Mortalities of workers at the Nitro plant with exposure to 2-mercaptobenzothiazole

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Abstract

Objectives—An update of a study of workers exposed to 2-mercaptobenzothiazole (MBT) at a rubber chemicals plant in Nitro, West Virginia is reported. The earlier study found high rates of lung cancer, prostate cancer, and bladder cancer in these workers who also had potential exposure to 4-aminobiphenyl (PAB), a potent bladder carcinogen.

Methods—This cohort mortality study examines the mortalities of 1059 full time white male production workers employed at the plant from 1955 to 1977. A detailed exposure assessment was done on the 600 workers with exposure to MBT. Nine years of additional follow up to the previous study are added.

Results—It was found that MBT workers have expected rates of lung (standardised mortality ratio (SMR)=1.0, 95% confidence interval (95% CI) 0.7 to 1.5) and prostate (SMR=0.9, 95% CI 0.2 to 2.3) cancer. There was an excess of bladder cancer among MBT workers who had definite exposure to PAB (SMR=27.1, 95% CI 11.7 to 53.4), and MBT workers with potential exposure to PAB (SMR=4.3, 95% CI 1.4 to 10.0). However, there were no deaths from bladder cancer among workers with no exposure to PAB (SMR=0.0, 95% CI 0.0 to 24.7), although there were only 0.2 deaths expected.

Conclusions—The potential confounding of exposure to an unknown portion of PAB in the MBT workers makes it impossible to evaluate risk of bladder cancer in this population at this time. However, exposure to MBT does not seem to increase the risk of most cancers including cancers of the lung and prostate.

Materials and methods

PLANT HISTORY

The Nitro plant started operations in 1922. The plant has produced or used agricultural chemicals, paper chemicals, plasticisers, fine chemicals, intermediates, and rubber chemicals, including MBT and PAB. This plant has been the subject of several epidemiology studies. Another study of MBT workers at a plant in Nitro, West Virginia reported high rates of bladder, lung, and prostate cancer. These high rates of cancers were limited to MBT workers with potential exposure to p-aminobiphenyl (PAB), a potent bladder carcinogen. However, the MBT workers without exposure to PAB had no bladder, lung, or prostate cancers, although few were expected.

The potential confounding from carcinogens in both these studies has made interpretation of the cancer findings for MBT workers difficult. Further follow up provides more precise risk estimates and more information on workers employed after the discontinuation of the confounding factors. Therefore, we have updated the study at the Nitro plant with 9 more years of vital status follow up to allow us to re-examine cancer rates among MBT workers.

Keywords: mercaptobenzothiazole; 4-aminobiphenyl; cancer; confounding exposure; exposure misclassification

2-Mercaptobenzothiazole (CAS No 149-30-4) (MBT) is a rubber chemical accelerator which improves the vulcanisation process. Vulcanisation is a procedure that stabilises rubber by creating crosslinks between polymers to provide strength and elasticity. There is some evidence of carcinogenic activity of MBT in one animal species. Rats developed dose related tumours of the adrenal gland but there is no carcinogenic activity in mice.

Two epidemiology studies reported on the cancer rates of workers with exposure to MBT at rubber chemicals plants. A study of MBT workers in Ruabon, Wales reported that rates of most cancers and other causes of death were lower than or equal to local population rates. This study, however, reported increased rates of bladder cancer, but many of these workers also had exposure to the suspect bladder carcinogen o-toluidine, phenyl-β-naphthylamine, which may contain β-naphthylamine, a bladder carcinogen, and MBT. Another study of MBT workers at a plant in Nitro, West Virginia reported high rates of bladder, lung, and prostate cancer. These high rates of cancers were limited to MBT workers with potential exposure to p-aminobiphenyl (PAB), a potent bladder carcinogen. However, the MBT workers without exposure to PAB had no bladder, lung, or prostate cancers, although few were expected.

Materials and methods

STUDY GROUP

We used the same study group presented in the study of Strauss et al. The study population was assembled from plant payroll, work
Methods of Assessing Exposure

2-Mercaptobenzothiazole is not very volatile so most of the exposure would be from dusts. Dermal exposure was not considered an important route of exposure due to the nature of the material and historical use of boots, gloves, and aprons to protect the skin. We estimated exposure to MBT using the method of Strauss et al. The MBT workers’ estimated average exposure for the years 1934–77 is shown in the figure. The highest estimated exposures occurred between the period of 1943–54 when the average exposures generally exceeded 2 mg/m³. The average estimated exposures for workers in this study were low during the first few years of production and after 1970.

The potential for exposure to PAB during the 20 years of manufacturing was limited to several areas where control analysis samples were taken, where distillation residues were removed, and where leaks occurred. Repairs to equipment and accidental leaks rather than normal operating conditions resulted in the greatest exposures. Most workers had some jobs with plantwide responsibilities and therefore had the potential to be involved in the clean up of spills. As we had no way of determining which workers were involved in the clean ups of PAB, estimates of exposure to PAB were impossible. We used two definitions for exposure to PAB as workers could be exposed either in the processes which used PAB or clean ups of accidental releases. A worker was considered to have potential exposure to PAB if he either had a job in a department where exposure to PAB was possible, or was employed between 1935 and 1955, the years when PAB was used in the plant. Use of PAB at the plant coincided with the highest mean exposures of the MBT workers between 1935 and 1955 (figure).

VITAL STATUS FOLLOW UP

We obtained vital status of workers from the beginning of 1955 to the end of 1996 from company payroll and pension files, Social Security Administration, the National Death Index, Motor Vehicle Bureau of West Virginia, and credit bureau records. Further details of how the data for these workers were assembled was presented previously.

At the end of the follow up period, 659 workers (62%) were verified as living, 393 (37%) were confirmed dead, and seven (1%) were lost to follow up. We obtained 99% of death certificates (388 of 393). Two nosologists coded underlying cause of death according to the rules of the eighth revision of the international classification of diseases (ICD-8). The nosologists resolved discrepancies in coding through discussion. Also, the National Death Index provided underlying cause of death for six decedents on whom we had not obtained the death certificate.

ANALYTICAL METHODS

Person-time for study subjects was accumulated across 5 year age and calendar year specific intervals. Accumulation of person-time began at the hire date or 1 January 1955, whichever was the latest. Accumulation of person-time ended at the end of the study (31 December 1996), the last day worked if lost to follow up, or the date of death, whichever was the earliest. We calculated standardised mortality ratios (SMRs) to compare mortalities with the white male population of the four counties of West Virginia (Caball, Kanawha, Lincoln, and Putnam) within a 20 mile radius of the plant. We used Fisher’s exact method for calculation of 95% confidence intervals (95% CIs). We followed guidelines for study conduct given by the Chemical Manufacturer’s Association.

We used cumulative exposure to MBT to evaluate the exposure-response for lung cancer, prostate cancer, and bladder cancer. Cumulative years of exposure are the sum of daily exposures divided by 365 days. Estimated exposures were cumulated before 1955 for workers who were active in 1955. The four categories of cumulative exposure were none, 0.01–1.9 mg/m³-years, 2–7.9 mg/m³-years, and 8–129 mg/m³-years. Person-years for workers not exposed to MBT and those who worked before exposure to MBT began are included in the none category. These exposure categories are the same as those of the earlier study and were developed by dividing the person-years into three equal cumulative exposure categories. A linear trend test was used to evaluate exposure-response. Rates were also evaluated by time since first exposure (<20 years and ≥20 years).

The SMRs are presented for the total plant population and those workers exposed to MBT. The group of workers exposed to MBT is also stratified by workers with and without a...
potential exposure to PAB to find the modifying effect of exposure to PAB.

Results
Table 1 shows the SMRs for all workers for the original study of Strauss et al, the SMRs for the 9 year update, and the results for both groups combined. The original study had 23,943 person-years of observation versus 64,040 in the update. There were 272 deaths reported in the original study versus 313.6 expected deaths (SMR=0.9, 95% CI 0.9 to 1.3). The observed numbers of deaths from lung cancer (SMR=1.2, 95% CI 0.8 to 1.7), prostate cancer (SMR=1.8, 95% CI 0.7 to 3.7), bladder cancer (SMR=8.0, 95% CI 4.2 to 13.6), and ischaemic heart disease (SMR=1.1, 95% CI 0.9 to 1.3) were greater than expected. The 1988–96 update added 121 additional deaths versus 115.8 expected deaths (SMR=1.0, 95% CI 0.9 to 1.3). The observed causes of death for the update period were at expected levels for most causes with the exception of bladder cancer (SMR=3.3, 95% CI 0.7 to 9.7), ischaemic heart disease (SMR=1.9, 95% CI 1.3 to 2.8), and non-malignant respiratory disease (SMR=1.4, 95% CI 0.8 to 2.2).

In the final column of table 1, we combine the follow up from the study of Strauss et al with the follow up from the update of 1988–96. For the entire follow up period, the SMR for all causes of death was 0.9 (95% CI 0.8 to 1.0). Although the number of all cancers in the original study was greater than expected (SMR=1.2, 95% CI 0.9 to 1.5), the number of cancers in the combined follow up was at expected levels (SMR=1.0, 95% CI 0.8 to 1.2). For the entire follow up period, lung cancer (SMR=1.0, 95% CI 0.7 to 1.3), prostate cancer (SMR=1.1, 95% CI 0.5 to 2.1), and the other cancer sites examined were at expected levels. Among the cancers, only rates of bladder cancer were greater than expected for the entire follow up period (SMR=6.3, 95% CI 3.6 to 10.3). Also, the SMR for ischaemic heart disease for the entire follow up period was 1.2 (95% CI 1.0 to 1.4). The remaining tables present results from the combined follow up periods only.

Table 2 shows the SMRs for the workers exposed to MBT and stratified by potential exposure to PAB. The SMR for total cancer among MBT workers was similar to the entire study group and to the population living near the plant (SMR=1.0, 95% CI 0.8 to 1.3). Rates for lung cancer (SMR=1.0, 95% CI 0.7 to 1.5) and prostate cancer (SMR=0.9, 95% CI 0.2 to 2.3) were also at expected levels. The SMR for bladder cancer (SMR=8.9, 95% CI 4.7 to 15.2) was greater than expected when compared with the external reference group. The number of total cancers was greater than expected (SMR=2.0, 95% CI 1.3 to 3.0) for MBT workers with one or more job with exposure to PAB during their career. The numbers

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>All MBT workers SMR (95%CI)</th>
<th>MBR workers with jobs with exposure to PAB SMR (95%CI)</th>
<th>MBR workers without jobs with exposure to PAB* SMR (95%CI)</th>
<th>MBR workers with no exposure to PAB (employed after 1955) SMR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>1.0 (0.8 to 1.3) [63/65.9]</td>
<td>2.0 (1.3 to 3.0) [23/11.5]</td>
<td>0.8 (0.5 to 1.0) [40/52.3]</td>
<td>0.3 (0.1 to 0.9) [39/77.7]</td>
</tr>
<tr>
<td>Lung</td>
<td>1.0 (0.7 to 1.5) [7/26.4]</td>
<td>2.4 (1.2 to 4.3) [1/14.6]</td>
<td>0.7 (0.4 to 1.2) [21/26.5]</td>
<td>0.6 (0.1 to 1.9) [22/6.6]</td>
</tr>
<tr>
<td>Prostate</td>
<td>0.9 (0.2 to 2.3) [4/4.4]</td>
<td>0.0 (0.0 to 4.4) [0/0.0]</td>
<td>1.1 (0.3 to 2.9) [4/3.6]</td>
<td>0.0 (0.0 to 11.9) [0/0.0]</td>
</tr>
<tr>
<td>Bladder</td>
<td>8.9 (4.7 to 15.2) [13/1.5]</td>
<td>27.1 (11.7 to 53.4) [8/0.3]</td>
<td>4.3 (1.4 to 10.0) [5/1.2]</td>
<td>0.0 (0.0 to 24.70 [0/0.0]</td>
</tr>
<tr>
<td>Workers</td>
<td>609</td>
<td>89</td>
<td>511</td>
<td>270</td>
</tr>
<tr>
<td>Person-years</td>
<td>17344</td>
<td>2405</td>
<td>14940</td>
<td>7405</td>
</tr>
</tbody>
</table>

*Includes workers who held plantwide jobs with potential exposure to PAB.
of lung cancers (SMR=2.4, 95% CI 1.2 to 4.3) and bladder cancers (SMR=27.1, 95% CI 11.7 to 53.4) for this group of workers were greater than expected. The MBT workers without a job with definite exposure to PAB during their careers had an observed total cancer rate (SMR=0.8, 95% CI 0.5 to 1.0) which was lower than expected mostly as a result of fewer than expected deaths from lung cancer (SMR=0.7, 95% CI 0.4 to 1.2). Observed deaths from bladder cancer (SMR=4.3, 95% CI 1.4 to 10.0), however, were greater than expected in this group based on five deaths. Workers with no potential exposure to PAB, or those workers hired after 1955, have a lower observed than expected risk of total cancer (SMR=0.3, 95% CI 0.1 to 0.9) and there were no deaths from bladder cancer (0.2 expected).

Table 3 presents the SMRs for lung, prostate, and bladder cancer by cumulative exposure for 511 MBT workers without a job with known exposure to PAB but who may have held plant wide jobs with potential exposure to PAB. The SMRs for lung cancer and prostate cancer varied around 1.0 for all exposure groupings and there was no trend with cumulative exposure. The SMRs for bladder cancer were at expected levels in the unexposed category (SMR=1.2, 95% CI 0.0 to 6.5), no deaths occurred in the low exposure category (SMR=0.0, 95% CI 0.0 to 13.8), one death occurred in the medium category (SMR=3.5, 95% CI 0.1 to 19.5), and four deaths occurred in the high exposure category (SMR=6.5, 95% CI 1.8 to 16.6). The p value for the linear trend test indicated that the increase in SMR with cumulative exposure was unlikely to be due to chance. All five deaths from bladder cancer in workers without a job with definite exposure to PAB occurred >20 years after first exposure to MBT (SMR=4.8, 95% CI 1.5 to 11.1). However, there was only 0.1 death expected from bladder cancer in the category of <20 years from first exposure to MBT.

Discussion
The original study on this group of MBT workers by Strauss et al found most cancers at expected levels. However, high rates of bladder, lung, and prostate cancer among MBT workers with potential exposure to PAB were reported. We have added 9 years of data, 6404 person-years of observation, and 121 additional deaths to the study of Strauss et al. During the update period, low cancer rates were observed relative to both the original study and the external comparison group. The high rates of lung and prostate cancer reported in the earlier study among MBT workers are now at expected levels with the addition of these new data. The risk of lung and prostate cancer do not seem to related to exposure to MBT as there was no trend with cumulative exposure. Further, the recently updated Ruabon study found no increase in lung or prostate cancer among MBT workers. Risks of lung and prostate cancer do not seem to related to exposure to MBT.

We observed high rates of bladder cancer among the 600 MBT workers. Many of these MBT workers had potential exposure to PAB, a potent bladder carcinogen. The manufacturing processes for MBT and PAB overlapped for 20 years, 1935–55. The highest mean exposure to MBT occurred during the period 1935–55 when PAB was used in the plant. In total 330 MBT workers either worked in the PAB department, or worked in the plant when PAB was used. Many of the group who worked in the plant when PAB was used had jobs with plantwide responsibilities. The association of exposure to MBT and bladder cancer has to be interpreted in the context of potential confounding with PAB.

Of the 13 deaths from bladder cancer which occurred among MBT workers, eight occurred among the 89 workers who held a job in the PAB department producing an SMR of 27.1 (95%CI 11.7 to 53.4). The five remaining deaths from bladder cancer occurred among the 511 MBT workers who did not have jobs listed in the PAB department on their work history. This group of workers also had increased rates of bladder cancer (SMR=4.3, 95% CI 1.4 to 10.0). If 65 of the 511 MBT workers employed when PAB was used at the plant had exposure to PAB, an SMR of 4.3 would be observed given a relative risk of 27.1 among PAB workers. The five workers who died of bladder cancer held jobs with plantwide responsibilities for 1 month, 5 months, 8 months, 20 months, and 10 years. These five workers had job titles of maintenance worker, yard labourer, or general production worker and thus may have had exposure to PAB. However, we have no definitive information that these workers were ever exposed to PAB. Although we found an association with increasing exposure to MBT and increasing risk of bladder cancer, the number of deaths in each exposure category was small, and at least some confounding with exposure to PAB seems likely given that the highest mean exposures to MBT occurred when PAB manufacturing was
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rates of bladder cancer are greater than expected among MBT workers, but an unknown portion of these workers had exposure to PAB. The potential confounding exposure to PAB, a potent bladder carcinogen, in an unknown portion of the MBT workers makes it impossible to evaluate risk of bladder cancer in this population. Although the lack of bladder cancers among workers hired after PAB manufacture ended would argue against a relation with exposure to MBT, the number of expected deaths in this group of workers is too small to be conclusive. However, exposure to MBT does not seem to increase the risk of most cancers including cancers of the lung and prostate.

Conclusion

The MBT workers have cancer rates that are lower than or equal to local population rates.