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Hematological, Myelotoxic, Clastogenic, Carcinogenic, and Leukemogenic Effects of Benzene

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INTRODUCTION

Many reviews on benzene simply enumerate publications that have appeared in the world literature, often using only the authors' own summaries without an evaluation, a discussion, or even an attempt to determine whether the results from reports from different sources are in agreement. The objective of this paper is not to give yet another review but rather to present a critical overview and an evaluation of those reports from the literature that deal with chronic benzene intoxication and would be germane to current rule making. This paper will deal then with hematological, myelotoxic, clastogenic, carcinogenic, and leukemogenic effects of benzene and with the dose–effect relationships involved.

STUDIES IN HUMANS

The association of leukemia with occupational exposure to high concentrations of benzene has been recognized for more than half a century (Delore and Borgomano, 1928; Emile-Weil, 1932). With the exception of the case of the small boy described by Mallory *et al.* (1939) **all confirmed cases of benzene-induced leukemia have occurred in workers occupationally exposed to high concentrations of benzene vapor, usually on the order of 150–1000 ppm.** Many "semiepidemiological" studies have been reported on hospital patients in whom a diagnosis of leukemia has been correlated with a retrospective occupational history of exposure to benzene. In other instances groups of workers with known exposures to benzene have been studied hematologically (Vigliani's group in Italy, Girard's and Cavigneaux's groups in France, and Aksoy's group in Turkey).[1]

[1] Penati and Vigliani (1938); Saita (1945); Vigliani and Saita (1964); Forni and Vigliani (1974); Vigliani (1976); Vigliani and Forni (1976); Revol *et al.* (1954); Goguel *et al.* (1967); Girard *et al.* (1968, 1970, 1971a,b); Girard and Revol (1970); Aksoy *et al.* (1971, 1972a,b, 1974a,b, 1976); Aksoy (1978, 1980).

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From these studies the cause-and-effect relationship between benzene and leukemia is sufficiently clear but there are few data from which a dose-effect or dose-response relationship can be established. **There is no evidence for a leukemogenic action of benzene at low concentrations.**

TYPES OF MYELOTOXICITY AND LEUKEMIA ASSOCIATED WITH BENZENE

Leukemia induced by radiation is usually myelogenous, the chronic form occurring more frequently than the acute. Rarely, acute lymphocytic leukemia may also result. Furthermore, ionizing radiation is also capable of inducing a variety of solid tumors in many organs and tissues. By contrast benzene induces only a single type of neoplastic response in a small percentage of people sufficiently overexposed to its vapor. **In most cases leukemia induced by benzene is of the small dark myeloblast/hemocytoblast/stem cell type** (Vigliani and Saita, 1964). It is becoming an increasingly held opinion (Vigliani and Forni, 1976) that some of the cases of pancytopenia, which were reported more frequently in the past, may well have been cases of aleukemic leukemia. Variants of myelogenous leukemia such as erythroleukemia, monocytic leukemia, paroxysmal nocturnal hemoglobinuria (PNH), and myelofibrosis with myeloid metaplasia have been associated with high levels of exposure to benzene. Although this association is not surprising in view of Dameshek's theory of the pluripotential stem cell their occurrence is very low indeed compared to AML.

There is general agreement on the causal relationship between exposure to high levels of benzene and the development of aplastic anemia, pancytopenia, and acute myelogenous leukemia (AML) and its variants. This has been accepted on account of the numerous case studies of aplastic anemia and AML or one of its variants in workers exposed to high concentrations of benzene. An association has been suggested for lymphatic leukemia, Hodgkin's disease, and non-Hodgkin lymphoma, but this is questionable.

A very small percentage of workers exposed to benzene get aplastic anemia. Very few of those develop leukemia (Jandl, 1977a,b; Goldstein, 1980). There are a number of case reports of benzene-induced aplastic anemia in which morphologically abnormal "preneoplastic" cells in the bone marrow became progressively more numerous, ultimately resulting in acute leukemia (Girard *et al.*, 1970; Aksoy *et al.*, 1972b; Mallein *et al.*, 1971). Aksoy (1980) recently reviewed his observations in Turkey, giving a follow-up of 44 pancytopenic patients observed over 2–17 years, and reviewed the reports on 42 patients with leukemia, 9 with malignant lymphoma, 2 with paroxysmal nocturnal hemoglobinuria, 2 with myeloid metaplasia, 5 with lung cancer, and 3 with multiple myeloma, a total of 63 patients with a history of exposure to benzene. Of these 63 patients 49 had previously been reported; 47 belonged to the group of 28,500 shoemakers in Istanbul, and the other 16 had been exposed to benzene in other occupations. Unfortunately, the figures are slightly confusing due to falling back on previous publications. The following, however, is a clear summary:

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Type of leukemia	Number of patients	Preceding pancytopenia
Acute myelogenous leukemia	16	3
Preleukemia	7	4
Acute erythroleukemia	8	2
Acute monocytic leukemia	3	1
Acute undifferentiated leukemia	1	1
Acute promyelocytic leukemia	1	0
Acute lymphocytic leukemia	4	0
Chronic myelogenous leukemia	2	0
Total	42	11

Thus among 42 patients with leukemia, 11 had had a previous period of pancytopenia, that is, 26%.

It is interesting to note that in the cases of acute lymphoid and chronic myelogenous leukemia there was no preceding period of pancytopenia. This contributes to the contention that for these types of leukemia the causality of exposure to benzene is not as convincing as it is for the acute myelogenous type and its varieties. It is, in this respect, important to note further the statement of the author that in a nonexposed group of hospital patients with leukemia 50% had chronic myelogenous leukemia, but in the exposed group this was only 5%. In a previous study (Aksoy *et al.*, 1976) of 34 patients with benzene-associated leukemia, only one case of CML was seen (3%).

According to Wolf *et al.* (1981), the association of lymphatic leukemia with solvent exposure is weaker than was previously described by McMichael *et al.* 1976). Further, in view of the common findings of chromosome aberrations in cultured peripheral lymphocytes from workers who have had significant exposure to benzene, it is of interest that Sandberg (1966) reported an absence of chromosome aberrations in almost all cases of chronic lymphatic leukemia.

HODGKIN'S DISEASE AND OTHER LYMPHOMAS

It has also been suggested (Aksoy *et al.*, 1974b; Bousser *et al.*, 1948) that Hodgkin's disease is in some way associated with exposure to benzene. In the earlier literature the distinction of a diagnosis of Morbus Hodgkin and non-Hodgkin lymphoma was not always quite clear. In 1947 Bousser *et al.* described a case of lymphosarcoma associated with exposure to benzene. In 1974 Aksoy *et al.* (1974b) described six cases of Hodgkin's disease in patients with exposure to benzene and in 1980 Aksoy reported an additional case as well as one case each of histiocytic and lymphocytic lymphoma. Viana and Polan (1979) examined the mortality from reticular cell sarcoma and solid tumors of the lymphoid system. The results suggested an increased relative risk in New York State for men employed in occupations in which benzene and/or coal tar is used. The increase was limited to men over 45 years of age. Enterline (1979) pointed out the methodological flaws in this study and showed that there was no excess mortality from lymphomas in the 14 relevant occupations when the appropriate proportionate mortality ratios are used.

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Smith and Nosella Lickies (1980) carried out a similar study in Tasmania and also did not find excess mortality from lymphoma in people with occupations involving exposure to benzene. The Wittings (1979) in Germany added an additional case history. As argued by Van Raalte (1981) this might well have been fortuitous.

ANIMAL STUDIES

Half a century ago Lignac (1928, 1932a,b) reported the induction of various types of leukemia and lymphomas in white mice following injections with benzene. Attempts to replicate the induction of leukemia by exposure of laboratory animals to benzene have failed (Hess, 1935; Morton and Burroughs Mider, 1941; Kirschbaum and Strong, 1942; Deichmann *et al.*, 1963; Ward *et al.*, 1975; Laskin, 1976). However, Deichmann's study is noteworthy in that, although at respiratory exposures to benzene in air at concentrations of 44 ppm and higher rats developed leukopenia, a no-effect level was shown at concentrations of 31 ppm and below.

Recently, three reports from Carroll Snyder's group at New York University Institute of Environmental Medicine have been published but the results *are difficult to interpret.*

(1) Snyder *et al.* (1978a), in an abstract of a paper (No. 106) presented at the seventeenth annual meeting (SOT), reported on a study, supported by Contract U-150-14 (PS-7) from the American Petroleum Institute, NIEHS Grant ES 00260, and NCI Grant CA 13343. Three strains of mice (AKR, C57BL, and Charles River CD 1) and Sprague-Dawley rats were exposed at 6 hr/day, 5 days/week, to 300 or 100 ppm of benzene vapor. Two rats, at the time still exposed to 100 ppm, displayed elevated white counts combined with a shift to the left, suggestive of possible chronic granulocytic leukemia. Two CD 1 mice exposed to 300 ppm of benzene developed pathologically confirmed myelogenous leukemia; one of these two was an acute AML. A third CD 1 mouse died with a blood profile suggestive of chronic myelogenous leukemia, the diagnosis awaiting pathological confirmation.

(2) Snyder *et al.* (1978b), Paper No. 3, was supported by the same contract and grants as the previous paper and therefore presumably deals with the same study. Here, the authors report on Sprague-Dawley rats and AKR strain mice exposed at only 300 ppm of benzene, 6 hr/day, 5 days/week for life. The authors conclude (p. 616): "No indications of a leukaemic or preleukaemic response were observed in either species."

(3) Snyder *et al.* (1980) reported the results of a study supported by the same contracts and grants and it might well be identical to the study or part of the study with three strains of mice discussed under (1), although in this 1980 report only *two* strains of mice are mentioned, AKR/J and *C57BL/6J*. The AKR strain of mice carries a virus that "spontaneously" gives rise to a high incidence of lymphoma and the C57BL strain carries a virus that yields a high incidence of lymphoma following exposure to radiation, carcinogens, and immunosuppressive agents. In this study the animals were exposed to 100 or 300 ppm benzene vapor, 6 hr/day, 5 days/week, for life. The AKR mice showed anemia and lymphocytopenia and 20% of these mice developed bone marrow hypoplasia (2% in controls) but in the AKR mice there was no change in incidence or induction time for the viral-induced lymphomas commonly seen in this strain. The C57BL mice showed anemia, lym-

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phocytopenia, and neutrophilia with a shift to the left and in 33% of the exposed animals, bone marrow hyperplasia. It should be noted that the AKR mice showed hypoplastic marrow. In these C57BL mice there was an *increase* in the incidence of hematopoietic neoplasms, including six cases (15%) of thymic lymphoma (two (5%) of the control C57BL mice died with lymphoma but neither of these tumors involved the thymus), one plasmocytoma (myeloma) and *one leukemia* of the hemocytoblastic type. Summarizing, these authors found:

CD 1 mice: one case of acute myelogenous leukemia, one case of chronic myelogenous leukemia, one possible—unconfirmed—case of chronic myelogenous leukemia.

CD 57 mice: one case of hemocytoblastic—presumably acute—leukemia.

SOLID TUMORS

Maltoni and Searnato (1979) carried out an experiment with oral administration of benzene to rats at 50 or 250 mg/kg daily by gavage, four to five times per week for 52 weeks. The authors reported a dose-response relationship and stated: "It causes Zymbal gland carcinomas. Moreover an enhancement of mammary carcinomas and leukemias and the appearance of miscellaneous otherwise rare malignancies have been observed." However, critical evaluation of this report reveals that the only statistical significance is in the number of Zymbal gland carcinomas in the female 250 mg/kg dose group, not in the 50 mg/kg group, not in the leukemia cases, and not even in the mammary carcinomas. Although the authors state that at these dosages no acute or subacute anomalies occurred, no information on hematology, bone marrow status, or chromosomes was given.

CLASTOGENICITY

The literature on chromosome aberrations in man is difficult to evaluate. Several cytogenetic studies have been carried out in patients with true and well-defined varieties of hemopathy associated with exposure to benzene. There is sufficient evidence for a causal association between a clear benzene hemopathy and chromosome aberrations in both bone marrow cells and cultured peripheral lymphocytes.[2] Some of the chromosome anomalies appear to persist for many years after clinical recovery.[3]

Hartwich and Schwanitz (1972) carried out a study in nine apparently healthy refinery (platformer) workers with 3–7 years exposure. Some of these workers might have had some exposure to benzene in previous jobs, and in their present job they had intermittent exposure to platformate containing between 1 and 10% benzene. The chromosome aberration rate in the peripheral blood lymphocytes of the exposed workers was 8–12%. The main anomalies were gaps and breaks. Trans-

[2] Pollini and Colombi (1964a,b); Pollini *et al.* (1964); Forni and Moreo (1967, 1969); Sellyei *et al.* (1970); Sellyei and Kelemen (1971); Hartwich *et al.* (1969); Haberlandt and Mente (1971); Manu and Popescu (1972).

[3] Pollini *et al.* (1969); Forni *et al.* (1971b); Liniecki *et al.* (1971); Pollini and Biscaldi (1976).

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location was rare. The rate of aneuploidy was not increased. The chromosome aberration rate in a control group of healthy blood donors was 5.1%. However, the rate in the refinery workers was still within the upper limit of normal in healthy people.

Gäth and Thiess (1972) examined 10 chemical workers with 11–38 years exposure to benzene. The urinary phenol excretion was 31–55 mg per liter, which would be equivalent to an exposure to benzene of 10 ppm for 8 hr. There were no hematological anomalies and no increase in the rate of chromosome aberrations.

Khan and Khan (1973) carried out cytogenetic studies in peripheral lymphocytes of 15 benzene workers and 14 controls and in bone marrow cells of 4 workers and 2 controls. One of the workers had a benzene myelopathy. There was an increased rate of stable and unstable chromosome changes in the exposed group.

Picciano (1979) examined 200 cells per person of 52 workers exposed to benzene and of 44 controls selected during preemployment examinations and matched "as closely as possible." Exposure of the workers to benzene was reported to have "averaged" 2 ppm (TWA) over the preceding 4-year period. No information on possible peak exposures was given. Complete absence of phenol in the urine of 52 persons, as reported by Picciano in the exposed workers, is extremely unlikely. A low concentration of phenol in the urine, 10–50 mg per liter, only indicates an exposure to benzene at concentrations below 10 ppm during the previous few days and gives no information at all about the level of exposure to benzene before that short period. The exposure periods ranged between 1 month and 26 years. The most recent exposures may well have been at concentrations less than 10 ppm. The far earlier exposures were apt to have been at much higher levels. It has been demonstrated (e.g., Pollini *et al.*, 1969; Forni *et al.*, 1971b; Pollini and Biscaldi, 1976) that chromosome abnormalities, particularly stable ones in peripheral lymphocytes, may persist for many years even after cessation of exposure.

In the Picciano study there was no difference between exposed persons and controls as regards abnormal cells (1.6 versus 1.4%) and there was no difference in chromatid breaks (1% versus 1.1%). However, the frequencies of chromosome breaks (0.67% versus 0.35%) and of "marker" chromosomes—rings, dicentrics, and exchanges (0.19% versus 0.06%)—was, as shown by χ^2 analysis, significantly elevated in the exposed group. In contrast to the findings of other studies (e.g., Tough *et al.*, 1970) no trend was seen with age. The difference in age between the exposed workers and the controls was large, a mean of 39 versus 27 years, respectively. Apart from the considerable difference in age, it is not clear if external variables which might have influenced the results (smoking, recent virus infections, use of drugs or pharmaceuticals, diagnostic X radiation, occupational or avocational exposure to chemicals other than benzene) were adequately controlled and taken into consideration in structuring both the exposed and the control group.

Second, while the difference in frequency for some types of chromosome aberration was statistically significant, the overall frequencies were quite low and would be considered within the normal range in many laboratories. Thus the biological and clinical significance of the findings is debatable.

Third, there is no repeat examination to show that the anomalies are still present after some time.

Fourth, the current trend seems to be of using the percentage of abnormal cells as a criterion for clastogenic activity rather than the total number of isolated

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individual aberrations. This is still under debate and the issue is far from being solved.

Fifth, no information about peak exposures to benzene is given and this failure makes it impossible to determine whether the small increase in aberration rate is due to benzene exposure or can be explained by long-term exposure to low concentrations or by short-term peak exposures to much higher concentrations.

Sixth, in addition, many of the workers had been exposed to a number of other chemicals.

From the above commentary, it is clear that Picciano's study fails to support the contention that exposure to benzene at concentrations below 10 ppm would pose a leukemogenic or any other blood dyscrasia hazard.

Fredga *et al.* (1979) report on a two-phase study which makes the reported results a bit difficult to unravel. In the first phase, the authors compared the rate of chromosome aberrations in cultured peripheral lymphocytes from drivers of gasoline road tankers to those from crew members of gasoline tanker ships and from petrol station attendants. The exposure of the different groups does not become quite clear. However, the authors state (page 193) that road tanker drivers had a mean time-weighted average exposure (they say "concentration") of 0.4 ppm. "Higher benzene exposure," the authors state, "was encountered in the crew members loading ship tankers, the mean time-weighted average concentration was 6.56 ppm" although the crew members were less frequently exposed than the road tanker drivers who were exposed daily. Frequency of chromosome and chromatid breaks in road tanker drivers was increased in a statistically significant way as compared to that for the other two groups. The rate of chromosome anomalies in these latter two groups approximated that of an unexposed control population examined at a different time.

In the second phase, lymphocyte chromosomes of a new group of gasoline road tanker drivers, with the same degree of exposure, were compared to those of an age- and job duration-matched group of milk truck drivers and with those from workers at an industrial gasworks exposed to benzene at a level of 5–10 ppm but occasionally much higher. Although the authors do not state so, it should be obvious that in the original design of this second phase study, the milk truck drivers were to serve as a control group. The rate of chromosome aberration was increased in comparison to that of an unexposed control group examined at a different time, but the aberration rate was virtually the same in all three groups. In other words, the milk truck drivers, who were also unexposed (diesel fuel does not contain benzene) had the same rate as the gasoline truck drivers, while the marine tanker crew in the first phase who had the higher exposure to benzene did not show an excess rate of chromosome aberrations.

Furthermore, it is not clear which preparations were harvested at 48 hr and which at 72 hr.

The results of this study simply do not provide good evidence to show that exposure to low levels of benzene causes chromosome aberrations.

Watanabe *et al.* (1980) examined 16 female workers exposed to benzene at concentrations up to 40 ppm over a period of 1–20 years. They found no increase in the rate of structural or numerical chromosome aberrations in cultured peripheral lymphocytes. They reported a slight decrease (!) in frequency of S.C.E. Their results

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are in agreement with those of Tough *et al.* (1970) showing no clastogenic effect from exposure to lower concentrations of benzene.

CHROMOSOME ABERRATIONS—SUGGESTED MECHANISM

Chromosome aberrations are known to be produced by compounds which bind covalently with DNA (e.g., alkylating agents) and are regarded by many as an indication of an affinity of a particular compound, or its metabolites, for DNA (Di Paolo *et al.*, 1976; Anderson and Richardson, 1981).

Recent evidence suggests that similar chromosomal abnormalities may be produced by compounds which inhibit tubulin polymerization or which accelerate its depolymerization (Irons and Neptun, 1980). Tubulin is a protein molecule of high molecular weight and is essential for the formation of microtubules, a system of intercellular structures which participate in a number of essential cellular processes. In particular, microtubules are essential for the formation of the mitotic spindle within which chromosomal rearrangement takes place during mitosis (Bryan, 1974). A number of compounds are known to interfere with the integrity of tubulin polymers, for example, colchicine, vinblastine, diphenylhydantoin, and selected sulfhydryl reagents. Exposure of cells to these agents *in vivo* or in culture results in metaphase arrest, uneven nuclear division, and other chromosomal abnormalities (Wilson *et al.*, 1968; MacKinney *et al.*, 1978; Himes and Himes, 1980). The principal dihydroxy metabolite of benzene, hydroquinone, also binds to tubulin and inhibits tubulin polymerization. In culture it inhibits cell division and produces chromosomal breaks in both human and animal lymphocytes. It may also be the agent responsible for such changes *in vivo* since polyhydroxy metabolites of benzene have been identified experimentally in the bone marrow, spleen, and thymus (Pfeifer and Irons, 1981).

It would thus appear that the clastogenic activity of benzene *in vivo* is a function of the disruption produced in the intracellular microtubules by its metabolites and hence cannot be taken as an indication of a direct interaction with DNA.

EPIDEMIOLOGY

In earlier studies the interest of the investigators was directed more to the type of disease and its symptomatology, hematological expression, and clinical course rather than to the incidence and relative risk of leukemia. Many reports of such studies, at times consisting of large series of case histories, have appeared in the literature.

In France, Goguel *et al.* (1966, 1967) reported fifty cases of leukemia in benzene workers in the Paris area in the period 1950–1965. Six of these cases had already been described earlier. Among the 44 new cases were 37 men and 7 women. Among them were 23 cases of acute leukemia, including 2 cases of erythroleukemia, 13 cases of chronic myelogenous leukemia, and 8 cases of chronic lymphoid leukemia.

Girard's group (Girard and Revol, 1970; Girard *et al.*, 1970) carried out a systematic case-control study among patients with blood diseases in a hospital in Lyon, France. Among 401 patients, 246 men and 135 women with mean ages of

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43 and 48 years, respectively, 257 cases of leukemia occurred. The diagnoses and the numbers of patients exposed to benzene were:

140 acute leukemia,	17 exposed (12%)
61 chronic lymphoid leukemia,	9 exposed (15%)
56 myelogenous leukemia,	4 exposed (7%)

Among the 124 control cases, 5 patients (4%) had been exposed. In addition (1970b) 13 cases of myelofibrosis were reported of whom 2 patients (4%) had been exposed.

Particularly among the patients with acute leukemias and aplasias was an association with occupational exposure to benzene found. In their first publication Girard *et al.* (1968) reported on 200 patients with hemopathies among whom they found 14 patients (7%) with confirmed and 3 (1½%) with probable exposures, involving the following categories:

Hemopathy	Number	Confirmed exposure	Probable exposure
Acute leukemia	70	7	1
Lymphatic leukemia	32	1	1
Myelogenous leukemia	30	1	—
Aplasia	17	3	—
Mono- or bicytopenia	27	1	—
Myeloid splenomegaly	7	1	—
Reticulo- or lympho-sarcoma	17	—	1

In a later publication the series was extended to 401 patients and this time an, although much smaller, control series was included which had been lacking in the previous study.

The high proportion of lymphoid leukemia in these French series is remarkable in that it is not in agreement with the results of the Turkish (Aksoy *et al.*) and Italian (Vigliani *et al.*) series. Neither is it in agreement with the more recent findings of Wolf *et al.* (1981). In the article by Girard a subdivision of the acute leukemias or of the myelogenous leukemias is not given. Although a suggestion of a causal relationship between leukemia and exposure to benzene is justified, there are no data on dose–response relationships. In 1971 these authors published the results of a study on 48 hospital patients with blood dyscrasias and the percentage exposed to benzene:

	No. patients	No. exposed (%)
Acute leukemia	24	15 (62.5)
Lymphoid leukemia	10	4 (40.)
Myelogenous leukemia	4	3 (75.)
Aplasias	10	4 (40.)

There is no information on the level of exposure.

Epidemiological studies have been carried out in the rubber industry, in the

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printing industry, in Istanbul shoemakers, and in the petroleum and petrochemical industry.

RUBBER WORKERS

Cohorts of rubber workers have been studied by Pagnotto *et al.* (1961, 1979), McMichael *et al.* (1974, 1975, 1976), Andjelkovic *et al.* (1976, 1978), Monson and Nakano (1976), and Infante *et al.* (1977).

Pagnotto *et al.* (1961) carried out a survey in a rubber coating industry where one 65-year-old benzene worker had died from panmyelophthisis. Among 52 workers, 16 had hematological deviations. In a follow-up study 18 years later (Pagnotto *et al.*, 1979), 38 workers who had been exposed for 1 to 24 years were reexamined. The exposure was reported to have been from 10 to 50 ppm (TWA) with short-term peaks which were higher. No occurrence of blood dyscrasia or leukemia was found.

In a study of rubber workers McMichael *et al.* (1974) reported an elevated standardized mortality ratio (SMR) for deaths from diseases of the hematopoietic and lymphatic systems and most notably a three fold excess mortality from leukemia. Deaths from lymphatic leukemia, particularly those from chronic lymphatic leukemia (CLL), showed the greatest excess. The solvent exposure group suffered a sevenfold excess of death from lymphatic leukemia with six out of eight deaths resulting from CLL. By contrast there was only a twofold excess of deaths from myeloid leukemia. Subsequently, (1975, 1976) the excess mortality from diseases of the hematopoietic and lymphatic systems, including leukemia, appeared to occur in workers exposed to solvents.

Andjelkovic *et al.* (1976) carried out a historic-prospective study in a cohort of rubber workers over the period 1964–1973 and determined standardized mortality ratios in 5-year age groups. They found an SMR greater than 100 for neoplasms of the hematopoietic and lymphatic systems in white males. In 1978 they reported the results in 1949 white female rubber workers in this cohort. No deaths from Hodgkin's disease or leukemia were observed. In the meantime, there has been some follow-up of these previous studies in rubber workers.

Wolf *et al.* (1981) carried out a case-control study of 72 cases of leukemia occurring in 1964–1973 in four rubber and tire companies. They found that in one company the association of lymphatic leukemia with exposure to a solvent was weaker than previously described and there was no association in other companies. Lymphatic leukemia was associated with general service jobs for the two larger companies from which 89% of the cases were derived. The authors found no increased risk for myelogenous leukemia. This would suggest that at moderate levels of exposure the risk of myelogenous leukemia is not significantly increased.

Delzell and Monson (1981) reported on the mortality among 29,087 men and women who had worked in a rubber plant for at least 2 years. The study included an update of a previous study (Monson and Nakano, 1976) which covered the period 1940–1974 and the authors compared the mortality pattern covering the years 1974–1978 to that of the previous period. For white male union members an excess mortality from leukemia was disclosed for both periods; there was no reduction over the last 4 years. The authors suggest that either an effective reduction

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in exposure might not have taken place during the valid period of causal exposure or due to the long induction period insufficient time had elapsed to result in reduction of incidence.

Infante *et al.* (1977) also carried out an epidemiological study on cohorts of rubber workers. They reported a fivefold increase of all leukemias and a tenfold increase in the combined incidence of myeloid and monocytic leukemias. The authors state that "the benzene levels themselves were generally below the limits recommended at the time of their measurements." This latter statement, referring to threshold limit values in force at the time of exposure (i.e., 100–35 ppm), and a second statement that exposure levels from 1969 onward, "in most instances ranging from zero to 10 or 15 ppm," do not quite seem to reflect the true facts. The paper has been severely criticized on account of the inaccuracy of some of the data and of some flaws in the methodology (Tabershaw and Lamm, 1977).

According to Lamm and Tabershaw (1977) measurements taken later showed that actual exposures were much higher ranging up to 350 ppm in one plant and from 120 to 1000 ppm in another, whereas the levels cited by Infante *et al.* and those reported in a survey conducted by the Industrial Commission of Ohio in 1946 were not quite accurate (see also: "Proposed standard fails to meet necessary criteria, Industry Groups say," *Occup. Safety & Health Reporter*, Vol. 7, No. 19, Part I, pp. 363–564.) In fact, Infante (1977a,b) indicated during the OSHA Benzene Hearings (Nov./Dec. 1977) that **the leukemia cases were more probably related to unknown but apparently very high (over 100 ppm) benzene exposures.** Infante further concluded that this epidemiology survey was only useful as a qualitative indicator of an association between benzene exposure and acute myelogenous leukemia (AML).

It is deplorable that the article by Infante *et al.* (1977) in the *Lancet* has been repeatedly uncritically cited and even proposed as a basis for rule making. A critical evaluation of the data presented, in the light of other articles, reveals the following:

> First, evidence from St. Mary's does not agree with results from Akron and, when viewed alone, is not statistically significant. Since results of the two separate cohorts do not agree, combining the data is inappropriate. Then, 404 "dry side" employees who were apparently exposed to benzene concentrations at least up to 20 ppm (64 mg/m³) and who otherwise fit the cohort definition, but among whom no leukemia deaths were discovered after 95% follow-up, were excluded from the cohort (748 workers) investigated by these authors. They "presumed" that the 404 workers had not been exposed "routinely" to benzene. Thus
>
> (a) the cohorts are neither adequately described nor appropriately chosen,
> (b) the true exposure data included levels far in excess of those reported by the authors,
> (c) alternative etiological factors that might have contributed to the incidence of leukemia were not considered, i.e., prior work experience, current exposure to benzene elsewhere (e.g., at home), exposure to pharmaceuticals or other chemicals.

Therefore, **a conclusion that exposure to benzene at concentrations of 0 to 10–15 ppm induces leukemia is not justified.**

Presently, in a new report (Rinsky *et al.*, 1982?) by Infante's co-authors, the above 1977 *Lancet* publication is now—but not then—designated as "preliminary" and a follow-up or completion of the original study is presented. The study population is now divided into "two temporal groups." Group 1 consisted of 748 individuals who worked at least 1 day in a department with exposure to benzene between January 1, 1940 and December 31, 1949. Group 2 consisted of 258 individuals who first worked in a department with benzene exposure from 1950

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through 1959. No examination was attempted of persons whose first exposure to benzene occurred after 1959 because the number of such individuals was small and because one of the plants ceased production in 1965. This, however, still represents an exposure period of up to 5 years and a period of observation (latency) of 16–21 years. The authors give a history of operations and describe the process and the work carried out and give some account of the results of the various measurements of benzene concentrations made by the different bodies involved at different times. This is helpful. Comparing the time the measurements were made with the time of the first exposure of the patients in whom leukemia developed, it appears that concentrations of benzene were or probably would have been well in excess of 100 ppm. Even in later years high concentrations occurred. In addition it was admitted that although under certain conditions "employees were required to wear a chemical cartridge respirator" these "were often not worn."

In order to facilitate a discussion on the interpretation of the clinical data, the leukemia cases reported in the study by Rinsky *et al.* (1982, p. 40a) are summarized:

Rinsky Leukemia Cases

Case	Leukemia	Exposure: Beginning	Exposure: Duration (years)	Latency (years)	Year of death	Age at death
Group 1: 748 men exposed 1940 through 1949; 7 cases observed, 1.25 expected.						
1	Monocytic	1940	3	17	1958	36
2	CML[a]	1948	1/12[b]	2	1950	29[a]
3	AML	1945	11½	13½	1958	60
4	AML	1949	9	10½	1960	65
5	di Guglielmo (AML)	1939	13	22	1961	62
6	AML	1941	20	20	1961	57
7	Acute monocytic	1942	5	15½	1957	57
Group 2: 258 men exposed 1950 through 1959; 1 case observed, 0.46 expected.						
8	Myelogenous	1950	1½	3½	1954	28[b]
Additional cases						
9	AML	1942	14	37 (!)	1979	67
10	AML	1940	6	12	1955	38
(not counted, salaried employees, not in cohort)						
11	Acute lymphocytic (aleukemia)	1937	4	13	1950	58
12	AML	1950	4	4	1954	48
(diagnosis on death certificate aplastic anemia, but hematologist said AML, therefore not counted)						

[a] Unusual: chronic ML after only 1 month exposure. Peak exposures, 1000 ppm.
[b] Exposed to peak concentrations up to 680 ppm.

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The following facts are of interest

(1) Case 2 (Group 1) is a case of chronic, not acute, myelogenous leukemia. It is unusual in clinical experience that a chronic leukemia occurs after only 1 month exposure to benzene.

(2) With one exception, case 9, acute myelogenous leukemia in a 67-year-old man, who died in 1979 with 37 (!) years latency, all cases occurred during the first 20 years, i.e., before 1961.

(3) With this one exception (case 9) all cases occurred between 1950 and 1961.

(4) Again with the exception of case 9, no new cases occurred after 1961, i.e., during the last 20 years.

Moreover, considering the details of the exception (case 9) one wonders whether in this case the association with exposure to benzene was coincidental or fortuitous rather than causal.

(5) There have been no cases at all in employees who were first exposed after 1951.

(6) The period of exposure for all cases started during the first 13 years since starting up the plants (1937–1950).

(7) With the exception of case 2, an unusual case of chronic, not acute, leukemia who had only 1 month exposure in 1948 and died at age 29 in 1950, and which might very well be fortuitous, the two cases with the most recent onset (cases 8 and 12) had the shortest latency periods: 3½ and 4 years.

(8) The mean latency period in the cases with the onset of exposure before 1945, when concentrations must have been higher, was 19½ years, whereas in the cases with onset after 1945, when concentrations were lower, the mean latency was only 6 years. In other words, patients exposed to the higher concentrations had the longer latency. This is not in agreement with general experience in experimental and clinical oncology.

(9) With the possibly coincidental exception of case 9, the 67-year-old man with a latency period of 37 years, all patients had a latency period of less than 20–22 years. Yet, the plant closed down in 1976; therefore in 26 years of employee exposure and 31 years of observation, no new cases occurred. The two possible exceptions, for which it has been suggested that the association with exposure to benzene might well be coincidental, would in that case represent two cases in 29 years (1950–1979), which even in such a small group would not be unexpected. This is in agreement with the results of the study by Monson and Fire (1978), who studied the mortality and morbidity among 13,570 white male rubber workers who worked for at least 5 years from 1940 to 1976 in a Goodrich Company plant in Akron, Ohio. They found, among other cancers, an excess of lymphatic cancer and leukemia in certain jobs. For men who started working after 1945, no excess leukemia or lymphatic cancer was seen.

In view of the above nine points, the results of Rinsky's study, rather than suggesting the association of leukemia with low-level exposure to benzene, suggest that at low levels of exposure no excess leukemia occurs.

PRINTING INDUSTRY WORKERS

A number of studies have been carried out in pressroom workers in the printing industry. In the United Kingdom an excess mortality from leukemia in printers

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was already evident in 1951 from the Registrar General's Report (Anonymous, 1968). In the United States, Viadaner and Bros (1972) found a nonsignificant excess of leukemia deaths among printers over the years 1959–1962. In the same tristate case-control study they found an elevated relative risk for leukemia deaths among painters in whose jobs solvents similar to those used in the printing industry may have been used.

Epidemiological studies in men in printing and press jobs where, in the past, people had been exposed to benzene-containing solvents, suggest (Kay, 1976) that this exposure might have been serious enough to give rise to an increased incidence of leukemia. In a proportional mortality study, Lloyd *et al.* (1977) found a slight increase in the number of deaths from leukemia in printing pressmen: 8 observed vs 5.1 expected. Greene *et al.* (1979) reported on a cancer mortality study among male U. S. Government Printing Office employees whose last job had been in the Printing Office during the period January 1948–April 1977. They found a "significantly higher proportion of deaths from multiple myelomas, leukemia, Hodgkin's disease." The excess deaths from leukemia occurred primarily in bindery workers where benzene was used to a limited extent until the early sixties. The authors considered four 5-year time periods. There was little or no variation between the mortality from leukemia in these time periods in spite of the fact that the use of benzene was discontinued. If anything, this suggests first that the low-level exposures to benzene may not have been associated with an excess incidence of leukemia, and second, that further lowering of an already low-level concentration of benzene does not give rise to a substantial decrease in the risk of leukemia.

Paganini *et al.* (1980) did a mortality study in Los Angeles of 1361 web-pressmen who had worked for more than 1 year during the period 1949–1965. They considered the vital status ultimo 1978 of 344 men out of 354 deceased. There were 7 cases of leukemia observed vs 2 8 expected in the U. S. white male population. Six of these seven cases were of the myelomonocytic type. In addition, myelogenous leukemia (presumably chronic) was mentioned in a secondary role in one case, and one other man had myelofibrosis.

PETROCHEMICAL WORKERS

In oil refining and certain petrochemical industries exposure to benzene is not uncommon. An important study is the one by Thorpe (1974) involving 38,000 persons employed by or on pension from a large oil company in the period 1962–1974 in Europe and the United States. No increased relative risk of leukemia was found among those employees who were expected to have been exposed to benzene. Over a 10-year period 18 cases of leukemia were recorded against an expected number from WHO age-corrected tables of 23,23. No precise statements of the exposure levels were given, but from experience in oil refineries it is known that such exposures varied in time and location from less than 1 to 20 ppm with occasional much higher peaks.

Ott *et al.* (1978) studied the mortality among 594 employees of a chemical company who had been occupationally exposed to benzene. The results are often cited and the authors are purported to have demonstrated significantly increased relative risk for leukemia among workers exposed to 1–30 ppm (3.2–96 mg/m^3) benzene. However, Ott *et al.* indicated in their publication that because of limited sampling and analytical information available prior to 1960, the estimates of av-

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erage exposure conditions for 20 of the 33 years included in the survey would be conservative. A careful analysis of the limited air sampling data presented in their paper indicates that the concentration of benzene ranged from zero to 937 ppm. The authors used these values to calculate assumed average benzene exposure levels for various job categories.

In the case of substances like benzene there is a flaw in the use of mean or average concentrations for conclusions on dose-response relationships when the range of concentrations is wide. As regards the concentrations at the upper end of the range, there is no problem. Certainly the observed effects are associated with this high exposure. A completely different situation, however, exists as regards the concentrations at the lower end of the range. These were determined at different moments which have no relationship with "peak" levels. The low levels might well have been, and probably were, still lower at still different times and the lowest points have been practically zero. Therefore, the concentration at the lower end of the range, as well as the so-called "mean concentration" are meaningless in dose-response relationships. The only meaningful relationship—in addition to an observed effect at a defined upper concentration—is a no-effect/no-response level *below* a defined *upper* concentration. Further to the figures of Ott *et al.*, the statistical significance associated with this observed (3) versus expected (0.8) ratio may be questioned on account of the relatively small (102) population. There is also some doubt regarding the accuracy of the leukemia diagnoses, which were based on death certificate information and lacked confirmatory autopsy or blood cytology data. One patient died at age 72, eight years after his retirement from a disease diagnosed as bilateral bronchopneumonia, with myeloblastic leukemia listed under "other significant conditions." This condition at that age might well have been a chronic, either lymphatic or myelogenous, rather than an acute leukemia, and would not in that case be likely to have been associated with exposure to benzene. The second patient had a prior work history in a veneer manufacturing plant, an activity which has been reported to be associated with increased incidence of myelogenous leukemia (Milham, 1976). All three patients had been exposed to other chemicals. Ott *et al.* (1978) stated:

> In these cases, varied work histories and the lack of medical history made a retrospective assessment of the possible relationship to benzene exposure very judgmental.

In short, their paper does not substantiate an association between *low-level* chronic exposure to benzene and the induction of ANLL. In an investigation on a smaller subgroup of the above cohort, Townsend *et al.* (1978) reported on health examinations of 282 men occupationally exposed to benzene at TWA concentrations of 1 to 35 ppm during the period 1940–1973. They found no effects of clinical importance. The three deaths reported by Ott *et al.* were already stated above.

In a small case-control study, Brandt *et al.* (1978) reported on 50 cases of acute nonlymphatic leukemia (ANLL) admitted to the University Clinic of Lund, Sweden. Of these 36% had been occupationally exposed to petroleum products (motor fuel) or their combustion products. In patients with chronic myelogenous leukemia (CML) 3 out of 22 (14%) were occupationally exposed and in patients with chronic lymphocytic leukemia none of the 9 patients had been occupationally exposed. In each of three clinical control groups 10 patients out of 100 (10%) were exposed.

Other epidemiologic studies have been carried out in petroleum refineries and

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petrochemical plants. The results are not unequivocal. Theriault and Goulet (1979) examined the mortality of 1205 men employed for more than 5 years in a Canadian oil refinery in East Montreal during the period 1928 through 1976. Survival status was determined and death certificates were reviewed. Expected numbers of deaths were estimated based on age- and cause-specific death rates for the province of Quebec. They found three deaths from leukemia and lymphoma versus 2.36 expected, indicating that there was no excess.

Hanis *et al.* (1979) studied employees of Imperial Oil Company who were exposed to petroleum products during the period 1964–1973 and compared the pattern of mortality to that of a nonexposed group. As regards tumors of the lymphatic and hematopoietic system they found an age-adjusted mortality ratio per 10,000 persons in the refinery exposed group of 1.7 (7 deaths) and in the nonexposed group, of 3.7 (15 deaths). The relative risk of the exposed group thus was 0.46.

Thomas *et al.* (1980) looked at 3105 union members in Texas who worked over the period 1947–1977. They found an increased relative frequency of leukemia and multiple myeloma in white males with more than 10 years membership. The numbers are small, and the type of leukemia and age at death are not mentioned. There was no increase in relative risk of leukemia with an increase in duration of membership or an increase in age.

Rushton and Alderson (1980, 1981) carried out a study on 35,000 workers with more than 1 year service at eight oil refineries in the United Kingdom during the period January 1950 through October 1975. There were 30 cases of leukemia plus 6 cases where leukemia was mentioned as a contributory factor. There was no excess of leukemia in the workers including "some" (say the authors, whereas we would say: many) who were exposed to benzene. There was even a deficit of observed deaths from leukemia compared to the expected national rates. There was no indication of an excess of ANLL. The authors also carried out on the same material a case-control study, using two sets of controls from the total refinery population, one set matched for refinery and year of birth and the other also for length of service. Exposure to benzene was estimated (by industrial hygienists) to be low, medium, or high. The risk of medium- plus high-exposure workers taken together relative to the risk of those with low exposure to benzene approached significance ($P = 0.05$) when length of service was taken into account. "If" the authors say, "there were an increased risk of leukaemia due to benzene exposure, it could only have been one that affected a very small proportion of men within the refinery force." The results were:

Type of leukemia	Number observed	Expected national
Acute lymphocytic (ALL)	3	2.66
Chronic lymphocytic (CLL)	5	5.96
Unspecified lymphocytic (ULL)	2	0.25
Acute myelogenous (AML)	6	12.17
Chronic myelogenous (CML)	4	5.89
Unspecified myelogenous (UML)	5	0.42
Acute monocytic (A. mon.)	4	0.94
Other acute leukemia (A other)	1	2.38
Acute nonlymphocytic (ANLL)	16	15.91

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ISTANBUL SHOEMAKERS

Aksoy and co-workers reported on leukemia and other blood disorders among shoemakers in Istanbul. Aksoy (1978), in a letter to the *Lancet*, refers to 34 cases of leukemia occurring between 1967 and 1975 among 28,500 shoemakers in Istanbul. This represents an incidence of 13 per 100,000 annually, whereas the incidence in the general population was stated to be 6 per 100,000. It should be noted that at the time the concentration of benzene in the air of the workroom of the shoemakers was 150–650 ppm and the exposure lasted from 4 months to 17 years (Aksoy and Erdem, 1978). After benzene was banned as a solvent in 1969, the incidence of leukemia after a peak in 1973 decreased in 1974 and 1975 with no cases reported in 1976, 1977, and 1978. However, in 1979 two new cases in one shoemaker and one rubber worker occurred (Aksoy, 1980). Although the author did not mention this, two cases (or rather one, because the rubber worker does not belong to the shoemaker cohort) in 4 years in 28,500 people is less than the expected incidence in the general population.

ENVIRONMENTAL EXPOSURE

Since benzene in community air derives primarily from petroleum products the following three studies are of interest. The results would indicate that current concentrations do not contribute to the incidence of leukemia.

Demopoulos and Gutman (1980) looked at mortality from lymphomas and leukemias in the period 1950–1960 in New Jersey and compared the rates to the U. S. average. The authors make the annotation:

> Benzene is supposed to be a common air pollutant where there is extensive petroleum refining; this chemical is also thought by some to be leukaemogenic in chronic low-dose exposures. Examination of heavy petroleum counties in New Jersey also fails to reveal any "excess" above the U. S. average.
> These neoplasms were not in "excess" in New Jersey compared to national averages.

For New Jersey white males they found mortality rates from lymphomas and leukemias of 4.93 and 8.74 versus U. S. averages of 4.89 and 8.81, respectively. Clemmesen *et al.* (1980) reported on the incidence of various types of leukemia in Denmark in 1943–1972. They found no major increase in the occurrence of leukemia in Denmark since 1943 and concluded:

(1) there is no excess in incidence from leukemia above the expected in any occupation; and

(2) if benzene should be involved in the overall leukemia pattern such as being a constituent of petrol we would expect a clear increase, considering the enormous increase in the use of petrol since 1943.

Van Raalte (1980) reported on the gasoline consumption and mortality from leukemia in three European countries. In Norway gasoline consumption in the period 1950–1964 increased by 150%; there was no increase in the mortality rate from leukemia 12 years later. In the Netherlands, gasoline consumption doubled from 1955 to 1964. There was no increase in the total number of deaths from leukemia 12 years later and the standardized mortality ratio from leukemia actually decreased. A similar pattern existed for men only. The available figures for Denmark allowed a study of acute nonlymphocytic leukemia as well as of total cases

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of leukemia related to gasoline consumption 15 years previously. Gasoline consumption increased 60% while the total number of cases of leukemia remained about constant and the incidence of acute nonlymphocytic leukemia decreased.

Conclusion. Experience in industry over the last half-century suggests that long-term exposure to high concentrations of benzene in the air of the work place is associated with the occurrence of various blood dyscrasias, including leukemia. There is, however, no evidence in the world literature showing that low-level exposure to benzene is associated with an increased risk of leukemia.

SUSCEPTIBILITY OF WOMEN AND THEIR OFFSPRING

Siou and Conan (1980) found with the micronucleus test in mice that adult females were only half as sensitive as males to intraperitoneally administered benzene. Siou and Sourdeix (1980) found that castrated male mice were as resistant as females whereas treatment with testosterone reversed this increased resistance.

Watanabe *et al.* (1980) reported on a study in 16 women who were exposed to benzene at concentrations up to 40 ppm over a period of 1–20 years. There was no increase in structural or numerical chromosome aberrations and there was a slight decrease in the frequency of sister chromatid exchange. No adverse effects on reproduction were shown in an inhalation study with rats (Bio-Dynamics, 1981) exposed at 300 ppm for 6 hr/day, 5 days/week, from 10 days before conception through the 21st day of lactation.

Murray *et al.* (1981) reported in mice and rabbits, inhaling 500 ppm of benzene, an absence of true teratogenic activity although, of course, signs of maternal and fetal toxicity were present at this high dosage.

Mehlman *et al.* (1981), in their review of the literature, concluded that benzene at nontoxic doses does not pose a teratogenic hazard.

Viadaner and Bros (1972) carried out a case-control study in three U. S. states, New York, Maryland, and Minnesota. They concluded that there was "no relationship between incidence and occupation in women."

Andjelkovic *et al.* (1978) studied a cohort of 1649 female rubber workers exposed during a period of 10 years. They found no case of leukemia.

Conclusion. There is no evidence in the literature which shows that women or their offspring are more susceptible to the clastogenic or leukemogenic action of benzene.

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