

Mortality From Lung Cancer Among Workers Employed in Formaldehyde Industries

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A historical cohort of 26,561 workers employed in ten facilities was assembled to evaluate cancer risks associated with exposure to formaldehyde. Historical exposures to formaldehyde by job, work area, plant, and calendar time were estimated using monitoring data available from participating plants, comments from long-term workers and company officials, exposure evaluations from walk-through surveys conducted by project industrial hygienists, and results from monitoring specifically performed for this project. A previous report of findings from this study noted a 30% excess mortality from lung cancer among wage workers. The relative risk for lung cancer (whether estimated by SMRs or SRRs) 20 or more years after first exposure did not generally rise with increasing exposure to formaldehyde. Various estimates of exposure were investigated including duration, intensity, peak, cumulative, and average, and by exposures lagged by 5, 10, 20, and 30 years. The excess did not appear to arise gradually, but emerged suddenly among workers whose total cumulative exposure was less than 0.1 ppm-years. Slightly positive, but nonsignificant, exposure-response associations between lung cancer and level of formaldehyde occurred in only a few out of a large number of comparisons (e.g., for persons hired before the start dates for the study and for workers also exposed to particulates). There was a lack of consistency among the various plants for risk of lung cancer, with six plants having elevated SMRs and four plants having deficits. Mortality from lung cancer was more strongly associated with exposure to other substances including phenol, melamine, urea, and wood dust than with exposure to formaldehyde. Workers exposed to formaldehyde without exposure to these substances did not experience an elevated mortality from lung cancer. The risk did not increase with cumulative levels of formaldehyde among those exposed to other substances and there was a slightly negative trend for those exposed to formaldehyde alone. Although some role for formaldehyde, particularly in association with other substances, in the excess of lung cancer seen among these workers cannot be ruled out, these findings suggest that exposure to phenol, melamine, urea, wood dust or other exposures also occurring in the area where these substances were used (i.e., production of resin and molding compounds) may play a more primary role. This association should be further evaluated in other studies that include workers from resin and molding compound operations.

Key words: respiratory cancer, exposure-assessment, formaldehyde-resins exposure, cohort study

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INTRODUCTION

In a study of workers from ten plants producing or using formaldehyde, a significant excess mortality from lung cancer (SMR = 132) was found among white male wage employees 20 or more years after their first exposure to formaldehyde [Blair et al., 1986]. Because the risk of lung cancer did not increase with increasing level or duration of exposure to formaldehyde and because the patterns of risk were inconsistent among the ten plants, we concluded that those results did not lend support to a causal interpretation of this association. Others, however, have drawn different conclusions [Department of Labor, 1987]. This report presents the results from additional analyses conducted to determine whether the association with formaldehyde may have occurred in a subgroup of the cohort and/or to identify other occupational risk factors that may be involved.

MATERIALS AND METHODS

The subjects and methods of this study have been described in detail elsewhere [Blair et al., 1986; Stewart et al., 1986]. Briefly, the cohort is composed of 26,561 workers first employed in any of ten plants before January 1, 1966, and traced to January 1, 1980, to determine vital status. This report includes only the 20,714 white men, the race-sex group that had an excess of lung cancer. Five of the plants in the study were located in the northeastern United States, one was in the southeast, two were in the south central, one was in the midwest, and one was in the north central section. The plants produced a variety of products, including formaldehyde (plants 2, 7, 10), formaldehyde resins and molding compounds (plants 1, 2, 7-10), molded plastic products (plants 8, 9), photographic film (plants 4, 5), decorative laminates (plant 6), and plywood (plant 3). Some workers from plant 2 (all those hired before 1977) and plant 10 (all deaths between 1950 and 1976) had been studied previously without a detailed evaluation of formaldehyde exposure [Wong, 1979; Marsh, 1982] and selected subjects from plants 4 and 5 were included in a case-control study of all cancers [Fayerweather et al., 1983].

Eight-hour time-weighted average (TWA) historical exposure levels to formaldehyde were estimated for job title/work area/plant/calendar-year combinations available from work histories covering all the years subjects were employed at the plants through 1982 [Stewart et al., 1986]. Estimates were based on job titles and job tasks, site visits by study industrial hygienists, discussions with workers and plant management, and monitoring data. Over 6,600 formaldehyde measurements were available for exposure assessment (4,600 from the companies and 2,000 from a monitoring program conducted by the investigators). As in the previous report [Blair et al., 1986], the estimate was used to place the jobs in exposure categories of <0.1, 0.1 to 0.5, 0.51 to 2.0, and >2.0 ppm. The midpoint of the category was then used as the exposure estimate for the job. These estimates should not be construed as "true" levels, but as approximations which were used to provide a relative ranking of job exposures. Peaks were defined as short-term excursions above the TWA exposure category. The potential for exposure to formaldehyde particulates, the use of respirators, and other exposure parameters were determined for each job. Exposure to suspect carcinogens identified by OSHA [Dept. of Labor, 1980] or EPA [Environmental Protection Agency, 1980] and other high volume substances used in the plant

were also identified for each job, however, no attempt was made to estimate exposure levels for these other substances.

A number of different estimates of exposure to formaldehyde were evaluated in these analyses because each measure has inherent strengths and weaknesses [Checkoway, 1986] and because the mechanism by which formaldehyde might exhibit carcinogenic effects in humans is not well understood. Duration of exposure can be measured very accurately from work histories, and although it is not dependent upon estimates of level of exposure, neither does it necessarily reflect level of exposure because level of exposure may change over time [Johnson, 1986]. Intensity was defined as the 8-hour TWA by job. Since intensity can change over time, in these analyses, individuals were placed in the highest intensity category achieved up to a particular point in time. Intensity and peaks were based on estimates of exposures, but they do not take into account duration of exposure. Estimation of peak exposures may be particularly crucial if during periods of very high, short-term exposures body defenses are overwhelmed. Cumulative exposure, a combination of duration and intensity, was used to approximate total dose. Average exposure was calculated by dividing cumulative exposure by the number of years exposed. These approaches classify workers differently. For example, a cumulative exposure of 10 ppm-years could be achieved by exposure to 2 ppm for 5 years, or from exposure to 0.5 ppm for 20 years. In an analysis by cumulative exposure these two individuals would fall in the same category, but by average exposure they would not. We also used analyses by intensity and duration of exposure to separate individuals into different exposure categories. Cumulative exposure also distributes person-years as exposure occur and individuals may contribute person-years to several exposure categories, while in analyses by average exposure, all person-years contributed by a subject occur in a single exposure category. Comparison of relative rankings of workers based on these different exposure measures indicated that they displayed considerable variation in the distribution of subjects and some measures, e.g., duration and average exposure, were entirely unrelated [Blair and Stewart, 1990]. This occurs because the level of exposure in jobs held by workers is unrelated to seniority at the plants. Since the patterns for lung cancer were similar for these different measures of exposure, cumulative exposure (a measure of total exposure) was selected for most subgroup analyses. Duration of exposure to substances other than formaldehyde was determined from the dates of jobs in which these chemicals were used.

Standardized mortality ratios (SMR) were used to compare the mortality experience of these workers to that of the total U.S. population using a program developed by Marsh and Preininger [1980]. Person-year accumulation in the cohort began on January 1 of the initial year of cohort identification, when subjects started employment at a plant, or upon the subject's first achieving the exposure and/or latency period of interest, depending upon the particular type of analysis performed. Person-year accumulation ceased on the closing date of the study, on the last date known alive, or on the date of death. Most analyses included stratification by time since first exposure (latency). Since the excess mortality from lung cancer was greatest 20 or more years after first exposure, many results are presented for only this latency period. SMR analyses, which lagged exposures by 5, 10, 20, and 30 years, were used to investigate the timing of exposure on lung cancer mortality. Statistical significance of SMRs was evaluated using the method of Bailar and Ederer [1964]. A chi-square test was used to evaluate statistical significance of SMR trends [Breslow et al., 1983]

TABLE I. SMRs and SRRs for Lung Cancer by Various Measures of Exposure to Formaldehyde (Wage White Men, ≥ 20 Years After First Exposure)

Measure of exposure	Exposure level				Total	X for trend
	1 (lowest)	2	3	4 (highest)		
Duration^a						
Obs./Exp. No.	49/36.0	32/23.9	28/14.4	33/29.5	142/103.8	
SMR	1.4 ^h	1.3	2.0 ^h	1.1	1.4 ^h	-0.54
SRR ^g	1.0	1.0	1.4	0.8		
Intensity^b						
Obs./Exp. No.	18/14.8	39/25.6	82/56.2	3/7.2	142/103.8	
SMR	1.4	1.5	1.5 ^h	0.4	1.4 ^h	-1.26
SRR	1.0	1.2	1.2	0.3		
Peak^{c,d}						
Obs./Exp. No.	28/17.5	22/15.8	48/32.1	41/36.4	139/101.8	
SMR	1.6	1.4	1.5 ^h	1.1	1.4 ^h	-1.41
SRR	1.0	1.0	0.9	0.9		
Average^e						
Obs./Exp. No.	29/23.8	42/27.6	69/47.3	2/5.2	142/103.9	
SMR	1.2	1.5 ^h	1.5 ^h	0.4	1.4 ^h	-0.15
SRR	1.0	1.2	1.2	0.3		
Cumulative^f						
Obs./Exp. No.	47/35.2	51/36.1	44/32.4		142/103.7	
SMR	1.3	1.4 ^h	1.4		1.4 ^h	0.11
SRR	1.0	1.1	0.9			

^aDuration categories: 1 = ≥ 1 day- ≤ 1 yr; 2 = 1-9 yr; 3 = 10-19 yr; 4 = ≥ 20 yr.

^bIntensity categories: 1 = >0 - <0.1 ppm; 2 = 0.1- <0.5 ppm; 3 = 0.5- <2.0 ppm; 4 = ≥ 2.0 ppm.

^cPeak categories: 1 = <0.5 ppm; 2 = 0.5- <2.0 ppm; 3 = 2.0- <4.0 ppm; 4 = ≥ 4.0 ppm.

^dWorkers with missing values for peak exposures were excluded.

^eAverage categories: 1 = >0 - <0.25 ppm; 2 = 0.25- <0.5 ppm; 3 = 0.5- <1.5 ppm; 4 = ≥ 1.5 ppm.

^fCumulative categories: 1 = >0 - <0.5 ppm-yr; 2 = 0.5- <5.5 ppm-yr; 3 = ≥ 5.5 ppm-yr.

^gDirect age and calendar year adjusted mortality rates for each exposure category was divided by the rate in the lowest category to obtain the SRR.

^h $p \leq 0.05$.

and chi values are presented to show the direction of the trend. For the trend tests, the midpoint of the categories was used to represent estimated exposure levels for all categories except the highest, for which the median value of the scores was used because the category is open-ended. Standardized rate ratios (SRR) for exposure subgroups, using mortality rates of each subgroup directly adjusted to the age and calendar-time person-year distribution of the entire cohort, were used to counter difficulties that may arise from comparing SMRs.

RESULTS

Table I shows mortality from lung cancer among white male wage workers exposed to formaldehyde by various measures of exposure. For these analyses, subjects were not considered at risk of lung cancer until 20 or more years after their first exposure to formaldehyde. Several measures of exposure were evaluated to minimize the limitations associated with each particular measure. Although not presented in a table, SMRs among workers exposed to formaldehyde were typically greater than

among those unexposed (non-exposed workers had an SMR of 0.9 (7 deaths vs. 8.1 expected)). Among the exposed, neither SMRs nor SRRs rose consistently with formaldehyde level for any measure of exposure and there were no statistically significant trends. The chi values for four of the five tests for trend were negative, indicating slight inverse associations. Subdivisions of the <0.5 ppm-year cumulative exposure category were created to determine at what exposure level the excess risk first occurred. For cumulative exposures of >0-<0.1, 0.1-<0.2, 0.2-<0.3, 0.3-<0.4, and 0.4-<0.5 ppm-years, respectively, the SMRs 20 or more years after first exposure among wage workers were 1.2 (19 obs./15.8 exp.), 1.7 (15 obs./8.8 exp.), 0.9 (4 obs./4.4 exp.), 1.6 (6 obs./3.7 exp.), and 1.2 (3 obs./2.4 exp.). Lung cancer was also elevated among those with a duration of exposure of less than one year (SMR = 1.4).

No significant exposure-response pattern was uncovered in analyses which included only jobs in which the industrial hygienists were more confident of exposure estimates, which included workers employed after the initial start date of person-year accumulation at each plant (new hires), which included persons also exposed to formaldehyde in solution, or which lagged exposures by 5, 10, 20, or 30 years (Table II). Among persons hired before the start date for cohort follow-up, SMRs rose with increasing cumulative exposure from an SMR of 1.3 among those with <0.5 ppm-years of exposure to an SMR of 1.7 for those with ≥ 5.5 ppm-years. SMRs for new hires were similar to workers hired before the start dates for person-years, except for the ≥ 5.5 ppm-year category (SMRs = 1.1 and 1.7, respectively). This latter excess among those hired before the person-year start dates was primarily a result of excess mortality in plant 6. SMRs also showed a slight increase with cumulative exposure to formaldehyde from 1.2 to 1.4 among persons also exposed to particulates from resin and molding compound operations. Although we lacked information on concentration of particulates, we were able to evaluate mortality from lung cancer by duration of time spent in particulate exposed jobs. The risk of lung cancer did not increase with duration of exposure to particulates alone for any latency category, nor in combination with different levels of exposure to formaldehyde. In several analyses, latency was defined as time since achieving a specific level of exposure instead of time since any exposure. None of these analyses revealed an exposure-response gradient.

SMRs for lung cancer among all wage workers were larger among those first exposed after age 35 than among those first exposed before age 35 (SMRs = 1.3 and 1.0, respectively) and larger among those exiting the study in later, rather than earlier, calendar years (SMRs = 1.4 and 1.1, respectively). The risk of lung cancer rose from an SMR of 1.0 based on deaths before 1955 to 1.2 based on deaths after 1975. Risks by year of entry for the >20 latency group were 1.4 for both those first employed before 1958 and for those first employed in 1958 or later. Finally, the risk of lung cancer did not decrease with increasing time since last exposure as might be expected for a substance acting as a promotor (SMRs of 0.8, 1.0, 1.4, and 1.2 by increasing years since last exposure <4, 4-9, 9-14, and ≥ 15 years, respectively).

Because cumulative exposure combines persons with heavy exposure for short durations with those having lower exposure for longer durations, we evaluated the independent effects of intensity and duration of exposure to formaldehyde on lung cancer mortality (Table III). No significant trends occurred either by intensity within duration categories, or by duration within intensity categories.

TABLE II. SMRs for Lung Cancer by Cumulative Exposure to Formaldehyde (Wage White Men, ≥ 20 Years After First Exposure)

Measure of exposure	ppm-years				X for trend
	>0-<0.5	0.5-<5.5	≥ 5.5	Total	
Cumulative using jobs with more confident estimates of exposure	1.4 (23/15.8) ^a	1.7 ^d (34/20.2)	1.6 (23/14.8)	1.6 ^d (80/50.8)	0.08
Cumulative excluding exposures during last 15 years	1.3 (48/36.3)	1.6 ^d (63/40.7)	1.2 (31/26.9)	1.4 ^d (142/103.9)	-0.89
Cumulative for new hires only ^b	1.3 (44/32.9)	1.4 ^d (35/24.2)	1.1 (19/17.5)	1.3 ^d (98/74.6)	-0.81
Cumulative for workers employed on start dates	1.3 (3/2.3)	1.3 ^d (16/11.9)	1.7 ^d (25/15.0)	1.5 ^d (44/29.2)	0.70
Cumulative (with potential exposure to formaldehyde in solution)	1.4 (16/11.2)	1.3 (28/22.2)	1.3 (31/24.6)	1.3 ^d (75/58.0)	-0.24
Cumulative (with potential contact to formaldehyde containing particulates) ^c	1.2 (32/26.6)	1.2 (32/25.6)	1.4 (26/18.6)	1.3 (90/70.8)	0.59
Exposures lagged 5 years ^c	1.3 ^d (78/61.0)	1.2 (80/67.5)	1.2 (49/39.8)	1.2 ^d (207/168.3)	-0.11
Exposures lagged 10 years ^c	1.4 (75/54.4)	1.2 (76/64.1)	1.2 (41/33.0)	1.2 ^d (192/156.5)	-0.05
Exposures lagged 20 years ^c	1.2 (56/45.0)	1.6 ^d (66/41.9)	1.2 (20/16.7)	1.4 ^d (142/103.7)	-0.23
Exposures lagged 30 years ^c	1.2 (18/14.3)	1.6 (18/11.4)	1.1 (3/2.7)	1.4 (39/28.3)	-0.12

^aObserved/expected Nos.

^bHired after start date of study.

^cTotal cohort; not restricted to ≥ 20 year latency.

^d $p \leq 0.05$.

A strength of multi-plant studies is the opportunity to evaluate the consistency of effects among different plants. Lung cancer patterns among wage workers by cumulative exposure to formaldehyde for individual plants are displayed in Table IV. Six plants had SMRs greater than 1.0 and four plants had SMRs of 1.0 or less. In plant 3 (a plywood plant), the SMR test for trend by increasing level of cumulative exposure was statistically significant, but it was based on only 3 deaths. Plant 4 (a photographic film plant) also showed a positive exposure-response gradient, based on 5 deaths. In plant 1, although the unexposed had an SMR of 2.8 (based on 2 deaths), the SMRs rose with increasing exposure levels among the exposed (from an SMR of 1.3 to 2.1). Four plants (Nos. 2, 6, 8, 9) had slightly negative trends of lung cancer by cumulative exposure. Risk varied by product with SMRs of 1.1 for photographic film (plants 4 and 5), 1.0 for formaldehyde (plants 2, 7, 10), 1.8 for plywood (plant 3), 1.2 for molding compounds or resins (plants 1, 2, 7-10), and 1.7 for plastic products (plants 6, 8, 9). Average estimated levels of formaldehyde in the plants ranged from 0.1 to 1.9 ppm, and the overall risk of lung cancer by plant did not appear to be correlated with the average formaldehyde level in the plant.

TABLE III. SMRs for Lung Cancer by Intensity and Duration of Exposure to Formaldehyde for Wage White Men ≥ 20 Years After First Exposure

Intensity	Duration (years)				Total	X for trend
	<1	1-<10	10 <20	≥ 20		
0 ppm ^a	1.4 (2/1.5) ^b	0.7 (1/1.5)	— (0/0.3)	1.0 (2/1.9)	1.0 (5/5.2)	-0.08
<0.1 ppm	1.2 (9/7.7)	1.3 (5/3.8)	— (0/1.0)	1.7 (4/2.4)	1.2 (18/14.8)	0.27
0.1-<0.5 ppm	1.2 (9/7.5)	1.7 (6/3.6)	2.7 ^c (12/4.4)	1.3 (12/9.5)	1.6 ^c (39/24.9)	0.06
0.5-<2.0 ppm	1.6 ^c (29/18.3)	1.6 (16/10.3)	1.4 (9/6.5)	1.3 (23/17.9)	1.4 ^c (77/53.0)	-0.80
≥ 2.0 ppm	— (0/0.6)	0.5 (1/1.9)	1.1 (1/1.0)	0.3 (1/3.3)	0.4 (3/6.7)	-0.20
Total	1.4 ^c (49/35.6)	1.4 (29/21.1)	1.7 ^c (22/13.2)	1.2 (42/35.0)	1.4 ^c (142/104.9)	-0.52
X for trend	0.51	-0.34	-0.91	-1.16	-0.84	

^aFor the unexposed, duration refers to duration of employment.

^bObserved/expected nos.

^c $p \leq 0.05$.

Evaluation of lung cancer mortality among further subdivisions of the highest latency and cumulative exposure categories showed no consistently increasing exposure-response pattern (Table V). The SMR was 1.4 thirty or more years after first exposure, the same as it was for the 20-29 year category. The risk of lung cancer was not elevated overall (SMR = 1.0) among persons with ≥ 25 ppm-years of exposure overall, or for the 20-29 year (SMR = 1.1) or the ≥ 30 year latency categories (SMR = 1.0). A significantly elevated SMR occurred among persons with <5.5 ppm-years of exposure, 20-29 years after first employment (SMR = 1.4).

Short-term and long-term workers may encounter different exposures in the workplace, may have different sensitivities to exposure, or may have different lifestyles which could influence their risk of cancer. To address this issue, we evaluated the risk of lung cancer by cumulative exposure, latency, and number of years employed in the plants (Table VI). Workers employed <1 year and ≥ 1 year both had significant excess risks of lung cancer 20 or more years after first exposure (SMRs = 1.4 and 1.3, respectively). For those in the ≥ 20 year latency category and employed ≥ 1 year, SMRs rose from 0.8 among the unexposed to 1.4 in each cumulative exposure category. Among those in the ≥ 20 year latency category and employed <1 year, excesses of lung cancer occurred among exposed and unexposed alike. Inspection of SMRs by cumulative exposure for those employed ≥ 1 year and with ≥ 20 year latency by individual plants revealed slight positive trends in plants 3 (plywood) and 4 (photographic film), but not in the other plants, as is consistent with the results in Table IV. There were too few deaths to provide meaningful analyses for short-term employees (<1 year) by individual plant. Short-term workers also experienced significantly elevated mortality from other causes, including all causes combined (SMR = 1.3), arteriosclerotic heart disease (SMR = 1.1), emphysema (SMR = 1.7), and diseases of the digestive system (SMR = 1.3). No such excesses occurred among long-term workers.

TABLE IV. SMRs for Lung Cancer by Plant and by Cumulative Exposure to Formaldehyde for Wage White Men, ≥ 20 Years After First Exposure

Plant No.	Cumulative exposure (ppm-yr)					X for trend	Estimated mean formaldehyde TWA (ppm)
	0	<0.5	0.5-<5.5	≥ 5.5	Total		
1	2.8 (2/0.7) ^a	1.3 (10/8.0)	1.5 (13/8.7)	2.1 ^b (11/5.3)	1.6 ^b (36/22.6)	1.01	0.9
2	— (0/0)	— (0/0.3)	0.8 (1/1.2)	0.4 (2/4.7)	0.5 (3/6.2)	-0.26	1.9
3	3.4 (1/0.3)	— (0/0.8)	1.7 (1/0.6)	42.5 ^b (1/<0.1)	1.8 (3/1.7)	4.24 ^b	0.2
4	— (0/3)	— (0/0.2)	0.6 (1/1.7)	2.1 (4/1.9)	1.2 (5/4.1)	1.54	0.4
5	— (0/0.7)	— (0/0.3)	1.8 (2/1.1)	0.7 (1/1.4)	0.9 (3/3.5)	0.06	0.5
6	— (0/0.2)	2.7 ^b (11/4.1)	2.1 ^b (15/7.2)	1.7 (17/10.0)	2.0 ^b (43/21.5)	-1.00	0.5
7	0.4 (1/2.4)	1.3 (18/13.0)	1.2 (6/5.2)	1.4 (1/0.7)	1.2 (26/21.2)	0.09	0.1
8	— (0/0)	1.0 (5/4.8)	0.5 (2/3.8)	0.5 (1/2.0)	0.8 (8/10.5)	-0.69	0.5
9	— (0/<0.1)	11.5 (1/0.1)	9.5 ^b (2/0.2)	— (0/0.1)	8.5 ^b (3/0.4)	-0.97	0.4
10	1.0 (1/1.0)	0.5 (2/3.8)	1.2 (8/6.4)	0.9 (6/6.4)	1.0 (17/17.6)	0.11	0.6

^aObserved/expected nos.^bp \leq 0.05.

TABLE V. SMRs for Lung Cancer by Latency and Cumulative Exposure to Formaldehyde for Exposed White Wage Men

Latency (years)	Cumulative exposure (ppm-yr)					X for trend
	> 0-<5.5	5.5-<10	10-<25	≥ 25	Total	
< 10	1.0 (16/15.8) ^a	2.3 (3/1.3)	1.7 (1/0.6)	— (0/0)	1.1 (20/17.7)	0.95
10-<20	1.0 (43/42.4)	1.1 (4/3.7)	0.5 (3/5.6)	— (0/1.0)	1.1 (50/52.7)	-1.42
20-<30	1.4 ^b (76/54.0)	1.2 (9/7.4)	1.4 (13/9.4)	1.1 (5/4.6)	1.4 ^b (103/75.4)	-0.52
≥ 30	1.3 (22/17.3)	1.9 (6/3.1)	1.7 (7/4.2)	1.0 (4/3.8)	1.4 (39/28.4)	-0.09
Total	1.2 ^b (157/129.5)	1.4 (22/15.5)	1.2 (24/19.7)	1.0 (9/9.5)	1.2 ^b (212/174.2)	-0.53

^a(Observed/expected nos.).^bp \leq 0.05.

Workers in this study also have exposures to substances other than formaldehyde. Although not presented in a table, lung cancer mortality among workers ever exposed to 17 different substances was evaluated, and elevated SMRs occurred among workers exposed to antioxidants, asbestos, carbon black, dyes and pigments, hexamethylenetetramine, melamine, phenol, plasticizers, urea, and wood dust. SMRs for workers

TABLE VI. SMRs for Lung Cancer by Cumulative Exposure to Formaldehyde by Latency, and by Years of Employment in the Study, Wage White Men

Latency and length of employment	Cumulative exposure (ppm-years)					X for trend
	0	<0.5	0.5-<5.5	≥5.5	Total	
<10 yr latency						
Employed < 1 yr	— (0/0.2) ^a	0.8 (4/5.2)	— (0/1.0)	— (0/0)	0.6 (4/6.4)	-0.85
Employed ≥ 1 yr	1.4 (1/0.7)	1.2 (3/2.6)	1.3 (9/7.1)	2.1 (4/1.9)	1.4 (17/12.3)	0.90
10-<20 yr. latency						
Employed < 1 yr	1.7 (1/0.6)	1.5 (22/15.1)	1.6 (5/3.1)	— (0/0)	1.5 (28/18.8)	0.19
Employed ≥ 1 yr	— (0/1.5)	0.9 (3/3.4)	0.6 (13/20.8)	0.7 (7/10.4)	0.6 ^b (23/36.1)	0.16
≥20 yr latency						
Employed < 1 yr	1.3 (2/1.5)	1.3 (39/29.3)	1.5 (10/6.6)	— (0/0)	1.4 ^b (51/37.4)	0.38
Employed ≥ 1 yr	0.8 (3/3.7)	1.4 (8/5.9)	1.4 (41/29.5)	1.4 (44/32.4)	1.3 ^b (96/71.6)	0.23
Total						
Employed < 1 yr	1.3 (3/2.3)	1.3 ^b (65/49.6)	1.4 (15/10.6)	— (0/0)	1.3 ^b (83/62.6)	0.26
Employed ≥ 1 yr	0.7 (4/6.0)	1.2 (14/11.9)	1.1 (63/57.5)	1.2 (55/44.7)	1.1 (136/120.0)	0.86

^a(Observed/expected nos.).^bp≤0.05.

exposed to these substances were typically ≥ 1.5 twenty or more years after first exposure and statistically significant, while SMRs among the nonexposed were about 1.1. Persons exposed to formaldehyde had an SMR of 1.4, while those not exposed had an SMR of 0.9. Since short-term workers (<1 year) had elevated mortality for several causes of death which may be unrelated to workplace exposures, we evaluated the risk of lung cancer associated with duration of exposure to substances other than formaldehyde among long-term wage workers separately (Table VII). Without latency considerations, statistically significant trends were found for melamine (SMRs = 0.8, 1.5, 1.5, and 2.0) and urea (SMRs = 0.8, 1.4, 1.5, and 2.1). Non-significant trends emerged by duration of exposure to phenol (SMRs = 0.8, 1.5, 1.1, 2.0) and wood dust (SMRs = 1.1, 1.2, 2.2, and 4.9). Similar patterns were observed among the ≥ 20 year latency group, except that workers exposed to these substances <1 year typically had SMRs in excess of 1.0.

To evaluate possible interaction between these substances and formaldehyde, we compared lung cancer risks by cumulative exposure to formaldehyde among persons ever exposed to at least one of the substances listed in Table VII to the risk among those never exposed to any of these substances (Table VIII). Among those exposed to formaldehyde, lung cancer mortality was elevated only when exposure to some other substance was present (SMR = 1.4 for formaldehyde plus other substances versus 1.0 for formaldehyde alone). The risk of lung cancer rose slightly with increasing level of exposure to formaldehyde in the <10 year latency period, but an inverse association occurred in the longer latency categories.

TABLE VII. SMRs for Lung Cancer Among Wage White Men Employed in Formaldehyde Industries ≥ 1 Year by Duration of Exposure to Selected Substances

Substance and latency	Duration of exposure (years)												Total	X for trend		
	< 1			1- < 10			10- < 19			≥ 20						
	O	E	SMR	O	E	SMR	O	E	SMR	O	E	SMR				
Antioxidants																
Total	9	7.9	1.1	21	13.9	1.5	6	6.4	0.9	11	5.6	2.0 ^a	47	33.9	1.4 ^b	0.76
≥ 20 yr latency	4	3.4	1.2	11	6.2	1.8	5	3.5	1.4	11	5.6	2.0	31	18.6	1.7 ^b	0.58
Asbestos																
Total	9	6.1	1.5	8	9.7	0.8	6	4.6	1.3	7	2.9	2.4	30	23.3	1.3	1.38
≥ 20 yr latency	6	2.4	2.5	4	4.4	0.9	3	2.4	1.2	7	2.9	2.4	20	12.1	1.6 ^b	0.65
Carbon black																
Total	6	3.4	1.7	5	6.0	0.8	3	3.6	0.8	6	2.5	2.4	20	15.6	1.3	0.88
≥ 20 yr latency	3	1.3	2.4	1	2.2	0.4	1	1.9	0.5	6	2.5	2.4	11	8.0	1.4	0.94
Dyes & pigments																
Total	12	7.2	1.7	7	9.1	0.8	6	2.9	2.0	3	1.7	1.8	28	20.9	1.3	0.65
≥ 20 yr latency	8	3.6	2.2	6	4.9	1.2	6	1.5	4.0 ^b	3	1.7	1.8	23	11.7	2.0	0.48
Hexamethylene-tetramine																
Total	9	6.6	1.4	12	8.5	1.4	9	4.3	2.1	3	2.2	1.4	33	21.5	1.5 ^b	0.47
≥ 20 yr latency	6	2.2	2.7	4	2.8	1.4	6	2.1	2.5 ^b	3	2.2	1.4	19	9.3	2.0 ^b	-0.47
Melamine																
Total	11	14.2	0.8	21	14.4	1.5	10	6.7	1.5	11	5.6	2.0	53	40.9	1.3	1.96 ^b
≥ 20 yr latency	8	6.1	1.3	10	6.5	1.5	7	3.6	1.9	11	5.6	2.0	36	21.9	1.6 ^b	0.99
Phenol																
Total	5	6.1	0.8	11	7.5	1.5	5	4.7	1.1	9	4.4	2.0	30	22.8	1.3	1.33
≥ 20 yr latency	3	2.4	1.2	5	3.7	1.4	3	2.8	1.1	9	4.4	2.0	20	13.4	1.5	0.93
Plasticizers																
Total	7	5.6	1.2	12	8.9	1.3	6	5.5	1.1	11	5.3	2.1 ^b	36	25.3	1.4	1.04
≥ 20 yr latency	5	2.4	2.1	6	4.1	1.5	5	3.0	1.7	11	5.3	2.1 ^b	27	14.7	1.8 ^b	0.32
Urea																
Total	8	9.7	0.8	18	13.4	1.4	10	6.8	1.5	12	5.8	2.1 ^b	48	35.7	1.3	1.96 ^b
≥ 20 yr latency	6	4.0	1.5	11	6.5	1.7	7	3.7	1.9	12	5.8	2.1 ^b	36	19.9	1.8 ^b	0.65
Wood dust																
Total	3	2.7	1.1	6	5.0	1.2	3	1.4	2.2	2	0.4	4.9	14	9.5	1.5	1.87
≥ 20 yr latency	3	1.1	2.8	4	2.2	1.8	2	0.6	3.4	2	0.4	4.9	11	4.3	2.6 ^b	0.97
Formaldehyde																
Total	7	8.3	0.8	63	51.1	1.2	36	33.6	1.1	33	28.1	1.2	139	121.0	1.2	0.02
≥ 20 yr latency	2	4.1	0.5	32	24.1	1.3	28	15.6	1.8 ^b	33	28.1	1.2	95	71.9	1.3 ^b	0.09

^aObserved and expected nos. for total and ≥ 20 year latency are identical.

^b $p \leq 0.05$.

Information was sought on smoking from medical records for 190 subjects with cancer and 950 age-matched controls from plants 1 and 6. Unfortunately, information was found for only one-third of these subjects. However, in this small sample where approximately 80% were, or had previously been, cigarette smokers, the prevalence of smoking did not appear to be strongly associated with exposure to formaldehyde (80% ever smoked among the unexposed, 67% among the >0 to >0.5 ppm-year exposure category, 84% among the ≥ 0.5 to <5.5 ppm-year category, and 70% among the ≥ 5.5 ppm-year category).

TABLE VIII. SMRs for Lung Cancer by Cumulative Exposure to Formaldehyde and Exposure to Other Substances, Wage White Men

Other exposures and latency ^a	Cumulative formaldehyde exposure (ppm-years)				X for trend
	>0-<0.5	0.5-<5.5	>5.5	Total	
<10 yr latency					
Other exposures ^a	1.0 (3/3.1) ^b	1.2 (5/4.4)	1.7 (2/1.2)	1.2 (10/8.7)	0.61
No others	0.9 (4/4.7)	1.1 (4/3.6)	2.9 (2/0.7)	1.1 (10/9.0)	1.46
10-19 yr latency					
Other exposures	1.0 (8/7.8)	0.8 (10/13.4)	0.8 (5/6.7)	0.8 (23/27.9)	-0.39
No others	1.6 (17/10.6)	0.8 (8/10.5)	0.5 (2/3.7)	1.1 (27/24.8)	-1.62
≥20 yr latency					
Other exposures	2.0 ^c (28/14.3)	1.5 ^c (28/18.5)	1.8 ^c (35/19.3)	1.8 ^c (91/52.1)	0.06
No others	0.9 (19/20.9)	1.3 (23/17.7)	0.7 (9/13.2)	1.1 (55/51.8)	-1.38
Total					
Other exposures	1.6 (39/25.2)	1.2 (43/36.3)	1.6 ^c (42/27.2)	1.4 ^c (124/88.7)	0.47
No others	1.1 (40/36.2)	1.1 (35/31.8)	0.7 (13/17.5)	1.0 (88/85.5)	-1.29

^aExposed to at least one of the following substances: asbestos, antioxidants, carbon black, dyes and pigments, hexamethylenetrarnine, melamine, phenol, plasticizers, urea, wood dust.

^bObserved/expected nos.

^cp≤0.05.

DISCUSSION

In the initial report regarding the mortality experience of workers exposed to formaldehyde [Blair et al., 1986], an excess of lung cancer was noted among workers ≥20 years after their first exposure to formaldehyde. No consistent patterns were seen by level or duration of exposure to formaldehyde, or by individual plant. Further analyses in the present report did not uncover any clear exposure-response gradients between lung cancer mortality and various estimates of exposure to formaldehyde. The excess occurred even among workers in the smallest cumulative exposure category (those with <0.1 ppm-years of exposure had an SMR of 1.2) and returned to unity among those with ≥25 ppm-years of exposure.

The lack of a clear exposure-response relationship between lung cancer and formaldehyde exposure seen in our data is consistent with other reports [Acheson et al., 1984; Bertazzi et al., 1986; Coggon et al., 1984; Partanen et al., 1985; Stayner et al., 1988; Gérin et al., 1989]. One plant in the study from the United Kingdom [Acheson et al., 1984] did show an increasing risk with level of exposure, but the remaining plants in the same study showed no such pattern. Studies of anatomists and pathologists who have exposure to formaldehyde have consistently shown deficits of lung cancer [Blair et al., 1985], but these results most likely reflect the low prevalence of smoking among professionals. In several studies of embalmers and funeral directors the mortality from lung cancer was about as expected [Blair et al., 1985] and

the prevalence of smoking in this occupation does not appear to be unusually low [Walrath et al., 1985].

Elevated risks (SMRs from 1.3 to 2.6) occurred among persons involved in the production of formaldehyde resins and molding compounds having contact with antioxidants, asbestos, carbon black, dyes and pigments, hexamethylenetetramine, melamine, phenol, plasticizers, urea, and wood dust, in addition to formaldehyde. Elevated SMRs for lung cancer occurred among persons with combined exposure to formaldehyde and at least one of these ten substances (SMR = 1.4 overall, and 1.8, twenty or more years after first exposure), but not among persons exposed to formaldehyde alone (SMRs of 1.0 and 1.1, respectively). Among long-term employees (≥ 1 year), the risk of lung cancer rose with duration of exposure to phenol, melamine, urea, and wood dust, suggesting that these substances may partially account for the lung cancer excess. These substances are used in the production of resins and/or molding compounds and it is possible that our findings simply identify the work area where exposures occurred which increased the risk of lung cancer, rather than indicating that these specific substances were directly involved. Wood dust is, however, an established nasal carcinogen [IARC Monographs, Suppl. 7, 1981] and excesses of lung cancer have been reported among furniture workers in Sweden [Esping and Axelson, 1980], woodworkers in the United Kingdom [Coggon et al., 1986], persons in wood and paper-related occupations in rural Georgia [Harrington et al., 1978], and workers exposed to wood dust in Montreal [Siemiatycki et al., 1986]. Another explanation could be that exposure to formaldehyde-containing particulates may lead to heavier actual exposure to formaldehyde than the estimates based on ambient air levels due to off-gassing of formaldehyde from the particulate. Among workers exposed to these other substances, however, mortality from lung cancer did not rise with increasing air levels of formaldehyde.

None of the different estimates of exposure to formaldehyde showed a consistent exposure-response gradient for lung cancer, although such a pattern could be missed if limited to specific industrial processes or selected subgroups of the cohort. Analyses by product revealed a significant excess among persons employed in plants producing plastic products, but risk did not increase with level of exposure to formaldehyde. Plant 3 (a plywood producer) had a statistically significant trend of lung cancer with cumulative level of exposure, based on 3 deaths and fairly low exposures. Plant 4 (a photographic film plant) also showed a slight positive trend with cumulative exposure, but the other plant producing photographic film (plant 5), using formaldehyde and somewhat different chemicals, showed no such trend. The lung cancer pattern by cumulative exposure to formaldehyde did not change when only recent exposures were included or excluded in the cumulative exposure analyses (patterns indicative of substances acting at late stages or early stages of carcinogenesis, respectively), when liquid exposures were considered, when exposures were lagged 5, 10, 20, or 30 years, or when the only jobs included were those for which the industrial hygienists were more confident about their exposure assignments. Among workers exposed to particulates, SMRs were slightly larger among those cumulative exposures to formaldehyde of ≥ 5.5 ppm-years than among those exposed to < 0.5 ppm-years (SMRs = 1.4 and 1.2, respectively). SMRs did not vary by year of entry into the cohort (SMRs = 1.4 for those entering before and after 1958) as might be expected since formaldehyde exposure levels were generally higher in the past.

An irritating substance such as formaldehyde might cause more sensitive per-

sons to leave jobs with high exposure, or cause them to leave the company. Sensitivity to the irritative properties of formaldehyde, however, would not necessarily indicate susceptibility to cancer. Because no actual measure of sensitivity to formaldehyde was available, length of employment at each plant was used as a surrogate for sensitivity. Among wage workers the lung cancer excess was greater among those employed <1 year (SMR = 1.3) than among those employed for more than 1 year (SMR = 1.1) for the total cohort, but the two groups were similar 20 or more years after first exposure (SMRs = 1.4 and 1.3, respectively). SMRs showed little association with level of cumulative exposure to formaldehyde among either short- or long-term workers. The excess among those employed for <1 year may have occurred because they represent a more transient group of workers with lifestyle factors that increase cancer risks. Excess mortality from arteriosclerotic heart disease, emphysema, and diseases of the digestive system was also noted among short-term workers. Excesses for such diverse diseases suggest that lifestyle factors are a more likely explanation than formaldehyde. Higher risks for short-term employees for some causes of death have been noted by others [Checkoway, 1986].

When interpreting these results, it is important to consider study limitations. First, detailed information was not available on cigarette smoking, a strong risk factor for lung cancer. Although differences in smoking habits by occupation occur, they seldom cause serious confounding [Axelson, 1978; Blair et al., 1985]. Information on smoking habits obtained from medical records for a small sample of workers from plants 1 and 6 suggests that the smoking habits among exposed workers were probably not radically different from those of the general population used for comparison [Sterling and Weinkam, 1979; Walrath et al., 1985] and that major differences in smoking prevalence did not occur by cumulative level of exposure. Although smoking would not appear to be a serious confounder in these data, slight under- or overestimates of the relative risks cannot be ruled out.

Another possibility is that formaldehyde has the capacity to increase the incidence of lung cancer at certain levels, but the levels of exposure experienced by the workers in this study may have been too low to cause a detectable effect. Separate analyses of workers who may have experienced short-term peak exposures above the TWA categories, however, did not confirm any additional risk, nor did it result in an exposure-response gradient. The levels of formaldehyde to which workers were exposed in this [Blair et al., 1986; Stewart et al., 1986, 1987] and other studies [Acheson et al., 1984; Bertazzi et al., 1986; Partanen et al., 1985; Stayner et al., 1988] are relatively low and the range is narrow. They do appear, however, to reflect those concentrations generally reported in inspection data from the Occupational Safety and Health Administration (OSHA) [Dept. of Labor, 1979-1986], the National Institute for Occupational Safety and Health [Berstein et al., 1984], and other sources [Consensus Workshop, 1984].

Estimating historical exposures is a difficult process, and some misclassification undoubtedly occurred [Checkoway, 1986; Stewart et al., 1986]. This issue was of particular concern at the Occupational Safety and Health Administration hearings on formaldehyde [Department of Labor, 1987]. We recognize that our estimates are approximations [Stewart et al., 1986]. For a number of reasons, however, it seems unlikely that misclassification would entirely account for our failure to note an exposure-response gradient. The risk of lung cancer by exposure level in our data (whether measured by duration, intensity, intensity by duration, average, cumulative,

or peak levels) consistently showed a pattern in which the risk in the highest exposure category was similar to that in the lowest exposure category or lower. Analysis by several measures of exposure decreases the chances of a false-negative finding because the relative ranking of workers varied considerably by these different exposure estimates [Blair and Stewart, 1990]. For example, average exposure and duration of exposure were entirely unrelated. Thus, the similarity in mortality patterns by different measures of exposure would not appear to be due to identical classification of the workers. Second, risk of lung cancer was greater among persons entering the cohort or dying in more recent years than in earlier years, even after controlling for latency, a pattern in contrast to changes in formaldehyde levels, which have decreased over time. Third, no exposure-response pattern was observed between mortality from lung cancer and duration of exposure, a more traditional measure of exposure that does not rely upon estimates of levels and which has proven to be useful in the evaluation of many well-documented occupational carcinogens [Checkoway, 1986; Rinsky et al., 1981; Schulte et al., 1985]. Fourth, the risk of lung cancer did not diminish as time since last exposure lengthened as would be expected if formaldehyde was operating at a late stage in the carcinogenic process. Fifth, there was no exposure-response association when analyses included only jobs where the industrial hygienists had greater confidence in the exposure estimates. Finally, in these data there was a sharp, but nonsignificant, exposure-response gradient between cancer of the nasopharynx and cumulative exposure to formaldehyde among persons also exposed to particulates [Blair et al., 1987], a cancer found to be associated with formaldehyde exposure in other studies [Olsen et al., 1984; Roush et al., 1987; Vaughan et al., 1986a,b]. Since exposure assessments were developed without knowledge of mortality status or cause of death, it seems unlikely that misclassification of exposures would have been limited to specific causes of death (e.g., lung cancer).

The failure to see an exposure-response gradient for the excess of lung cancer in these data could be due to the "healthy worker effect," which may lead to an underestimate of relative risks. There is considerable evidence, however, that the healthy worker effect is not a problem in this analysis of lung cancer and formaldehyde. First, there was little evidence of a healthy worker effect in this cohort. The mortality from all causes was about as expected (SMR = 97 among those exposed to formaldehyde and 99 among those unexposed). Second, others have found that the healthy workers effect diminishes with time from entry and that it has largely disappeared 15 years of follow-up [Fox and Collier, 1976; McMichael, 1976]. By design, entry into this cohort had to occur before 1966, which was 15 years prior to the closing date of the study. Third, SRRs based on internal comparisons, which were also used in these and earlier analyses [Blair et al., 1986] are less influenced by the "healthy worker effect" than SMRs, and we found no exposure-response gradient using SRRs to estimate relative risks. Robins et al. [1988], in a reanalysis of our data using a procedure specifically designed to adjust for the healthy worker survivor effect, found "no suggestion of an adverse effect of formaldehyde on lung cancer mortality." Sterling and Weinkam [1988], in a reanalysis using log-linear modeling, reported significant excess mortality from all causes, all cancer, and lung cancer. In these analyses, however, deaths were incorrectly counted, resulting in approximately three times as many events as actually occurred in the data set [Blair and Stewart, 1989]. In a letter correcting this problem, Sterling and Weinkam [1989] report from

a new reanalysis an excess only for lung cancer that rose with level of exposure. The number of lung cancer deaths in Sterling and Weinkam's [1989] new analysis ($N = 299$) differs from the number of deaths from lung cancer in the original data set (280). Sterling and Weinkam's new analyses [1989] may have included deaths from lung cancer that were from contributing causes ($N = 19$) as well as those that were from underlying causes ($N = 280$), although the number of deaths from all cancers ($N = 873$) in their analyses was not sufficient to also have included contributing causes.

In summary, these additional analyses have not fully explained the excess mortality from lung cancer seen among wage workers 20 or more years after first exposure, but one finding stands out. Excesses are particularly striking among workers from areas producing formaldehyde resin and molding compounds where, in addition to formaldehyde, exposure to phenol, urea, melamine, wood dust, and other substances may have occurred. Analysis by a number of different measures of level of exposure to formaldehyde failed to detect a consistent increase in the risk of lung cancer, although small, non-significant trends were seen for cumulative exposure for persons hired before the start dates for the study and for persons also exposed to particulates. The latter may be another indication of risks associated with substances in resin and molding compound operations. Interpretation of these slight exposure-response patterns is difficult because of the small increases in risk, the lack of statistical significance, and the inconsistency among the individual plants. The association between lung cancer and exposure to phenol, melamine, urea, and wood dust and other substances suggests that these substances might account for some, or all of the excess observed and therefore deserve further attention in other cohorts of workers employed in resin and molding operations.

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