Lung cancer mortality among workers in a factory manufacturing chlorinated toluenes: 1961-84

T SORAHAN,¹ M CATHCART²

From the Cancer Epidemiology Research Unit,¹ Department of Social Medicine, University of Birmingham, Edgbaston, Birmingham B15 2TH, and Albright & Wilson Ltd,² Warley, West Midlands, UK

In 1982 IARC published a monograph that included an evaluation of the carcinogenic risk to man of exposure to the following chlorinated toluenes: benzyl chloride (BYL), benzal chloride (BAL), benzotrichloride (BTC), and benzoyl chloride (BOL).¹ The evaluations may be summarised as follows. In experimental animals there was inadequate evidence for the carcinogenicity of BOL, limited evidence for the carcinogenicity of BYL and BAL, and sufficient evidence for the carcinogenicity of BTC. The epidemiological data were inadequate to evaluate the individual carcinogenicity of the above chemicals, but there was limited evidence that employment in the production of these chemicals represents a carcinogenic risk to man.^{2,3}

In 1983 we published a report of mortality among 953 men from an organic chemicals factory, of whom 163 were considered to have been exposed to chlorinated toluenes (CT+).⁴ Although there was a possible bias in the coding of exposures, we concluded "that there is evidence of an increased mortality from cancer but no increase in mortality from other causes amongst the (more highly exposed) group."

The present report provides results for a further period of follow-up (1977-84) for 951 workers (two individuals have been removed from the original cohort, one duplicate, one woman incorrectly coded as male).

Materials and methods

The definition of the study cohort and details of the work process have been described before.⁴ At the closing date of the study (31 December 1984), the Office of Population, Censuses and Surveys (OPCS) traced 182 who had died, 30 who had emigrated, and 728 survivors; 11 were untraced. Copies of death certificates were obtained for the 182 employees known to have died and, for each, the underlying cause

of death was classified according to the 8th revision of the International Classification of Disease (ICD).

Two analyses were performed. The first approach used the method of SMRs in which the mortality of the study population was compared, after suitable adjustments for age and calendar year, with mortality for men in England and Wales as a whole.

In an attempt to provide more detailed information on any likely occupational risks we also carried out a "nested case-control study," choosing, for each death from lung cancer, three controls (matching survivors or referents) from the study cohort. We matched on year and age at starting employment: 50 controls were within ± 1 year of the year and age at start of employment of the case; 16 controls were within ± 2 years, 11 controls were within ± 3 years, and one control was within ± 5 years. When more than three potential controls were available for a particular case, random number tables were used.

The period from first employment until death was calculated for each case. Employment histories were then assessed for this period for each case and for its matching controls.

Information on (1) total number of years of employment with "higher" levels of exposure to BTC, (2) total number of years of employment with higher levels of exposure to other chlorinated toluenes, and (3) cigarette smoking category (smoker, ex-smoker, non-smoker) was collated by the factory nurse from personnel records, medical records, and discussions with other employees.

These matched sets were analysed by conditional logistic regression.⁵ The approach assumes that separate risk factors combine multiplicatively.

Results

Compared with the general population of England and Wales, and for the period 1961-84, SMRs for all causes, all cancers, and all non-cancers, were 138, 163, and 129 respectively. These SMRs were based on 182 deaths, 57 deaths, and 125 deaths respectively. For site

Table 1 Mortality from lung cancer† for two periods of follow up

Subgroup	Period of follow up						Total		
	1961-76			1977-84					
	Exp‡	Obs	SMR	Exp‡	Obs	SMR	Exp‡	Obs	SMR
CT +	1.64	5	305	1.38	5*	362	3.02	10**	331
CT -	5.57	8	144	5.90	8	136	11.47	16	139
Total	7.21	13	180	7.28	13	179	14.49	26**	179

*p < 0.05; **p < 0.01 (two tailed tests, Poisson).

†ICD 8th rev: 162, 163.

‡Expectations calculated from quinary quinquennial rates of mortality for England and Wales 1961-83. No contributions made to expectations or observed deaths past 85th birthday.

CT - = "Low" exposure to chlorinated toluenes (n = 788).

CT + = "Higher" exposure to chlorinated toluenes (n = 163).

specific cancer mortality, statistically significant excesses were found for lung cancer (exp = 14.5, obs = 26, SMR = 180, p < 0.01) and for Hodgkin's disease (exp = 0.4, obs = 3, SMR = 714, p < 0.05). There were no statistically significant deficits.

Observed and expected numbers of deaths from lung cancer are shown by periods of follow up for the CT+ and CT- groups in table 1. Although numbers of deaths are small, the SMRs for the CT+ group are similar for the two periods of follow up shown (305 and 362), as are those for the CT- group (144 and 136).

Table 2 shows relative risks for four variables, estimated by conditional logistic regression. The left hand part of the table shows the results of considering each variable singly, and the right hand part the results of considering all four variables together. All the 95% confidence intervals include unity, indicating that no relative risk differs significantly from unity.

The estimated relative risk of 0.27 for the "indicator variable for smoking" indicates that the risk of lung cancer was much lower among workers for whom we had smoking data. The most likely explanation for this unexpected finding is that lack of information on smoking history was not random, and that the "no information" group contained, in fact, a much higher proportion of smokers than did the group for which we had some smoking data. When the difference between the information and no information groups was taken into account, an excess relative risk for cigarette smoking was obtained (2.97).

The relative risks calculated for the two "chemical exposure" variables were above unity. The 95% confidence intervals for these estimated risks, however, were large, and these risks did not approach statistical significance.

Discussion

The excess mortality from lung cancer in the CT+

group for the period 1977-84 cannot be explained by systematic bias in the exposure coding of individual workers, since the coding was carried out before 1977. Expectations have been calculated on the basis of death rates for England and Wales, and there is no doubt that regional and social class adjustments would lead to lower SMRs for both groups. Nevertheless, the differences between the CT+ and CT- groups would remain.

The nested case-control study did not provide convincing evidence of occupational involvement, although the positive non-significant effect for the "BTC exposure" variable was not due to a confounding effect of smoking, as judged from the available smoking data.

Chlorinated toluenes should continue to be considered as potential human carcinogens and further work on this topic could consider, as an

Table 2 Conditional logistic regression of 26 matched case-control sets (the "case" for each set is a death from lung cancer)

Variable	Estimated relative risk* (with 95% CI)	Estimated relative risk† (with 95% CI)
BTC‡	1.32** (0.71-2.44)	1.36** (0.43-4.24)
Other chlorinated toluenes§	1.31** (0.66-2.61)	1.12** (0.30-4.22)
Cigarette smoker	0.83 (0.28-2.50)	2.97 (0.34-25.83)
Indicator variable for smoking¶	0.27 (0.05-1.42)	0.09 (0.01-1.18)

*Four variables considered separately, ignoring other three variables.

†Four variables considered together.

‡Total number of years of employment with higher levels of exposure to BTC (given as completed integer years—for instance, two periods of exposed employment, one year three months and one year five months, total = two years eight months, completed integer years = 2).

§Total number of years of employment with higher levels of exposure to other chlorinated toluenes.

||Known to be smoker, or ex-smoker, variable = 1; non-smoker or no information, variable = 0.

¶Known to be smoker, ex-smoker, or non-smoker, variable = 1; no information, variable = 0.

**Relative risk expressed per 10 years of exposed employment.

priori hypothesis, that lung cancer may result from occupational exposure to certain chlorinated toluenes.

We thank Professor M A Cooke for his work in initiating this study, Dr J R Jackson and Dr J A H Waterhouse for their earlier involvement, Sister S F Carson for the difficult job of gathering data from many sources, Ann Balnaves for checking of data and work processing, and the directors and staff of the factory concerned.

References

1 International Agency for Research on Cancer. *Monograph on the*

evaluation of the carcinogenic risk of chemicals to humans. Vol 29. *Some industrial chemicals and dyestuffs*. Lyon: IARC, 1982:49–92.

- 2 Sakabe H, Matsushita H, Koshi S. Cancer among benzoyl chloride manufacturing workers. *Ann NY Acad Sci* 1976;**271**:67–70.
- 3 Sakabe H, Fukuda K. An updating report on cancer among benzoyl chloride manufacturing workers. *Ind Health* 1977;**15**:173–4.
- 4 Sorahan T, Waterhouse JAH, Cooke MA, Smith EMB, Jackson JR, Temkin L. A mortality study of workers in a factory manufacturing chlorinated toluenes. *Ann Occup Hyg* 1983;**27**:173–82.
- 5 Lubin JH. A computer program for the analysis of matched case-control studies. *Computers and Biomedical Research* 1981;**14**:138–43.