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by Paddle GM, Osborn AJ, Parker GD

Affiliation: ICI Epidemiology Unit, Nr Macclesfield, Cheshire, United Kingdom.

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Mortality of employees in plants manufacturing 4,4'-bipyridyl

by Geoffrey M Paddle, PhD,[1] A John Osborn, PhD,[2] Gabrielle DJ Parker, BSc[1]

PADDLE GM, OSBORN AJ, PARKER GDJ. Mortality of employees in plants manufacturing 4,4'-bipyridyl. *Scand J Work Environ Health* 1991;17:175—8. A historical-prospective cohort study was conducted of 729 male employees of plants manufacturing 4,4'-bipyridyl. The cohort was studied because employment in some of the plants had been linked to malignant and nonmalignant skin lesions attributed to exposure to tarry by-products. The overall mortality experience of the cohort did not show any statistically significant findings. More-detailed analysis by subdivision of the cohort gave results that justified further inquiry into lung cancer incidence. A nested case-referent study did not indicate that any occupational factor other than employment in a bipyridyl plant was related to the incidence of lung cancer. The epidemiologic, toxicologic, and industrial hygiene information was assessed, and it was concluded that there was no evidence of a plausible occupational hazard of lung cancer to the bipyridyl workers, but that a follow-up of the cohort after an interval of five years should be undertaken.

Key Terms: cohort, diglyme, lung cancer, skin lesions.

4,4'-Bipyridyl has been manufactured from pyridine at Widnes in the northwest part of England since 1961. The process has taken place in three plants, a high-temperature sodium (HTS) plant from 1961 to 1963, a magnesium (M) plant from 1962 to 1967, and a low-temperature sodium (LTS) plant from 1966 to the present. During 1976, several shift process workers who had worked in one or more of the plants were found to be suffering from skin lesions. These lesions included cases of solar keratosis, squamous cell carcinoma, and Bowen's disease. A thorough investigation, which included examination of many past employees and toxicologic assessment of the chemicals handled, led to the conclusion that exposure to tarry by-products at the HTS and M plants was the most likely cause of the lesions (1).

At the time of the skin lesion investigation, the mortality and morbidity data that were available in the records showed no cause for concern about the health of the employees on grounds other than skin conditions. Nonetheless, it was considered prudent to assemble the mortality and cancer incidence on a more formal and comprehensive basis and to initiate regular reviews of the data. Therefore, a retrospective cohort study was conducted on the employees of the three 4,4'-bipyridyl plants. One objective of this study was to monitor the mortality and cancer incidence of the cohort to detect adverse mortality trends in a population among whom an excess incidence of nonfatal skin conditions had been reported. A second objective was to provide a system for continued management of the medical surveillance program set up to diagnose and initiate treatment of new cases of skin lesions as they occur.

[1] ICI Epidemiology Unit, Alderley Park, Nr Macclesfield, Cheshire, United Kingdom.
[2] ICI Chemicals and Polymers Ltd, The Heath, Runcorn, Cheshire, United Kingdom.

Reprint requests to: Dr GM Paddle, ICI Epidemiology Unit, Alderley Park, Nr Macclesfield, Cheshire SK10 4TJ, United Kingdom.

Subjects and methods

A formal protocol was written for the study and approved by the Office of Populations, Censuses and Surveys. The cohort consisted of all past employees that had manufactured 4,4'-bipyridyl in the three plants at Widnes, and all employees working in the existing plant when the cohort was established in 1983. No minimum restriction was imposed on the length of service at the plants. Identification and occupational details for the 761 members of the cohort were extracted from the Company's manual and computerized systems. Cards for 188 ex-employees were sent to the National Health Service Central Register at Southport for tracing. The other 573 were traced through the Company's records for employees and members of the pension fund (2). The tracing by the National Health Service met the second objective of the study by reducing the untraced proportion of the cohort to less than 4 %. The records for the 25 past employees who remained untraced lacked key identification details, largely because they were only employed for very short periods. No further cases of skin cancer appeared as a result of this search.

A computer file for the analyses was created from all the available information. It contained identification, date of birth, date of first employment at a 4,4'-bipyridyl plant, plants worked at and jobs held, and date of exit from the study (due to death, emigration, or untracibility).

The Man Years Computer Language (MYCL) program written by Hill (3) was used to calculate the figures for expected deaths for the complete cohort and selected subcohorts.

An analytical strategy was agreed upon prior to the results being known so that hypotheses would be tested in a structured manner, and the chance of discovering coincidental clusters would not be exaggerated. Standardized mortality ratios were calculated as the ratios of the observed deaths to the calculated expected figures after the application of a suitable correction factor for the town in which the plants were situated.

The northwest of England has higher mortality rates than England and Wales as a whole for most common causes of death, and Widnes has higher mortality rates than the northwest of England (4). The selection of a comparison group for this study, therefore, involved a choice between the stable but inappropriate figures for England and Wales and the northwest region, and the unstable but appropriate figures for Widnes (5). It was decided to use the England and Wales figures, which are widely available for a comprehensive range of diagnoses, to calculate the expected figures. Multiplicative correction factors were then applied to derive figures more representative of the Widnes conurbation for all causes, all cancer, lung cancer, and cardiovascular disease.

All the significance tests were based on one-sided Poisson distributions. In the absence of any prior hypotheses, it could be argued that two-tailed tests are more even-handed, and therefore more valid, but there is then no obvious way of interpreting a significantly low standardized mortality ratio (SMR), such as was found for cardiovascular disease in this study.

For causes of death that merited further investigation, MYCL calculations were performed for subcohorts defined by job and plant, and the occupational histories of the cases were compared with those of referents in a nested case-referent study (6).

For the analyses by jobs and plants, the jobs were dichotomized into process workers and other jobs, and the plants considered were the HTS, M, and LTS plants and, to give continuity with the skin lesion investigation, the M and LTS plants combined. Then the ICI Occupational Health Team and Widnes Works collaborated to produce assessments of exposure to various chemicals according to plant and job. Estimated exposure levels were based on engineering and chemical process considerations and recollections of the plants by those who operated and maintained them. Descriptions of the levels of exposure were restricted to high, medium, low, none, and unknown.

The purpose of the nested case-referent study was to investigate the possibility that occupational factors other than those in the bipyridyl plants had affected the mortality pattern of the cohort. For each of the cases, one live referent and one dead referent were selected from the cohort after matching to the cases on sex, date of birth (to within 10 years), and, to permit study of prior occupations, date of first joining the cohort (to within one year) (7).

Table 1. Mortality analysis for the male members of the cohort. (SMR = standardized mortality ratio)

	Observed number of deaths	Expected number of deaths[a]	SMR (Widnes)
All causes	75	96.3	78
All cancers	29	27.1	107
Lung cancer	13	10.5	124
Cardiovascular	28	45.2	62
All other	18	24.0	75

[a] Based on England and Wales mortality rates and Widnes correction factors.

Table 2. Mortality analysis allowing for ten years of latency. (SMR = standard mortality ratio)

	Observed number of deaths	Expected number of deaths[a]	SMR (Widnes)
All causes	51	57.2	89
All cancers	23	16.4	140
Lung cancer	11	6.4	172

[a] Based on England and Wales mortality rates and Widnes correction factors.

Table 3. Lung cancer mortality analyzed by latency period. (SMR = standardized mortality ratio)

Latency	Lung cancer mortality		
	Observed number of deaths	Expected number of deaths[a]	SMR (Widnes)
< 5 years	1	1.5	67
5—10 years	1	2.3	43
10—15 years	3	2.6	115
>15 years	8	3.8	211

[a] Based on England and Wales mortality rates and Widnes correction factor.

Results

The vital status of the 761 members of the cohort on 31 December 1985 was as follows: 75 had died, 652 were traced and alive, 9 had emigrated, and 25 were untraced. The tracing rate was, therefore, 96.6 %; those lost were, on the whole, short-stay employees who were inadequately identified in the records.

As there were only 32 women in the cohort, and their mortality and cancer incidence records contained nothing noteworthy, all the analyses were restricted to the male employees. No cancer incidence data were received that have not been included in the mortality data; therefore the analyses were restricted to mortality calculations.

In table 1 the observed and expected figures are shown for all causes, all cancers, lung cancer, cardiovascular disease, and all other causes combined for all the men in the cohort. The expected figures were based on England and Wales quinquennial mortality rates for age and calendar year, multiplied by correc-

tion factors for Widnes. These correction figures were taken from the data used to construct the atlases of mortality published by the Environmental Epidemiology Unit of the Medical Research Council. They are 1.174 for all causes, 1.213 for all cancers, 1.185 for lung cancer, and 1.143 for cardiovascular disease. There were no more than two cases of cancer for any target organ other than the lung.

The all causes SMR of 78 is indicative of the healthy worker effect typical of an occupational cohort for which the period of follow-up is short and overlaps the cohort definition period. The observed number of cardiovascular deaths was substantially fewer than the expected number. The all cancers SMR of 107, and the lung cancer SMR of 124 were somewhat elevated, but not significantly so.

Analysis of the entire experience of a cohort can, in some circumstances, obscure the presence of an excess occupational risk because such an excess risk will not have any effect until a latency period has elapsed. Table 2 presents the results of an analysis in which the 10 years immediately after first employment in a bipyridyl plant have been excluded for each subject.

Some employees were omitted from this and subsequent calculations because their work histories were not sufficiently precise for valid latency determinations. As none of these employees had died, the expected figures in table 2 have a negative bias, and the SMR values are, therefore, overestimates. Predictably, the all cause SMR of 89 shows a much reduced healthy worker effect. The all cancers and lung cancer SMR values of 140 and 172 are in excess of 100, but the excesses are not statistically significant at the 5 % level.

As the choice of 10 years of latency was arbitrary, the calculation for lung cancer was repeated for latency periods of 5 and 15 years, there being too few person-years at risk to justify a calculation for 20 years. The results, in table 3, show that the cases were predominantly clustered in the latency period of over 15 years, for which the SMR of 211 would just achieve statistical significance at the 5 % level. It was, therefore, felt advisable to investigate the cases further.

Two approaches were adopted. We subdivided the cohort to see whether the lung cancer cases were significantly clustered into particular jobs and plants. This approach was considered to be more penetrating than analysis by duration of employment because the study included three distinct plants, one of the plants was run in campaigns rather than continuously, and employees in jobs such as maintenance and instrumentation were only in the plants intermittently. In parallel, a nested case-referent study was conducted within the cohort to determine whether the cases had a risk factor in common that was not associated with employment in a bipyridyl plant.

Subcohort analyses were performed for two job categories (process workers and others), four plants (HTS, M, LTS, and M and LTS combined), and 11 chemicals (10 of which were specific compounds, and the 11th was called tars). Some job and plant combinations were also considered, and each calculation was repeated for a latency of 10 years. The MYCL runs were carried out for each chemical by dividing the cohort into two suitable groups of higher and lower exposure, or, in some cases, exposed and unexposed.

The analyses showed that the lung cancer cases were largely concentrated among the process workers in the HTS plant and all the workers at the LTS plant. For all but one of the chemicals investigated, there was no indication that exposure was a risk factor for lung cancer. Indeed, in most cases, the SMR for the less exposed group was higher than that for the more exposed group. The exception was diethylene glycol dimethyl ether, or diglyme, as it is commonly called. This apparent relationship between lung cancer incidence and diglyme arose because the pattern of exposure estimates provided for diglyme matched the pattern of lung cancer indicated by the job and plant analyses. Diglyme had been used in the LTS plant, but not in the M or HTS plant. However, diglyme was manufactured at a batch plant adjacent to the HTS plant, which also operated in batch mode. As the process operators worked at these, and other, plants in rotation and as these plants had common maintenance and trade teams, it was assumed that the HTS employees had worked at some time in the diglyme plant.

Another possibility was that prior or contemporaneous employment in another facility in the neighborhood of the bipyridyl plants was related to the lung cancer incidence. This possibility created the need to collect detailed lifetime occupational histories. The advantage of the nested case-referent study is that it concentrates attention on a small number of subjects, 39 in this case, which means that detailed employment histories, both during and prior to joining the Company, and social histories do not have to be collected for everybody. The employment histories of the cases and referents, apart from their service in bipyridyl plants and the diglyme plant, proved to be very diverse, and no new hypotheses came to light. It was interesting, and to some extent a vindication of the approach, that four cases had probable exposure to asbestos, as opposed to one referent, but as an excess risk for asbestos exposure might be expected in any such lung cancer study, it does not mean that the excess in the cohort study can be attributed to asbestos exposure.

Discussion

The analyses of this study with zero latency gave negative results and suggested that there are no grounds for anxiety about the mortality pattern of the cohort. However, as the study was of a cohort known to have been exposed to a skin carcinogen, a more thorough analysis was set in progress in a structured fashion. An excess of lung cancer that merited further investigation was found when latency periods of 10 years and

more were used in the analyses. The study of lung cancer in an occupational setting is always hampered by the confounding effects of smoking habits, social class, geographic region, and past exposure to asbestos. The use of a Widnes correction factor took account of one of these factors, but, in a small cohort, the calculation of an expected value for lung cancer cases always leaves some residual doubts about its validity.

In the absence of precise exposure data, two appropriate tools for investigating a possible cluster of disease are subdivision of the cohort by job, plant, and categories of exposure to chemicals, and a nested case-referent study. Calculations for over 40 subdivisions were undertaken even though it was realized that this procedure increased the probability that a false positive relationship would emerge.

For only one of the agents used in the plants did the subcohort analyses show a positive relationship with lung cancer. The possibility of a synergistic effect between two of the chemicals, though remote, cannot be dismissed, but neither can it be investigated adequately with the available data.

The attention that this approach drew to diglyme led to a full appraisal of the technical, toxicologic, epidemiologic, and exposure data for the compound. The toxicologic review gave no reason to believe that diglyme would pose a carcinogenic hazard. No epidemiologic studies have been reported on diglyme. Exposure to diglyme at the plants was assessed through a review of the data collected during the history of the plants, and it was estimated that the average level would have been below the limit of detection of about 3 ppm.

When the exposure of each of the lung cancer cases to diglyme was assessed, it was concluded that they were all low, or very low, even in relation to the time-weighted average figures of about 1 ppm. In addition, for some cases, the elapsed times since exposure were less than one year. A causal relationship between diglyme and lung cancer in this cohort is, therefore, considered to be implausible.

The failure of the nested case-referent study to generate any new hypotheses is not surprising in view of the size of the study and the unexceptional excess of cancer. In addition, however, the number and diversity of jobs and exposures reported for as few as 39 employees served to illustrate the difficulties involved in recording and analyzing such information in the chemical industry.

Concluding remarks

The initial analysis of this study did not produce any disturbing results or any serious grounds for anxiety about the mortality experience of a cohort among whom an excess of skin lesions had been reported, but detailed analysis of the data produced a mortality ratio for lung cancer that justified further inquiry. The outcome of this inquiry was that the epidemiologic evidence did not demonstrate any definite occupational hazard of lung cancer to the bipyridyl workers. The investigation drew attention to diglyme, but, when the toxicology of diglyme was reviewed and when the exposures of the cases were investigated, a causal relationship between diglyme and lung cancer was considered to be implausible.

However, it was felt that the mortality experience of this cohort should be reviewed after five years of follow-up.

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