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Risk assessment of leukaemia and occupational exposure to benzene

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ABSTRACT Experimental toxicological studies have offered clear evidence that benzene induces haematopoietic neoplasms, and it is generally accepted that exposure to benzene is a risk factor for leukaemia, in particular for acute non-lymphatic leukaemia. Quantitative aspects of benzene risk assessment are still a matter of controversy, however. In several risk assessments an estimated 50 deaths from leukaemia per 1000 deaths would arise from exposures to benzene of 10 ppm during a working life of 30 years. The assessment presented in this paper leads to lower estimates, which are more in agreement with the weak toxicological data. Furthermore, an approach is presented to incorporate the results of low exposure epidemiological studies into the process of quantitative risk assessment.

In the past decades a substantial body of knowledge has accumulated regarding the long term health effects of occupational exposure to benzene. In addition to experimental data, this consists of epidemiological data mainly from retrospective cohort studies of workers occupationally exposed to benzene. Except for the ability of benzene to cause non-malignant blood anomalies, the main chronic health effect of concern is the increased mortality due to leukaemia and, in particular, acute non-lymphatic leukaemia: several investigators have stated that this is the only increased risk after exposure to benzene. Nevertheless, other investigators have pointed out that benzene induces a variety of malignant neoplasms, including lymphatic leukaemia and lymphomas.'" The relation between exposure to high concentrations of benzene and the risk of leukaemia is well documented and generally accepted. Case reports and epidemiological confirmations have led to regulatory legislation throughout the world in the field of occupational exposure, and exposures experienced by the general population.[1–10] Several risk assessments have been conducted for occupational exposures.[11–15] In a recent review the authors presented a risk assessment based on the results of a retrospective cohort study of 1006 exposed workers, applying a linear dose-response relation."

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Following a request from the Minister of Welfare, Public Health and Culture, a committee of the Health Council of The Netherlands has drawn up a somewhat different risk assessment for the risk of leukaemia after exposure to benzene in ambient air. It is the purpose of this article to apply this risk assessment to occupational exposures to benzene.

Several weaknesses of epidemiological data can be identified that may form a source of controversy. The first weakness is the lack of accurate and reliable data regarding the exposure levels that existed in the past and have been experienced by the studied cohorts. This is not a particular problem in the course of a qualitative risk assessment: in other words to assess if exposure to high concentrations of a certain chemical is a risk factor for a particular neoplasm. In the course of a quantitative risk assessment, however, the estimation of past exposure will have substantial impact on the outcome of the assessment. A second weakness of epidemiological data is the lack of information regarding the mechanisms, leading to the increased risk observed. Insight into the mechanism thereof is of great importance in the determination of the extrapolation model to be applied to assess the risks related to low exposure levels. The choice of extrapolation model may also have a great impact on the outcome of the risk assessment. A major issue is whether or not the chemical should be considered as genotoxic or not. In the case of a non-genotoxic agent it is customary to take a no-effect level approach and

pply a safety factor to be on the safe side. In the case f a genotoxic agent a non-threshold approach is ener lly applied because it may be argued that even a mall dose may provide a carcinogenic effect. The non-hreshold approach does not imply that the extrapola-on model is linear or logistic. After a brief review of xperimental toxicologic data of the carcinogenic otency of benzene, several remarks will be made egarding the available epidemiological data. Then the sk assessment proposed by the Health Council of he Netherlands will be described.

xperimental toxicological data

adioactive labelled benzene has been reported to be corporated into nucleic acids in the liver, spleen, one marrow, and kidney cell of mice and rats.[16–18] veral recent publications have made covalent bind-g of benzene metabolites to DNA even more ausible.[19 20] These investigations were conducted by eans of isolated bone marrow mitochondria and ir levance for in vivo genotoxicity is at least estionable. Investigations of the effects of benzene DNA repair and the occurrence of unscheduled NA-synthesis in mammalian cell cultures''[22] and in cteria[23] have so far not yielded any evidence of DNA teraction. Despite extensive efforts there are no dications that benzene is capable of inducing gene utations in bacteria, yeasts, drosphila, or mam-alian cells if tests not capable of discriminating tween gene mutations and recombinations are clud d.[24] Benzene has been shown to be capable of duci g chromosome aberrations in yeast, fungi, ects. and somatic mammalian cells, including man lymphocytes. Chromosome breakage pheno-ena such as translocations have been found in vitro d in vivo in mammalian cells. These chromosome errations were observed with benzene concen-ations lower than 10 ppm. Several in vivo experi-nts indicate that the sensitivity of laboratory mals to clastogenic effects indicate that the sensi-ity of laboratory animals to clastogenic effects rea es with containing exposure.[25 26] Benzene has en tested for neoplastic transformation in a variety test systems. Only in Syrian hamster cells was an rease in the incidence of transformed cell clones served.[27 28] Benzene is also capable of increasing the currence of tumours in Zymbal's gland, a compara-ely rare organ for tumour formation in laboratory mals.[29] On the basis of the multiple site carcino-nicity in animals, benzene may be considered as a ent carcinogen in animals and the carcinogenic oces should in principle be viewed as a stochastic oces

Epidemiological data

After case reports were published indicating a possible relation between exposure to benzene and the occurrence of leukaemia, many epidemiological studies in this field were started and an extensive review has recently been published." The findings of these studies leave no doubt that workers exposed in the past to high concentrations of benzene have experienced an increased mortality from leukaemia. Both case-control studies and retrospective cohort studies have confirmed this relation. Several studies, however, in low exposure groups have reported contradictory results. For instance, in a retrospective cohort study of about 13 500 workers in the rubber industry an excess mortality risk for lymphatic leukaemia was observed[9] and not for non-lymphatic leukaemia as has been reported by other epidemiologists. In several other large studies of workers exposed to low concentrations of benzene no indications were found that these cohorts had experienced increased mortality for leukaemia. In a study of 38 800 workers employed in the petrochemical industry 18 cases of leukaemia were observed compared with an expected number of 23.[30] In a study of similar size (34781 workers) in the oil industry 30 deaths from leukaemia were observed, compared with an expected number of 32." In this study, however, a dose response relation appeared to exist, which was shown by means of a nested case-control study design.[32] Again this *case*-control study confirmed the existence of a risk of leukaemia after exposure to high concentrations of benzene. A third study of workers exposed to benzene that should also be regarded as negative is the study conducted by Parkes *et al* in the British rubber industry." In this study of 33 815 workers, 31 cases of leukaemia were observed compared with an expected number of 28.

As has been pointed out by Hernberg, the interpretation of negative results of epidemiological studies is complicated.[34] With a negative outcome, it is not always clear whether the finding is an effect of methodological deficiencies or if there actually is no increased risk present in the cohort and exposure level under investigation.

The greatest weaknesses of the three large studies of low exposures are the lack of quantitative exposure data and the possibility that a proportion of the "exposed cohort" had not been exposed to benzene at all. Despite these weaknesses, the committee of the Health Council of The Netherlands decided not to disregard these findings in establishing a risk assessment. Thus the committee was left with the task of incorporating positive results of high exposure studies and negative results of low exposure studies in a risk assessment, low exposures being defined as lower than

a time weighted average exposure of 10 ppm which is the current threshold unit value in many countries. This contradictory conception has also been supported by the European Chemical Industry Ecology and Toxicology Centre." As a consequence it was decided not to estimate an overall relative risk for leukaemia after exposure to benzene, as has been done in the evaluation of vinyl chloride.[36] Two separate risk assessments were made, both based on the findings of epidemiological studies. The first departed from the findings in high exposure studies, the second from the findings in low exposure studies. Although the risk assessment conducted by the committee was intended for risks experienced by the general population, it may also be applied to the occupational environment.

RISK ASSESSMENT BASED ON STUDIES OF HIGHLY EXPOSED WORKERS

Before embarking on a risk assessment several assumptions must be made. The first deals with the magnitude of risk after a particular exposure dose. The second is concerned with the extrapolation model. The first assumption may be derived from several cohort studies. A reasonable estimate of this risk, based on Rinsky's risk assessment, is that workers exposed on average to 40 ppm over a period of 10 years have experienced a fivefold increase in the risk of dying from acute non-lymphatic leukaemia (SMR = 500).[13] Assuming a stochastic working mechanism, if a doubling of the dose also implies a doubling of the risk, a linear extrapolation model is suitable. Such a model may be formulated as:

$$SMR = 100 + b \times d$$

where SMR is the standardised mortality ratio (observed/expected × 100), b is the tangent of the angle between the straight line and the horizontal axis (dose), and d is the benzene dose in ppm-years. By means of this model the number of additional deaths from leukaemia per 1000 deaths which may arise from a benzene dose of 300 ppm-years may be calculated, as done by Austin *et al*[15]:

$$500 = 100 + b \times 400 \rightarrow b = 1$$

if d = 300 ppm-years then SMR =

$$100 + 1 \times 300 = 400$$

Thus workers having received a total benzene dose of 300 ppm-years may experience a SMR of 400.

In a western country such as The Netherlands the age adjusted death rate for acute non-lymphatic leukaemia in men is 1.6 per 100 000[37] and the total mortality is 923.2 per 100 000. This implies that about 1·7 deaths per 1000 deaths are due to acute non-lymphatic leukaemia. In a population in which an SMR of 400 exists 4 × 1.7 = 6.8 deaths due to acute non-lymphatic leukaemia may occur per 1000 deaths, which is an excess of about five deaths. This estimate differs from that proposed by Austin" which is in the range of about 50 excess deaths per 1000 deaths.

RISK ASSESSMENT BASED ON THE RESULTS OF LOW EXPOSURE STUDIES

There are three large epidemiological studies of workers exposed mainly to low concentrations of benzene,"""[33] Thorpe conducted a study of 38 000 workers in petroleum refineries.[30] Although this study has several methodological weaknesses, the study could have detected a risk if there was one. Rushton and Alderson studied the mortality patterns of 35 000 male employees with a minimum of one year's continuous service in the United Kingdom oil industry.[34] There was no excess of leukaemia. A third large study of workers potentially exposed to benzene based on the rubber industry. Parkes *et al* followed up 34 000 British rubber workers for whom no increased risks could be detected.[33] In these three studies combined a total number of 18 + 30 + 31 = 79 deaths from leukaemia were observed. A 95% two sided confidence interval may be calculated around this combined finding, which is:

$$e^{[\ln(SMR) \pm 1.96\sqrt{1/obs}]} = e^{(4.605 \pm 0.1125)} = 89 - 112$$

This upper limit can serve as a point of departure for the risk assessment. Again no accurate data on past exposures to benzene are available. Since 10 ppm was the threshold limit value in the early 1970s, it may be reasonable to use 5 ppm during a period of ten years as an estimate of the exposure. Subsequently it is possible to calculate b in the linear model.

$$SMR = 100 + b \times d$$
$$112 = 100 + b \times 50$$
$$b = 12/50 = 0{\cdot}24$$

which may be used to calculate the SMR given a total dose of 300 ppm-years.

$$SMR = 100 + 0.24 \times 300$$
$$SMR = 172$$

Since the confidence limits were based on total leukaemia mortality, it seems appropriate to extrapolate for total leukaemia mortality, even though the risk is probably restricted to acute non-lymphatic leukaemia. The age adjusted death rate for total leukaemia among men in The Netherlands is 7·6 per 100000. The total mortality is 923.2 per 100 000, which implies that 8.2 deaths per 1000 deaths will be due to leukaemia if no exposure to benzene occurs. Thus in a group of workers experiencing a dose of 300 ppm-years of benzene, associated with an estimated SMR of 172, 8·7 × 1·72 = 15 deaths from leukaemia may occur, of which 8.7 are attributable to the "natural" background incidence of leukaemia.

By analogy, a risk assessment may be made limiting

e potential risk to acute non-lymphatic leukaemia. his perspective is probably more realistic given the bser ations cited earlier in this article.

In he Netherlands the annual age adjusted death ate from acute non-lymphatic leukaemia is 1·6 per 00 000 men. For total leukaemia this rate is 7·6 per 00 000 men, which implies that approximately 21% f deaths from leukaemia occurring in men are of the cute non-lymphatic type. Thus generalising this gure to the three low exposure studies, an estimated 7 (21%) of the 79 deaths from leukaemia observed in ese studies may have been of the acute non-mphatic type giving a two sided 95% confidence ter l of 62–161 for the SMR. This upper limit may gain serve as the SMR resulting from a benzene dose f 50 ppm-years. Next b may be calculated:

$$\text{SMR} = 100 + b \times d$$
$$161 = 100 + b \times 50$$
$$b = 61/50 = 1.22$$

a dose of 300 ppm-years is experienced an SMR for cute non-lymphatic leukaemia may be estimated by eans of the linear model as follows:

$$\text{SMR} = 100 + 1.21 \times 300 = 466$$

his implies that instead of the 1·7 deaths from acute on-lymphatic leukaemia an estimated eight deaths ay occur per 1000 deaths, of which 1.7 are attributble to the "natural" background incidence of acute on-lymphatic leukaemia.

Discussion

There is no doubt that relatively long exposure to high oncentrations of benzene increases the risk of dying from cute non-lymphatic leukaemia. This observaion has frequently been confirmed in epidemiological udies. In studies of workers exposed to low oncentrations, however, this relation has been absent r was confined to those workers who had been xposed to high concentrations in the past. It did not eem justified to disregard these negative findings in sk assessments as being merely an effect of methodoogical shortcomings in these studies. Several risk ssessments have been conducted, giving risks in the ang of 50 excess deaths from leukaemia per 1000 eaths among workers exposed to 300 ppm-years of enzene. The nsk assessment presented in this article early leads to lower results than, for instance, the one repared by Austin *et al.*[15] Both assessments are based n several assumptions which are difficult, if not mpossible, to verify. Thus it remains of great mportance to conduct updates of cohorts already entified as having been exposed to benzene. Although it is up to the policy makers to decide whether or not to alter the current occupational tan rd, perhaps a guideline might be given as to what level of risk would be regarded as acceptable in an occupational setting. This is more a matter of ethics than of science. Nevertheless, it should be remembered that benzene is not the only chemical to which workers can be exposed. and that the interindividual susceptibility for the haematapoietic effects of benzene can differ widely. Perhaps one additional death per 1000 deaths after a working life of exposure can serve as a guideline.

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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 28460 benzene aposed 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-years in the benzene cohort and 2/100 000 person-years in the control cohort; the standardized mortality ratio was 5·74 ($p < 0.01$ 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 to 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 additia to its presence in the general environment as a pollutant benzene is still used in various industries and in China some 500 000 workers are 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 leukaemia has been reported by several authors including Vigliani 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,[1] 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 benzene group were selected from 233 painting, shoe-making, rubber synthesis, leather, and adi .ve and organic synthesis factories in the 12 cities cited. 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 occupational carcinogens. The sex and age distribution 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 during the same period. 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, 12 817 women) and the control cohort of 28 257 subjects (16 621 men, 12 336 women). Both cohorts were followed up from 1972 to 1981 so that 178 556 person-years were obtained for the benzene cohort and 199 201 the control cohort.

Items investigated included the occupational history of the individuals, a history of benzene poisoning

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T l *Mortality and relative risk of leukaemia*

Sex	Benzene			Controls				
	Person-years	*Death*	*Mortality*	*Person-years*	*Death*	*Mortality*	*RR**	*p*
Men	100025	17	7.00	122268.5	3	2.47	6·88	<0.01
Women	78531	a	10.19	77932.5	I	1.28	7.24	<0.05
Total	178 556	25	14·00	199201.0	4	2.01	6.97	<0.01

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

Table 2 *Standardired morrality ratio (observed/expected) for benzene leukaemia*

Sex	Deaths				
	Observed	*Expected*	*SMR*	*U*	*P*
Men	17	3·392	5·01	3.30	<0.01
Women	a	0.964	8.30	2.49	<0·05
Total	25	4.356	5·74	4.13	<0·01

Table *3* *Mortality rate of leukaemia in various industries*

Ind.	*Workers*	*Person-years*	*Leukaemia*	*Mortality**
Painting	13604	87935·5	14	15·9
Paint producing	4533	26859	2	7.4
Rubber	2208	I3544	2	14.8
Glueing	1512	I1082	I	9.0
Shoemaking	3811	23117	1	4·3
Leather	323	I795	—	—
Organic synthesis	I976	I2037	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 workplace; 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 leukaemia, 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, a 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 cohort.

Results

MORTALITY AND RELATIVE RISK OF LEUKAEMIA

In total, 30 cases of benzene leukaemia were found in the benzene cohort, of whom **25** had died and five were alive in 1972–81; four cases of leukaemia were found in the control cohort (all dead). The mortality rate of leukaemia was 14/100 000 person-years in the benzene cohort and **2·01/100 000** person-years in the control cohort. The relative risk of leukaemia 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 (table 2). When the mortality due to benzene leukaemia was compared in the various industries, the rate was highest in organic synthesis factories followed by the painting and rubber synthesis industries (table 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 leukaemia was lower in the ben-

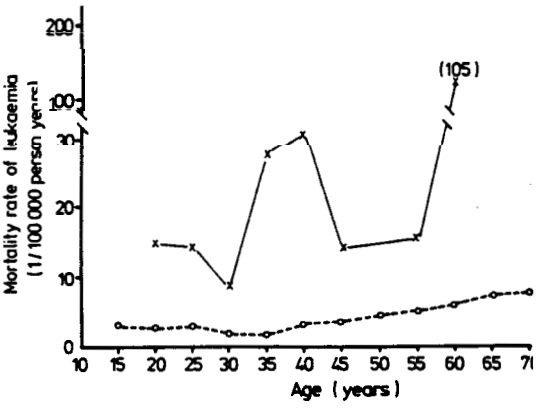

Fig 1 *Leukaemia mortality rate in male workers at various ages. Solid line indicates mortality rate among workers in benzene cohort. Broken lme indicates values among male adults in big cities in China (data obtained from the National Control Office of the Ministry of Health. 1979).*

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 workers 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 average latency was 11·4 years (minimum 0·8, maximum 49·5 years, respectively). The cumulative mortality of leukaemia was in proportion to the duration of exposure up to 20 years and then levelled off (fig 3), as

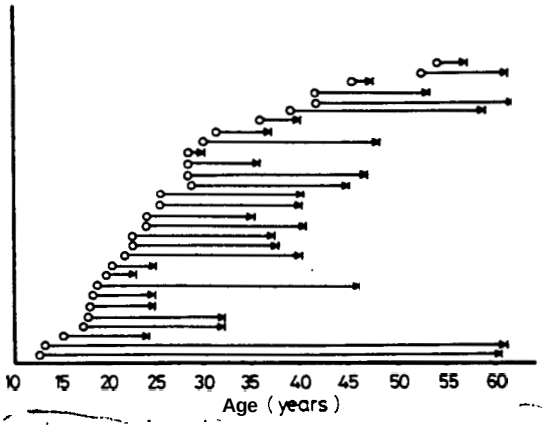

Fig 2 Age at start of exposure, of diagnosis of leukaemia, and latency of 30 cases of leukaemia. O indicates ages of the initiation of the exposure and ▶| ages at which diagnosis of leukaemia was established. Connecting lmes show period of latency.

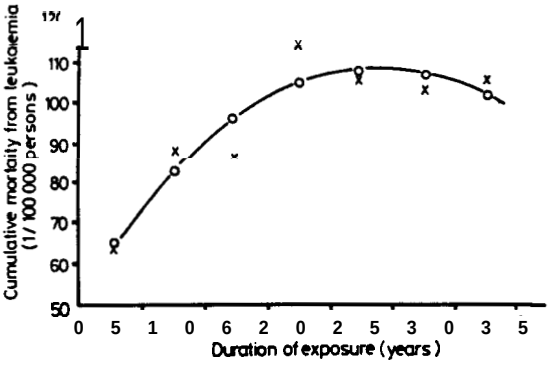

Fig 3 Relation of cumulative mortality of leukaemia with duration of exposure. Crosses indicate cumulative mortality of leukaemia observed. Open circles indicate value estimated by an orthogonal polynomical curve of

$$y = 55.56 + 4.4471\,x - 0{\cdot}09248\,x^2$$

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

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

$$y = 55{\cdot}56 + 4{\cdot}4471\,x - 0.09248\,x^2$$

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

Table 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	283.1 (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 (13·7–550
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.

'ENE CONCENTRATION IN THE W .KPLACES 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 BF ZENE POISONING

In .e benzene cohort 196 cases of chronic benzene poisoning and aplastic anaemia were found; seven of the 25 patients with leukaemia had 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 leukaemia. The leukaemia 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 *etal* have presented data suggesting that benzene may cause leukaemia in rodents.*[9] About 289 benzene exposure related cases of leukaemia have been reported in Italy, China, France. Japan, the Soviet Union, Turkey, and the United States:[7] In the past 20 years several epide- logical studies have shown that long term occupational exposure to benzene at high concentration is associated with the occurrence of various blood dyscasias including leukaemia.[11] For example, Aksoy reported 34 cases of leukaemia among shoemakers in Istanbul in 1967–75[3]; the incidence of leukaemia was 13/100 000 in shoemakers by contrast with 6/100 000 in the general population. Rinksy *etal* Investigated two pliofilm manufacturing plants and found that the SMR for benzene leukaemia was 560.[4] In a recent study of a chemical plant where benzene ha .cn used as a material for organic synthesis Decouflé *et al* observed four deaths due to lymphoreticular cancers (2 leukaemia, 1 leukaemia multiple myeloma, 1 multiple myeloma) in a 30 year follow up study of 259 male workers by contrast with 1·1 expected deaths[12]; 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 leukaemia had spent more time in jobs with potential exposure to coal tar based benzene and xylene.[13] Tsai *etal* by contrast found no deaths from leukaemia 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 cohort (SMR 574 for men + women; 501 for men, 830 for women) being in line with the findings by Rinsky *et al*.[4]

The mean latency period 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,[7] 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 leukaemia was 27.8 years. When 11.4 years of latency is added the sum is about 39 years, which falls in the age range (35–45) of peak leukaemia mortality (fig 1). This may explain why the leukaemia mortality was highest in those aged 31-45.

With regard to the benzene concentration to which patients with leukaemia were exposed, some authors have estimated that it ranged from 200 to 600 ppm without exact details.[17,18] Recently, Rinsky etal 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 being similar to the observation by Rinsky *et al*.[4] There remains a possibility that leukaemia may develop among the less heavily exposed workers. In fact in the present study three cases of leukaemia were associated with a benzene concentration of 10 mg/m^3 in the workplace air even though the occupational 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 chromatid exchanges (SCE) in peripheral 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.'' 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.'' Thus a close 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 to be established.

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ABSTRACT Atopy is o allergenic substan f what is largely cor uggest that atopy is rue for other occup amely, atopy define llergens—has also b iably. Different conc

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