British Journal of Industrial Medicine 1993;50:888–893

Mortality experience of employees exposed to 2-mercaptobenzothiazole at a chemical plant in Nitro, West Virginia

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Abstract

Mortality trends for 1059 production workers at a rubber chemicals plant in Nitro, West Virginia were examined to find whether they had increased mortality from cancer associated with exposure to 2-mercaptobenzothiazole (MBT). This chemical and its derivatives are vulcanising agents that have been manufactured at the plant since 1935. Analyses were conducted on MBT exposed employees by cumulative exposure and time since first exposure, and were also stratified by past assignment to *p*-aminobiphenyl (PAB) related departments; PAB is a potent bladder carcinogen that was used at the plant between 1935 and 1955. There was an excess of bladder cancer in MBT workers who had PAB related assignments (standardised mortality ratio (SMR) = 3200, 95% confidence interval (95% CI) 1286–6593). In employees without a job assignment with exposure to PAB, there were no associations between exposure to MBT and increased rates of most malignant neoplasms. The SMR for bladder cancer was increased based on three deaths (SMR = 455, 95% CI 94–1328), although these results were too few to evaluate trends by cumulative exposure category. The possibility of confounding by PAB for exposures for jobs that covered all areas of the plant for these three cases must be considered in the light of the potency of PAB as a bladder carcinogen. There were no deaths from bladder cancer among MBT workers hired after the end of manufacture and use of PAB, but the expected number of deaths was only 0·03.

(*British Journal of Industrial Medicine* 1993;50:888–893)

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A study by the National Toxicology Program (NTP) reported the results of a chronic gavage study with 2-mercaptobenzothiazole (MBT) in rats and mice.[1] Some evidence of carcinogenic activity was reported for male and female rats. The study reported no increased incidences of tumours in male mice and the findings in female mice were equivocal. A second chronic feeding study with MBT in mice showed no neoplastic effects related to treatment.[2] The findings in the Program studies were not considered sufficient to list MBT on the Department of Health and Human Services Annual Report on Carcinogens.[3]

Because the animal studies on MBT were inconclusive, investigations of workers exposed to MBT were initiated at a manufacturing plant in Nitro, West Virginia, and a similar plant in North Wales, United Kingdom.[4] Both plants had long histories of MBT manufacture and use. We report the results for the study of workers in West Virginia.

Materials and methods

DATA COLLECTION METHODS

The study population included 1059 full time, white, male production employees who were paid an hourly rate and who were active at the Nitro plant between 1955 and 1977 for one day or more. Workers who left before 1955 were not included because many of the early personnel records were missing from the plant files. The study population was enumerated from a computerised plant payroll file and social security tax records. Information on demographic and work history was taken from plant personnel records. Five employees with missing or incomplete work histories were not included. Salaried personnel were excluded because many had limited exposures to the plant environment and many of their work histories could not be ascertained from plant records. Thirty one female and 32 non-white male employees were excluded because of small numbers.

Vital status to the end of 31 December, 1987

was obtained for 98% of the 1059 employees eligible for the study. Death certificates were available for all but one known death. At the end of the follow up period, 769 employees (73%) were verified as living, 271 (26%) were confirmed dead, and 18 (2%) were lost to follow up. Information on vital status was obtained from the company payroll, pension and mortality databases, the Social Security Administration, the National Death Index, the Motor Vehicle Bureau of West Virginia, and credit bureau records. Underlying cause of death was coded by two independent nosologists according to the rules of the eighth revision of the International Classification of Diseases (adapted).[5] Discrepancies were resolved by discussions between the two nosologists.

EXPOSURE ASSESSMENT METHODS

Production of MBT at the Nitro plant began in 1934 and continues at present. The manufacturing process has been constant, combining aniline, sulphur, and carbon disulphide to produce MBT. Hydrogen sulphide is a significant byproduct. Over the years, various grades of MBT have been produced; MBT has been purified and sold as a rubber accelerator or converted to the sodium salt, which is an intermediate in the production of other rubber accelerators (table 1). There is some evidence that the amino substituted MBT derivatives are metabolised to MBT and the corresponding amine in vivo.[6 7] Therefore, it was assumed that exposure to 1 mg/m^3 of an MBT derivative was biologically equivalent to exposure to 1 mg/m^3 MBT.

Employees were considered exposed if they had jobs with potential exposure to MBT dust or any of the MBT related derivatives. Animal studies have indicated a minimal potential for human dermal absorption, so dermal exposure to the dry product was not thought to be an important route of entry.[7 8] Annual air borne exposure estimates throughout the study period were developed for all hourly production jobs by a former plant industrial hygienist with sampling data available from 1977 to 1989, historical company documents, and interviews with knowledgeable retirees for the period before 1977. All jobs with potential exposure to MBT were assigned to one of four exposure categories: very low (>0 to 0·5 mg/m^3), low (>0·5 to 2·0 mg/m^3), medium (>2·0 to 5·0 mg/m^3), and high (>5·0 to 20·0 mg/m^3). A cumulative exposure index for each job was calculated by multiplying the midpoint of each exposure category by duration in an MBT exposed job. Altogether, 600 of 1059 employees had a history of exposure to MBT. General maintenance, production, and pilot plant jobs could not be classified conclusively and were considered unexposed.

Because of concern about the potential confounding effect of exposure to para-aminobiphenyl (PAB), a potent human bladder carcinogen used at the plant between 1935 and 1955,[9 10] we also identified employees who worked in a PAB related department. The employees exposed to PAB were defined as those employees who worked in certain areas of the plant where PAB had been used. Those employees whose work covered all parts of the plant, such as yard labour, maintenance, or general production jobs were not considered exposed to PAB, although it was recognised that some of these jobs may have involved such exposure.

ANALYTICAL METHODS

A cohort study design was used to compare death rates of workers with rates for the general population. Standardised mortality ratios (SMRs) were calculated by taking the ratio of observed deaths to expected deaths multiplied by 100.[11] Person–years of follow up were counted from 1955 to the date of death or the study end date, 1987, whichever came first.

Mortality for the white male populations of the counties located within a 20 mile radius of the plant and of the United States as a whole were used to calculate expected death rates. Precision of the SMRs were found with approximate 95% confidence intervals (95% CIs) when the number of observed deaths exceeded five, and Fisher's exact 95% CIs in all other instances.[12]

Table 1 Derivatives of MBT included in study

Chemical name	*CAS No*	*Start and stop production dates*
2-Mercaptobenzothiazole	000149304	1934-present
Sodium mercaptobenzothiazole	002492264	1937-present
n-Cyclohexyl-2-benzothiazole sulphenamide	000095330	1937-present
Benzothiazyl disulphide	000120785	1942-present
n-Tertiary-butyl-2-benzothiazole sulphenamide	000095318	1953-present
2-(morpholinothio) Benzothiazole	000102772	1961-82
2-(2,6-dimethylmorpholinothio) Benzothiazole	000102783	1958-71
2-(hexamethyleneiminothio) Benzothiazole	016832625	1972-74
1,3 Bis(2-benzothiazolylmercaptomethyl) urea	CAS number not available	1935-68

The SMRs were calculated for the total plant population and the subgroup exposed to MBT. To evaluate potential confounding from PAB, the cohort exposed to MBT was stratified by those with and those without a PAB job assignment. The SMRs were also calculated for MBT exposed workers hired after 1955, the year after use of PAB at the plant was discontinued.

Cumulative exposure analyses were conducted for the subgroup of workers exposed to MBT without job assignments in the PAB areas. The SMRs that were based on three or more deaths were evaluated for an internal comparison population without exposure to MBT or PAB according to our definitions, and three categories of cumulative exposure to MBT (<2 mg/m^3, 2–7 mg/m^3, 8–129 mg/m^3). These categories are subsequently referred to as low, medium, and high. The cumulative exposure categories were developed by dividing the person-years into three nearly equal groups and with the upper and lower cumulative exposure value of each group. Trend tests were used to find whether rates of disease increased with exposure level.[13] Death rates were also evaluated for time since first exposure (<20 and ⩾20 years).

Direct comparisons of cancer rates used Mantel-Haenszel techniques for estimation of the age adjusted rate ratio (RR_{M-H}), with 95% CIs based on the variance of the natural logarithm of the RR_{M-H}.[13] The data were stratified into four age categories (15–34 years, 35–54 years, 55–64 years, and 65 or more years). Trend tests were also used.[13]

The unexposed employees in the plant wide cohort became part of an internal comparison population that was used for developing baseline mortalities.

Results

A comparison of results with local *v* United States population rates showed small differences. Therefore, the tables include results from comparisons with the local population. Table 2 shows SMRs for all workers for 1955–1987. Mortality from all causes was significantly lower than local mortality (SMR = 87, Obs = 272, 95% CI 77–98), whereas the SMR for all cancers was slightly raised at 118 (Obs = 78, 95% CI 93–147). This was attributable to the raised rates seen for lung cancer (SMR = 122, Obs = 32, 95% CI 83–172), prostate cancer (SMR = 180, Obs = 7, 95% CI 72–370), and bladder cancer (SMR = 797, Obs = 13, 95% CI 424–1363). SMRs for other site specific cancers and for non-neoplastic diseases were either near or considerably lower than 100.

Table 3 shows SMRs calculated for the total subcohort exposed to MBT, and then by PAB exposure state. Table 3 also shows that mortality from all causes in the total MBT subcohort was slightly lower than local mortality, (SMR = 90, Obs = 158, 95% CI 76–105), whereas the SMR for all cancers was slightly raised at 119 (Obs = 46, 95% CI 87–158). Increased death rates were seen for lung cancer (SMR = 132, Obs = 21, 95% CI 82–202), prostate cancer (SMR = 201, Obs = 4, 95% CI 55–514), and bladder cancer (SMR =

Table 2 Standardised mortality ratios and observed (Obs) and expected (Exp) number of cause specific deaths during 1955–1987 for white hourly employees

Causes of death (ICD-8)	*SMR (Obs/Exp)*	*(95% CI)*
All causes (0–999)	87 (272/313·56)	(77–98)
All cancers (140–209):	118 (78/66·35)	(93–147)
Buccal cavity and pharyngeal (140–149)	64 (1/1·57)	(2–354)
Oesophageal (150)	— (0/1·56)	(0–237)
Stomach (151)	45 (1/2·25)	(1–248)
Colon (153)	63 (3/4·79)	(13–183)
Rectal (154)	73 (1/1·38)	(2–404)
Liver (155–156)	98 (1/1·03)	(2–543)
Pancreatic (157)	33 (1/3·04)	(1–183)
Lung (162)	122 (32/26·26)	(83–172)
Prostate (185)	180 (7/3·90)	(72–370)
Kidney (189·0–189·2)	— (0/1·63)	(0–226)
Bladder (188, 189·9)	797 (13/1·63)	(424–1363)
Central nervous system (191–192)	63 (1/1·58)	(2–353)
Leukaemia (204–207)	85 (2/2·36)	(10–306)
All other cancers	112 (15/13·37)	(63–185)
Ischaemic heart disease (410–414)	107 (116/108·80)	(88–128)
Cerebrovascular disease (430–438)	49 (9/18·44)	(22–93)
Non-malignant respiratory disease (460–519):	59 (13/22·11)	(31–101)
Bronchitis, emphysema, and asthma (490–493)	37 (2/5·41)	(5–133)
Other non-malignant respiratory disease (460–466, 500–519)	104 (9/8·67)	(48–197)
External causes (800–999)	72 (22/30·49)	(45–109)
All other causes	49 (33/67·37)	(34–69)
Unknown causes	1	

No of employees = 1059; person-years = 23 943 and includes five employees with missing work histories.

Table 3 Standardised mortality ratios and observed and expected numbers of cause specific deaths during 1955–1987 for white hourly male employees exposed to MBT and stratified by PAB exposure

	Total MBT cohort (n = 600, p-y = 13 760)		*MBT with PAB job assignment (n = 89, p-y = 2161)*		*MBT without PAB job assignment (n = 511, p-y = 11 599)*		*MBT employees hired after 1955 (n = 270, p-y = 5104)*	
Causes of death	*SMR (obs/exp)*	*(95% CI)*	*SMR (obs/exp)*	*(95% CI)*	*SMR (obs/exp)*	*(95% CI)*	*SMR (obs/exp)*	*(95% CI)*
All causes	90 (158/176·17)	(76–105)	134 (52/38·87)	(100–175)	77 (106/137·29)	(63–93)	37 (8/21·81)	(16–72)
All cancers	119 (46/38·81)	(87–158)	238 (20/8·41)	(145–367)	86 (26/30·40)	(56–125)	— (0/4·26)	(0–87)
Large intestine	37 (1/2·73)	(1–204)	— (0/0·60)	(0–615)	47 (1/2·13)	(1–262)	— (0/0·28)	(0–1315)
Rectal	126 (1/0·80)	(3–700)	— (0/0·18)	(0–2072)	162 (1/0·62)	(4–902)	— (0/0·08)	(0–4662)
Liver	166 (1/0·60)	(4–925)	— (0/0·13)	(0–2822)	212 (1/0·47)	(5–1182)	— (0/0·06)	(0–5851)
Lung	132 (21/15·92)	(82–202)	294 (10/3·40)	(141–541)	88 (11/12·52)	(44–157)	— (0/1·64)	(0–225)
Prostate	201 (4/1·99)	(55–514)	— (0/0·49)	(0–759)	266 (4/1·51)	(72–680)	— (0/0·05)	(0–7418)
Bladder	1138 (10/0·88)	(546–2093)	3200 (7/0·22)	(1286–6593)	455 (3/0·66)	(94–1328)	— (0/0·03)	(0–14683)
Leukaemia and aleukaemia	76 (1/1·32)	(2–421)	356 (1/0·28)	(9–1983)	— (0/1·04)	(0–354)	— (0/0·22)	(0–1645)
All other cancers*	48 (7/14·6)	(19–99)	64 (2/3·11)	(7–232)	44 (5/11·45)	(14–102)	— (0/1·90)	(0–194)

*Cause of death included in 'All other cancers' category if observed = 0; p-y = person-years.

1138, Obs = 10, 95% CI 546–2093).

The SMRs for MBT employees with PAB exposed job assignments were significantly increased for all cancers (SMR = 238, Obs = 20, 95% CI = 145–367), lung cancer (SMR = 294, Obs = 10, 95% CI 141–541), and bladder cancer (SMR = 3200, Obs = 7, 95% CI 1286–6593). There were no deaths due to prostate cancer (expected = 0·49).

The SMRs for MBT employees without job assignments with exposure to PAB were slightly lower than expected for all cancers (SMR = 86, Obs = 26, 95% CI 56–125), but were increased for bladder cancer (SMR = 455, Obs = 3, 95% CI 94–1328) and prostate cancer (SMR = 266, Obs = 4, 95% CI 72–680). The SMR for lung cancer was lower than expected (SMR = 88, Obs = 11, 95% CI 44–157).

Table 3 shows SMRs for MBT employees hired in 1956 or later. The total number of deaths from all causes was significantly lower than expected (SMR = 37, Obs = 8, 95% CI = 16–72), and there were no deaths due to cancer (expected = 4·26), or bladder cancer (expected = 0·03).

Table 4 shows SMRs by cumulative exposure for all cancers, lung, prostate, and bladder cancers. The SMRs for all cancers and lung cancer varied around 100 with no trend with exposure. The SMRs for prostate cancer were greater than 200 for non-MBT workers and the three exposure categories, although the 95% CIs included 100. The SMRs for bladder cancer were slightly higher in the internal unexposed group (SMR = 174, Obs = 1, 95% CI 4–967) and showed no deaths in the low cumulative exposure group (expected = 0·15), and were increased in the medium (SMR = 623, Obs =

Table 4 Standardised mortality ratios for selected causes of death among white hourly male employees exposed to MBT at the Nitro plant 1955–1977 by cumulative exposure with test for trend

		Cumulative exposure to MBT (in mg/m³ y) in employees without PAB job assignment			
	Internal control	*<2 (low)*	*2–7·9 (medium)*	*8–129 (high)*	*Trend test*
All cancers:					
SMR (obs/exp)	106 (23/21·76)	45 (3/6·62)	136 (12/8·82)	74 (11/14·96)	p_{TREND} = 0·36
(95% CI)	(67–159)	(9–132)	(70–238)	(37–132)	
Lung cancer:					
SMR (obs/exp)	98 (8/8·16)	38 (1/2·63)	135 (5/3·72)	81 (5/6·18)	p_{TREND} = 0·77
(95% CI)	(42–193)	(1–212)	(44–314)	(26–189)	
Prostate cancer:					
SMR (obs/exp)	205 (3/1·47)	299 (1/0·33)	286 (1/0·35)	243 (2/0·82)	p_{TREND} = 0·94
(95% CI)	(42–598)	(8–1669)	(7–1591)	(29–879)	
Bladder cancer:					
SMR (obs/exp)	174 (1/0·58)	(0/0·15)	623 (1/0·16)	573 (2/0·35)	p_{TREND} = 0·31
(95% CI)	(4–967)	(0–2455)	(16–3473)	(69–2069)	
Persons at risk	721	366	257	171	
Person-years at risk	9064	3344	3956	4299	

1, 95% CI 16–3473) and high CE categories (SMR = 573, Obs = 2, 95% CI 69–2069). Trend tests were not statistically significant. The RR_{M-H} for bladder cancer with the internal comparison population as the standard were 0 for the low cumulative exposure category, 4·10 for the medium cumulative exposure category (95% CI 0·11–150·47), and 3·21 for the high cumulative exposure category (95% CI 0·22–86·23). The trend test was not statistically significant (p = 0·26).

All three deaths from bladder cancer in the MBT group occurred 20 or more years after first exposure. The SMR for all cumulative exposure groups combined in the 20 years or more since first exposure was 545, (95% CI 112–1591). The SMR for bladder cancer was 363 for the internal unexposed group after 20 or more years since first employment (Obs = 1, 95% CI 9–2024), 0 in the low cumulative exposure group (Exp = 0·12), 792 in the medium cumulative exposure group (Obs = 1, 95% CI 20–4415) and 655 in the high cumulative exposure group (Obs = 2, 95% CI 79–2367). Confidence intervals in the cumulative exposure analyses indicated imprecise estimates of the SMR by exposure category.

Discussion

There were no associations between exposure to MBT and its derivatives and increased rates of most malignant neoplasms in employees without a job assignment with exposure to PAB. The SMRs were increased for prostate and bladder cancer. Prostate cancer was high in all cumulative exposure categories and an unexposed internal comparison group. These results suggested that the findings for prostate cancer were related to some extraneous personal or occupational factor that was affecting all groups equally.

The association between exposure to MBT and bladder cancer was based on only three deaths and was very imprecise. There was no strong trend of increasing rates with increasing exposure, although there were too few deaths for meaningful trend analysis. All three deaths from bladder cancer in the group exposed to MBT occurred in the two highest cumulative exposure categories, and with at least 20 years since first exposure.

Evaluation of bladder cancer results for MBT may also have been confounded by exposure to PAB, even though these findings related to workers never assigned to PAB departments. The processes involving PAB and MBT overlapped for a 25 year period and workers exposed to MBT may have had undocumented exposure to PAB if they had a job working in many parts of the plant between 1935 and 1955. Analysis of the MBT cohort hired after the end of work with PAB showed no deaths due to bladder cancer although only 0·03 deaths were expected.

Review of the work histories of the three employees exposed to MBT who died of bladder cancer showed that all held plant wide jobs during the period of PAB use at the plant. Two employees worked one month in either yard labour or a general production job before 1956, and a third employee worked for 10 years before 1956 as a maintenance worker. Whereas very short term exposure to PAB would seem unlikely to be of aetiological importance, a previous report also suggested that a relatively short exposure to PAB may have been related to bladder cancer.[14]

A study at a rubber chemicals factory in North Wales also examined the association between exposure to MBT and bladder cancer.[4] There were three deaths from bladder cancer among MBT workers at this plant (SMR = 271, Obs = 3, 95% CI 60–792). One death was in the low cumulative exposure category (SMR = 184, Obs = 1, 95% CI 5–1024), two deaths were in the medium category (SMR = 561, Obs = 2, 95% CI 68–2028), and there were no deaths in the high category (expected = 0·20). The internal unexposed group had a bladder cancer SMR of 80 (Obs = 6, 95% CI 29–174). The authors raised concern about potential confounding exposures for these workers as other substances—namely, phenyl-β-naphthylamine, o-toluidine, and aniline when evaluated separately, were also associated with increased rates of bladder cancer in exposed subcohorts.

Possible confounding by cigarette smoking was also considered in our study. Cigarette smoking has been shown to be associated with a two to fourfold risk of bladder cancer among male smokers compared with non-smokers.[15,16] The effect of cigarette smoking as a confounding variable was indirectly evaluated by the method of Axelson,[17] as smoking data was unavailable for the plant population. These results indicated that cigarette smoking would only explain up to a 20% increase in the SMR for this study population.

A major limitation of the investigations at both the West Virginia and North Wales plants is the small number of deaths from bladder cancer in the cohorts. The results of both studies may also have been influenced by the presence of overlapping confounding exposures that were found to be associated with increased rates of bladder cancer. Future study updates of the group of employees hired after 1955 at the West Virginia plant and of the North Wales cohort should provide more definitive information as to whether there is an association between MBT and increased rates of bladder cancer.

Conclusion

An excess of bladder cancer was seen for MBT workers who also had job assignments with exposure to PAB. For MBT workers who did not have a job assignment with exposure to PAB, there were no excesses for most malignant neoplasms. The SMR for bladder cancer was raised, although there were too few deaths to evaluate trends by exposure category. The possibility of confounding by PAB for MBT workers who had plant wide jobs not directly related to departments with exposure to PAB must be considered in the light of the potency of PAB as a bladder carcinogen. There were no deaths from bladder cancer among MBT workers hired after the end of PAB use at the plant although only 0·03 deaths were expected.

This work was sponsored by Monsanto Company, 800 North Lindbergh Boulevard, St Louis, Missouri 63167.

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Accepted 18 January 1993