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Projections of Leukemia Risk Associated With Occupational Exposure to Benzene

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In 1982, White et al published an assessment of quantitative leukemia risk associated with lifetime occupational exposure to benzene. At about the same time, IARC (1982) published estimates of quantitative cancer risk associated with industrial chemicals. Benzene was one of the two chemicals selected by IARC for its risk estimation. This paper presents a summary of these assessments along with new study results demonstrating adverse effects on bone marrow and peripheral blood cells as a result of low-level benzene exposure.

Mathematical extrapolations based on epidemiologic studies are consistent with a finding of significant risk of dying from leukemia under the current occupational permissible exposure limit of 10 ppm. Although a significant reduction of risk could be expected to be achieved by reducing exposure to 1 ppm, a significant risk may still remain. The uncertainty of the dose-response projections rests on the underlying estimates of relative risk of death from leukemia, the estimates of benzene exposure (dose), and the appropriateness of the mathematical model.

Recent findings in experimental animals demonstrate chromosomal damage to bone marrow cells, significant depression of the bone marrow, and disturbances of immune system function as a result of less than 1 week of exposure to the current permissible benzene exposure limit of 10 ppm. This was the lowest dose tested. These experimental findings provide further evidence of a potentially significant risk of bone marrow proliferative cancer (leukemia) as a result of low-dose benzene exposure.

Key words: benzene, leukemia, cancer, occupation, risk assessment, bone marrow

INTRODUCTION

Quantitative estimation of human cancer risk is uncertain because judgements must be made about conditions which lie outside the range of scientific observation. While risk estimates based on single compound exposures to experimental animals can readily determine dose and response. they pose some difficulty in extrapolation to humans. Interspecies variability in metabolism and exposure in the environment to a host of other chemicals may interact to potentiate the carcinogenic response in

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humans. For example, the incidence of angiosarcoma of the liver in experimental animals administered vinyl chloride (VC) alone is much lower than the incidence when ethyl alcohol is added to the drinking water [Radike et al, 1981]. Thus, extrapolation of cancer risk to societies that consume ethanol, based solely on VC administration to experimental animals, might result in an underestimate of the cancer risk. Likewise, in humans where interaction has been studied, as in the case of asbestos and cigarette smoking and alcohol and cigarette smoking, a synergistic interaction resulting in a higher risk of lung cancer [Hammond et al, 1979] and esophageal cancer [Tuyns, 1982], respectively, has been demonstrated in contrast to the summation of risk from exposure to these agents independently.

In the study of humans, other difficulties, as well, complicate the process of determining the dose-response relationship. Among these are the following: the long induction period, typically of many years duration, between the beginning of exposure and the appearance of cancer; the paucity of data for determining relative risk and dose for most chemical compounds; the mixed nature of most chemical exposures and the previously mentioned modification of carcinogenic response by a variety of other chemical exposures in the environment. Despite these and other difficulties, quantitative risk assessments are being used to help policy makers determine whether a "significant" health risk exists under certain conditions of exposure [White et al, 1980].

Although numerous cases of aplastic anemia had been reported since 1897 [Le Noir and Claude, 1897; Santesson, 1897] and well over a hundred cases of leukemia had been reported in association with benzene exposure since 1928 [Delore and Borgomano, 1928; Vigliani. 1976], it was not until the 1970s that detailed epidemiologic studies of clearly defined cohorts of workers exposed to benzene were carried out. Since that time. studies of relatively small cohorts of workers exposed to benzene have demonstrated a significant excess of leukemia [Infante et al, 1977; Rinsky et al, 1981; Ott et al, 1978; DeCoufle et al, 1983]. The relative risks of leukemia for the entire cohorts in these studies have ranged from 3.75 to 8.57. Significant excesses of leukemia also have been reported among benzene-exposed petroleum refinery workers employed by Conoco (Baltimore), Gulf (Port Arthur. TX), Mobile (Beaumont, TX), Texaco (Port Arthur. TX), and Shell (Wood River, IL and Deer Park, TX) when data were analyzed for the entire cohorts [Thomas et al. 1982; Joyner. 1983] or when data were analyzed for those employees known to have had relatively higher benzene exposure [DeCoufle et al. 1983; Divine and Kaplan. 1983].

COHORT SELECTION

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

As a result of a review of the literature [White et al. 1982], two epidemiologic studies were identified as meeting the minimum requirements for inclusion in the quantitative risk assessment for benzene. The first was the NIOSH cohon study

[Infante et al, 1977, Rinsky, et al, 1981]; the second was the DOW study [Ott et al, 1978]. The study of petrochemical workers exposed to benzene by DeCoufle et al [1983] was not used because exposure information was not presented in the study. Additional studies of petroleum refinery workers indicating an excess of leukemia as cited above were not used because documentation of exposure was lacking.

In the NIOSH study [Infante et al, 1977], 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 from specific causes between January 1, 1950 and June 30, 1975, was compared to the expected number based on U.S. white male mortality rates, using a modified life-table approach. More recently, Rinsky et al [1981] reported that most of the 748 workers had been exposed to benzene for a relatively short period of time; 58% of this cohort had been employed for less than 1 year. When the data were analyzed by length of employment, a significant excess of leukemia was observed among workers employed 5 or more years but not among workers employed for less than 5 years. Among the latter group, two workers had died from leukemia compared to 1.02 expected, an excess which was not statistically significant. Among workers employed for more than 5 years, however, five had died from leukemia compared to 0.23 expected, yielding a relative risk of 21.

The second epidemiologic study selected for this quantitative risk assessment was a mortality study of Dow Chemical Company employees exposed to benzene conducted by Ott et al [1978]. A total of 541 white males were identified who had been exposed to benzene in three chemical production areas of a Michigan plant. There were three cases of myelogenous leukemia observed versus 0.8 expected, resulting in a relative risk of 3.75.

EXPOSURE CONDITIONS

Estimates of exposure for the NIOSH cohort are shown in Table 1. Based on the years for which actual exposure information was available, these values in general tend to overestimate benzene exposure [Rinsky et al, 1981]. Benzene exposures to the cohort were generally within the limits recommended at the time, that is, the 8-hour time-weighted average (TWA) exposures ranged between 10 ppm and 100 ppm. A few individuals [Van Raalte et al, 1984] have questioned this assessment. In order to clarify this important issue, we shall summarize the available benzene exposure data for the NIOSH cohort as published in 1981 by Rinsky et al.

For one Pliofilm manufacturing facility, information on benzene concentrations between 1946 and 1976 was available from a series of reports by the Industrial Commission of Ohio, the Ohio Department of Health, the company, the University of North Carolina, and a NIOSH survey. According to NIOSH investigators, most of the data in these reports appear to have been derived from area samples measured with detector tubes over a sampling period ranging from 2 to 3 minutes. The company surveys of 1973–1975 and the NIOSH walk-through survey conducted in 1976 measured concentrations in personal breathing zone air. While the short-term area samples measured over the years indicated that some benzene levels were above the concen-

TABLE I. Estimates of 8-Hour Time-Weighted Average (TWA) Benzene Concentrations for NIOSH Cohort Based on Best Available Information[a]

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

[a]See references in Infante et al [1977] and Rinsky et al [1981].
[a]No recommended level was available before 1941.
[b]Recommended level was expressed as a maximum allowable concentration.
[c]Recommended level was expressed as a ceiling concentration.

trations recommended at the time, most wen below. These latter data points quite often seem to be ignored by those who take issue with the exposure assessment.

In addition, area samples arc often measured in an effort to determine point source emissions, and they may exaggerate actual worker exposure. Furthermore, exposures determined from short-term area samples correspond to relatively lower personal 8-hour average concentrations, because workers are mobile and take breaks away from manufacturing areas.

The Rinsky et al [1981] report cites documents indicating that workers were required to wear respirators when exposed "even momentarily" to levels considered above those recommended at the time. These levels ranged from a maximum allowable concentration of 100 ppm in 1941 to an 8-hour TWA of 10 ppm from 1969 to the present. One of the several documents does indicate that respirators were not used. Overall, the evidence indicates that respirators generally wen used when exposures wen over the recommended limit, but the actual level of protection provided by respirator use is unknown.

The actual exposure levels for individual workers comprising the NIOSH study will never be known precisely. Much effort. however, has been made to characterize their exposure. resulting in reasonable estimates that are better in quality and in detail than those for most historical prospective occupational mortality studies. Only studies of asbestos-, arsenic-, and radon-daughter-exposed workers have provided better exposure data [OSHA, 1983, 1984; Lundin et al, 1971].

Limited information on exposure levels was available from the second location. One report from the Ohio Department of Health dated 1948 indicated there were "a few conditions wherein an employee might be subjected to an extremely high concentration of benzol." but that employees were "well aware of the toxicity of benzol and have been instructed to. and do. wear respirators when they are required to enter" these areas. Environmental data from this location believed to have been derived around 1957, when the recommended 8-hour TWA was 25 ppm, indicate atmospheric levels ranging between zero and 100 ppm based on short-term area samples. Because respirators were used at this facility and management was aware of the toxicity of

benzene, the assumption that personal exposure to benzene at this facility was generally within the recommended limits at the time of exposure seems reasonable. Upon review of the Rinsky et al [1981] report, it seems that our assumption, in fact, may overestimate average exposure for the cohort.

For the NIOSH study, the risk assessment was based on those individuals with 5 or more years of exposure, since the data were statistically significant for this data point only. The length of employment for these individuals ranged from 5 to 30 years. For those exposed for 5 or more years, their average exposure was estimated to be 83 ppm, or 415 ppm-years (5 years x 83 ppm). For those exposed for 30 years, their average exposure was estimated to be 50 ppm, or 1,500 ppm-years (30 years x 50 ppm). (See White et al [1982] for further details on calculation for estimates of exposure.)

Estimates of benzene doses for the study by On et al (1978) were determined by the authors for each individual. Workers were then grouped by cumulative career-dose categories of 0–499 ppm-months, 500-999 ppm-months and 1,000 or more ppm-months.

None of the three leukemia cases worked in the area of the plant where the highest exposures occurred. On the contrary, two of the individuals who died from leukemia worked in areas characterized as having low benzene exposures, 2–9 ppm TWA, while the third worked in an area characterized as having very low exposures, that is, TWA exposures were less than 2 ppm. Further assessment of atmospheric benzene levels in the three production areas from which workers were selected for study by Ott et al [1978] indicated that exposures to the cohort had always been fairly low, reflecting the use of closed continuous systems. In production area 1, estimated TWA benzene exposures based mostly on breathing zone samples ranged between 0.1 and 6.2 ppm for the years 1944 to 1973. In production area 2, the TWAs ranged between 0.3 and 14.7 ppm between 1953 and 1972, while in production area 3, the averages ranged between 4 and 35.5 ppm for the years 1952–1974. It is clear from the On et al [1978] report that a single benzene exposure level of 937 ppm was measured in production area 3. (See Infante et al [1984] for more discussion on exposures of the NIOSH and DOW cohorts.)

On the basis of data presented in the Ott et al study [1978], the average exposure for the entire cohort is estimated to be about 5 ppm. Thus, in the absence of any mathematical modeling for this study, one could be left with the impression that fairly low average exposure to benzene can result in a significantly elevated risk of developing leukemia.

From these data we estimated that the range of exposure was between 500 and 1500 ppm-months or 42 and 125 ppm-years. It should be noted that the estimated cumulative doses for the three workers who died from leukemia were 545 ppm-months (45 ppm-years). 29 ppm-months (1.6 ppm-years), and 305 ppm-months (25 ppm-years).

Given that one-half of the study population and two of the three leukemia cases may have had cumulative benzene exposures of less than 42 ppm-years. we believe that our range of 42–125 ppm-years is unlikely to be an underestimate of the benzene exposure that was associated with a 3.75-fold relative risk of leukemia in this study.

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 exposure level. We selected the one-hit, or linear, model because the biological mechanism of benzene-induced leukemia is not understood well enough to suggest that a more complicated model would be more appropriate and because the information available from epidemiologic studies regarding the relative risks of leukemia at different levels of benzene exposure was inadequate to test statistically the appropriateness of more complex models. Furthermore, several indications of toxicity to bone marrow and peripheral blood cells have demonstrated a linear dose-response in relation to benzene exposure.

The one-hit, or linear, nonthreshold model assumes that every increment of dose is accompanied by an increment in the excess cancer risk. The use of the linear nonthreshold model has been recommended for extrapolation of risks from relatively high dose levels, where cancer responses *can* be measured, to relatively low dose levels, where such risks are too small to be measured directly through animal or epidemiologic studies [WHO, 1981]. This model also has been accepted by regulatory groups in the U.S., the World Health Organization, and other international scientific bodies for low-dose extrapolation of cancer risk [WHO, 19811.

EXCESS LEUKEMIA RISK UNDER VARIOUS EXPOSURE CONDITIONS

Table II shows the results of analyses indicating the estimates of excess risk of dying from leukemia under different assumptions of level and length of exposure. Exposure for an occupational lifetime (45 years) to an average concentration of 10 ppm benzene is estimated to result in 44 to 152 excess leukemia deaths per 1,000 workers based on the NIOSH study [Infante et al, 1977; Rinsky et al, 1981] or 48 to 136 excess leukemia deaths based on the DOW study [Ott et al, 1978]. For 45 years of exposure to 1 ppm, the excess risk of death from leukemia ranged between 5 and 16 per 1,000 workers. The range of projected risk represents different assumptions about exposure. If confidence limits of the relative risks were also incorporated into the estimates, the range of risk would be wider.

IARC [1982] conducted a quantitative cancer risk assessment for benzene and leukemia using the results of four studies. IARC assumed a linear relationship between cumulative benzene dose and the relative risk of deveioping leukemia. It made slightly different assumptions from us regarding the length of exposure for the NIOSH and DOW studies.

TABLE II. Estimate of Excess Leukemia Deaths per 1,000 Workers Exposed to Benzene by Number of Years Exposed and Exposure Level*

	Exposure levels			
	10 ppm		1 ppm	
Years exposed	NIOSH study	DOW study	NIOSH study	DOW study
45	44-152	48-136	5-16	5-15
30	30-104	32-93	3-11	3-10
15	15-54	16-48	1.5-5	2-15
5	5-18	5-16	0.5-2	0.5-2
1	1-4	1-3	0.1-0.4	0.1-0.3

*From White et al [19821

For the DOW study, IARC assumed that the *cohort* was exposed for approximately 8–9 years, that benzene exposures ranged between 1 and 30 ppm and that the relative risk of developing leukemia was 3.75.

For the NIOSH study, IARC made two assumptions *about* both relative risk and length of exposure for the cohort. Under the first set of assumptions, IARC assumed that the relative risk of developing leukemia was 21 for those individuals with at least 5 years of exposure. These assumptions resulted in a risk of 140 excess leukemia deaths per 1,000 employees exposed for at least 5 years. Since the risk of cohort members' developing leukemia increased with length of exposure, IARC assumed the estimation based on at least 5 years of exposure to be a lower bound for the excess leukemia risk associated with benzene exposure.

Under its second set of assumptions, IARC assumed that the entire cohort was exposed to benzene for 8.5 years based on the average length of exposure for the Seven leukemia deaths. Using the relative risk of 5.6 for the entire cohort as observed in the study, IARC estimated the risk of leukemia to be 170 excess leukemia deaths per 1,000 workers exposed for an occupational lifetime of 45 years.

For purposes of comparing results, a summary of the IARC benzene risk assessment and linear extrapolation of the risks associated with exposure levels of 10 ppm and 1 ppm, based on IARC methodology, is shown in Table III. IARC did not perform all the calculations in the last three columns. These were performed using IARC methodology employed for the Infante-Rinsky study (cumulative dose and linear extrapolation) and the IARC's opinion that "risk calculations. . . reflect the degree of uncertainty in the estimates of dose rate . . . by citing upper and lower bounds of such estimates" [IARC, 1982]. The excess leukemia risk per 1,000 workers

TABLE III. Analysis of Relative Risk and Excess Leukemia Risk per 1,000 Workers Exposed to Benzene for an Occupational Lifetime by study, Based on Methodology IARC [1982] Used for Infante-Rinsky Study Results*

Authors	RR	Estimated exposure to cohort	Cohort's Occupational lifetime excess risk per 1,000	Excess risk per 1,000 exposed to 10 ppm	Excess risk per 1,000 exposed to 1 ppm
Ott et al [1978]	3.75	1–30 ppm for 8–9 years	72[a]	24–720	2.4–72
Infante et al [1977]	5.6	10–100 ppm, 8.5 years average exposure for cases[b]	170	17–170	1.7–17
Rinsky et al [1981]	21	5 years exposure	140	14–140	1.4–14
Vigliani [1976]	20	200–500 ppm, 9 years average exposure for *cases*	475	9.5–23.8	1.0–2.4
Aksoy [1977]	25	150–210 ppm[c], 9.7 years average	534	25.4–35	2.5–3.6

[a]Based on exposure of 8.5 years.
[b]IARC extrapolated average length of exposure for cases (8.5 years) to average length of exposure for cohort for this analysis.
[c]Based on testimony of Aksoy at 1977 OSHA Benzene Hearing.
*IARC did not perform all calculations in the last three columns. These were performed using IARC methodology. See text.

from lifetime occupational benzene *exposure* to 10 ppm ranges from 9.5 to 720, while the risk from exposure *to* 1 ppm ranges from 1.0 to 72. With the exception of the upper bound *estimate* based on the Ott et al [1978] study, the results of estimated excess leukemia risk using IARC methodology are remarkably *similar* to each other as well as to those *estimated* by us using a mathematical model as *shown* in Table II.

DISCUSSION

There are many uncertainties in quantitative risk assessment. These relate particularly to confidence in exposure estimates and *case* ascertainment with its resultant effect on the estimate of relative risk. Efforts have been made to utilize all of the exposure information available as particularly demonstrated by Rinsky et al [1981] as well as by Ott et al [1978].

With regard to relative risk, there may be underascertainment of leukemia deaths in the Rinsky et al [1981] cohort, as indicated by the testimony of Sakol during the 1977 OSHA benzene hearings [Sakol, 1977]. Exhaustive efforts were made by the NIOSH investigators to identify these additional leukemia deaths without *success* [Rinsky et al, 1981]. Their addition, however, would result in a higher excess risk.

Different assumptions of exposure and slightly different methodologies were used in the risk assessments presented above; however, the results seem to be similar. The exception is the upper-bound estimate based on extrapolation of IARC methodology using the study by Ott et al [1978], as shown in Table III. In this —, the upper-bound risk was 720 and 72 deaths per 1,000 workers exposed for an occupational lifetime to 10 and 1 ppm benzene, respectively. These risk projections when compared with all other projections seem too high.

The upper-bound estimate of risk based on the Ott et al [1978] *study* (136/1,000 for 10 pprn and 15/1,000 for 1 ppm) using our risk assessment model as presented in Table II appears to be virtually identical to the upper-bound estimate based on the NIOSH study (152/1,000 for 10 pprn and 16/1,000 for 1 pprn).

Using estimates from Table II based on the NIOSH *study,* lowering a worker's benzene exposure from 10 ppm to 1 ppm over an occupational lifetime of 45 years would result in a reduction of 39–136 excess deaths from leukemia per 1,000 workers. Based on the DOW study, the reduction would be 43-121 leukemia deaths. The remaining risk as a result of benzene exposure to 1 ppm for 45 years is estimated to be 5–16 excess leukemia deaths (based on projections from the NIOSH *study)* or 5–15 excess leukemia deaths (based on the DOW study) per 1,000 workers.

The magnitude of the above-mentioned risks are considered significant by OSHA. In the evaluation of risk associated with exposure to inorganic arsenic, OSHA concluded that a reduction in risk from 373–465 excess deaths from lung cancer per 1,000 workers to 7.7-10 excess deaths for workers exposed over a working lifetime to the new 10 $\mu g/m^3$ standard constituted a significant reduction in cancer risk [OSHA, 1983]. OSHA further concluded that the excess risk remaining (7.7-10 per 1000 over a working lifetime) at the new exposure level of 10 $\mu g/m^3$ was also significant. Due to problems of feasibility, exposures could not be lowered further.

Thus. all of the mathematical extrapolations are consistent with a finding of significant excess risk (as defined by OSHA in its final determinations of the inorganic arsenic standard) of developing leukemia as a result of 45 years of occupational exposure to the current permissible exposure limit of 10 ppm averaged over an 8-

hour work shift. Although a large reduction in risk could be expected to be achieved by lowering the lifetime occupational exposure to 1 ppm (Table II), the extrapolations indicate that a significant risk may still be present as a result of exposure to this lower level.

while some continue to argue [Van Raalte et al, 1984] that only peak benzene exposure above 100 ppm can cause leukemia or bone marrow toxicity, the results of several epidemiologic and experimental studies do not support such arguments.

Although dose-related effects on human DNA and bone marrow resulting from benzene exposure quite often have to be estimated on the basis of the best available industrial hygiene information, experimental studies in which dose can be controlled serve to augment epidemiologic observations. In this regard, several recent experimental studies have demonstrated adverse effects on chromosomes and bone marrow in relation to low-level benzene exposure. Several of these new and significant findings were presented earlier at this conference.

Tice [Tice et al, 1985] presented a paper demonstrating that exposure to benzene at a concentration of 10 ppm in air, 6 hours/day for 9 days, induced a significant increase in micronuclei (a measure of bone marrow chromosomal damage) in peripheral blood cells of C57BL/6 male mice. These investigators also demonstrated that mice exposed to 28 ppm benzene for a total of only 4 hours had a twofold increase in sister chromatid exchanges (SCEs) in mouse bone marrow cells. The effect on mouse bone marrow cells increased linearly with increasing levels of 4-hour benzene exposure, indicating a linear dose response by level of 4-hour exposure.

Gad-El-Karim et al [1984] also reported a dose response and a twofold increase in micronuclei in bone marrow erythrocytes of CD-1 mice administered a total of two oral doses of benzene at concentrations as low as 8.8 mg/kg body weight. Assuming that the CD-1 mice weighed 25 g and their minute volume of air intake is 24 ml, this dosage would be equivalent to two 8-hour atmospheric exposures of approximately 6 ppm.

Kilgerman recently reported findings at the International Symposium on Sister Chromatid Exchange held at Brookhaven National Laboratory [Kilgerman et al, 1983]. Male DBA/2 mice exposed to 10 ppm benzene by inhalation for only 6 hours demonstrated a significant increase in SCE in peripheral blood lymphocytes and in micronuclei in bone marrow erythrocytes.

Collectively, these studies demonstrate chromosomal damage in bone marrow cells as a result of only one 6-hour exposure to 10 ppm or one 4-hour exposure to 28 ppm. or two daily benzene exposures equivalent to 6 ppm. or 9 days (6 hours/day) of exposure to 10 ppm. They also demonstrate a linear dose-response for benzene exposure and chromosomal damage to both marrow and peripheral blood cells.

These experimental findings Serve to support epidemiologic observations reported over 5 years ago. Picciano studied DOW chemical workers exposed to benzene at the Freeport, Texas facility [Picciano, 1980]. Fifty-two workers exposed to average benzene concentrations below 10 ppm demonstrated a significant excess of chromosomal damage as compared to such damage observed among 44 workers who served as controls. Furthermore. the percentage of workers exhibiting both chromosome breaks and marker chromosomes was 20. 25. and 32% for workers categorized as exposed to average benzene concentrations below 1. 1.0–2.5, or 2.5–10.0 ppm, respectively. Less than 3% of the controls exhibited both chromosome breaks and marker chromosomes.

Snyder presented earlier the results from two studies recently completed. In the Baarston et al [1984] study, C57BL mice were exposed by inhalation to 10 ppm benzene for 6 hours/day, 5 days/week for 32, 66, and 178 days. Since most leukemias and related disorders in man seem to involve stem cell anomalies, the response to hematopoietic stem cells was investigated. Progenitor cells from benzene-exposed mice showed markedly reduced abilities to form colonies compared to cells from control mice. Both marrow and splenic colony-forming unit-erythroid (CFU-E) were depressed to 5% and 10% of control values, respectively, after 178 days of exposure. Marrow burst-forming unit-erythroid (BFU-E) colonies were significantly reduced to 55% of control values after 66 days of exposure, but they returned to control values at 178 days. The mice also exhibited significant depressions in the numbers of circulating red cells and lymphocytes.

In the second recently completed study, short-term exposure (6 hours/day for 6 days) to 10 ppm benzene in air significantly depressed mitogen-induced blastogenesis of both B- and T-lymphocytes in mice [Rosen et al, 1984]. Moreover, 6-days exposure to 10 ppm benzene was just as effective in reducing blastogenesis as 6-days exposure to higher benzene concentrations. The authors concluded that benzene exposure at or near the current occupational Limit may affect immune functions.

Thus, less than 1 week of exposure to the current permissible limit (10 ppm) for benzene is associated with chromosomal damage to bone marrow cells, significant depression of the bone marrow, and disturbances of immune system function. Since most leukemias and related disorders in man seem to involve stem cell abnormalities and immune system deficiencies, these findings may be highly relevant to benzene exposure and leukemia in humans. These experimental findings provide further support for the conclusion that an elevated risk of a bone marrow proliferative cancer (leukemia) could be expected as a result of exposure to 10 ppm benzene.

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