

Different Types of Malignancies due to Occupational Exposure to Benzene: A Review of Recent Observations in Turkey

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Since the first description of a case of leukemia due to occupational exposure to benzene, several types of malignancies following the use of this chemical agent have been reported: leukemia, malignant lymphoma, lung cancer, myeloid metaplasia, paroxysmal nocturnal hemoglobinuria, and multiple myeloma. The evidence suggesting a causal relationship between occupational exposure to benzene and development of the various types of malignancies is discussed.

INTRODUCTION

Since the first description of a leukemia case related to occupational exposure to benzene (Le Noire, 1897), several types of malignancies associated with the use of this chemical have been reported. The overwhelming part of these malignancies occurred in the hematopoietic tissue: leukemia, malignant lymphoma, myeloid metaplasia, paroxysmal nocturnal hemoglobinuria (PNH), and multiple myeloma. Despite the lack of evidence showing a causal relationship between chronic exposure to benzene and carcinoma, we have recently observed lung cancer in five patients with long-term exposure to this chemical. The purpose of this presentation is to discuss our recent observations of various types of malignancies associated with occupational exposure to benzene.

MATERIALS AND METHODS

During the period of 1967-1979, we studied 42 patients with leukemia, 9 with malignant lymphoma, 2 with PNH, 2 with myeloid metaplasia, 5 with lung cancer, and 3 with multiple myeloma (total, 63 patients), all chronically exposed to benzene. Fifty-one of the patients were examined at the Hematology and Outpatient Departments of Istanbul Medical School. The remaining 12 subjects (10 with acute leukemia, 1 with PNH, and 1 with multiple myeloma) were seen in other hematology departments of Istanbul and Cerrahpasa Medical Schools and Istanbul Social Insurance Hospital. Forty-nine of these patients have previously been described (Aksoy, 1977; Aksoy *et al.*, 1972a, 1974a, b, c, 1975, 1976a, b). Forty-seven of the cases occurred among a group of 28,500 shoe workers chronically exposed to benzene (Aksoy, 1977; Aksoy *et al.*, 1972a, 1974a, b, c, 1975, 1976a, b). The other 16 patients were employed at different facilities such as print shops, furniture manufacturing workshops, painters' workshops, etc. The working conditions and measurements of benzene in the working environment and in the adhesive sol-

vents used have been described elsewhere (Aksoy, 1977; Aksoy and Erdem, 1978).

RESULTS AND COMMENTS

Leukemia

A causal relationship between chronic occupational exposure to benzene and development of leukemia has now been established beyond doubt. The apparent absence of convincing animal experiments concerning development of leukemia by inhalation or parenteral administration of benzene (Leong, 1977) is of little importance, since three studies have related leukemia to occupational exposure to benzene in Istanbul.

(1) *Incidence of leukemia among shoe workers in Istanbul during the Period 1967–1975.* Studies on workers at shoe manufacturing facilities where benzene was used have demonstrated an increased risk of leukemia (Aksoy, 1977; Aksoy *et al.*, 1974a; 1976a). During 1967–1975 40 leukemic patients with benzene exposure were admitted to the hematology departments of the medical schools in Istanbul, 34 of them being detected among a group of 28,500 shoe workers. The crude incidence of leukemia among this group was 13/100,000 which is significantly higher ($P < 0.01$) than the incidence of 6/100,000 in the general population. This observation provides a more definite evidence than the clinical impression of leukemogenic effect of benzene in man. Our calculation of the incidence of leukemia was probably an underestimation since we were not able to include the leukemic workers who may have been admitted to other hospitals in Istanbul. Table 1 shows the annual number of leukemic shoe workers in Istanbul between 1967 and 1975.

(2) *Decline of leukemia after phaseout of benzene in Istanbul.* As can be seen in Table 1 the peak of occurrence of leukemia among these shoe workers with chronic exposure to benzene occurred in 1973. The number of leukemic workers decreased in 1974 and 1975 to the level of 1969–1970, and none were reported in the subsequent 3 years. In 1979, however, we have observed two new cases associated with long-term exposure to benzene, one in a shoe worker and one in a worker from a rubber plant. The decline in the annual occurrence of leukemia in this group of workers may be attributed to the gradual prohibition and discontinuation of the use of benzene in Istanbul from 1969. The substitutes for benzene at the workplaces studied were analyzed by gas chromatography (Aksoy, 1977; Aksoy and Erdem, 1978). The results showed that most of the substitutes contained no benzene. This decline of leukemia after the phaseout of benzene sup-

TABLE 1
ANNUAL NUMBER OF LEUKEMIA CASES IN SHOE WORKERS WITH CHRONIC BENZENE
EXPOSURE IN ISTANBUL BETWEEN 1967 AND 1975

	Year								
	1967	1968	1969	1970	1971	1972	1973	1974	1975
No. of cases	1	1	3	4	6	5	7	4	3

ports the assumption of a leukemogenic effect of benzene on the shoe workers studied.

(3) *Development of leukemia in pancytopenic patients exposed chronically to benzene.* According to Cronkite (1961) "The finger of suspicion must be pointed at any agent which is able to produce an aplasia of the bone marrow, assuming it will probably be able to produce leukemia also." Indeed, as can be seen in Table 2 a preceding pancytopenic period was present in 26% of these patients. The interval between the onset of the preceding pancytopenic period and that of acute leukemia varied between 6 months and 6 years. Quite often the clinical and hematological appearance of the pancytopenia improved considerably, or the condition even disappeared completely. Despite any such improvement, leukemia developed later. Furthermore, we have performed a follow-up study over 2-17 years of 44 pancytopenic patients with chronic benzene exposure (Aksoy and Erdem, 1978). They had been subjected to high concentration of benzene (150-650 ppm) in their working environment for 4 months to 15 years. The benzene content of the adhesives varied between 9 and 88% (average 50%). Complete remission was seen in 23 patients (52%) and fatal outcome due to complications was observed in 14 pancytopenic patients (32%). In 6 pancytopenic patients (14%) leukemia developed after a period of 6 months to 6 years. The development of leukemia in 6 out of 44 pancytopenic patients is a further evidence for the leukemogenic effect of benzene in man.

(4) *Difference in the distribution of the types of leukemia found in the individuals chronically exposed to benzene and those of nonexposed leukemic patients.* In order to illustrate this difference we summarized our results on the distribution of the types of leukemia in both the exposed and nonexposed groups (Table 3). The age distributions of nonexposed and exposed leukemic individuals were similar. Acute myeloblastic leukemia was the most frequently observed type of leukemia in exposed workers, followed by acute erythroleukemia and preleukemia. The nonexposed group showed chronic lymphoid leukemia in 26% of the cases while

TABLE 2
OCCURRENCE OF PANCYTOPENIC PERIOD PRECEDING LEUKEMIA IN 42 CASES WITH
LONG-TERM EXPOSURE TO BENZENE

Types of leukemia	No. of leukemic patients with preceding pancytopenic period (total number in parenthesis)	Percentage
Acute myeloblastic leukemia	3 (16)	19
Preleukemia	4 (7)	57
Acute erythroleukemia	2 (8)	25
Acute monocytic leukemia	1 (3)	33
Acute undifferentiated leukemia	1 (1)	100
Acute lymphoblastic leukemia	0 (4)	0
Acute promyelocytic leukemia	0 (1)	0
Chronic myeloid leukemia	0 (2)	0
Total	11 (42)	26

none of the exposed group exhibited this form of leukemia. More importantly, 50% of the nonexposed group had chronic myelogenous leukemia while this condition was only found in 5% of the exposed group. As shown in Table 3, the distribution of leukemia types in the exposed group is significantly different from the one in the nonexposed group (Aksoy, 1977; Aksoy *et al.*, 1976a). Previous studies by Vigliani and Saita (1966) and Forni and Vigliani (1974) indicated, in accordance with our studies, that acute myeloblastic leukemia is the most frequently observed type following chronic exposure to benzene. Furthermore, the high frequency of acute erythroleukemia and preleukemia and the rarity of chronic leukemia are very striking findings.

Malignant Lymphoma

In contrast to leukemia, a causal relationship between chronic exposure to benzene and malignant lymphoma has not been proven. Very few case reports suggest exposure to benzene as a possible etiological factor for the development of malignant lymphoma. In 1947 Bousser *et al.* reported a case of lymphosarcoma which occurred 3.5 years following the cessation of exposure to benzene. A few cases of malignant lymphoma associated with chronic exposure to benzene have been described later (Paterni and Sarnari, 1965; Casirola and Santagati, 1969). In 1974 Aksoy *et al.* described six cases of Hodgkin's disease associated with a history of benzene exposure. These patients were chronically exposed to benzene for a period ranging from 1 to 28 years with a mean of 11 years. The patients comprised three shoe workers, a compass repairman, a car painter, and a television repairman. Their ages varied between 27 and 61 years with a mean of 39 years. These six patients belonged to a series of 94 cases of Hodgkin's disease, of whom 25 were workers, all admitted to the Internal Medicine Clinic of Istanbul Medical School during the period of 1968 to 1972. Despite the lack of exact

TABLE 3
OCCURRENCE OF DIFFERENT TYPES OF LEUKEMIA IN 42 INDIVIDUALS WITH CHRONIC EXPOSURE TO BENZENE AND IN 50 NONEXPOSED PATIENTS^a

Types of leukemia	Patients exposed to benzene		Nonexposed patients	
	No.	Percentage	No.	Percentage
Acute myeloblastic leukemia	16	38	8	16
Acute lymphoblastic leukemia	4	10	13	26
Acute erythroleukemia	8	19	1	2
Preleukemia	7	17	2	4
Acute monocytic leukemia	3	7	3	6
Acute promyelocytic leukemia	1	2	0	0
Acute undifferentiated leukemia	1	2	0	0
Chronic myeloid leukemia	2	5	10	20
Chronic lymphoid leukemia	0	0	13	26
Total	42	100	50	100

^a χ^2 Test (acute leukemia and preleukemia vs chronic leukemia): $P < 0.001$.

statistical data, we suggested that chronic exposure to benzene may play a role in the development of Hodgkin's disease or malignant lymphoma. Some clinical and experimental data suggest that benzene has a deleterious effect on lymphocytic or reticuloendothelial tissue. Wirtschafter and Bischel (1960) showed that reticuloendothelial responses could be observed in the lymphnodes, spleen, thymus, and bone marrow of the rat after a single injection of benzene. Reticuloendothelial cells of the macrophage type were increased in the lymph nodes and thymus following benzene injections and decreased to normal level after a short time. On the other hand, the existence of relative or absolute lymphopenia in chronic benzene poisoning is well known (Goldwater, 1941; Aksoy *et al.*, 1972b). The lymphopenia found in chronic benzene poisoning can be considered a result of deleterious effect of benzene on the lymphocytic tissue. In view of the above-mentioned facts and malignant lymphoma being a proliferative disorder of lymphoreticular tissue, an etiological relationship between chronic exposure to benzene and malignant lymphoma may not be surprising. In addition to the six patients with Hodgkin's disease (Aksoy *et al.*, 1974c) we recently studied three cases of malignant lymphoma: histiocytic lymphoma in a 42-year-old worker, lymphocytic lymphoma in a 47-year-old worker, and Hodgkin's disease in a 36-year-old shoe worker. All were chronically exposed to benzene with a duration varying from 10 to 17 years.

Lung Cancer

A causal relationship between chronic exposure to benzene and the occurrence of lung cancer in man has so far not been described. We have recently observed five patients with lung cancer associated with long-term exposure to benzene. Table 4 shows some clinical and laboratory data of these patients. In these cases duration of exposure to benzene varied between 8 and 35 years. Despite this exposure only three patients showed hematologic abnormalities such as mild leucopenia or lymphopenia. In addition, these patients were heavy or moderate smokers, and in two cases the histopathological diagnosis was oat-cell carcinoma. It should be stressed that no benzo[a]pyrene has been detected by ultraviolet spectrophotometry of benzene available in Turkey (Aksoy and Erdem, 1978); thus, the malignancies described above cannot be attributed directly to this carcinogenic agent in benzene. Benzene is mainly absorbed via the lungs and about 40% of the absorbed portion of benzene is exhaled unchanged; after 24 hr a small percentage of benzene can still be detected in the expired air (Sherwood and Carter, 1970). Therefore, a local carcinogenic effect of benzene on the lungs is possible. On the other hand, because our patients were also smokers, the possible role of smoking in the development of lung cancer should also be considered. Thus, chronic benzene exposure may not be the only causative factor in the development of lung cancer in our patients. Furthermore, if one considers Cronkite's (1961) suggestion that any agent capable of producing an aplasia of the bone marrow may produce leukemia and that any agent which will cause a cancer may give rise to leukemia when transported to the hematopoietic system, one may assume that the reverse may also be true. Benzene, a leukemogenic substance, may therefore cause lung cancer and this possibility deserves further attention.

TABLE 4
SOME CLINICAL AND LABORATORY DATA IN FIVE PATIENTS WITH LUNG CANCER ASSOCIATED WITH LONG-TERM EXPOSURE TO BENZENE

Case No.	Age	Profession	Duration of exposure (years)	Smoking habits (cigarettes per day)	Diagnosis	No. of white blood cells/ μ l	Histopathology
1	31	Shoe worker	17	10/day for 10 years	Bronchogenic carcinoma of right upper lobe	4900	Small anaplastic cell (oat cell)
2 ^a	54	Physician	15	20/day for 40 years	Bronchogenic carcinoma of right upper lobe	7300	Small anaplastic cell (oat cell)
3 ^a	49	Orthopedic shoe manufacturer	8	20/day for 10 years	Bronchogenic carcinoma of right middle lobe	3000	Not performed
4	40	Shoe worker	15	40/day for 15 years	Bronchogenic carcinoma of right middle lobe	6800	Undifferentiated epithelioma
5 ^c	57	Dyer	35	20/day for 27 years	Bronchogenic carcinoma of left lower lobe	5200	Undifferentiated carcinoma

^a Worked in a laboratory of gynecological endocrinology.

^b Died from cerebral and liver metastases.

^c Had liver metastases and absolute lymphocyte count of $312/\mu$ l, i.e., 6% lymphocytes in the differential count, possibly as the result of chronic benzene poisoning.

Myeloid Metaplasia

The causal relationship between chronic exposure to benzene and myeloid metaplasia was already suggested by Gall in 1938. Three years later Rawson *et al.* (1941) claimed that benzene was an etiologic factor in three out of six workers with myeloid metaplasia; unfortunately no details of the cases were given. One case of myeloid metaplasia associated with chronic exposure to benzene was described by Port and Hyman (1965). In 1975 the present author and his associates described a case of fatal myeloid metaplasia 8 years after the occurrence of aplastic anemia due to chronic exposure to benzene (Aksoy *et al.*, 1975). During the pancytopenic period, the bone marrow was hypercellular with marked erythropoietic hyperactivity. In 1977 we have observed another case of myeloid metaplasia associated with chronic benzene exposure. A 21-year-old technician was exposed to benzene for 4 years before the development of myeloid metaplasia. Surprisingly, the incidence of myeloid metaplasia in chronic benzene poisoning is lower than that of leukemia, aplastic anemia, and even that of malignant lymphoma. Our series included at least 46 patients with aplastic anemia, 42 with leukemia, and 9 with malignant lymphoma. However, only 2 cases of myeloid metaplasia, 1 following aplastic anemia, were found.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Patients with aplastic anemia and PNH often develop acute leukemia and, during the course of leukemic disease, red cell properties characteristic of PNH may occur. As Goldstein (1977) pointed out, these facts suggest that PNH is a paraneoplastic disorder. PNH is considered a rare disease. Hitherto only three cases of PNH associated with chronic exposure to benzene have been reported. As early as 1948, Croizat described a case of PNH associated with chronic exposure to benzene. The present author and his associates (Aksoy *et al.*, 1975) described an atypical case of PNH following 10 years of exposure to benzene. The patient was 74 years old. Akman *et al.* (1971) previously reported a case of PNH with the features of intravascular consumption coagulopathy. Although not mentioned in the paper, this patient had been exposed to benzene (Aksoy *et al.*, 1975).

Multiple Myeloma

Only one report dealing with the relationship between chronic exposure to benzene and multiple myeloma has been published. Torres *et al.* (1970) described two cases of IgG multiple myeloma in patients chronically exposed to benzene for 6 and 11 years. In our series a possible causal relationship between multiple myeloma and chronic exposure to benzene was found in three individuals (Table 5). Only in one of them, a technician in an airplane repair plant, we found a short period of moderate pancytopenia associated with hypoplastic bone marrow. Rapidly, a severe myeloma kidney and Bence-Jones proteinuria developed. Despite the low percentage of atypical plasma cells in bone marrow, 21% plasma cells were found in the peripheral blood smear. The second case, a manager in a plastic plant who was occasionally exposed to benzene for 15 years, had monoclonal hypergammaglobulinemia, IgG of lambda type, and 35% of atypical plasma cells in the bone marrow. Despite this finding, no sign of bone involvement ap-

TABLE 5
SOME CLINICAL AND LABORATORY DATA IN THREE INDIVIDUALS WITH MULTIPLE MYELOMA ASSOCIATED WITH CHRONIC EXPOSURE TO BENZENE

Case No.	Age	Profession	Duration of exposure (years)	Preceding pancytopenic period	Bone marrow cellularity (% of plasma cells)	Percentage plasma cells in blood film	Immunoglobulin (mg/liter)	Bence-Jones protein-uria	Kidney involvement	Osteolytic lesions	Type of multiple myeloma
1	36	Technician in airplane plant	7	+	Hypoplastic (5)	21*	IgG 3400	++	+	-	Bence-Jones
2	59	Manager in plastic plant	15	-	Normocellular (35)	0	IgG 4888	-	-	-	IgG, Lambda
3	63	Shoe worker	15	-	Normocellular (41)	0	—*	-	-	++	—

* Appeared in final stage.
* Not performed.

peared for a subsequent 10-year period. The last patient, a shoe worker with 15 years of chronic exposure to benzene, had classical findings of multiple myeloma such as osteolytic lesions in cranium and vertebrae and 41% of myeloma cells in the bone marrow. In agreement with the observations by Torres *et al.* (1970), our findings of multiple myeloma associated with chronic exposure to benzene indicate that benzene may be an etiologic factor in the development of multiple myeloma.

CONCLUSIONS

Until recently, heavy occupational exposures to benzene were frequent in Turkey. Several types of malignancies have been observed with association to such exposures. An increased incidence of leukemia occurred among shoe workers during 1967–1975, but the incidence has recently declined, possibly as a result of phaseout of benzene. A pancytopenic period was found in 26% of the benzene-associated cases of leukemia. Further, acute myeloblastic leukemia, acute erythroleukemia, and preleukemia were the most frequent types of leukemia, a distribution which was significantly different from that in a control group of leukemia patients without benzene exposure. Malignant lymphoma, another malignancy, was observed in nine cases associated with chronic exposure to benzene; one case of paroxysmal nocturnal hematuria related to benzene was also found. Further, occupational benzene exposure was verified in three cases of multiple myeloma. Five patients with carcinoma of the lung, all smokers, had been chronically exposed to benzene. Though these case reports do not prove a causal relationship between benzene exposure and the various malignancies, the frequent finding of this association suggests that benzene may not only cause leukemia but also be involved in other types of malignancy.

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