

# Increased bladder cancer risk among workers exposed to *o*-toluidine and aniline: a reanalysis

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Accepted 19 October 2009

## ABSTRACT

**Introduction** In 1991, the US National Institute for Occupational Safety and Health (NIOSH) reported an increased bladder cancer risk in a cohort of 1749 workers potentially exposed to *o*-toluidine and aniline at a chemical manufacturing plant. As additional information showed that workers in certain departments had been misclassified regarding *o*-toluidine exposure, we therefore conducted a reanalysis of the data using updated exposure categories.

**Methods** We updated exposure categories based on information ascertained during a plant walkthrough, documents on file at the plant, interviews with current and former employees, and answers provided by company and union officials to specific questions. Bladder cancer incidence was determined through 31 December 1988 and mortality through 31 December 1994.

**Results** Thirteen cases of bladder cancer were observed versus 3.57 expected (New York State rates excluding New York City) (standardised incidence ratio (SIR) 3.64, 95% CI 1.94 to 6.23). Among workers classified as definitely exposed, increasing risks were observed for longer duration of employment (for  $\geq 10$  years, standardised rate ratio (SRR) 6.07, 95% CI 0.77 to 48.17) and time since first employment in the exposed departments (for  $\geq 20$  years, SRR 3.39, 95% CI 0.40 to 29.03). One bladder cancer death was observed among those definitely exposed.

**Conclusions** These findings are comparable to the results reported earlier by NIOSH, and confirm that workers in this plant have an increased risk of bladder cancer.

## INTRODUCTION

*o*-Toluidine is an aromatic amine used primarily in the manufacture of dyestuffs, and also in the production of synthetic rubber, chemicals and pesticides and as a curing agent for epoxy resin systems. *o*-Toluidine was recently classified by the International Agency for Research on Cancer (IARC) as 'carcinogenic to humans' (group 1).<sup>1</sup> This classification was based largely on the results of a retrospective cohort study conducted by the US National Institute for Occupational Safety and Health (NIOSH) in a chemical manufacturing plant in New York State. From 1973 through 1988, NIOSH identified 13 cases of bladder cancer (versus 3.61 expected based on the population of New York State, excluding New York City) among 1749 workers employed at the plant.<sup>2</sup> A 6.5-fold bladder cancer risk was observed among workers in the rubber chemicals department, where *o*-toluidine, aniline and other chemicals were used.

## What this paper adds

- In earlier papers, NIOSH reported an increased bladder cancer risk in a cohort of workers potentially exposed to *o*-toluidine and aniline at a chemical plant.
- Exposure to *o*-toluidine was likely associated with this risk because it is a more potent carcinogen than aniline in animals and was found in the urine of workers at higher levels than aniline.
- Additional information showed that workers in certain departments had been misclassified regarding *o*-toluidine exposure.
- Using revised exposure categories, our findings were comparable with those reported in the earlier NIOSH studies, and confirm that workers in this plant have an increased risk of bladder cancer.

A strong exposure-response effect was observed with duration of employment and time since first employment in the rubber chemicals department.<sup>2</sup> In a subset of workers, NIOSH found that urinary *o*-toluidine and aniline levels were elevated over background (population) levels pre- and post-shift, even in those workers considered not exposed to *o*-toluidine.<sup>3</sup>

In 2004, Markowitz and Levin<sup>4,5</sup> reported 19 additional cases of bladder cancer in this cohort. The authors questioned the exposure classification used in the NIOSH studies. They indicated that, at a minimum, laboratory workers should be considered definitely exposed since they routinely handled samples of *o*-toluidine and aniline. The aim of this paper is to present a reanalysis of the original study data<sup>2,6</sup> using updated exposure categories.

## METHODS

The cohort consisted of 1749 workers employed for 1 day or more at the plant between 1946 and 1988. The plant, processes and substances used and the study design and methods have been described previously.<sup>2,6</sup> Briefly, personnel records were microfilmed for all workers employed at the plant since 1946, including office and salaried personnel. The data were coded and entered into an electronic database. Bladder cancer cases were identified by the company and the union and confirmed through review of medical records. Additional cases were identified through the New York State Cancer Registry, but these were not confirmed through

**Table 1** Bladder cancer risk by exposure group in the original and updated studies

Study	Exposure group	Number of workers†	PYAR	Bladder cancer			
				Observed	Expected	SIR	95% CI‡
Ward <i>et al</i> (1991) <sup>2</sup>	Probably not exposed	753	9956	2	1.43	1.39	0.17 to 5.02
	Possibly exposed	288	3811	4	1.09	3.66	1.0 to 9.37
	Definitely exposed	708	9144	7	1.08	6.48*	2.61 to 13.35
	Total	1749	22911	13	3.61	3.60*	1.92 to 6.16
Current update	Probably not exposed	600	8077	1	1.15	0.87	0.02 to 4.86
	Possibly exposed	187	2460	1	0.54	1.86	0.05 to 10.39
	Definitely exposed	962	12373	11	1.88	5.84*	2.91 to 10.45
	Total	1749	22911	13	3.57	3.64*	1.94 to 6.23

\* $p<0.001$ .

†Workers were classified in their highest exposure group, that is, once workers were classified as definitely exposed, they were definitely exposed from that point on; once workers were classified as possibly exposed, they were possibly exposed from that point on unless they became definitely exposed.

‡Original study reported 90% CI; 95% CI were calculated based on the estimates reported in the manuscript.

PYAR, person-years-at-risk; SIR, standardised incidence ratio.

medical record review. Vital status and cause of death were ascertained by linking with records of the Social Security Administration and the National Death Index. This study was approved by the NIOSH Human Subjects Review Board.

In the original NIOSH studies,<sup>2,6</sup> workers were classified into three mutually exclusive groups: (1) 'definitely exposed', workers who had ever worked in the rubber chemicals department, even if they had periods of employment outside of that department; (2) 'possibly exposed', workers ever employed in maintenance, shipping, janitorial or yard work; and (3) 'probably not exposed', all other workers who were not likely to have been exposed to *o*-toluidine and aniline. Consequently, we adjusted the original exposure groups to reclassify some departments based on updated information ascertained during a plant walkthrough, interviews with employees, management and union representatives, and review of records. We also developed a list of questions seeking clarification of worker-reported jobs and departments and differences between similar job titles and potential for exposure, and obtained responses from company and union representatives.

For this analysis, work in the maintenance, rubber chemicals, quality control, laboratory, and research and development depart-

ments was considered to be definitely exposed; work in the shipping/packaging/warehouse and yard/janitor departments, and in certain positions including temporary assignment from headquarters, was considered to be possibly exposed; and work in the remaining departments plus all work prior to 1 January 1957 was considered to be probably not exposed. Previous analyses<sup>2,6</sup> considered only work in the rubber chemicals department as definitely exposed and work in maintenance, shipping/packaging/warehouse and yard/janitor departments as possibly exposed. Workers were assigned to the highest exposure category of all the departments where they had worked. Work histories were truncated for 295 workers who were actively employed on 1 August 1988, when the records were obtained.

We conducted the cancer incidence analysis using New York State (excluding New York City) as the comparison population, as done previously.<sup>2</sup> For those considered definitely exposed, we also calculated the standardised rate ratio (SRR) for bladder cancer by duration of employment and time since first employment. Person-years-at-risk began at the later of 1 January 1973 (the rate file begin date) or the date of first employment. Person-years-at-risk ended at the earliest of the date of bladder cancer diagnosis (for bladder cancer incident cases), the date of

**Table 2** Bladder cancer risk by duration of employment and time since first employment in the departments with definite exposure to *o*-toluidine and aniline, in the original and updated studies

Study	Characteristic	Number of workers‡	Bladder cancer				SRR	95% CI
			Observed	Expected	SIR	95% CI§		
Ward <i>et al</i> (1991) <sup>2</sup>	Duration of employment							
	<5 years	584	0	0.75	—	—		
	5–<10 years	51	1	0.11	8.8	0.22 to 49.0		
	≥10 years	73	6	0.22	27.2*	9.98 to 59.2		
	Time since first employment							
	<10 years	196	0	0.22	—	—		
Current update	Duration of employment							
	<5 years	678	1	0.80	1.25	0.03 to 6.97	1.0	—
	5–<10 years	95	1	0.27	3.67	0.09 to 20.44	2.0	0.13 to 32.05
	≥10 years	189	9	0.81	11.09*	5.07 to 21.05	6.07†	0.77 to 48.17
	Time since first employment							
	<10 years	78	1	0.28	3.63	0.09 to 20.23	1.0	—

\* $p<0.001$ .†Tests for trend:  $p<0.0001$  for duration of employment and  $p=0.12$  for time since first employment.

‡Number of workers whose duration of employment or time since first employment (as of the study end date, the date of diagnosis, date of death, or date last observed) was in the category stated.

§Original study reported 90% CI; 95% CI were calculated based on the estimates reported in the manuscript.

SIR, standardised incidence ratio; SRR, standardised rate ratio.

death (for deceased cohort members), the date last observed (for cohort members lost to follow-up) or 31 December 1988.

We conducted the bladder cancer mortality analysis using the US population as the reference, as done previously.<sup>6</sup> Person-years-at-risk began at the later of 1 January 1960 (the rate file begin date) or the date of first employment. Person-years-at-risk ended at the earliest of the date of death (for deceased cohort members), the date last observed (for cohort members lost to follow-up) or 31 December 1994. We used the NIOSH Life Table Analysis System (LTAS.NET V. 2.0.16) to conduct the statistical analyses.

## RESULTS

The possibly exposed category now includes 30 workers previously assigned to the probably not exposed category, and the definitely exposed category now includes 131 and 123 workers previously assigned to the possibly exposed and probably not exposed categories, respectively (table 1). Work in the yard/janitor and shipping/packaging/warehouse departments continues to be possibly exposed and work in rubber chemicals continues to be definitely exposed, but work in maintenance (185 workers), quality control (8 workers), the laboratory (146 workers), and research and development (28 workers) is now considered definitely exposed, and work in certain positions including temporary assignment from headquarters (99 workers) is now considered possibly exposed.

The observed and expected bladder cancer cases for each exposure group and for the total cohort are shown in table 1. Increased standardised incidence ratios (SIR) of the same magnitude as observed in the previous study<sup>2</sup> were obtained using the updated exposure categories. Among those workers classified as 'definitely exposed', SIR estimates were comparable to those reported earlier, and SRR showed increasing risks with longer duration of employment and time since first employment in the exposed departments (table 2).

Two bladder cancer deaths were observed, one among those definitely exposed and one among those probably not exposed (standardised mortality ratio (SMR) 1.98, 95% CI 0.05 to 11.05 and SMR 3.0, 95% CI 0.08 to 16.71, respectively). These results are comparable to the SMR of 3.8 (95% CI 0.1 to 21.1) for workers definitely exposed and 2.6 (95% CI 0.07 to 14.3) for those probably not exposed, reported previously.<sup>6</sup> In contrast, the SMR for all cancers among the definitely exposed group was 0.97 (95% CI 0.62 to 1.42) and for all causes of death was 0.87 (95% CI 0.70 to 1.05).

## DISCUSSION

Using revised department-based exposure categories, we have confirmed the results of an earlier study that reported an

increased risk of bladder cancer among workers exposed to *o*-toluidine and aniline. Exposure to *o*-toluidine is likely associated with this risk because it is a more potent carcinogen than aniline in animals and was found in the urine of workers at higher levels than aniline.<sup>3</sup> It was, however, not possible to determine workers' exposures to *o*-toluidine and aniline separately.

A limitation of the exposure classification scheme used in this study is that it is based on department only and workers were assigned to the highest exposure category of all the departments where they had worked, even if it was for only a short period of time. This classification does not consider the job performed, date of employment (since exposures have changed throughout the years), and length of exposure in each specific job. It is therefore possible that exposures were misclassified.

Low-grade, superficial bladder cancers have minimal risk of progression to death; consequently, the SMR may not be a good indicator of risk. Even though the number of bladder cancer deaths was small and the results were not statistically significant, an increased risk of bladder cancer mortality was observed among those definitely exposed, whereas the risks for all cancers and all causes of death were not increased in this group.

These findings are consistent with those of a recently published study in the United Kingdom<sup>7</sup> and support the IARC classification of *o*-toluidine as a human bladder carcinogen.

**Acknowledgements** The authors wish to thank Lian Luo and Jean Geiman for programming assistance, and the company workers, management and union staff for their valuable input. We also thank the reviewers for helpful comments.

**Funding** This study was funded by CDC/NIOSH operating funds.

**Competing interests** None.

**Ethics approval** This study was conducted with the approval of the NIOSH Human Subjects Review Board.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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