

# Cancer incidence and exposure to 4,4'-methylene-bis-ortho-chloroaniline (MbOCA)

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<b>Aims</b>	To monitor the occurrence of cancer in a recently defined cohort of UK workers engaged in the manufacture of polyurethane elastomers using 4,4'-methylene-bis-ortho-chloroaniline.
<b>Methods</b>	A cohort of 308 male production workers from seven factories have been enumerated. All employees had a minimum of 12 months employment and were first employed at one of the participating factories in the period 1973–2000. Mortality and cancer incidence data for the period 1979–2007 were compared with expected values based on national rates.
<b>Results</b>	Mortality from all cancers combined was below the expected value [observed (Obs) 5, standardized mortality ratio (SMR) 68]. There was a single death from bladder cancer (SMR 560). The incidence of all cancers combined was also below expectation [Obs 9, standardized registration ratio (SRR) 77]. Site-specific incidence was unexceptional except there was a non-significant excess of bladder cancer based on two cases (SRR 328).
<b>Conclusions</b>	The findings for bladder cancer should be treated with caution as they relate to a relatively early period of follow-up and are based on very small numbers.
<b>Key words</b>	Bladder cancer; MbOCA; 4,4'-methylene-bis-ortho-chloroaniline; polyurethane elastomers.

## Introduction

The evidence of a carcinogenic risk from exposure to 4,4'-methylene-bis-ortho-chloroaniline (MbOCA) was reviewed in detail recently by the International Agency for Research on Cancer (IARC) and MbOCA was reclassified as a Group I carcinogen on the basis of experimental animal studies (dogs, mice and rats) and mechanistic considerations; epidemiological studies in humans provided only inadequate evidence of carcinogenicity [1,2].

The present study was initiated in 2001 as part of a study of cancer risks in UK rubber workers [3]. Findings for the MbOCA subcohort were not included in the recently published report on cancer risks in UK rubber workers [3] but are shown here to determine whether there are discernible excess risks of bladder cancer in

workers engaged in the manufacture of polyurethane elastomers (polymers) using MbOCA. These polymers are high-performance, specialized, castable polyurethane products providing greater load-bearing capability than conventional elastomers and are used in diverse engineering applications including solid industrial tyres, feed and drive rollers and shock absorption pads.

In the UK, it is estimated that 25 companies currently use ~200 tonnes of MbOCA each year and ~300 workers are exposed to it during polyurethane elastomer production. Although occupational exposure to MbOCA may occur through inhalation, ingestion and skin absorption, exposure primarily occurs via skin absorption. In a recent study conducted during 2005/06 by the UK Health & Safety Executive, the exposure profile for employees working in 20 of these companies (including the companies participating in the current mortality survey) was studied in detail [4]. MbOCA exposures were found to have declined significantly over the last 30 years with a gradual decline in the 90th percentile value for post-shift urinary MbOCA from ~50 µmol/mol creatinine in 1977 to <10 µmol/mol creatinine between 1995 and 2006. (In 1987, the UK Biological Action Limit for MbOCA was 30 µmol/mol creatinine. This figure was reduced in 1996 to 15 µmol/mol creatinine and became a Biological Monitoring Guidance Value.)

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## Methods

A total of seven polymer manufacturing facilities from the UK supplied identifying particulars, work histories, MbOCA-in-urine data and smoking status information for 308 male workers first employed in the factory environment of the participating facilities during the period 1973–2000, for whom personnel records were still available. MbOCA is no longer manufactured in the UK and was never manufactured at any of the seven study plants. Office workers are excluded, whereas maintenance workers are included in the cohort. A further 19 former employees were identified but were excluded as dates of birth were unavailable. At the time of data collection, all facilities were members of the former British Rubber Manufacturers' Association; this industry sector is now represented by the British Rubber and Polyurethane Products Association. All study subjects were employed for a minimum period of 12 months. Information on cigarette smoking at the time of hire was available for 161 study subjects, but only in terms of current smoker ( $n = 55$ ), ex-smoker ( $n = 38$ ) and lifelong non-smoker ( $n = 68$ ). It was known that personnel records were not available at any of the plants for leavers who had left employment many years ago, and a comparison of plant-specific study populations classified by year of hire and by year of leaving employment indicated that personnel records were complete from 1979 at Plant 3, 1987 at Plant 4, 1988 at Plants 1 and 2, 1990 at Plant 5, 1993 at Plant 6 and 1996 at Plant 7. Routine urine cytology is carried out on employees at five of the seven plants.

The Office for National Statistics (ONS), has with the approval of the South Birmingham Research Ethics Committee, provided information on the vital status of each study subject up to the current closing date of the survey

(31 December 2007): 293 (95%) subjects were alive, 10 were deceased (all ages) and 5 subjects were untraced. The underlying cause of death was coded according to the contemporaneous revision of the International Classification of Diseases (ICD). The ONS also supplied information on cancer registrations (incident cancers) for the period 1971–2007.

Expected numbers of deaths were calculated by applying sex-, age- and period-specific mortality rates for UK to corresponding person-years-at-risk (pyr). Each study subject contributed pyr from the end of the first 12 months of employment or the date when company records were judged to be complete to the closing date of the study, death or date last known alive, whichever was the earliest. Standardized mortality ratios (SMRs) were calculated as the ratio of observed (Obs) deaths to expected deaths, expressed as a percentage. These procedures were carried out using the PERSONYEARS programme [5]. Standardized registration ratios (SRRs) were calculated in the same way for the cancer morbidity data.

## Results

Observed and expected numbers of deaths and cancer registrations are shown for selected causes in Table 1. Statistically significant deficits in mortality are shown for all causes of death combined (Obs 9, SMR 46) and for all causes excluding neoplasms (Obs 5, SMR 37). Non-significant deficits are shown for all neoplasms, both for mortality (Obs 4, SMR 68) and for cancer incidence (Obs 9, SRR 77). For bladder cancer, there was a single death with an expected number of 0.18 and two cancer registrations with an expected number of 0.61. Neither of these findings was statistically significant. The first case

**Table 1.** Overall mortality and cancer incidence in 308 male UK workers engaged in the manufacture of polyurethane elastomers using MbOCA, 1979–2007

Disease	ICD9	Mortality (1979–2007)				Cancer registrations (1979–2007)			
		Obs	Exp	SMR	95% CI	Obs <sup>a</sup>	Exp <sup>a</sup>	SRR	95% CI
All causes	1-999	9(*)	19.38	46	21–88	–	–	–	–
All neoplasms	140-239	4	5.89	68	19–174	9	11.64	77	35–147
Stomach cancer	151	0	0.29	0	–	0	0.46	–	–
Lung cancer	162	1	1.51	66	2–368	1	1.80	56	1–310
Bladder cancer	188	1	0.18	560	14–3122	2	0.61	328	40–1184
Kidney cancer, other urinary	189	0	0.17	0	–	0	0.39	–	–
Other neoplasms	remainder 140-239	2	3.74	53	6–193	6	8.38	72	26–156
All other causes	1-139, 240-999	5(*)	13.49	37	12–87	–	–	–	–

\* $P < 0.05$ , (\*) indicates deficit. Exp, expected.

<sup>a</sup>All malignant neoplasms (ICD9, 140–208) excluding non-melanoma skin cancer (ICD9, 173) for which cancer registration data are unreliable. Findings for benign tumours were not included in the incidence findings because of the variable quality of registrations for such tumours in the different cancer registries.

was employed for 10 years, the cancer was diagnosed 23 years after first employment and no information was available on use of cigarettes; the second case was employed for 6 years, the cancer was diagnosed 12 years after first employment and the man was a former smoker. There was also a single case of bladder carcinoma *in situ* (ICD-10 D09.0); national incidence rates for *in situ* and benign tumours are not available for the period under study, and observed and expected numbers of *in situ* tumour registrations are excluded from the table.

## Discussion

There was an excess occurrence of bladder cancer in this study based only on two cases (one death and two cancer registrations). Both of the bladder cancer cases were employed at factories not participating in routine urine cytology. It is not possible to argue, therefore, that these cases represent an artefact of the screening programme (screened populations by definition undergo more diagnostic tests than unscreened populations and identify asymptomatic cases for which it is usually not possible to calculate an appropriate expected number).

This study of UK workers engaged in the manufacture of polyurethane elastomers using MbOCA is still at an early stage of follow-up and confident interpretation of findings based on small numbers of deaths and cancer registrations is not possible. Overall health, as judged by overall mortality, is better than the national average.

The epidemiological literature provides little information to place these findings in a broader context. The company medical records of 209 employees with potential contact with MbOCA at a chemical plant in Deepwater, NJ, USA, were examined. MbOCA had been manufactured at the plant since 1954; no case of bladder cancer was identified for the period 1954–70 [6]. Expected numbers were not provided, follow-up was relatively short and any cases occurring after employees left the company would not have been detected. A brief mention was made by Cartwright [7] of an excess of bladder cancer cases at a plant in the UK engaged in the manufacture of MbOCA. This factory was also involved with the manufacture of magenta, the manufacture and use of ortho-toluidine and the use of other aromatic amines. No attempt to separate the likely role of these various agents has ever been published. A total of 552 workers from a plant in Michigan, USA, producing MbOCA in the period 1968–79 were invited to take part in a telephone interview study and to participate in urine cytology screening [8,9]. A total of three asymptomatic bladder cancers were identified; no valid comparison rates of asymptomatic bladder tumours were available to calculate a corresponding expected number.

Our study provides early evaluation of morbidity and mortality outcomes for a cohort whose exposure profile, as determined by urinary MbOCA results, has been well de-

finied. In the course of time, there may be a sufficient number of events in this cohort to make use of the more detailed work history, MbOCA-in-urine monitoring and smoking status information in a single analysis; the position relating to bladder cancer will need to be monitored carefully.

## Key points

- The first cohort study of workers using rather than manufacturing 4,4'-methylene-bis-ortho-chloroaniline have been established.
- Overall cancer incidence and mortality was below average, although follow-up is at an early stage.
- There was a non-significant excess of malignant bladder cancer, based on two cases only.

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## Conflicts of interest

None declared.

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