Monitoring of Aromatic Amine Exposures in Workers at a Chemical Plant With a Known Bladder Cancer Excess

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Background: **In April 1991, an excess of bladder cancer cases among workers employed at a chemical manufacturing facility in Niagara Falls, NY, was reported. This excess was primarily confined to 708 workers who had ever been employed in the rubber chemicals manufacturing area of the plant, where the aromatic amines aniline and *o*-toluidine have historically been used. *Purpose:* An environmental and biological monitoring survey was conducted to evaluate current exposures to aniline and *o*-toluidine in the rubber chemicals department. *Methods:* Personal air sampling for aniline and *o*-toluidine was conducted with the use of a modified Occupational Safety and Health Administration (OSHA) 73 method. Urine samples were collected before and after work (i.e., pre-shift and post-shift, respectively) and stored at –70 °C. Base hydrolysis was used to convert acetanilide and *N*-acetyl-*o*-toluidine, metabolites of aniline and *o*-toluidine present in the urine, to the parent compounds. The parent compounds were extracted from the alkaline urine into butyl chloride and then back-extracted from the butyl chloride into aqueous hydrochloric acid. An aliquot of each acidic extract was subjected to ion-interaction reversed-phase liquid chromatography with coulometric electrochemical detection. Hemoglobin (Hb) was extracted from blood and stored at –70 °C. For the measurement of adducts of aniline, *o*-toluidine, and 4-aminobiphenyl (4-ABP), precipitated Hb was dissolved in 0.1 *M* sodium hydroxide in the presence of recovery standards, and the hydrolysate was extracted with hexane, derivatized with pentafluoropropionic anhydride, and analyzed by gas chromatography–mass spectrometry with negative chemical ionization. *Results:* A total of 73 workers, including 46 of 64 exposed workers who were employed in the rubber chemicals department and had the potential for exposure to aniline and *o*-toluidine and 27 of 52 unexposed workers employed in other departments where aniline and *o*-toluidine were not used or produced, had data available for both aniline and *o*-toluidine and Hb adducts; 28 of the workers in the former group also had personal air-sampling data. Personal air sample measurements showed that airborne concentrations of aniline and *o*-toluidine were well within the limits allowed in the workplace by OSHA. Urinary aniline and *o*-toluidine levels, however, were substantially higher among exposed workers than among unexposed control subjects. The most striking differential was for post-shift urinary *o*-toluidine levels, which averaged (± standard deviation) 2.8 μg/L (±1.4 μg/L) in unexposed subjects and 98.7 μg/L (±119.4 μg/L) in exposed subjects (P = .0001). Average aniline–Hb and *o*-toluidine–Hb adduct levels were also significantly higher (P = .0001) among exposed workers than among unexposed control subjects. Average levels of adducts to 4-ABP, a potential contaminant of process chemicals, were not significantly different (P = .48), although three exposed workers had 4-ABP levels above the range in unexposed workers. *Conclusions:* The adduct data suggest that, among current workers, *o*-toluidine exposure substantially exceeds aniline exposure and that 4-ABP exposure, if it occurs at all, is not widespread. These data support the conclusion that occupational exposure to *o*-toluidine is the most likely causal agent of the bladder cancer excess observed among workers in the rubber chemicals department of the plant under study, although exposures to aniline and 4-ABP cannot be ruled out. [J Natl Cancer Inst 1996;88:1046-52]**

In April 1991, an excess of bladder cancer cases among workers employed at a chemical manufacturing facility in Niagara Falls, NY, was reported (*1*). This excess was confined primarily to 708 workers who had ever been employed in a department that used aniline and *o*-toluidine to make products used in the manufacture of rubber; no increased risk was observed among 753 workers who had also been employed at the plant but who had never worked in this department. Among workers in the rubber chemicals department, the standardized incidence ratio (SIR) was 6.48 (seven cases observed and 1.08

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See "Notes" section following "References."

expected); among workers employed in the rubber chemicals department for more than 10 years, there were six cases observed and 0.22 expected (SIR = 27.2). The chemical manufacturing facility under study opened in 1946 for the production of polyvinyl chloride. In 1957, the rubber chemicals department was opened in a new and separate building. Two products, an antioxidant and an accelerator, are produced in the rubber chemicals department. The antioxidant is produced by the mixing of *o*-toluidine, aniline, hydroquinone, and toluene. The accelerator used in the production of rubber is produced by the mixing of carbon disulfide, sulfur, aniline, benzothiazole, and a proprietary chemical. Among the major chemicals used or formed in the two processes, only *o*-toluidine, aniline, and hydroquinone have been evaluated as potential carcinogens by the International Agency for Research on Cancer (IARC); only *o*-toluidine was classified as demonstrating sufficient evidence of carcinogenicity in animals (*2*), whereas the evidence supporting carcinogenicity of aniline was limited (*3*). 2-Mercaptobenzothiazole, a byproduct in the accelerator process, has been found by the National Toxicology Program (NTP) (Research Triangle Park, NC) to have some evidence of carcinogenic activity in male and female rats, no evidence of carcinogenic activity in male mice, and equivocal evidence of carcinogenic activity in female mice (*4*). Investigators at the NTP found some evidence for carcinogenicity of hydroquinone in male and female mice (*5*). On the basis of the reactants used in the process and the process chemistry, it is thought that 4-aminobiphenyl (4-ABP), a known human bladder carcinogen (*6*), may be present as a low-level contaminant.

In February through March 1990, an environmental and biological monitoring survey was conducted at the plant under study. The objective of this survey was to characterize airborne and dermal exposures to aniline and *o*-toluidine and to detect internal absorption. The survey focused on *o*-toluidine and aniline because they were known to be present in large quantities at the plant and, because of the chemicals evaluated by the IARC or tested in the NTP, the evidence for carcinogenic effects was strongest for those compounds. Personal (i.e., monitored on an individual basis) air samples were collected during workshifts, and samples of urine were collected before and after workshifts to allow characterization of exposures on each day of the survey, since previous studies in humans (*7,8*) and in laboratory animals (*9,10*) suggested that 50%-90% of administered aniline and *o*-toluidine are excreted in the urine in the first 24 hours. Blood samples were also collected to measure the levels of adducts of aniline and *o*-toluidine with hemoglobin (Hb), which are biomarkers that reflect longer term exposures. As a local referent group, workers employed in a department of the plant in which aromatic amines were not used or produced were asked to provide blood and urine samples; air sampling was conducted only in the rubber chemicals department.

4-ABP is a potential contaminant in process chemicals (*11-14*). Adducts of 4-ABP on Hb molecules have been extensively studied as a biological marker related to cigarette smoke and have been well characterized in population groups with no occupational exposure (*15-24*). Therefore, the levels of 4-ABP adducts in the Hb of study participants were measured to determine whether employment in the rubber chemicals department results in 4-ABP exposure.

Subjects and Methods

All 64 workers employed in the rubber chemicals department at the time of the survey were invited to participate in the biological monitoring survey. Fifty-two workers in another department, which manufactured polyvinyl chloride polymer, were invited to participate as unexposed controls. The study was approved by the Human Subjects Review Board of the National Institute for Occupational Safety and Health (NIOSH); the week before the biological samples were collected, written informed consent was obtained from all workers who participated in the biological monitoring survey. Personal air sampling was conducted on three of four workshifts by use of a modified Occupational Safety and Health Administration (OSHA) 73 method (*25*). Persons for whom personal air sampling was conducted were not required to participate in the biological monitoring survey. At the time they volunteered for the study, the participants in the survey were asked to complete a questionnaire concerning work history, smoking habits, and medication use. Participants were provided with 500-mL polypropylene containers and were asked to collect a urine sample immediately before reporting to work (pre-shift) and immediately after leaving for the day (post-shift). Urine was frozen on dry ice for transport to the laboratory and subsequently stored at –70 °C. Levels of *o*-toluidine and aniline, but not of 4-ABP, were analyzed in urine. The details and validation of the urine analysis method have been reported previously (*26*). Base hydrolysis was used to convert acetanilide and *N*-acetyl-*o*-toluidine, metabolites of aniline and *o*-toluidine present in the urine, to the parent compounds. The parent compounds were extracted from the alkaline urine into butyl chloride and then back-extracted from the butyl chloride into aqueous hydrochloric acid. An aliquot of each acidic extract was subjected to ion-interaction reversed-phase liquid chromatography with coulometric electrochemical detection. Urine and blood samples were randomly coded, and laboratory analysts were unaware of the exposure or smoking status of the individual from whom the samples were obtained.

The workers who volunteered for the biological monitoring survey were scheduled to have a blood sample collected by a NIOSH phlebotomist in the plant medical department during their workshift. A total of 40 mL of blood was collected in heparinized vacutainers. Blood was transported at room temperature to the Robert A. Taft Laboratory of NIOSH in Cincinnati, OH. Upon arrival at the laboratory, within 24 hours of collection, blood was placed in 15-mL centrifuge tubes and centrifuged at 1500*g* for 20 minutes at 4 °C. The plasma and buffy-coat layer were removed. Packed red blood cells were washed with phosphate-buffered saline and centrifuged at 700*g* for 10 minutes at 4 °C. The red blood cells were washed twice more in the same manner and then transferred to a 50-mL centrifuge tube. Two 10-mL aliquots of cold (2-8 °C) osmosis-purified water were added to lyse the red blood cells. The lysate was spun at 4500*g* for 25 minutes at 4 °C to remove cellular debris. After centrifugation, 25 mL of the lysate was added to a beaker. Four volumes of cold (2-8 °C) ethanol were added dropwise to precipitate the Hb. The Hb was collected by centrifugation at 400*g* for 10 minutes at 4 °C and then washed three times with cold acetone (2-8 °C), dried under a stream of nitrogen, and stored at –70 °C.

The details and validation of the method for the determination of Hb adducts have been published recently (*24*). For the present study, Hb (100-200 mg) was dissolved in 0.1 *M* sodium hydroxide (3-4 mL). The following mixture of internal standards was added in 20 μL hexane to the Hb solution: 2 ng d_5-aniline, 2 ng d_4-*o*-toluidine, 0.5 ng d_4-*m*-toluidine, 1 ng d_4-*p*-toluidine, 1 ng d_3-2,4-dimethylaniline, 2 ng $^{13}C_6$-4-chloroaniline, 1 ng d_9-4-aminobiphenyl, and 1 ng 4′-fluoro-4-aminobiphenyl. After 1 hour of shaking at room temperature, the Hb solution was extracted once with hexane (6 mL). Drying with sodium sulfate was followed by derivitization with pentafluoropropionic anhydride and by careful evaporation to dryness under a light stream of nitrogen. The residue was taken up to 15 μL ethyl acetate and analyzed by gas chromatography–mass spectrometry involving use of negative chemical ionization. Aniline, *o*-toluidine, and 4-ABP were quantified by comparison with the internal standards of d_5-aniline, d_4-*o*-toluidine, and 4′-fluoro-4-aminobiphenyl.

Workers were divided into two groups for the analysis: unexposed workers and exposed workers. Unexposed workers were assigned to the polyvinyl chloride department and did not have any known potential for contact with aniline or *o*-toluidine, except that they shared a lunchroom with the rubber chemicals department workers. Exposed workers included individuals with

production, maintenance, or supervisory responsibilities in the rubber chemicals department. Individuals who had transferred from the exposed to the unexposed area within the 4 months before the survey were considered to be exposed for the purpose of the analysis; with this cutoff, only three workers who were not currently in the exposed department were reclassified as exposed. Data were analyzed by use of the SAS 6.10 Statistics Software Package (SAS Institute, Inc., Cary, NC) for personal computers. For Student's *t* tests requiring normality, *P* values were determined from log-transformed data; Spearman correlation coefficient significance tests based on ranks that do not assume normality are reported. Laboratory values below the limit of detection were assigned a value of the limit of detection divided by the square root of 2 for statistical calculations (*27*). All *P* values resulted from the application of two-sided statistical tests.

Results

A total of 73 workers, including 46 of 64 exposed workers from the rubber chemicals department and 27 of 52 unexposed workers, had data available for both aniline and *o*-toluidine and Hb adducts[1]; 28 of the workers in the former group also had personal air-sampling data. A total of 10 additional workers (five exposed and five unexposed) provided blood samples, but adduct levels could not be determined because the Hb was depleted by earlier analyses in another laboratory. The exposed and unexposed groups did not differ with respect to sex (only four unexposed and three exposed individuals were female) or smoking habits (37.0% smokers in the unexposed group and 37.0% smokers in the exposed group), but unexposed subjects were somewhat younger (mean ages of 37 years in the unexposed group and 45 years in the exposed group). Measurements of *o*-toluidine and aniline in air monitored by personal air sampling for exposed workers documented that exposure to aniline and *o*-toluidine was ubiquitous throughout the rubber chemicals department. Among 28 individuals with both Hb adduct and personal air-sampling data, the mean air concentration (± standard deviation) of aniline was 187 μg/m^3 (±181 μg/m^3) and that of *o*-toluidine was 412 μg/m^3 (±366 μg/m^3), well within the 1989 OSHA time-weighted average permissible exposure limit of 8000 μg/m^3 for aniline and 22 000 μg/m^3 for *o*-toluidine (*28*). Mean air concentrations measured for seven study participants who had personal air samples but no Hb adduct measurements were 153 μg/m^3 (±95.1 μg/m^3) aniline and 516 μg/m^3 (±513 μg/m^3) *o*-toluidine, similar to average air concentrations among individuals with Hb adduct data. Personal air sample measurements were not collected in the polyvinyl chloride department.

Unexposed workers had urinary aniline concentrations in their pre-shift and post-shift urine samples (Table 1) that were approximately equivalent to those reported in a previous study (*29*) using a different analytical method. el-Bayoumy et al. (*29*) found 2.5 μg aniline/24 hours in the urine of nonsmokers and 3.1 μg aniline/24 hours in the urine of smokers, which, based on the average 24-hour urine volume of 1.5 L (*30*), is equivalent to 1.7 μg/L and 2.1 μg/L, respectively. We found approximately 2 μg/L aniline in the urine of unexposed nonsmokers and 4-6 μg/L aniline in the urine of unexposed smokers. el-Bayoumy et al. (*29*) found 4.1 μg *o*-toluidine/24 hours (approximately 2.7 μg/L) in the urine of nonsmokers and 6.3 μg *o*-toluidine/24 hours (approximately 4.2 μg/L) in the urine of smokers. We found approximately 2 μg/L *o*-toluidine in the urine of unexposed nonsmokers and smokers. In the current study, urinary concentrations of aniline, but not *o*-toluidine, were significantly higher among unexposed smokers than among unexposed nonsmokers. Both aniline and *o*-toluidine levels in post-shift urine samples were increased over those in pre-shift urine samples from unexposed workers, which was statistically significant for *o*-toluidine ($P \leq .05$).

Both pre-shift and post-shift levels of *o*-toluidine and aniline in the urine samples were significantly elevated among all worker groups in the rubber chemicals department compared with those among unexposed control workers (Table 1). Within the exposed group, smokers had higher *o*-toluidine and aniline levels, particularly in their post-shift samples, than nonsmokers, but this difference was statistically significant only for post-shift *o*-toluidine levels (Table 1). Post-shift concentrations of aniline among exposed workers were 7.6 times higher than those among unexposed workers, whereas post-shift concentrations of *o*-toluidine among exposed workers were 35 times higher than those among unexposed workers. Thus, the urine data provide substantial evidence that aniline and *o*-toluidine are absorbed by workers in the rubber chemicals department.

The levels of aniline and 4-ABP adducts in the unexposed group were in the same range as those that have been reported

Table 1. Mean (standard deviation) of *o*-toluidine and aniline concentrations in pre-shift and post-shift urine samples of chemical workers*

	Nonsmoker				Smoker				Total			
	No. of pre-shift subjects	Pre-shift mean (SD)	No of post-shift subjects	Post-shift mean (SD)	No. of pre-shift subjects	Pre-shift mean (SD)	No. of post-shift subjects	Post-shift mean (SD)	No. of pre-shift subjects	Pre-shift mean (SD)	No. of post-shift subjects	Post-shift mean (SD)
						Aniline in urine, μg/L						
Unexposed	16	1.6 (1.1)	16	2.6 (1.8)	10	4.2† (3.1)	9	6.2†,‡ (2.9)	26	2.6 (2.4)	25	3.9 (2.8)
Exposed	28	11.3 (11.9)	27	22.6‡ (11.9)	15	19.4 (22.4)	15	42.9†,‡ (37.3)	43	14.1 (16.6)	42	29.8‡ (25.7)
P		.0001		.0001		.0009		.0001		.0001		.0001
						o-Toluidine in urine, μg/L						
Unexposed	16	1.3 (1.3)	16	2.8 (1.6)	10	0.9 (0.7)	9	2.8‡ (1.2)	26	1.2 (1.1)	25	2.8‡ (1.4)
Exposed	28	16.1 (33.0)	27	80.1‡ (94.0)	15	14.3 (10.2)	15	132.1‡ (153.1)	43	15.4 (27.1)	42	98.7‡ (119.4)
P		.0001		.0001		.0001		.0001		0001		.0001

*Pre-shift = urine samples collected before work; post-shift = urine samples collected after work.
†Significant difference between smokers and nonsmokers in post-shift or pre-shift concentrations (Student's *t* test [two-sided]).
‡Significant difference between post-shift and pre-shift concentrations within individual (paired Student's *t* test [two-sided]).

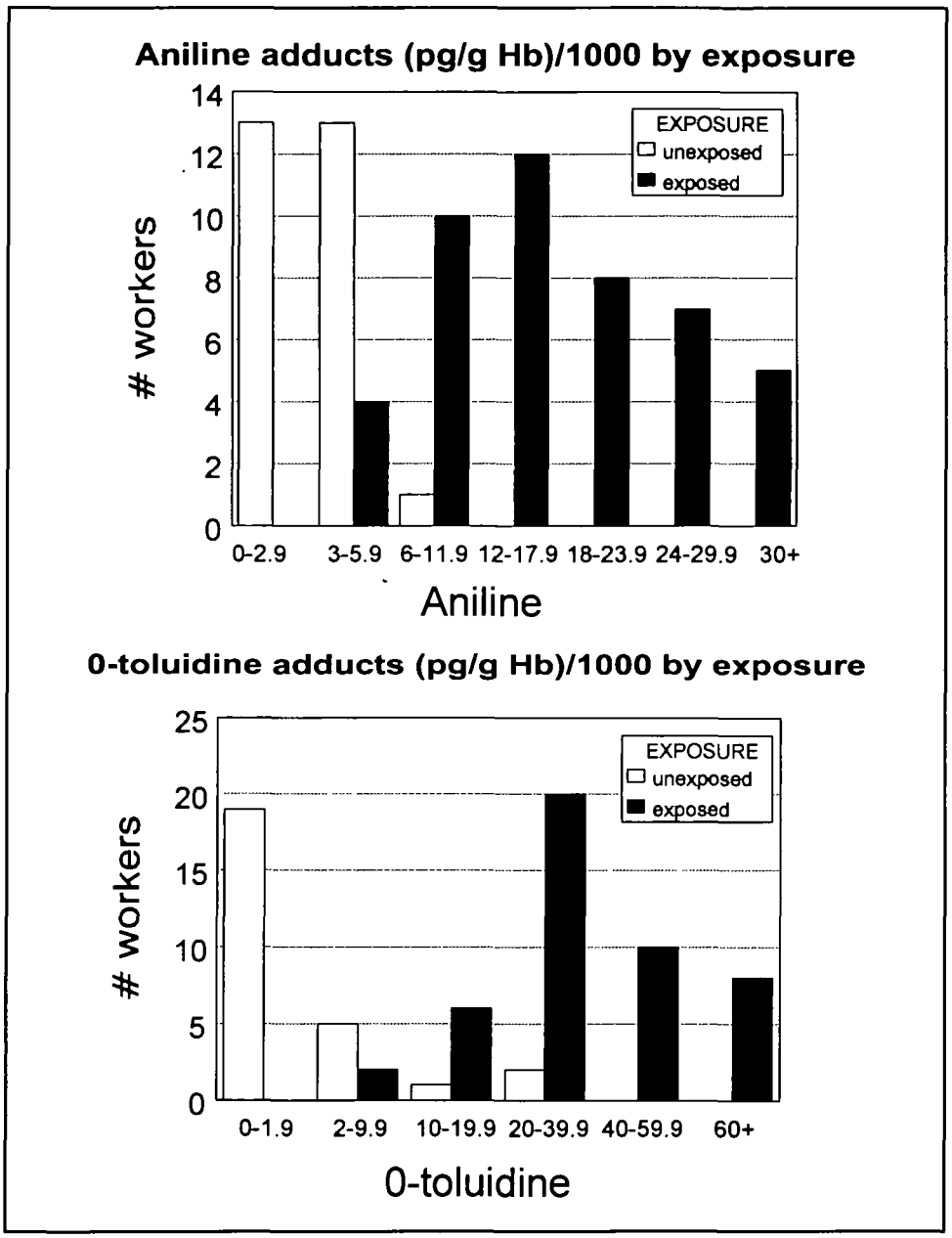

Fig. 1. Distribution of aniline–hemoglobin (Hb) and *o*-toluidine–Hb adduct levels by exposure status.

Table 2. Aromatic amine–hemoglobin (Hb) adducts among chemical workers*

Adduct		Nonsmoker No.	Nonsmoker Mean level (SD), pg/g Hb	Smoker No.	Smoker Mean level (SD), pg/g Hb	*P*	Mean level of total group (SD), pg/g Hb
Aniline	Unexposed	17	3118 (1513)	10	3240 (905)	.49	3163 (1302)
	Exposed	29	16 072 (7422)	17	19 776 (10 748)	.36	17 441 (8867)
	P		.0001		.0001		.0001
o-Toluidine	Unexposed	17	3518 (5581)	10	3510 (7064)	.82	3515 (6036)
	Exposed	29	41 028 (37 679)	17	40 494 (22 120)	.68	40 830 (32 518)
	P		.0001		.0001		.0001
4-Aminobiphenyl (4-ABP)	Unexposed	17	48.2 (52.3)	10	119.3 (58.1)	.0003	74.5 (63.8)
	Exposed	27†	72.7 (117.0)	15‡	97.7 (84.3)	.12	81.7 (106.1)
	P		.99		.12		.48

*All *P* values were determined by use of the two-sided Student's *t* test.
†Adduct levels of 4-ABP with Hb were not determined for two exposed nonsmokers.
‡Adduct levels of 4-ABP with Hb were not determined for two exposed smokers.

(*15,16-18,20-22*) in other nonoccupationally exposed populations (Fig. 1, Table 2). Only one previous study (*15*) reported aniline adducts; this study found a mean of 3800 pg/g Hb in nonsmokers and a mean of 4400 pg/g Hb in smokers. Numerous studies (*15-18,20-22*) have reported levels of 4-ABP adducts; the means ranged from 25-50 pg/g Hb in nonsmokers to 130-290 pg/g Hb in smokers. On the other hand, mean levels of *o*-toluidine–Hb adducts are about 10 times higher in our unexposed population than those reported in three other published studies (*15,16,18*). Skipper et al. (*16*) reported mean *o*-toluidine adduct levels ranging from 89 pg/g Hb in nonsmokers in Boston to 290 pg/g Hb in smokers in Turin, Italy. Bryant et al. (*18*) reported mean *o*-toluidine adduct levels ranging from 188 pg/g Hb in nonsmokers to 329 pg/g Hb in smokers of black tobacco. Stillwell et al. (*15*) reported mean *o*-toluidine adduct levels of 34 pg/g Hb in nonsmokers and 100 pg/g Hb in smokers. *o*-Toluidine adduct levels in blood samples from German control subjects, measured in the laboratory that analyzed the samples in this study, were similar to those measured by Stillwell et al. (*15*). The mean *o*-toluidine level in the unexposed group in our study was approximately 3500 pg/g Hb for both smokers and nonsmokers. This mean value is not the result of a few high observations; in fact, only three of the 27 study participants in the unexposed group had *o*-toluidine adduct levels at or below 500 pg/g Hb. These data, along with the significant increase in *o*-toluidine concentrations in the course of the workday, suggest that some exposure to *o*-toluidine may have occurred in the "unexposed" workers.

Aniline–Hb and *o*-toluidine–Hb adduct levels were significantly higher among exposed workers than among unexposed workers (Fig. 1, Table 2). Average *o*-toluidine adduct levels were approximately 11 times higher in exposed workers than in unexposed workers at the plant under study and more than 100 times higher than the means in other unexposed populations

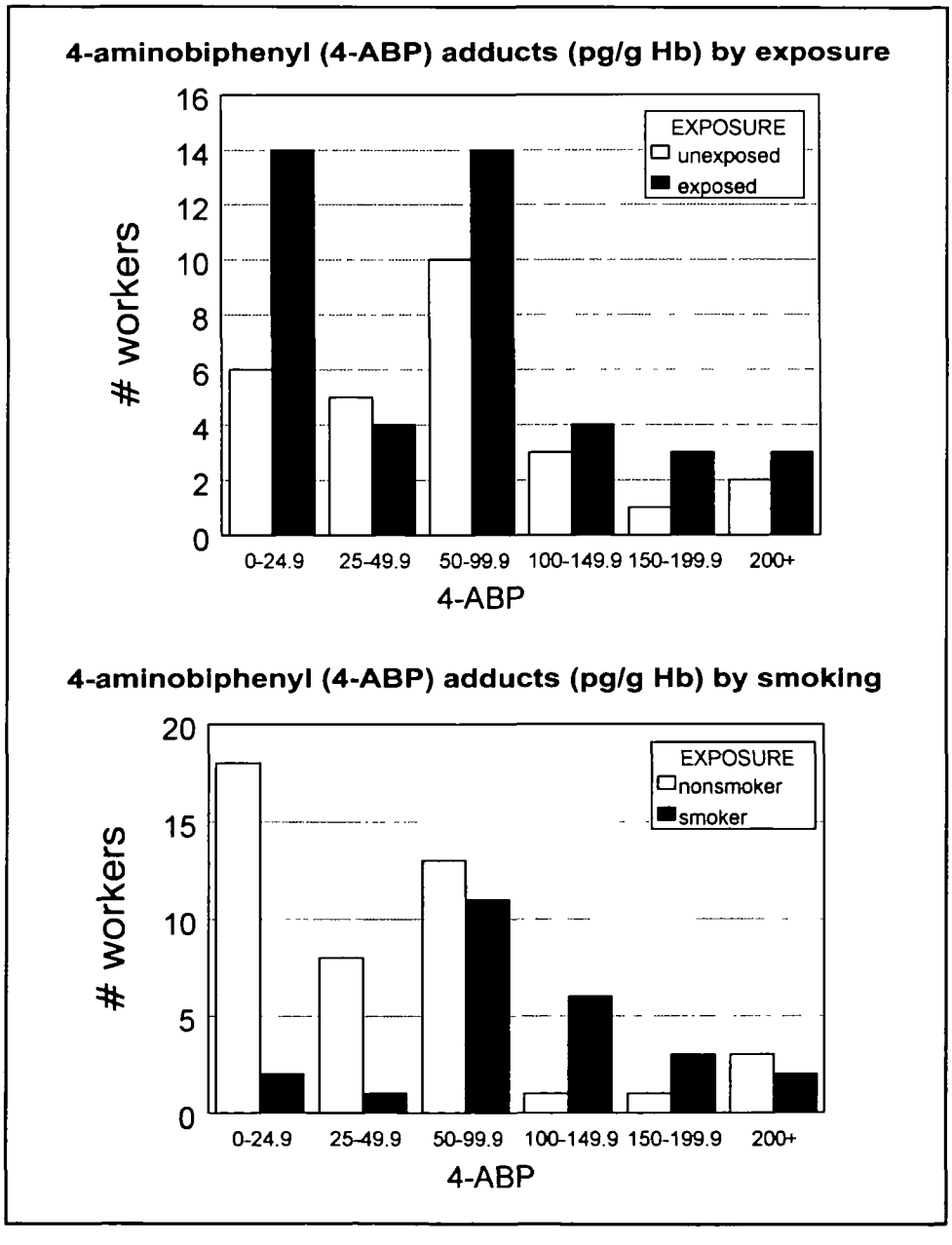

Fig. 2. Distribution of 4-aminobiphenyl–hemoglobin (Hb) adduct levels by exposure and smoking status.

studied (*15,16,18*). In contrast, mean 4-ABP levels did not differ significantly between exposed and unexposed subjects ($P = .48$) (Fig. 2, Table 2). 4-ABP levels were significantly higher in unexposed smokers than in unexposed nonsmokers, but there was no difference among the exposed smokers and nonsmokers (Table 2). Three exposed workers had 4-ABP levels above the range of the unexposed group; the highest number of 4-ABP adducts (pg/g Hb) observed in the unexposed group was 240, whereas the top three high values in the exposed group were 292, 335, and 573 (Fig. 2). These values were within the range reported for smokers in some other populations (*17,21*). Two of the three exposed workers with high values, however, were nonsmokers.

In the total population studied, aniline and *o*-toluidine adduct levels were highly correlated ($r = .94$; $P = .001$), whereas 4-ABP adduct levels were not correlated with either aniline adduct levels ($r = .09$; $P = .47$) or *o*-toluidine adduct levels ($r = .04$; $P = .75$). Regression analyses found that 4-ABP levels were positively associated with smoking status ($P = .06$), whereas aniline and *o*-toluidine levels were not. Regression analyses indicated that none of the covariates considered (smoking status, sex, and birth year) had a consistent or strong relationship with aniline and *o*-toluidine adduct levels; therefore, the relationship between air and urine levels and adduct levels was explored with the use of a simple correlation analysis (Table 3). Aniline–Hb and *o*-toluidine–Hb adduct levels were more strongly correlated with post-shift urine concentrations than with air levels, whereas 4-ABP–Hb adduct levels were correlated with neither (Table 3).

Discussion

This study was undertaken to characterize current exposure to *o*-toluidine and aniline at a chemical plant where an excess risk of bladder cancer had been observed. There were insufficient historical data to characterize exposures at the plant 10-30 years ago, the time period most relevant to the development of industrially related bladder cancers, which have a latent period (time from first exposure to onset of disease or death) averaging 20 years and ranging from 4 to 40 years (*31*). Questions have also been raised about the possibility that contamination of workers with 4-ABP 10-30 years ago might be responsible for the bladder cancer excess (*11,13*).

There were several important findings from the biological monitoring survey. First, urine and Hb adduct data were concordant in documenting that workers in the rubber chemicals department are absorbing substantial quantities of aniline and *o*-toluidine into their bodies during the course of their workshift. Environmental and biological monitoring data are consistent in documenting that air concentration, urinary excretion, and adduct levels of *o*-toluidine are two to three times higher than those of aniline but that the two exposures are highly correlated. Data collected during the survey could not determine the relative contribution of airborne and dermal exposures. Second, urine and Hb adduct data are concordant in suggesting that workers in the "unexposed" department may have had potential occupational exposure to *o*-toluidine. This is based on the observation that post-shift urine concentrations of *o*-toluidine were significantly higher than pre-shift concentrations and that *o*-toluidine adduct levels were 10 times higher in the unexposed than those reported for three other unexposed populations (*15,16,18*). Third, the data on 4-ABP adducts provide no evidence for widespread contamination of the process area with 4-ABP at the time that the survey was conducted. The elevated 4-ABP levels among three workers may be related to nonoccupational causes, since levels in this same range have been reported (*17,21*) in studies of the general population (but only in smokers). It is also possible that exposure to 4-ABP occurred through contact with process chemicals. NIOSH chemists, who reviewed the process description, concluded that 4-ABP may form at one point in the reaction but that it is unlikely to persist in the reaction mixture. Thus, contact with process chemicals at that point in the process, which might occur among workers taking quality-control samples or making repairs, could result in low levels of 4-ABP exposure. The relatively low contamination of the current process with 4-ABP does not rule out the possibility that contamination was higher in the past. Fourth, workers in the exposed department have *o*-toluidine–Hb adduct levels averaging 100 times, and ranging as high as 1000 times, greater than the adduct levels previously observed among unexposed populations.

In rats, the proportion of the administered dose of aniline that binds to Hb is higher than that of *o*-toluidine; therefore, the finding of higher levels of *o*-toluidine adducts than aniline adducts is likely to reflect their relative concentration in the environment

Table 3. Correlation between aromatic amine–hemoglobin adducts and the concentrations of the aromatic amines in air and in urine

	Air concentration of		Post-shift* urine concentration of	
	Aniline	*o*-Toluidine	Aniline	*o*-Toluidine
Aniline adducts				
Correlation coefficient	.52	.38	.84	.80
P†	.004	.04	.0001	.0001
o-Toluidine adducts				
Correlation coefficient	.45	.38	.80	.75
P†	.01	.04	.0001	.0001
4-Aminobiphenyl adducts				
Correlation coefficient	.27	.18	.16	−.04
P†	.20	.39	.20	.75

*Post-shift = urine samples collected after work.
†Determined by use of the two-sided Student's *t* test.

rather than binding efficiency (*32*,*33*). The finding of higher Hb adduct concentrations for *o*-toluidine and aniline is consistent with the environmental and urine data in suggesting that, among current workers, *o*-toluidine exposure substantially exceeds aniline exposure. In addition, there is little evidence of widespread 4-ABP contamination. These data support the conclusion that occupational exposure to *o*-toluidine is the most likely cause of the bladder cancer excess observed among workers in the rubber chemicals department of the plant under study. Exposure to aniline is also substantial, and aniline cannot be ruled out as a potential cause of the bladder cancer excess. Exposure to 4-ABP is an unlikely cause, based on current exposure data, although historic exposure (i.e., exposure 10-30 years earlier) to 4-ABP cannot be ruled out. In 1990, NIOSH (*34*) recommended that aniline and *o*-toluidine be treated as potential occupational carcinogens and that exposure to these chemicals be reduced to the lowest feasible limit. The urinary and Hb adduct data reported here indicate that, even at airborne exposure levels significantly below the OSHA time-weighted average permissible exposure limit, substantial absorption and accumulation of aniline and *o*-toluidine may occur.

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Notes

[1]*Note added in proof:* Among the 46 exposed workers with Hb adduct data, 44 had data on urinary aniline and *o*-toluidine concentrations (41 from both pre-shift and post-shift, two from only pre-shift, and one from only post-shift determinations). Among the 27 unexposed workers with Hb adduct data, all 27 had data on urinary aniline and *o*-toluidine concentrations (25 from both pre-shift and post-shift, one from only pre-shift, and one from only post-shift determinations).

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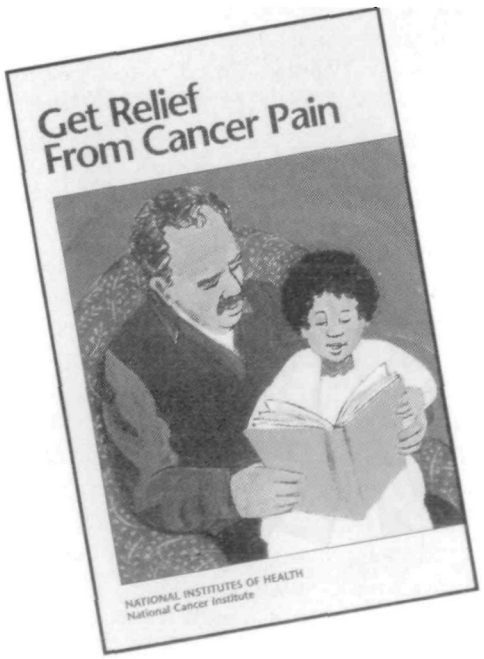
A New Brochure to Increase Patient Awareness of the Importance of Treating Cancer Pain



Patients have a right to pain control. • *Patients have a role in communicating their pain.* • *Patients should talk to their doctors or nurses as soon as pain begins.* • *Patients should not let fears keep them in pain.*

Get Relief From Cancer Pain is written at a 5th grade reading level and is available through the National Cancer Institute's Cancer Information Service at 1-800-4-CANCER or the American Cancer Society at 1-800-ACS-2345.