

Occupational Health

LEUKAEMIA IN BENZENE WORKERS

PETER F. INFANTE
JOSEPH K. WAGONER

*Industry-wide Studies Branch, Division of Surveillance,
Hazard Evaluations and Field Studies, National Institute for
Occupational Safety and Health, Center for Disease Control,
Cincinnati, Ohio 45202, USA.*

ROBERT A. RINSKY
RONALD J. YOUNG

Summary Workers occupationally exposed to benzene in 1940-49 were followed for vital status up to 1975. In comparison with two control populations, a significant ($P < 0.002$) excess of leukaemia was observed. A five-fold excessive risk of all leukaemias and a ten-fold excess of deaths from myeloid and monocytic leukaemias combined are demonstrated in the study population compared with controls. These figures underestimate the true leukaemia risk to benzene-exposed workers, because follow-up is only 75% complete and the untraced 25% of the study population were all regarded, in the statistical analysis, as being alive at the end of the study period.

The environment of the workers in the study population was not contaminated with solvents other than benzene, and existing records indicate that the benzene levels themselves were generally below the limits recommended at the time of their measurement.

INTRODUCTION

ONE of the earliest reports of benzene-related blood disorders consistent with what is now known to result from benzene poisoning was published in Paris in 1897.¹ In 1928, a clearly established case of leukaemia was associated with benzene exposure in Italy.² Since then, many cases of leukaemia associated with exposure to benzene have been reported from various parts of the world.³⁻⁹ A significant excess of chromosomal aberrations has also been observed in benzene-exposed workers.¹⁰

Ishimaru et al.⁶ demonstrated a significant association between leukaemia and occupations with probable exposure to benzene, and Aksoy et al.⁷ reported a significantly greater incidence of leukaemia in shoe workers exposed to benzene than in the general population. In 1976 Vigliani⁴ reported that 150 cases of leukaemia attributed to benzene had been identified in Italy. McMichael et al.¹¹ demonstrated an excess of leukaemia among rubber workers previously exposed to solvents, including benzene. However, in that study the leukaemogenic effect could not be attributed directly to benzene because of concomitant exposure to other solvents used in the manufacture of rubber products.

Before the 1914-18 war, benzene was used mainly as a solvent in the rubber industry, but during the war the demand for toluene in the manufacture of explosives greatly stimulated benzene production. Currently, 87% of benzene is used as a raw material in the synthesis of compounds such as styrene, phenol, and cyclohexane. Approximately 10.2 billion lb (4.6 billion kg) were pro-

duced in the U.S. in 1973, 3.5 billion lb (1.6 billion kg) in Japan in 1972, and 1.2 billion lb (0.5 billion kg) in the U.K. in 1972.¹² In the 50 years since the first reported case of benzene-associated leukaemia, benzene has been neither widely acknowledged nor uniformly controlled as a carcinogen in the U.S.¹³ The failure to control benzene as a carcinogen has resulted primarily from the reluctance of industry and Government to accept the accumulated case-reports and epidemiological observations as scientific evidence of the leukaemogenic properties of benzene. Today, in the U.S. alone, an estimated two million workers are at risk of exposure to benzene.¹⁴ For these reasons we have studied mortality patterns in workers occupationally exposed to benzene in the production of a natural rubber cast film (rubber hydrochloride, marketed under the trade name 'Pliofilm') at two localities in Ohio.

INDUSTRIAL-HYGIENE ASSESSMENT

Production Methods

In the production of 'Pliofilm', natural rubber was masticated in an internal mixer, passed through a mill, and conveyed to mixing-tanks, where benzene was added and the mixture was agitated. The resulting solution was pumped to a blending-tank, then transferred into a reactor vessel, where it was treated with hydrochloric acid to form rubber hydrochloride. At this stage, more benzene was added to adjust the proportion of solids in the solution. The rubber hydrochloride was transferred to a neutralising-tank, where pliofilm straps, soda ash, steam, plasticisers, and more benzene were added. After filtration, the rubber hydrochloride solution was pumped to a casting-unit, then it was spread on a continuous conveyor, where the benzene was evaporated, and the finished film was taken up on a roll. The gas containing benzene was exhausted from the casting-unit, passed through a wet scrubber, and channelled into an activated-charcoal absorber unit, where benzene was recovered and recycled. The rolls of pliofilm were transferred to another room, where they were inspected, trimmed, cut to customer specification, and packed (primarily for food wrapping). In the production of pliofilm, the only material known to be associated with blood disorders was benzene. Other materials used included hydrochloric acid, soda ash, and small amounts of antioxidants and plasticisers. The manufacturing process was essentially identical at both Ohio localities.

Environmental Monitoring

In 1942, Wilson, as a former member of corporate management, recommended a policy for the rubber industry, which would include pliofilm operations, of periodic air monitoring and a complete blood-count for all new employees.¹⁵ It was his view that "a closed system of ventilation where the workman comes in contact with no fumes is ideal. Any other type of ventilation is not entirely safe." Shortly thereafter, extensive exhaust ventilation equipment was installed in the pliofilm department in one locality. The Industrial Commission of Ohio, after surveying that department in 1946, reported that, "Tests were made with benzol detectors and the results indicate that concentrations have been reduced to a safe level and in most instances range from zero to 10 or 15 parts per million". A further investigation of benzene exposure in that department in 1956 concluded that exhaust ventilation controls were of excellent design. In the early 1960s benzene point-source concentrations were measured by company personnel using detector tubes. A total of 112 surveys were conducted in the period 1963-74. These and earlier surveys have indicated that employees' benzene exposure was generally below the recommended limit in effect at the time of each survey.^{13,14,16,20} (table 1).

Aksoy & STAMM

TABLE I—CHRONOLOGY OF RECOMMENDED BENZENE CONCENTRATIONS IN WORKPLACES IN U.S.A.

Year	Concentration (p.p.m.)	Reference
1941	100 M.A.C.	16, 17
1947	50 8h T.W.A.	14
1948	35 8h T.W.A.	14
1957	25 8h T.W.A.	14
1963	25 Ceiling	14
1969	10 8h T.W.A.	18
1971	10 8h T.W.A.	13

M.A.C.=Maximum allowable concentration.
T.W.A.=Time-weighted average.

Historical environmental data for the second locality in Ohio is less well defined. However, our own observations, discussions with company personnel, and the meagre environmental data that have been retained suggest that employees' benzene exposure at this location was generally well within the recommended limits.

RETROSPECTIVE COHORT STUDY

Methods

All White men who had had direct exposure to benzene at any time between Jan. 1, 1940, and Dec. 31, 1919, were studied. The departments and jobs involving direct exposure to benzene were determined by a survey by N.I.O.S.H. personnel, which included a review of the pliofilm process, engineering controls, and air-sampling data. Company personnel also assisted in these determinations. Job classifications involving benzene exposure were determined without knowledge of the workers' vital status.

Follow-up of all study-cohort members was attempted for the time period from first employment to June 30, 1975. To date, vital status has been determined for approximately 75% of the 748 cohort members. The remaining 25% were assumed to be alive to avoid overestimating the true risk of lymphatic and haemopoietic malignancies associated with benzene exposure. Causes of death were determined from death certificates and were coded according to the International Classification of Diseases in effect at the time of death; these codes were then converted to I.C.D. 7th revision numbers. A modified life-table technique was used to generate person-years at risk of dying according to 5-year age-group and 5-year calendar periods.

Person-years of observation and causes of death were determined for the period Jan. 1, 1950, to June 30, 1975. Person-years of observation and deaths occurring before Jan. 1, 1950, were excluded from analysis since vital statistics on lymphatic and haemopoietic malignancies were not published before that date.

Two populations were chosen as control groups for generating the numbers of expected deaths in the study population. The first group consisted of the U.S. White male general population standardised for age and time period over which the study cohort lived. The second group consisted of 1447 White men who had been employed in Ohio at a fibrous-glass construction-products factory between Jan. 1, 1940, and Dec. 31, 1949, and who had achieved 5 or more years of employment by June 1, 1972 (which was the cut-off date for vital-status ascertainment in the fibrous-glass control population)."

Results

There were 140 observed deaths from all causes among benzene-exposed workers compared with 187.6 expected deaths (table II). This deficit reflects in part the incomplete follow-up of the study population. There was a significant excess of deaths from malignancy of the lymphatic and haemopoietic systems (I.C.D. 200-205) compared to that expected on the basis of death-rates of U.S. White males. This is due almost entirely to an excess of leukaemia deaths (I.C.D. 204). To date, 7 leukaemia deaths have been observed, compared with an expected 1.38 ($p < 0.002$) based on rates for U.S. White males and an expected 1.48 ($p < 0.002$) based on rates for fibrous-glass workers. Even more striking is the observation that all 7 leukaemia deaths were from either the myelogenous or monocytic type. Data for cell type, age at death, and interval since initial exposure to benzene are shown in table III. The period between initial exposure and death ranged from 2 to 21 years. These observations, indicating a specific type of leukaemia, are consistent with the data of Vigliani,⁴ which show a predominance of acute myelogenous leukaemia among workers exposed to benzene in the rotogravure and shoe-manufacturing industries in Italy. Since data for specific

Causes of death (I.C.D. codes)*	Benzene-exposed workers		Comparison group	S.M.R.
	Deaths observed	Deaths expected		
All causes (200-205)	140	187.5809	(U.S.W.M.)	075
(204)	9	3.4497	(U.S.W.M.)	260†
200-205)	7	1.3831	(U.S.W.M.)	506†
(204)	9	5.1020	(F.G.)	
(204)	7	1.4758	(F.G.)	474†

TABLE III—CASES OF LEUKAEMIA IDENTIFIED BY APRIL, 1977, AMONG WORKERS EXPOSED TO BENZENE BETWEEN 1940 AND 1949 DURING PLIOFILM MANUFACTURE

Case no.	Type of leukaemia	Age at death (yr)	Period from initial exposure to death (yr)
1	Acute myelogenous	60	13
2	Acute myelogenous	65	10
3	Acute myelogenous	62	21
4	Acute myelogenous	57	19
5	Monocytic	57	15
6	Chronic myelogenous	29	2
7	Monocytic	36	17
8*	Myelogenous	28	3

*Indicates leukaemia case which did not fit into cohort definition. The subject began employment in 1950.

types of leukaemia mortality in the U.S. are not readily available for the study period, incidences for myeloid, monocytic, and total leukaemia from the Connecticut Tumor Registry²² for the period 1960-62 were applied to the age-distribution of the benzene-exposed cohort to generate the specific proportion of total-leukaemia cases which would be of the myelomonocytic types. Of the total expected number of incidence cases of leukaemia, 50.37% were calculated to be of the myelogenous and monocytic types. This proportion was applied to the total number of expected leukaemia deaths in the study cohort which had been previously generated on the basis of rates for the U.S. White male population. The results indicated an expected 0.6967 ($0.5037 \times 1.3831 = 0.6967$) deaths from myelogenous and monocytic leukaemia, compared with 7 observed, the standardised mortality-ratio being 1004. Thus, pliofilm workers exposed to benzene have an estimated 10-fold risk of dying from myelogenous and monocytic leukaemia.

As a result of past failure to control benzene as a carcinogen, millions of people, without knowledge of the haemopoietic dangers, are continually being exposed to benzene at work. In addition, unknown numbers of consumers, including children, are exposed to benzene at home, from sources such as model-aeroplane glue and paint strippers (some containing up to 50% benzene).

We hope that our findings, which demonstrate overwhelmingly an increased risk of leukaemia in workers exposed to benzene, will stimulate efforts to control occupational and consumer exposure to benzene, an agent known for almost a century to be a powerful bone-marrow poison.

We thank Ms Betsy Egan and Mr David Brown and the entire support staff of the biometry section, National Institute for Occupational Safety and Health, for their dedication and assistance during the study.

Requests for reprints should be addressed to P. F. I.

REFERENCES

1. LeNoir, C. *Bull. Mém. Soc. méd. Hôp. Paris* 1897, 3, 1251.
2. Delore P., Borgamano, C. *J. Méd. Lyon* 1928, 9, 227.
3. Glogue, A., Cavignaux, A., Bernard, J. *Nouv. Revue fr. Hémat.* 1967, 4, 465.
4. Vigliani, E. C. *Ann. N.Y. Acad. Sci.* 1976, 271, 143.
5. Ludwig, V. H., Werthemann, A. *Schweiz. med. Wschr.* 1962, 92, 378.
6. Ishimaru, T., Okada, H., Tomiyasu, T., Tsuchimoto, T., Hoshino, T., Achimaru, M. *Am. J. Epidemiol.* 1971, 93, 157.
7. Akutsu, M., Erdem, S., DinCol, G. *Blood*, 1974, 44, 837.
8. Mallory, T. B., Gall, E. A., Brickley, W. J. *J. ind. Hyg. Toxicol.* 1939, 21, 355.
9. Jarrell, E. M., Kontchalovskaya, N. M., Zorina, L. A. *Acta. Un. int. Cancer*, 1963, 19, 751.
10. Form, A., Pacifico, E., Limonta, A. *Archs envir. Hlth*, 1971, 22, 373.
11. McMichael, A. J., Spirtas, R., Kupper, L. L., Gamble, J. F. *J. occup. Med.* 1975, 17, 234.
12. I.A.R.C. *Monographs on Evaluation of Carcinogenic Risk of Chemicals to Man. Some Anti-thyroid and Related Substances, Nitrofurans and industrial Chemicals*, 1974, 7, 203.
13. Code of Federal Regulations, Title 29, Subtitle B, Chapter xvii, Occupational Safety and Health Administration, Part 1910.93, U.S. Washington, D.C., 1971.
14. Criteria for a Recommended Standard: Occupational Exposure to Benzene. U.S. Dept. Health, Education and Welfare, Public Health Service Washington, D.C., 1974.
15. Wilson, R. H. *J. Lab. clin. Med.* 1942, 27, 1517.
16. Industrial Commission of Ohio, Report, Nov. 1946.
17. Ohio Department of Health, Report, Jan. 1956.
18. Brinker, P. Criteria of Industrial Health Hazards. In United States Department of Labor: Protecting Plant Manpower. Washington, D.C., 1941.
19. Sappington, C. O. *Essentials of Industrial Health*. Philadelphia, 1943.
20. U.S.A. Standard Acceptable Concentrations of Benzene, Z37.4. United States of America Standards Institute, Inc. New York, 1967.
21. Bayless, D. L., Dement, J. M., Wagoner, E. K., Blejer, H. P. *Ann. N.Y. Acad. Sci.* 1976, 271, 324.
22. Cancer in Connecticut, Incidence and Rates, 1935-1962. Connecticut State Dept. of Health, Hartford, Connecticut, 1966.

Before Our Time

OPIUM AND THE HISTORICAL PERSPECTIVE

VIRGINIA BERRIDGE

Addiction Research Unit, Institute of Psychiatry, London SE5

The literature produced over the last ten years analysing and describing the "drug scene" in the United Kingdom has almost totally neglected the historical examination of English drug, and especially opiate, use. The familiar examples are quoted and re-quoted; references to the mid-19th-century opium wars abound. But how did ordinary people use opium in the 1820s, when De Quincey was writing his *Confessions*? How great a danger did the unrestricted sale of opium pose? How did the medical profession, the chemists, and the public at large react? Such questions have remained largely unanswered; and yet responses to them are needed if a properly informed perspective is to be given to the current worries, and a more rational appraisal made of contemporary attitudes and policies.

UNRESTRICTED OPIATE USE

Narcotics have been under strict legal control almost as long as anyone can remember — there can be few doctors now in practice whose professional experience goes back to the years before the first Dangerous Drugs Act became law in 1920. It is therefore instructive to recall that, up to 1868, opium and cannabis (in fact then rarely used) were available over the counter without any form of restriction. Imported opium, mostly Turkish in origin, could be bought almost anywhere—not just from chemists, druggists, or pharmacists, but in village shops, from grocers, general stores, and corner shops in the back streets of the growing industrial cities. The Hull coroner, for instance, noted in 1854 after an inquest on an infant poisoned with laudanum sold in mistake for syrup of rhubarb, that the liquid opiate "was kept with several other bottles of similar shape and appearance on a shelf in the shop window of a Grocer in a district thickly inhabited by factory operatives, and was given to a messenger between six and seven years old".

Acceptance of the drug went so far as to encourage enterprising farmers, doctors, and market gardeners to experiment with the cultivation of a British variety. Messrs Cowley and Staines, for instance, who cultivated several acres at Winslow in 1823, managed to produce 186 lbs of opium from 12 acres of land. Their profit, including the yield from a crop of turnips prudently planted in addition, was over £96 an acre; others reported similar successes, although "the precariousness of our climate" was universally recognised as a drawback.^{2,3} British opium was never generally used; hut opiates—chiefly laudanum, the camphorated tincture known as paregoric elixir, and raw opium, sold in pills and penny sticks—were widely used both on medical prescription and as self-medication by those who could not afford medical treatment. In one area of the country, the low-lying, marshy, ague-ridden Fens, it was accepted that opiate use on a regular and sustained basis was