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Response of the National Institute for Occupational Safety and Health to an occupational health risk from exposure to *ortho*-toluidine and aniline

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In 1988, union representatives at a New York chemical plant requested a health hazard evaluation by the National Institute for Occupational Safety and Health (NIOSH). There was an apparent increase in bladder cancer incidence among rubber additives workers, with nine cases diagnosed from 1973 to 1988. Since 1957 the plant has made a rubber antioxidant from *ortho*-toluidine (*o*-toluidine), aniline, hydroquinone, and toluene, and since 1970 a rubber accelerator has been produced from carbon disulfide, sulfur, aniline, benzothiazole, and a proprietary chemical. Among the major chemicals used or formed in the processes, only *o*-toluidine has been classified as an animal carcinogen (1).

Subjects and methods

In response to the request for a health hazard evaluation, NIOSH conducted an epidemiologic study of cancer incidence and case-referent biomonitoring and made notifications of the findings. In the retrospective cohort study (2), the bladder cancer incidence of the workers was compared with the New York State rate. Cases identified by the company and union were confirmed from requested medical records. Additional cases were identified from matching with the New York State Cancer Registry. Biological monitoring of *o*-toluidine and aniline began with the collection of pre- and postshift urine samples and 8-h personal air samples. Workers in a department where *o*-toluidine and aniline were not used were enlisted as referents for the urine tests. Blood samples were collected from some subjects for adduct determinations (results will not be discussed as the adduct analyses are incomplete). The participants provided urine samples shortly before starting work and immediately after the shift. The procedures for the sample preparation and laboratory analysis of the urine have been described elsewhere (3). Each participant was asked for a smoking history because *o*-toluidine and aniline are both found in cigarette smoke (4) and in the urine of smokers and nonsmokers (5). In addition, airborne exposure to *o*-toluidine and aniline among 33 study participants in the rubber additives department was monitored for an entire shift with personal air samplers. Extracted samples were analyzed by gas chromatography (6).

Results

During the cancer incidence study period (1973—1988), 13 individuals were diagnosed with bladder cancer, seven from the rubber additives department, with definite exposure to *o*-toluidine and aniline, four from maintenance, janitorial or yard and shipping departments, with possible exposure, and two who had worked only in other areas and were probably unexposed. Table 1 presents the numbers of observed and expected bladder cancer cases for the entire cohort and for each exposure group. Excess bladder cancer occurred at the plant among possibly exposed maintenance, yard and shipping workers and definitely exposed workers in the rubber additives department. Those employed less than five years in the exposed department had no increased risk, those who worked 5—10 years had a standardized incidence ratio (SIR) of 8.8 [95% confidence interval (95% CI) 0.1—50.6], and workers employed 10 years or more had an SIR of 27.2 (95% CI 10.0—59.4). A linear test for trend indicated a strong positive relationship with length of exposure ($P < 0.001$). Risk also increased with latency, those with < 10 years since first employment in the exposed department having no increased risk, those with 10—20 years' latency having an SIR of 2.0 (95% CI 0.03—11.4), and those with ≥ 20 years of latency having an SIR of 16.4 (95% CI 5.9—35.3).

Because of the strong association between bladder cancer and exposure to *o*-toluidine and aniline, NIOSH investigators were concerned about current levels of exposure at the study plant. The lack of air monitoring data prior to 1975 made it difficult to estimate past exposure and compare it to present levels, which are well below the limits set by the Occupational Safety and Health Administration (OSHA). [It should be

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noted that all of the workers diagnosed with bladder cancer began working at the plant before 1970, when exposures may have been considerably higher.] The hypothesis was that despite the low air levels of *o*-toluidine and aniline, workers in the rubber additives department might still have significant exposure. In addition, air monitoring does not reflect dermal absorption, possibly an important route of exposure for both chemicals (7).

The biological monitoring study showed that workers in the rubber additives department had high levels of both chemicals in their urine. The preshift mean concentration of aniline was 2.7 $\mu g \cdot l^{-1}$ for the unexposed workers and 17.4 $\mu g \cdot l^{-1}$ for the exposed workers. The postshift means were 3.8 $\mu g \cdot l^{-1}$ for the unexposed workers and 32.3 $\mu g \cdot l^{-1}$ for the exposed workers. Both differences were significant ($P < 0.0001$) in unpaired t-tests. [All data were log-transformed to achieve normality.] The increases during the shift, from 2.7 to 3.8 $\mu g \cdot l^{-1}$ for the unexposed and from 17.4 to 32.3 $\mu g \cdot l^{-1}$ for the exposed, were also statistically significant in paired t-tests. For *o*-toluidine, the preshift means were 1.1 $\mu g \cdot l^{-1}$ for the unexposed and 18.5 $\mu g \cdot l^{-1}$ for the exposed workers. The postshift means were 2.7 $\mu g \cdot l^{-1}$ for the unexposed and 103.7 $\mu g \cdot l^{-1}$ for the exposed workers. Both differences were significant ($P < 0.0001$) in unpaired t-tests. The increases during the shift, from 1.1 to 2.7 $\mu g \cdot l^{-1}$ for the unexposed and from 18.5 to 103.7 $\mu g \cdot l^{-1}$ for the exposed workers, were significant ($P < 0.0001$) in paired t-tests. The postshift differences between the nonsmokers and smokers within the exposure groups were significant for aniline (table 2). However, exposure had a stronger effect. The difference in smoking and exposure effects was more pronounced for *o*-toluidine (table 2).

Air samples of 33 exposed workers were consistent with company and NIOSH sampling since 1975, showing *o*-toluidine and aniline levels well below the OSHA exposure limits. Although the air levels were low, they correlated significantly with the urine levels in postshift samples. Both the air and urine levels of *o*-toluidine and aniline were 2—2.5 times as high in the antioxidant section as in the accelerator section of the exposed department.

The results of the epidemiologic and biomonitoring studies were sent to the company and the union. A letter describing the results of the epidemiologic study was sent to nearly 2000 current and former workers in the rubber additives department, and the participants in the biomonitoring study were sent their individual results. The highly correlated urine and air data pinpointed jobs and activities with potential high exposure to aromatic amines which should be the focus of efforts to reduce exposure. Periodic screening of the exposed workers was also recommended.

In a "NIOSH Alert" (8), NIOSH also communicated the results of the epidemiologic investigation and

Table 1. Observed and expected numbers of bladder cancers among the chemical workers by exposure group. (N = number of persons, O = observed number of bladder cancers, E = expected number of bladder cancers, SIR = standardized incidence ratio, 95% CI = 95% confidence interval)

Probability of exposure to *o*-toluidine and aniline[a]	N	O	E[b]	SIR	95% CI
Definitely exposed	708	7	1.08	6.5	2.6—13.4
Possibly exposed	288	4	1.09	3.7	1.0—9.4
Probably unexposed	753	2	1.43	1.4	0.2—5.1
Total	1749	13	3.61	3.6	1.9—6.2

[a] Definite exposure to *o*-toluidine and aniline in the rubber additives department; possible exposure in maintenance, janitorial and yard and shipping departments; or probably unexposed, working only in other areas.
[b] Expected based on total person-years at risk and New York State cancer incidence rates.

Table 2. Urinary aniline and *o*-toluidine concentrations[a] by exposure group and smoking status.

Exposure group	Aniline				*o*-Toluidine			
	Preshift		Postshift		Preshift		Postshift	
	Number of workers	Concentration ($\mu g \cdot l^{-1}$)	Number of workers	Concentration ($\mu g \cdot l^{-1}$)	Number of workers	Concentration ($\mu g \cdot l^{-1}$)	Number of workers	Concentration ($\mu g \cdot l^{-1}$)
Unexposed group								
Nonsmokers	20	1.8	21[b,c]	2.7	20[b]	1.2	21[c]	2.8
Smokers	12[d]	4.1	11[b,d]	5.8	12[b]	1.0	11[c]	2.6
Exposed group								
Nonsmokers	29	14.6	32[c]	23.6	29	17.5	32[c]	83.9
Smokers	19	21.8	20[c,d]	46.1	19	20.0	20[c,d]	135.6

[a] The median coefficient of variation from combined laboratory and split data was 0.16 for aniline and 0.13 for *o*-toluidine.
[b] Among the unexposed workers, 11 of 20 preshift and 4 of 21 postshift nonsmoker samples and 1 of 12 preshift and 1 of 11 postshift smoker samples were below the limit of detection of 1.4 $\mu g \cdot l^{-1}$ for aniline and 10 of 20 preshift nonsmoker samples and 5 of 12 preshift smoker samples were below the limit of detection of 0.6 $\mu g \cdot l^{-1}$ for *o*-toluidine.
[c] Significant ($P < 0.05$) differences between the preshift and postshift samples by individual in paired t-tests.
[d] Significant ($P < 0.05$) difference between the smokers and nonsmokers in the unpaired t-test.

information on engineering and personal protective measures to reduce potential exposure to companies throughout the United States in which *o*-toluidine and aniline were potentially in use. In the NIOSH Alert and in its communications to the Occupational Safety and Health Administration (OSHA), NIOSH has recommended that exposure to *o*-toluidine and aniline be reduced to the lowest feasible concentration (8).

Discussion

A major collaborative effort by several NIOSH divisions has involved a study of the results of exposure to *o*-toluidine and aniline in the workplace. The incidence study found a significant risk of bladder cancer at the study plant, highest among workers considered to have definite exposure to *o*-toluidine and aniline, intermediate among workers considered to have possible exposure, and lowest among workers considered unexposed. The risks among those definitely exposed increased with length of exposure and time since first exposure.

Efforts to develop methods to monitor exposures to these chemicals were first implemented to evaluate current exposures at the plant where the bladder cancer incidence study was done. Biological monitoring determined that workers considered to have definite exposure to *o*-toluidine and aniline had significantly higher levels of both chemicals in their urine before the workday than did unexposed workers, possibly reflecting "steady state" levels of the chemicals in their bodies. At the end of the workday, the levels of both chemicals in the urine were 10—40 times higher in the exposed workers than in the unexposed ones. Recommendations have been made on reducing exposures at the plant. Recently NIOSH initiated a project to identify a cohort to study bladder cancer incidence among workers exposed to *o*-toluidine and no other aromatic amines. NIOSH estimates that, during 1981—1983, 28 500 workers were potentially exposed to *o*-toluidine (and 35 800 to aniline) [unpublished provisional data as of 1 January 1990, NIOSH, National occupational exposure survey (NOES), 1981—1983, data on *o*-toluidine and aniline]. In collaboration with the National Cancer Institute, NIOSH conducted a search for a cohort exposed only to *o*-toluidine. Over 50 facilities, from a list NIOSH compiled of over 300 that definitely or probably used *o*-toluidine, were evaluated for their use of aromatic amines. Information from the study is currently being evaluated. The NIOSH response to a request from the public has led to a series of research and notification activities which have had and will continue to have a major public health impact. All of these activities were undertaken to fulfill the NIOSH mandate to assure a safe workplace for every American worker.

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