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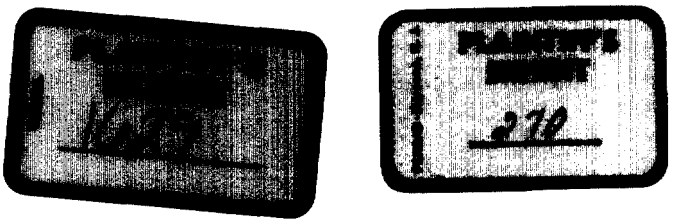

A Quantitative Estimate of Leukemia Mortality Associated with Occupational Exposure to Benzene'

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In 1980, the U S Supreme Court vacated a revised occupational standard for benzene. stating that the Occupational Safetv and Health Administration (OSHA) had failed to demonstrate that significant health nsks existed under the current standard. This decision has been interpreted by OSHA as requiring the consideration of quantitative nsk assessments. whenever possible. in the development of regulations for occupational carcinogens. In light of this deasion. the available epidemiologic evidence was used to generate a quantitative nsk assessment for benzene. Uncertainties regarding the levels and lengths of benzene exposure for the studied cohorts were incorporated into the analvsis Based on the one-hit model. the assessment indicates that a working lifetime exposure to benzene at the current permissible exposure level (10 ppm) poses a substantial excess nsk of death from leukemia This report, discusses the calculation of the nsk estimates. the basis for relying on certain assumptions, and the inherent limitations of using epidemiologic studies to quantify cancer risks

KEY WORDS: *nsk* assessment; benzene: leukemia; occupational cancer; regulation

1. INTRODUCTION

The risk of developing leukemia from occupational exposure to benzene at the current. 8-hr time-weighted average (TWA), permissible exposure level of 10 parts per million (ppm)[1] has been vigorously debated since the mid-1970s. when epidemiologic evidence conclusively demonstrated benzene's leukemogenic potential in humans. In 1978. the Occupational Safety and Health Administration (OSHA) promulgated a revised standard of 1 ppm TWA for occupational exposure to benzene.'" OSHA took the position that "once the carcinogenicity of a substance has been established qualitatively, any exposure must be considered to be attended by risk when considering any given population." OSHA concluded that it was not possible to demonstrate a threshold level for benzene-induced carcinogenicity, or to establish a safe level for benzene exposure, and therefore decided that the permissible exposure level to benzene should be reduced to the lowest feasible level.

The revised standard was challenged in the courts. and in July 1980. the U.S. Supreme Court upheld a lower court's decision to vacate the revised standard.'" A pluralitv of justices. in a split 5 to 4 decision. stated that OSHA had failed to make the threshold finding that exposure to benzene at the current standard is unsafe. in the sense that significant risks are present and can he eliminated or lessened bv a change in practices. OSHA has interpreted the U.S. Supreme Court decision as requiring the consideration of significance of risk in the devel-

'The opinions. findings. and views expressed in this paper are those of the authors and should not be attributed to the Occupational Safety and Health Administration or the National Toxicology Program.

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opment of regulations for occupational carcinogens. including nsk assessments when thev can be appropriately performed. However. OSHA has stated that "when data are not available to perform a formal quantitative risk assessment. qualitative evidence. expert testimony and other evidence may be appropriately utilized to based a determination of significance of risk."[4]

Following the **U.S.** Supreme Court decision. the available epidemiologic evidence was evaiuated for use in a quantitative risk assessment, since appropriate experimental data were not available. **Although** benzene also has been shown to induce nonmalignant blood disorders, chromosomal aberrations, and perhaps lymphomas.'" attention was focused on the quantificativn ot the **risk** of death from leukemia.

Risk assessments have been developed by the Environmental Protection Agency for environmental exposure to benzene[6] and by the Consumer Product Safety Commission for consumer exposure to benzene.[7] These **risk** assessments were prepared with regard to regulatory considerations at the time and have not been published. Our purpose in publishing this **risk** assessment **for** occupational exposure to benzene is to stimulate interest and discussion on the methodology and assumptions which can be used when the underlying scientific evidence **is** less than ideal **for** the development of a quantitative risk assessment, in a scientific rather than a regulatory context. We invite critical evaluations of the relative merits of our approach to the epidemiologic evidence as compared to other approaches that could be or have **been** taken.

2. EPIDEMIOLOGIC EVIDENCE

From epidemiologic studies, relative **risk** values and the corresponding exposure estimates may be used to develop a mathematical model for predicting carcinogenic risk. **Most** often in studies of occupationally exposed persons. the relative **risk** of a given cause of death can **be** approximated by the standardized mortality ratio **(SMR).** However. because the number **of** workers who die from a particular cause of death in a population usually is small. the confidence interval surrounding the SMR may he quite large. In addition, adequate exposure measurements for the time period of interest may not be available.

The error component of the mathematical model used to predict carcinogenic risk will he a function ot many factors, including the measurement errors associated with the SMR and exposure values. However, measurement error in the exposure values is an especially important problem, as exposure is the independent variable of anv model. **A** large amount of' error in the independent variable could lead to seriously biased results in the risk estimates.

Thus. in order for an epidemiologic studv to contribute useful information to the development of a quantitative risk assessment. it must meet two absolutely minimum requirements. First. the studv must provide an estimate of the excess risk in a population which was exposed to :he substance in question. based on the experience of an appropriate control population. Second, reliable industrial hygiene measurements must he available to permit a reasonable characterization of previous exposure conditions.

The scientific literature is filled with case reports. case series. and epidemiologic studies which qualitatively Link benzene exposure with leukemia in humans. This literature has been reviewed and summarized many times.[2,5,8] However, most of this scientific evidence has not been presented in a manner that can be used to quantify the magnitude **of** the risk of benzene-induced leukemia at a given exposure level. Only a handful of studies are available which attempt to measure the relative **risk** of leukemia under specified benzene exposure conditions.

Aksoy has published a series of reports which examined the incidence of leukemia among shoeworkers and other persons exposed to benzene in Istanbul.[9-11] Aksoy reported that 31 shoeworkers had been diagnosed as having leukemia in one Istanbul hospital between 1967 and 1975, out of a population of approximately 28.500 shoeworkers."'' Aksoy calculated a crude incidence rate of leukemia in this group of 13.5/100,000, which was more than double the leukemia incidence rate of 6/100,000 for the general population. This comparison does not take into consideration differences in ages between shoeworkers and the general population. the fact that persons diagnosed as having leukemia at other hospitals in Istanbul would not have been counted. or the absence of an accurate leukemia incidence rate for Turkey.

Moreover. very little is known about past benzene exposures among the *28,500* shoeworkers in

Istanbul. An early report by Aksoy[9] indicated that the duration of exposure to benzene ranged from 3 months to 17 years for a sample of 217 apparently healthy shoeworkers. and that the concentration of benzene in the working environment ranged from 15 to 30 ppm during nonworking hours to a peak of 210 ppm when benzene adhesives were being used. Another report[10] indicated that benzene levels as high as 640 ppm had been measured in the shoeworking environment. The representativeness of these few measurements to the entire shoeworking industry, on which the incidence rates are based, is impossible to judge. Therefore, nsk values and exposure measurements based on Aksoy's work were considered too speculative to be included in a quantitative risk assessment.

In Italy, Vigliani and his co-workers also sought to assess the risk of leukemia among persons exposed to benzene. An early report[12] stated that 12 persons with leukemia attributed to benzene exposure had been diagnosed in the provinces of Milan and Pavia between 1960 and 1963: 11 had been diagnosed in 1962 or 1963. Assuming that about 5,000 people were exposed to benzene in these 2 provinces, Vigliani and Saita estimated that the incidence of acute leukemias in 1962 and 1963 was about 20 times higher than expected. The investigators acknowledged that an analysis of the incidence of acute leukemia based on a control group would have been preferable.

Even though there is considerable uncertainty in the relative risk of leukemia among these benzene-exposed workers, there is even greater uncertainty in the levels of previous benzene exposures. The only exposure information available is that benzene levels in some shoe factories in Pavia ranged from 25 to 600 ppm. with most between 200 and 500 ppm.[13] It is unknown how representative these figures may be of the exposure conditions of the 5,000 workers in Milan and Pavia who were estimated to be exposed to benzene. Thus, as with Aksoy's work, the information available from Vigliani's reports concerning relative risks of leukemia and past benzene exposure levels were considered too imprecise to be used as other than a qualitative indication of benzene's leukemogenic potential.

Only two epidemiologic studies were identified as meeting the minimum requirements for inclusion in a quantitative risk assessment for benzene.

The first was a mortality study of rubber workers in Ohio, conducted by Infante and his colleagues at the National Institute for Occupational Safety and Health (NIOSH). Initial results of this study were published in 1977,[14,15] and a more detailed presentation of the NIOSH study was published recently by Rinsky *et al.*[16]

In this study, 748 white male workers were identified who had been exposed to benzene in the production of Pliofilm, a rubber film material, in two essentially identical production facilities. To be included in the study, workers had to have worked for at least 1 day between January 1, 1940, and December 31, 1949, in a department with benzene exposure. The number of workers who died between January 1, 1950, and June 30, 1975, was compared to the expected based on U.S. white male mortality rates, using a modified life-table approach.

With the follow-up more than 90% complete,[15] the investigators found that 7 workers had died from leukemia, compared to an expected figure of 1.25. This excess in the number of workers who died from leukemia was statistically significant (SMR = 560, $P < 0.001$).

Six of these seven workers had been diagnosed with acute myelogenous or monocytic leukemia. In order to take into account the distribution of specific cell types of leukemia, an expected number of deaths was generated using mortality rates for acute and monocytic leukemias from the National Cancer Institute.[17] The number of workers who died from acute or monocytic leukemia was found to be more than 8 times the expected figure of 0.70, yielding an SMR of 857.

In the most recent report of this study,[16] Rinsky *et al.* reported that most of the 748 workers had been exposed to benzene for a relatively short period of time; 58% of this group had been employed for less than 1 year. When the data were analyzed by length of employment, a significant excess in leukemia was observed among workers employed 5 or more years, but not among workers employed for less than 5 years. Among the latter group, 2 workers had died from leukemia compared to 1.02 expected, an excess which was not statistically significant. However, among workers employed for more than 5 years, 5 had died from leukemia compared to 0.23 expected, yielding an SMR of 2100.

The second epidemiologic study selected for this quantitative risk assessment was a mortality study by Ott *et al.* of Dow Chemical Company employees exposed to benzene.[17] A total of 541 white males were

identified who had been exposed to benzene in 3 chemical production areas of a Michigan plant, excluding workers who also had been exposed ti, arsenicals, vinyl chloride, or asbestos. **All** workers were emplnved at the plant between 1940 and 1970, and no minimum length of emplovment was required for inclusion in this study.

From 1940 to 1973, 91 workers had died. Three of these workers had died from leukemia; all were classified as myelocytic and two as acute myelmy·tic leukemia. This observed number was significantly ($P < 0.048$) greater than the expected number of cases of leukemia of other than lymphocytic or monocytic cell types, (essentially acute and chronic myelocytic leukemia), which was calculated to be 0.8 based on incidence rates from the Third National Cancer Survey. If we assume that the expected incidence of myelocytic leukemia was very similar to the expected mortality from myelocytic leukemia, then the relative risk of death from myelogenous leukemia among these workers can be approximated by an **SMR** of **375.**

3. EXPOSURE CONDITIONS

In recreating the exposure conditions of the workers included in both the NIOSH and Dow studies, an attempt was made to describe the range of average exposures. both by level and by duration.

With regard to the NIOSH study, the initial conclusion of the investigators was that "employees' benzene exposure was generally below the recommended **limit** in effect at the time of each survev," (see Table I). During the **1977 OSHA** rulemaking for benzene. some parties disputed this conclusion and suggested that benzene exposures may have been higher than the recommended limits. The recent report **of** the **NIOSH study**[16] presented a very detailed description of the processes and exposure levels at the studied facilities. The available information generally supports the **NIOSH** investigators' initial conclusion concerning exposure conditions. Although a few higher exposures to benzene were recorded (up to **680** ppm). often these measurements were taken in areas where workers were present infrequently for brief periods of time or not present at all. Moreover. records at the plant indicated that the company was aware of benzene's toxicity and that respirators were worn during some operations. For this risk assessment, we assumed that exposures were at the recommended standard for that time. We recognized that some workers may have been exposed occasionally to higher levels. However, we believed that the average exposure experience for the entire study population is adequately represented by the levels in Table I. and that the use of these levels actually may have overestimated average benzene exposures for many workers.

Table I. Estimates of 8-hr. TWA Benzene Concentrations for NIOSH Cohort Based on Recommended Environmental Levels[a]

Year	Benzene level
1937–1940	150[b]
1941–1946	100[c]
1947	50
1948–1956	35
1957–1962	25
1963–1968	25[d]
1969–1975	10

[a]References provided in infante *et al.*[14] and Rinsky *et al.*[16]
[b]No recommended level was available before 1941.
[c]Recommended level was expressed as a maximum allowable concentration.
[d]Recommended level was expressed as a ceiling concentration.

The length of employment varied widely among the workers included in the NIOSH study. The minimum length of employment for inclusion in the study was 1 day, and the maximum length of time that anyone could have worked in one of the plants was **37** years. Well over half (58%) of the study population were employed for less than 1 year. In addition. the length of employment for the 7 workers who died from leukemia ranged from 1 month to 20 years. with an average of 8.5 years.

It was decided to base the risk assessment on the experience of workers who had been employed for **5** or more years, because most of the elevated leukemia risk was observed in this group. In addition, we did not know what proportion of the person–years for the total cohort had been contributed bv persons with only verv brief employment. The range of duration of employment was determined to be 5–30 years; the upper limit was based on the fact that workers who had been employed for more than 30 years contributed less than 0.01 to the number of espected leukemia deaths.

The range of average benzene exposures was estimated as follows. The earliest date any employee was exposed to benzene **was** 1937, since this was the date the oldest facility began Pliofilm production. Workers could have begun emplovment **as** late as

1949 and still have been included in the study. Follow-up ended in 1975, so exposure *to* benzene after this date could not have contributed to the observed risks. Thus. workers employed for 5 years could have been employed for any 5-year period between 1937 and 1954. and workers employed for 30 years could have been employed for any 30-year period between 1937 and 1975. Because benzene-exposure measurements were not available for the earliest years of Plioiilni production. we arbitrarily assumed that benzene exposures before 1941 were 50% higher. or 150 ppm TWA. The average henzene exposure over the period of 1937 to 1954. using 15U ppm for 1937–1940 and the values from Table I. was 83 ppm. Over the period 1937–1975, the average benzene exposure was 50 ppm. Thus, the exposure to benzene which was associated with a **21-fold** excess risk of leukemia was estimated to range from 83 ppm x 5 yr, **or 415** ppm-yr, to **50** ppm × 30 yr, or 1500 ppm-yr.

Within the three production areas included in the Dow study,[17] the results of exposure monitoring from 1944 to 1974 indicated that benzene exposures were considerably lower than at the facilities studied by NIOSH. Although peak levels of benzene as high as 937 ppm were measured. estimated time-weighted average exposures ranged from 0.1 to 35.5 ppm for different job categories. The length of employment among workers in this study varied greatly; 23% were employed for less than 1 year and 17% were employed for **20** or more years. Ott and his colleagues examined the job histories of these workers and calculated cumulative ppm-month career doses for each worker. Their method was to multiply the mean TWA value for each job category by the number of months spent in that category. Information was not provided concerning the distribution of workers by ppm-months. However. the observed and expected number of deaths were analyzed bv cumulative dose (see Table II). From this analysis, we determined that workers who had exposures of less than 500 ppm-mo, **or 42** ppm-yr, contributed 57% of the number of expected deaths from all causes. Workers who had exposures of more than 1.000 ppm-mo. or 83 ppm-yr, contributed 29% of the number of expected deaths. From this information. we estimated that approximately one-half of the study group were exposed for less than **42** ppm-yr. and nearly one-third were exposed for more than **83** ppm-yr. The investigators did not state what the largest number of ppm-months was for any worker in the study group. We estimated an upper limit of 1,500 ppm-mo. or 125 ppm-yr. for our range of exposure. Therefore. the range of benzene exposures estimated for the Dow study was **42**– 125 ppm-vr. It should be noted that the estimated cumulative doses for the three workers who died from leukemia **were** 545 ppm-mo (45 ppm-yr), 19 ppm-mo (1.6 ppm-yr). and 305 ppm-mo (25 ppm-yr). Given that one-half of the study population and 2 of the 3 leukemia cases ma); have had cumulative benzene exposures of less than **42** ppm-yr, we believe that our range of **42–125** ppm-yr is unlikely to be an underestimate of the benzene exposure that was associated with a 3.75-fold excess risk of leukemia in this study.

Table II. Number of Observed and Expected Deaths from all Causes for Dow Cohort bv Estimated Career Benzene Dosages[a]

Career dose category	Observed	Expected
0–499 ppm-mo	41	65.1
500–999 ppm-mo	18	16.2
1000 + ppm-mo	32	32.8
Total	91	114.1

[a] From Ott *et al.*[17]

4. SELECTION OF A MODEL

Several mathematical models have been developed to describe the relationship between the level of exposure to a carcinogen and the probability of developing cancer associated with that level.[18] We selected the one-hit model for a quantitative **risk** assessment for benzene, primarilv because it is a simple model. The current biological evidence concerning the chemical induction of leukemia was considered insufficient to defend the use of a more complex model. In addition. the information available from epidemiologic studies regarding the relative risks **of** leukemia at different levels **of** benzene exposure was inadequate to statistically test the appropriateness of more complex models.

The one-hit model **is** based on an assumption that a single dose of a carcinogen can affect some biological phenomenon in the organism which subsequently will lead to the development of cancer. This model is a nonthreshold model; i.e., it assumes that every level of dose is accompanied by some amount of excess cancer risk.

Expressed mathematically, the one-hit model states that the excess cancer risk (P_d) **is** related to the

dose (d) bv the equation

$$P_d = 1 - \exp(-B \times d). \quad (1)$$

If a "background" cancer risk (P_0) exists in the absence of exposure to d. then P_d is not equal to the total probability of developing leukemia (P_t), but rather is related to P_t and P_0 by the equation

$$P_d = (P_t - P_0)/(1 - P_0) \quad (2)$$

as explained bv Mantel and Bryan."'

Therefore, the excess risk (P_d) was redefined as

$$P_d = [1 - \exp(-B \times d)](1 - P_0) \quad (3)$$

and the total leukemia risk as

$$P_t = P_0 + [1 - \exp(-B \times d)](1 - P_0). \quad (4)$$

5. CONVERTING INFORMATION FROM EPIDEMIOLOGIC STUDIES TO THE MODEL

The relative risk of leukemia mortality from both the NIOSH[16] and Dow [17] studies was approximated by the SMR. The SMR represents the ratio of observed deaths due to leukemia in the benzene-exposed group. divided by the number of expected leukerma deaths based on the death rates of a comparable age and sex-specific group

$$\text{SMR} = \frac{\text{number of deaths observed}}{\text{number of deaths expected}} \times 100.$$

For the risk assessment, the SMR is assumed to represent

$$\text{SMR} = (P_t/P_0)100$$

and thus,

$$P_t = \frac{\text{SMR}}{100}(P_0). \quad (5)$$

To determine the excess probability (P_d) of developing leukemia from a given level of benzene (d) over a defined period of time, using Eq. (3), two values needed to be calculated.

The first was the working lifetime probability (P_0) of death due tu leukerma (all cell types combined) and myelogeneous leukemia, independent of exposure to benzene. The P_0 values were calculated, using standard life-table methods. as the sum over 5-year age intervals (from 20 to 84) of the probability of death due to leukemia during the specific interval times the probability of survival to the beginning of that interval. This life-table method assumes the independence of these events.[20] Death rates for all causes and for all types of leukemia were taken from the 1975 mortality rates for U.S. white males."'' Death rates for cell-specific leukemia were average annual rates for U.S. white males from 1973 to 1977, and were abstracted from mortality rates collected through the National Cancer Institute SEER Program.[22] The calculated P_0 values were 0.00707 for ail types of leukemia and 0.00495 for myelogenous leukemia. (Appendicies providing detailed information concerning the calculation of these P_0 values are available upon request from the authors.)

The second value was B, which is associated with the rate at wtuch the excess probability of leukemia increased with each increment in dose. It can be shown from Eqs. (4) and (5) that the solution for B is:

$$B = -\ln[(1 - (\text{SMR}/100)P_0)/(1 - P_0)]/d. \quad (6)$$

The SMR values and dose estimates which were used in these calculations are presented in Table III.

As explained earlier. upper and lower estimates of the dose associated with the SMR were generated for both the NIOSH[16] and Dow[17] studies. Treating each study separately, the upper and lower dose estimates were used to calculate two E values from Eq. (6). These B values also are presented in Table

Table III. Values for SMR. Dose. and B[a] Used to Calculate Excess Leukemia Risk

Studv	SMR	Benzene dose estimate	B value corresponding to dose estimate
Rinsky *et al.*[16]	2100	415 ppm-yr (lower)	0.000370
		1500 ppm-yr (upper)	0.000102
Ott *et al.*[17]	375	42 ppm-vr (lower)	0.000328
		125 ppm-vr (upper)	0.000110

[a] B is associated with the rate at which the excess probabilitv of leukemia increases with each increment in dose. as calculated by Eq. (6).

III. Separate risk estimates were calculated using each B value and Eq. (3). The two resultant risk estimates represent a range of nsk which reflects the uncertainty in the exposure conditions for each study.

6. ESTIMATED EXCESS LEUKEMIA RISK UNDER DIFFERENT EXPOSURE CONDITIONS

Risk estimates were made for a working lifetime exposure to benzene, assumed to be 45 years. at both the current 10 ppm standard (450 ppm-yr) and at the vacated 1 pprn standard (45 ppm-yr). Recognizing that few employees would be exposed to benzene for as long as 45 years, estimates also were made for lengths of employment equal to 1, 5, 15, and 30 years at 10 ppm and at 1 ppm benzene.

Table IV presents the estimates of additional lifetime leukemia risk (per 1,000 workers) due to occupational exposure to 10 ppm or 1 ppm benzene for different lengths of time, based on the NIOSH study. Table V presents the corresponding risk estimates for myelogeneous leukemia based on the Dow study. We believe that the NIOSH study provides stronger evidence of an association between benzene and leukemia than does the Dow study, as well as better information on benzene exposure levels. Therefore, we have greater confidence in the risk estimates based on the NIOSH study and our discussion will focus on these risk estimates. The risk estimates based on the Dow study are consistent with those from the NIOSH study. In fact, the risk estimates in Tables IV and V are much more similar than one may have expected, given the uncertainty associated with quantitative risk assessments.

Table IV. Estimates of Additional Lifetime Leukemia Risk per 1000 Workers" from Occupational Exposure to Benzene[b]

	Exposure level	
Years exposed	10 ppm	1 ppm
45	44–152	5–16
30	30–104	3–11
15	15–54	1.5–5
5	5–18	0.5–2
1	1–4	0.1–0.4

[a] Estimates were rounded to the nearest whole number (per 1,000) for risks greater than 1 per 1,000 workers.
[b] Based on Data from Rinsky *et al.*[16]

Table V. Estimates of Additional Lifetime Leukemia[a] Risk per 1000 Workers' from Occupational Exposure to Benzene

	Exposure level	
Years exposed	10 ppm	1 ppm
45	48–136	5–15
30	32–93	3–10
15	16–48	2–15
5	5–16	0 5–2
1	1–3	0 1–0 3

[a] Estimates are based on leukemia cell types other than lymphocytic or monocytic.
'Estimates were rounded to nearest whole number (per 1,000) for nsks greater than 1 per 1,000 workers
'Based on data from Ott *et al.*[17]

As can be seen in Table IV, 45 years of occupational exposure to benzene at 10 ppm was estimated to result in an excess lifetime leukemia risk of between 44 and 152 per 1,000 exposed workers. At 1 ppm benzene for 45 years. the excess Lifetime leukemia risk was estimated to be between 5 and 16 per 1,000 exposed workers. A certain magnitude reduction in either length or level of exposure produced a reduction in risk of equal magnitude. The linear relationship between dose and excess risk resulted from the fact that the one-hit model is essentially linear at low doses.[23]

7. DISCUSSION

Because any risk assessment must apply study results obtained under one set of conditions to another and sometimes very different set of conditions. the estimated risk contains uncertainty. Although the best available scientific data were used in this risk assessment for benzene, certain assumptions had to be made for several unknown variables. The use of these assumptions might have resulted in a large amount of error in the risk estimate. So that the risk estimates are viewed in the proper perspective, the major assumptions on which these estimates were based are discussed below.

First. it was assumed that the 748 white males in the NIOSH cohort and the 541 white males in the Dow cohort do not differ in their susceptibility to benzene-induced leukemogenesis from the more than 629,000 men and women, white and nonwhite, who

are estimated to be occupationally exposed to benzene.[2] Even though this risk assessment was based on information derived from human populations, and therefore no species-to-species extrapolation was necessary. extrapolation from one population to another still may be problematic. Populations may vary from one another in their sensitivity and susceptibility to carcinogenic agents due to variations in genetic factors, age distributions, and exposures to potentially interacting environmental and social factors. However, no means are currently available to determine such variatian in susceptibility.

With regard to age distributions, the SMR of a study population has been shown to be a useful approximation for the relative risk when the excess in mortality is consistent across all age groups.[24] It is not known whether the relative risk of benzene-induced leukemia is different at different ages. However, if the relative risk of benzene-induced leukemia is age-dependent, then the SMRs obtained from the NIOSH or Dow cohorts could overestimate or underestimate the relative risk of benzene-induced leukemia among another group with a different age composition.

Second, it was assumed that the risk ratios obtained from these studies represented working lifetime risks of benzene-induced leukemia. However, the risk ratios obtained from the NIOSH and Dow cohorts were based on exposure and follow-up periods which occurred over a limited fraction of the cohort member's Lifetimes. For instance. in the Rinsky *et al.* report,[16] only 181 deaths were reported, meaning that 76% of the cohort was still alive or presumed to be alive at the end of the follow-up period. Similarly, only 91 deaths were reported in the Ott *et al.* study,[17] leaving 83% of the cohort still alive at the time of follow-up. The assumption of a constant SMR could either underestimate or overestimate the true risk, if the relative risk of leukemia among the cohort members actually increased or decreased during the period after the date of follow-up.

In addition, it also was assumed that the relative risk of leukemia would remain constant after exposure to benzene had ceased. Day and Brown[25] have demonstrated that, under the multistage theory, the effect of cessation of exposure will depend largely on whether the carcinogen affects an early or late stage of the cancer's development. If benzene were a late-stage carcinogen, then one would expect the excess leukemia risk to eventually decline in these cohorts as the length of time since termination of exposure increased.

However. Peto[26] has argued that the multistage theory probably is not applicable to nonepitheliai cell cancers such as leukemia. Moreover, 3 of the 12 case reports described by Rinsky *et al.*[16] were of men who had died from leukemia 9 or more years after they left the Pliofilm operations. To date. there is no evidence to suggest that benzene may be a late-stage carcinogen or .that the excess leukemia risk will decline after exposure has ceased.

Third, many of the industrial processes where benzene exposure occurs, such as petroleum refining, rubber manufacturing, and chemical processing, contain other known or suspected carcinogens. The presence of other, carcinogens in the workplace might enhance (synergistically) the carcinogenic effect of benzene. However, it was assumed that no such synergism had occurred in the workplaces studied or would occur in other occupational settings.

Fourth, one of the most important assumptions made in this risk assessment was that the dose-response relationship between benzene exposure and leukemia development follows the one-hit model. Although this model is generally considered to be conservative at low exposure levels, it may actually underestimate the risk at lower levels if the risk of leukemia no longer increased with increasing dose after a certain level of exposure, i.e., the dose-response curve plateaus, and if the studied workers had been exposed to benzene at a level above the point at which the curve flattens out.

Fifth, it was assumed that for benzene exposure levels which are generally not associated with acute toxicity (TWA less than 100 ppm), a cumulative dose-effect relationship exists. That is, the level of risk associated with a certain dose was assumed to be constant. regardless of whether exposure occurred over a short period of time or at lower levels over a longer period of time. At present, there is no available method to test the validity of this frequently made assumption.

The cumulative dose model also assumes that the total amount of benzene to which a worker was exposed contributed to his risk of death from benzene-induced leukemia. Theoretically, a worker could be exposed to benzene after the point at which the irreversible but subclinical development of benzene-induced leukemia had begun. Thus, any exposure to

benzene after leukerma had been induced would not add to the risk of mortality from leukema and could be viewed as a "wasted" dose in terms of generating a dose-response curve. Therefore, a dose-response relationship which is based on total dose could overestimate the amount of dose that is responsible for a given level of excess risk.

Sixth. although these risk estimates take into consideration some of the uncertainty in the benzene levels from the NIOSH and Dow studies. these estimates do not reflect the uncertainty associated with the risk ratios from these studies. For instance. the upper 95% confidence interval for the SMR of 2100 from the Rinsky *et al.* report[16] is 5073. The use of this value would have resulted in much higher risk estimates. Thus, even though these risk estimates are expressed as ranges, the upper range of the risk estimates actually would have been greater if the uncertainty of the SMRs had been included in the analysis.

8. CONCLUSION

The risk estimates generated for total leukemia from the NIOSH study[16] and for myelogeneous leukemia from the Dow study[17] were almost identical. We estimated that a working lifetime exposure of 45 years to benzene at 10 ppm (the current OSHA standard) would result in a leukemia risk ranging from approximately 44 to 152 excess leukemia deaths per 1,000 exposed workers. A working Lifetime exposure to benzene at 1 ppm would result in a leukemia risk ranging from 5 to 16 excess leukemia deaths per 1,000 exposed workers. At different lengths of exposure, the risk associated with 10 ppm was consistently 10 times greater than the risk at 1 ppm. This order of magnitude difference in risk was expected because the risk estimates were based on the one-hit model, and the one-hit model has been shown to be essentially linear at low doses.

This report demonstrates how some types of epidemiologic evidence can be used to estimate the level of Carcinogenic risk associated with a certain level of exposure. However. it is far easier to quantify a level of carcinogenic risk than it is to quantify the level of confidence that should be placed in the risk estimate. When viewed in the context of scientific evidence which qualitatively indicates that benzene is a relatively potent human carcinogen, these risk estimates suggest that workers exposed to benzene at the current OSHA permissible exposure level oi 10 ppm are at a substantially elevated nsk of death from leukemia.

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