighted average (weighted according to the expected number of total deaths) of the cumulative benzene exposures sustained by the men in these cohorts is about 42 ppm-years. Thus, an overall estimate of the number of excess leukemia deaths associated with 300 ppm-years of occupational exposure to benzene is obtained as:

$$(19 - 9.6)/1.273$$

$$\times (300 \text{ ppm-years}/42 \text{ ppm-years})$$

$$= 53 \text{ per } 1{,}000.$$

Using the lower and upper 95 per cent confidence limits of the overall standardized mortality ratio, a lower and upper bound for the number of excess leukemia deaths for 300 ppm-years of benzene exposure are 10 and 113 per 1,000, respectively. The estimates for 30 years of exposure beginning at age 20 years to the proposed new standard of 1 ppm benzene are one-tenth of these results.

SUMMARY

Benzene is widely recognized as a leukemogen, and the Occupational Safety and Health Administration is currently attempting to limit exposure to it more strictly. The proposed new regulation is a limit of an eight-hour time-weighted average of 1 ppm in place of the current limit of 10 ppm. The fundamental rationale for the change is a perception that the current standard is associated with an inordinate excess of leukemia.

The epidemiologic literature on benzene and leukemia supports the inference that benzene causes acute myelocytic leukemia. However, the available data are too sparse, or suffer other limitations, to substantiate the idea that this causal association applies at low levels (i.e., 1–10 ppm) of benzene. Nonetheless, under the assumption that causation does apply at such low levels, a number of authors, including ourselves, have performed risk assessments using similar data but different methodologies. The assessments that we consider acceptable suggest that, among 1,000 men exposed to benzene at 10 ppm for a working lifetime of 30 years, there would occur about 50 excess deaths due to leukemia in addition to the baseline expectation of seven deaths. However, this estimate is speculative and whether or not enough confidence can be placed in it to justify a lower occupational benzene standard remains a decision for policy makers.

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