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Leukaemia in benzene workers: a retrospective cohort study

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ABSTRACT A retrospective cohort study was conducted in 233 benzene factories and 83 control factories in 12 cities in China. The benzene cohort and the control cohort consisted of 28 460 benzene exposed workers (178 556 person-years in 1972–81) and 28 257 control workers (199 201 person-years). Thirty cases of leukaemia (25 dead and 5 alive) were detected in the former and four cases (all dead) in the latter. The leukaemia mortality rate was 14/100 000 person-yean in the benzene cohort and 2/100 000 person-years in the control cohort: the standardized mortality ratio was 5·74 (p c 0·01 by U test). The average latency of benzene leukaemia was 11·4 years. Most (76.6%) cases of benzene leukaemia were of the acute type. The mortality due to benzene leukaemia was high in organic synthesis plants followed by painting and rubber synthesis industries. The concentration of benzene to which patients with a leukaemia were exposed ranged from 10 fo 1000 mg/m^3 (mostly from 50 to 500 mg/m^3). Of the 25 cases of leukaemia. seven had a history of chronic benzene poisoning before the leukaemia developed.

In addition to its presence in the general environment as a pollutant benzene is still used in vanous industnes and in China some 500 000 workers arc exposed to benzene or a benzene containing mixture (SN Yin *et al*, reported at scientific committee on maximum permissible limits meeting, London. 1983). The aetiological relation between exposure to benzene and leukaema has been reported by several authors including Vigliaru and Saita,[1] Ishimaru *et al*,[2] Aksoy,[3] and Rinsky *et al*.[4] Whereas the leukaemogenic property of benzene in man has been well established,[5] the epidemiological data are still considered insufficient and. especially, there has been no epidemiological report on benzene leukaemia in China To study the causal relation between benzene and leukaemia a further retrospective cohort study was undertaken in 1982–3. The present paper reports the major findings of the study The relation of other malignancies to exposure to benzene will be described in a separate report.[6]

Materials and methods

The study was conducted in the cities of Shanghai, Tianjin, Chengdu, Chongqing, Haerbin, Shenyang, Jinzhou. Zhengzhou, Luoyang, Guangzhou, Nanchang. and Kaifeng, China. in 1982–3 The members of the benzcne group were selected from 233 painting, shoe-making, rubber synthesis. leather. and adhesive and organic synthesis factories in the 12 cities ated. The subjects had worked in those factories for at least half a year between 1 January 1972 and 31 December 1981. Those in the control cohort were from 83 machine production. textile, and cloth factories in which there were no known exposures to benzene or other occupauonal carcinogens. The sex and age distnbution in the control group were similar to that of the benzene group. The controls had also worked in the same cities for at least half a year dunng the same pcnod. The drop out rate was 0 8% in the benzene cohort and 1·3% in the control cohort. Thus the benzene cohort consisted of 28 460 workers (15 643 men. 12817 women) and the control cohort of 28 257 subjects (16621 men. 12336 women). Both cohorts were followed up from 1972 to 1981 so that 178556 person-years were obtained for the benzene cohort and 199201 the control cohort.

Items investigated included the occupauonal history of the individuals. a history of benzene poisoning

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Table 1 *Mortality and relative risk of leukaemia*

	Benzene			*Controls*				
Sex	*Person-years*	*Deaths*	*Mortality*	*Person-years*	*Death*	*Mortality*	*RR**	*p*
Men	100 025	17	7·00	122 268·5	3	2·47	6·88	<0·01
Women	78 531	8	10·19	77 932·5	1	1·28	7·24	<0·05
Toul	178 556	25	14·00	199 201·0	4	2·01	691	<0·01

*RR = Relative risk defined as the ratio of mortality B to mortality C

Table 2 *Standardised mortality ratio (observed expected) for benzene leukaemia*

	Deaths				
Sex	*Observed*	*Expected*	*SMR*	*U*	*P*
Men	17	*3.392*	5·01	3 3 0	<0·01
Women	8	0·964	*8.30*	2 49	<0·05
Toul	25	4 3%	5 74	4 13	<0·01

Table 3 *Mortality rate of leukaemia in various industries*

Industry	*Workers*	*Person-years*	*Leukaemia*	*Mortality**
Painting	13604	87935·5	14	15·9
Paint producing	4533	26859	2	7·4
Rubber	2208	13544	2	14·8
Glueing	1512	11082	1	9·0
Shoemaking	3811	23117	1	4·3
Leather	323	1795	—	—
Organic synthesis	1976	12037	5	41 5
Miscellaneous	493	2685 5	—	—
Total	28460	178556	25	14·0

*Mortality rate: unit, 1 100 000 person-years

and other specific disease, death certificates (for all known deaths). working conditions. and atmospheric benzene concentrations in the workplaa: this information was collected from factory records. Benzene concentrations were determined by means of grab samples followed in the main by gas chromatographic analyses. The cases of kukaemia. aplastic anaemia. and benzene poisoning were obtained from hospital records; the diagnosis of benzene poisoning was established based on China national criteria for diagnosis of benzene poisoning' including occupational history. 8 peripheral leukocyte count of less than 4000 cells/mm^3, and symptoms or signs in the central nervous system. The vital status was followed up until 31 December 1981. The standardized mortality ratio (SMR) was calculated with reference to the deaths in the control cohon

Results

MORTALITY AND RELATIVE RISK OF LEUKAEMIA

In total. 30 cays of benzene leukaemia were found in the benzene cohort. of uhom 25 had died and five were alive in 1972–81. lour cases of leukaemia were found in the control cohort call dead) The mortality rate of leukaemia was 14 100 000 person-years in the benzene cohort and 3 01 100 000 person-years in the control cohort The relative nsk of kukaemia for *the* benzene workers was *6* 97 and was significantly high both in men and women (table 1)

As 25 cases of benzene leukaemia (excluding five live cases) were observed compared with 4 3 expected. the SMR was 5·01 for men. 8 30 for women. or 5.74 for both (tabk 2) When the mortality due to benzene leukaemia was compared in the various industries. the rate was highest in organic synthesis factona followed by the painting and rubber synthesis industnes (tabk 3)

AGE AND LATENCY IN CASES Of LEUKAEMIA

The ages of the patients with leukaemia in the benzene cohort ranged from 24 *to 62* with a mean of *39.7* years (38.1 for men. 36·0 for Women). The mean age of the patients with kukaemia was lower in the ben-

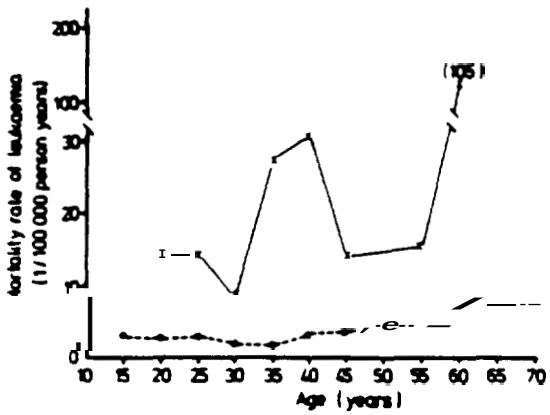


Fig 1 *Leukaemia mortality rate in male workers at various ages Solid line indicates mortality rate among workers in benzene cohort Broken line indicates values among male adults in big cities in China (data obtained from the National Control Office of the Ministry of Health, 1979)*

zene cohort (38·1 years when both sexes combined) than in the control cohort (46·7 years). The mortality for leukaemia increased in the age range 35–45 in the benzene cohort (fig 1) The average age of the worken when exposure began was 27·8 years. Figure 2 shows the relation between the start of exposure and the time of diagnosis (the latency period). Among the 30 cases of leukaemia in the benzene cohort the avenge latency was 11·4 years (minimum 0·8, maximum 49·5 years, respectively). The cumulative mortality of kukaemia was in proportion to the dunuon of exposure up to 20 years and then levelled off (fig 3), as

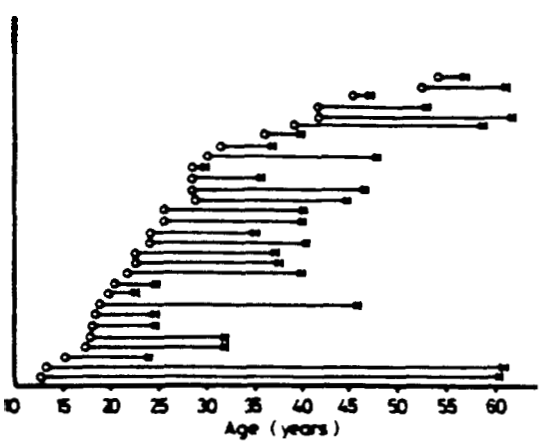


Fig 2 *Age at start of exposure, of diagnosis of leukaemia, and latency of 30 cases of leukaemia. ○ indicates ages of the initiation of the exposure and ● ages at which diagnosis of leukaemia was established. Connecting lines show period of latency.*

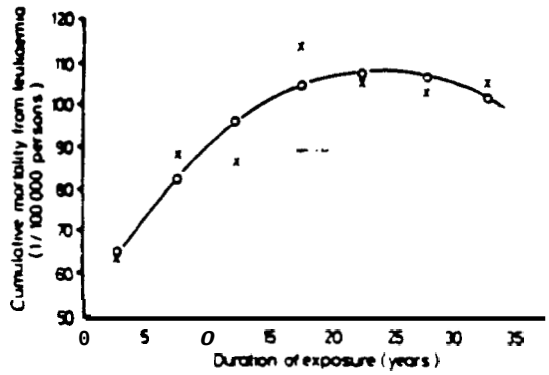


Fig 3 *Relation of cumulative morralrrv of leukaemia with duration of exposure Crosses indicate cumulative mortality of leukaemia observed Open circles indicate value estimated by an orthogonal polynomical curve of*

$$y = 55\,56 + 4\,4471\,x - 0\,09248\,x^2$$

where y is cumulative mortality (1/10⁵ persons) and x is duration of benzene exposure (wars)

was well described by an orthogonal polynominal curve of the form:

$$y = 55{\cdot}56 + 4{\cdot}4471\,x - 0{\cdot}09248\,x^2$$

where y is the cumulative mortality (1 10^5 persons) and x is the duration of benzene exposure (years).

Tabk 4 *Benzene concentration in workplaces where cases of leukaemia were observed*

No of cases	Industry	Benzene concentration (mg/m³)
1	Laboratory in rubber factory	136·2 (99·3–173·1)
2	Chemical reagent	253·9 (20–440·2)
3	Paint	50·2 (0–220)
4	Glue	100 (30–150)
5	Paint	190·6 (5–1200)
6	Paint	26·5 (0–250)
7	Paint	15·5 (3–39·4)
8	Paint	15 (10–20)
9	Paint	203·1 (25–500)
10	Paint	239·3 (0–4736)
11	Paint	30·2 (0–341·3)
12	Benzene refined	474·2 (0–4024)
13	Chemical analysis	87·8 (5·3–170·2)
14	Paint	1104·7 (3·5–3826)*
15	Cleaning	6·5 (1·6–11·4)
16	Organic synthesis	15·4 (1·4–50·0)
17	Paint	243·6 (0–618)
18	Shoemaking	13·3*
19	Paint	190·8 (42–453)
20	Paint	468·1 (13·7–5508)
21	Paint	301 (250–352)
22	Paint	118·9 (31·3–206·4)
23	Paint	575·2 (2·2–6102)
24	Paint producing	21·4 (0·7–80·1)
25	Paint	96·8
26	Paint	68·2 (54·7–138·8)
27	Organic synthesis	8·3 (6·5–10)*
28	Paint	37·1 (2·1–94·1)
29	Rubber	86·4 (4·9–116·2)
30	Paint producing	159·5 (10–733)

*Single measurement.

BENZENE CONCENTRATION IN THE WORKPLACES WHERE CASES OF LEUKAEMIA WERE OBSERVED

Table 4 shows the benzene concentrations in the workplaces where the 30 patients with leukaemia had worked. The mean concentrations varied in a wide range of 10 to 1000 mg/m^3 but were mostly in the range 50–500 mg/m^3.

LEUKAEMIA MORTALITY AMONG CASES OF BENZENE POISONING

In the benzene cohort 1% cases of chronic benzene poisoning and aplastic anaemia were found; seven of the 25 patients with leukaenua bad a history of chronic benzene poisoning (for criteria of the diagnosis, see materials and methods) or aplastic anaemia, or both, before being diagnosed as having a kukaerma. The kukaemia mortality among benzene poisoning cases was 700·70/100 000 person-years, and was 49 times higher than that in the benzene workers (14/100 000).

TYPES OF BENZENE LEUKAEMIA

Among the 30 cases of benzene leukaemia, 23 (76.7%) were acute and seven (23·3%) chronic. The cases of acute leukaemia comprised 13 myelogenous, four monocytic, two myelocytic-monocytic, one erythromyelocytic, and three lymphocytic leukaemia. Chronic leukaemia included five with myelogenous leukaemia, one lymphosarcomatous leukaemia, and one unidentified case.

Discussion

Benzene is a well established human carcinogen.[5] In addition, Goldstein *et al* and Maltoni *et al* have presented data suggesting that benzene may cause kukaemia in rodents.[8 9] About 289 benzene exposure related cays of kukaemia have been reported in Italy, China, France, Japan, the Soviet Union, Turkey, and the United States.[10] In the past 20 years several epidemiological studies have shown that long term occupauonal exposure to benzene at high concentration is associated with the occurrence of vanous blood dyscasias including leukaemia.[11] For example, Aksoy reported 34 cases of leukaenua among shoemakers in Istanbul in 1967–75[3]; the incidence of leukaemia was 13 100 000 in shoemakers by contrast wth 6,100 000 in the general population. Rinksy *et al* investigated two pliofilm manufacturing plants and found that the SMR for benzene kukaerma was 560.[4] In a recent study of a chemical plant where benzene had b a n used as a matenal for organic synthesis DeCouflé *et al* observed four deaths due to lympho-reticular cancers (2 leukaemia, 1 leukaenua multiple myeloma, 1 multiple myeloma) in a 30 year follow up study of 259 male workers by contrast with 1·1 expected deaths". no quantitative data on benzene exposure were available, however Arp *et al* reviewed the history of solvent use, raw materials specification, and the job description of 15 cases of lymphatic leukaemia in a rubber industry and comparing them with 30 matched controls found that patients with leukaenua had spent more time in jobs with potential exposure to coal tar based benzene and xylene." Tsai *et al* by contrast found no deaths from kukaerma in a study of 454 workers who had been employed in a refinery from 1952 to 1978 and exposed to benzene either at 0·14 ppm (median; refinery workers) or 0·53 ppm (median; workers in benzene related units).[14] In the present retrospective cohort study of workers exposed to benzene the mortality from leukaemia was higher than that in the control cohon (SMR 574 for men + women. 501 for men. 830 for women) being in line mtb the findings by Rinsky *et al*.[4]

The mean latency pcnod of benzene leukaemia was 11·4 years (range 0·8 to 49·5) (fig 2). It is similar to the observation by Vigliani and Saita of 1–46 years,[1] Goguel *et al* of 1–20 years,[15] and Infante *et al* of 2–21 years.[16] The average age of initial exposure to benzene among the cases of kukaerma was 27.8 years. When 11·4 years of latency is added the sum is about 39 years, which falls in the age nnge (35–45) of peak kukaemia mortality (fig 1). This may explain why the kukaemia mortality was highest in those aged 35–45.

With regard to the benzene concentraton to which patients mth kukaemia were exposed, some authors have estimated that it ranged from 200 to 600 ppm without exact details.[17 18] Recently, Rinsky *et al* reported that their patients were exposed to benzene at 16–100 ppm, only slightly over the current OSHA standard of 10 ppm.[4] In the present study the benzene concentrations in the workplaces where the patients had worked were reported to be 10–100 mg/m^3 (about 3–300 ppm) and mostly in the range 50–500 mg/m^3 (about 16–160 ppm), the levels king similar to the observation by Rinsky *et al*.[4] There remains a possibility that kukaemia may develop–among tbe less heavily exposed workers. In fact in the present study three cases of leukaemia were associated with a benzene concentraton of 10 mg/m^3 in the workplaa air even though the occupauonal hygiene data were not adequate for quantitative estimation of exposure intensity. In this connection Infante *et al*[20] cited the fact that Kligerman *et al* (paper presented at the international symposium on sister chromatid exchange, Brookhaven, 1984) had detected a significant increase in sister chromaud exchanges (SCE) in pcnpheral lymphocytes and in the micronuclei in bone marrow erythrocytes of mice exposed

to benzene at 10 ppm for only 10 hours. By contrast, Sarto *et al* found no significant increase in SCE in the blood of the workers exposed to benzene in the range of 0·2 to 12·4 pm. although changes in chromosomal aberration were significant.[20] Thus this possibility apparently deserves further attention.

It should be noted that seven of the 25 patients had had a history of chronic benzene poisoning such as leukopaenia or aplastic anaemia, or both, before the leukaemia developed. The leukaemia mortality was as high as 700·70/100 000 person-years in cases of chronic benzene poisoning. Aksoy also observed the development of 13 cases of leukaemia in 51 pancytopaenic patients with benzene exposure.[21] Thus a clox relation between leukaemia and benzene poisoning should be considered. Accordingly, it may be deduced that the prevention of benzene poisoning, is the best way to prevent benzene leukaemia. The way to monitor preleukaemic changes in benzene poisoning, however, remains lo be established.

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