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Lung Cancer Mortality in a Dutch Cohort of Asphalt Workers: Evaluation of Possible Confounding by Smoking

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Background *Using data from a Dutch cohort of workers in road construction and asphalt mixing companies, this article describes possible confounding of the association between exposure to bitumen fume and lung cancer mortality by smoking.*
Methods *A retrospective cohort of 3,714 workers with at least one season of employment was identified. Semi-quantitative exposure to bitumen fume was assessed by a job-exposure matrix. Information on smoking habits was available for a sub-cohort of 1,138 workers, who underwent medical examinations by the occupational health services in the past.*
Results *Smoking habits differed between occupational title groups and there was a positive association between cumulative exposure and smoking. Internal analyses using the non-exposed subjects as reference category, showed a positive association between semi-quantitative bitumen fume exposure and lung cancer risk. After adjusting for differences in smoking habits, all relative risks were reduced, but a weak positive association could still be observed.*
Conclusion *Confounding by smoking on the association between exposure to bitumen fume and lung cancer mortality is possible, although the positive trend (not statistically significant) for lung cancer mortality remained. Only a nested case-control study may allow proper treatment of potential (residual) confounding by smoking in this population.*
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KEY WORDS: occupational exposure; asphalt; bitumen; mortality; lung cancer; smoking

INTRODUCTION

Evaluation in experimental animal studies has raised suspicion about the carcinogenic properties of bitumen. Bitumen is used as the binder in asphalt mix (in North America the binder is usually referred to as ‘‘asphalt’’). To address the question if bitumen is a human carcinogen, a large-scale international retrospective cohort of workers with bitumen exposure from road construction and asphalt mixing companies has been assembled by the International Agency for Research on Cancer (IARC) [Boffetta et al., 2001]. The study focused on a possible increased risk for lung cancer mortality due to occupational exposure to bitumen fume in road paving and asphalt mixing.

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Results from the pooled study, comprising 29,820 workers from eight countries, showed a statistically significant increased risk for lung cancer mortality among workers ever employed in jobs entailing bitumen exposure, further referred to as ''asphalt workers'' (330 observed deaths, standardized mortality ratio (SMR) = 1.17, 95% confidence interval (CI) = 1.04–1.30). Compared to an internal reference group of workers in building and ground construction, asphalt workers had a similar risk for lung cancer (relative risk (RR) = 1.09, 95% CI = 0.89–1.34) [Boffetta et al., 2002a]. Exposure–response analyses for the subgroup of workers only employed in paving with modeled quantitative estimates of bitumen fume exposure showed increasing lung cancer mortality with increasing career-average exposure (with and without a 15 year lag) and unlagged cumulative exposure, but not with lagged cumulative exposure. Analyses (for all workers) with semi-quantitative exposure estimates showed no positive association [Boffetta et al., 2003a,b].

Smoking is the most important potential confounding factor for any association of lung cancer with occupational exposures. However, direct information on smoking habits was not available from all national cohorts, and, therefore, the association between bitumen exposure and lung cancer risk could not be corrected for potential differences in smoking habits. Smoking habits were available for some of the national cohorts in the IARC study [Kauppinen et al., 2003; Randem et al., 2003] including the Dutch cohort. The current article describes evaluation of possible confounding by smoking in the Dutch cohort.

METHODS

Population

Data for the Dutch cohort were collected in six companies involved in asphalt production and road construction. These companies were selected from a pilot-study on availability and quality of historical employee records. Personnel records were available since 1969–1984. The first date of employment was in 1927, the last worker entered the cohort in 1998. End of cohort enumeration was August 30, 1999, except for one company where employment ended due to reorganization on January 1, 1999. The total number of identified subjects was 6,171 workers. Eleven subjects were excluded because of missing date of birth and eight subjects were excluded because of missing dates of start of employment. Follow-up for mortality was completed until 31 December, 1999. Vital status of workers, who left employment before 1995, was ascertained through community registers. For workers employed after 1995, records of the Social Security and Pension Fund for Building and Construction Workers were used. At the end of follow-up, 5,285 subjects (86%) were known to be alive, 664 (11%) had died, 39 (1%) had emigrated, and 164 (3%) were lost to follow-up.

Exposure Assessment

For each worker, detailed information was abstracted from the personnel files about date of start of employment, date of end of employment, and positions held. Employment records were coded according to a protocol for the international study. The main job classes were: (1) asphalt road paving and production, (2) building or ground construction, (3) unspecified worker (mainly foremen and unspecified blue-collar worker), (4) office, administration, and management, and (5) unknown. A substantial part of the workers (46%) was coded only as unspecified worker, because the information extracted on the job held was not sufficient to code them more specifically. For analyses based on job classes, subjects were classified as subjects who *ever* worked in asphalt road paving or production (further referred to as ''asphalt workers''), subjects who *only* worked in building or ground construction, subjects who *only* worked as unspecified worker, and lastly others.

From each company, a questionnaire was obtained with information on temporal changes in production characteristics and work organization. Coal tar had been used in the past in five companies, the last year of coal tar use varied between 1969 and 1990. Mastic asphalt was occasionally applied in three companies, but mastic workers were usually not coded with a separate job-title. The duration of the working season differed from 8 to 12 months per year between job classes and companies.

A Road Construction Workers' Exposure Matrix (ROCEM) was constructed based on statistical modeling of 2,007 exposure measurements gathered in the participating countries [Burstyn et al., 2000], expert assessment of relative exposure intensities, and information on determinants of exposure obtained from company questionnaires. The ROCEM estimates the exposure to bitumen fume and other relevant exposures based on calendar period, country, company, and job. Semi-quantitative exposure estimates of intensity of bitumen fume for workers in all job classes were based on the combination of statistical models and expert evaluation of relative exposure intensities between different working conditions. Results on semi-quantitative exposure to bitumen fume are expressed in exposure intensity units. Quantitative estimates were computed for workers only employed in road paving [Burstyn et al., 2003]. In the Dutch cohort, analyses with quantitative estimates were not meaningful due to small numbers.

Exposed subjects were divided into quartiles, each including approximately one fourth of the lung cancer deaths in the international cohort. For national analyses, we used the same cut points to permit a direct comparison.

Cohort Restrictions

Several differences exist between the current cohort and the Dutch component in the analyses performed by IARC [Boffetta et al., 2001]. An update of the cohort removed two duplicate subjects and one female subject, and decreased the number of subjects lost to follow-up from 393 to 164. Improvements in cohort definition caused a decrease in total number of person years. For 498 workers from two companies, there was no information on job-histories from date of first employment to entry into the cohort (respectively, 1974 and 1970). At IARC these periods were removed and date of first employment was set at date of entry in cohort. We coded these periods with unknown job class and assumed exposure to bitumen fume was equal to the mean exposure of all job classes in corresponding time periods. This caused a shift of 41 workers (seven observed deaths, one case of lung cancer) from job class ‘‘only employed in building or ground construction’’ to ‘‘other.’’

The analyses were restricted to workers who had at least one full season of employment (n = 3,714 subjects (60%)). Table I shows vital status and employment characteristics. Most of the excluded short-term workers with less than one season of employment were employed as unspecified blue-collar workers (n = 1,154), student trainees (n = 428), or holiday workers (n = 180).

Smoking Habits

Workers in the Dutch construction industry are regularly invited for a voluntary medical evaluation. These evaluations are carried out by regional occupational health services. As part of the medical examination, subjects are asked to fill in a self-administered questionnaire on health and working conditions. Results of these questionnaires have been available in electronic files since 1993. The overall response rate is ~50%. Response rates vary 2% between different sectors within the construction industry.

Subjects could be identified in the questionnaire database by their social-fiscal identification number. For 5,392 subjects (87%) this identification number was available, 1,533 (25%) subjects could be linked, and 1,191 (19%)

TABLE I. Vital Status and Employment Characteristics for 3,714 Subjects With at Least One Season of Employment, in a Dutch Cohort of Workers From Road-Construction Companies, 1969–1999

	Entire cohort	Known smoking habits	Unknown smoking habits
Number of workers	3,714	1,138 (31%)	2,576 (69%)
Person years	63,140	16,835	46,305
Vital status			
Alive	3,181 (86%)	1,128 (99%)	2,053 (80%)
Dead	470 (13%)	9 (1%)	461 (18%)
Emigrated	15 (0%)	1 (0%)	14 (1%)
Lost to follow-up	48 (1%)	0	48 (2%)
Age at first employment (years)			
Before 20	523 (14%)	171 (15%)	352 (14%)
20–29	1,527 (41%)	544 (48%)	983 (38%)
30–39	844 (23%)	265 (23%)	579 (22%)
40 or more	820 (22%)	158 (14%)	662 (26%)
Year of first employment			
Before 1975	1,328 (36%)	229 (20%)	1,099 (43%)
1975–1984	1,223 (33%)	346 (30%)	877 (34%)
1985 or later	1,163 (31%)	563 (49%)	600 (23%)
Duration of employment (years)			
0–4	1,886 (51%)	391 (34%)	1,495 (58%)
5–9	703 (19%)	261 (23%)	442 (17%)
10–14	425 (11%)	181 (16%)	244 (9%)
15–19	260 (7%)	112 (10%)	148 (6%)
20 or more	440 (12%)	193 (17%)	247 (10%)
Time since first employment (years)			
0–9	748 (20%)	314 (28%)	434 (17%)
10–19	1,114 (30%)	423 (37%)	691 (27%)
20–29	1,318 (36%)	310 (27%)	1,008 (39%)
30 or more	534 (14%)	91 (8%)	443 (17%)

subjects were included in the analyses. Smoking status (never, former, or current smoker) was ascertained for 1,138 workers (Table II). If a subject filled in multiple questionnaires from several medical surveys, the most recent one was used in our analyses.

The following items were included in the questionnaire about tobacco smoking habits: ever smoking (yes/no), currently smoking (yes/no), amount smoked per day (for cigarettes, hand-rolled cigarettes, or small cigars: less than 10 (light smoker), 10–20 (moderate), or more than 20 (heavy), and for pipes or cigars: less than 5 (light smoker), 5–10 (moderate), or more than 10 (heavy)), for former smokers: time since quitting smoking (last year, 1–5, or more than 5 years ago), and duration of smoking (less than 1, 1–5, 5–10, 10–20 years, or more than 20 years). We aggregated data to define semi-quantitative categories for smoking consumption, taking into account both cigarette and pipe/cigar smoking: (1) light smokers (light cigarette smoker and light pipe/cigar smoker), (2) moderate smokers (moderate cigarette smoker and light pipe/cigar smoker, or light cigarette smoker and moderate pipe/cigar smoker), and (3) heavy smokers (moderate cigarette smoker and moderate pipe/cigar smoker, or heavy cigarette smoker, or heavy pipe/cigar smoker).

Statistical Analyses

Causes of death for subjects deceased before 1996 were converted from the eighth to the ninth revision code of the International Classification of Diseases (ICD), according to a table prepared at IARC. Lung cancer was defined as cancer of trachea, bronchus, and lung, ICD (9)-code 162.

Person-years at risk were calculated using a SAS program developed at IARC [SAS Institute, Inc., 1996]. SMRs were calculated to compare mortality to the general population. Expected numbers of deaths were calculated using age-, calendar year, and gender-specific mortality rates for The Netherlands, obtained by the World Health Organization mortality databank. Ninety-five percent CIs based on Poisson distribution, were calculated using Byar's approximation when the observed number of deaths exceeded 30.

TABLE II. Smoking Habits of 3,714 Subjects With at Least One Season of Employment, in a Dutch Cohort of Workers From Road-Construction Companies, 1969–1999

		Known smoking status			
	Smoking status unknown	Never smoker	Former smoker	Current smoker	Total
Job class					
Ever in asphalt road paving or mixing	317 (12%)	47 (21%)	71 (32%)	106 (47%)	541 (15%)
Only building/ground construction	416 (16%)	71 (28%)	80 (32%)	99 (40%)	666 (18%)
Only unspecified worker	1,199 (47%)	106 (23%)	138 (31%)	208 (46%)	1,651 (44%)
Other	644 (25%)	66 (31%)	66 (31%)	80 (38%)	856 (23%)
Duration of bitumen exposure (years)					
Non-exposed	206 (8%)	44 (35%)	37 (29%)	45 (36%)	332 (9%)
$>$ 0–1.8	628 (24%)	29 (26%)	21 (19%)	60 (55%)	738 (20%)
$\geq$ 1.8–4.6	592 (23%)	36 (22%)	52 (32%)	73 (45%)	753 (20%)
$\geq$ 4.6–9.9	402 (16%)	53 (28%)	50 (26%)	88 (46%)	593 (16%)
$\geq$ 9.9	460 (18%)	78 (23%)	125 (37%)	138 (40%)	801 (22%)
Unknown	288 (11%)	50 (24%)	70 (33%)	89 (43%)	497 (13%)
Semi-quantitative cumulative bitumen exposure (units $\times$ years)					
Non-exposed	206 (8%)	44 (35%)	37 (29%)	45 (36%)	332 (9%)
$>$ 0–3.87	1,027 (40%)	85 (28%)	76 (25%)	142 (47%)	1,330 (36%)
$\geq$ 3.87–10.05	462 (18%)	59 (28%)	57 (27%)	97 (46%)	675 (18%)
$\geq$ 10.05–26.83	342 (13%)	40 (21%)	76 (41%)	71 (38%)	529 (14%)
$\geq$ 26.83	251 (10%)	12 (12%)	39 (39%)	49 (49%)	351 (10%)
Unknown	288 (11%)	50 (24%)	70 (33%)	89 (43%)	497 (13%)
Semi-quantitative average bitumen exposure (units)					
Non-exposed	206 (8%)	44 (35%)	37 (29%)	45 (36%)	332 (9%)
$>$ 0–1.29	888 (34%)	155 (27%)	167 (29%)	255 (44%)	1,465 (39%)
$\geq$ 1.29–3.21	1,139 (44%)	39 (18%)	79 (37%)	98 (45%)	1,355 (36%)
$\geq$ 3.21–4.76	44 (2%)	2 (22%)	2 (22%)	5 (56%)	53 (1%)
$\geq$ 4.76	11 (0%)	0	0	1 (100%)	12 (0%)
Unknown	288 (11%)	50 (24%)	70 (33%)	89 (43%)	497 (13%)

For smaller numbers, exact limits were calculated [Breslow and Day, 1987].

Poisson regression analysis was applied for internal comparison of mortality rates, using GLIM [Royal Statistical Society, 1987]. Estimated RRs with 95% CIs were calculated, controlling for age (10 5-year groups), calendar period at end of follow-up (before 1972, 1975–1979, 1980–1984, 1985–1989, and 1990 or later), and duration of employment (1 season—4, 5–9, 10–14, 15-19, and 20 or more years). A test for linear trend was performed by linear regressing of the RRs and taking the exposure variable as a continuous variable, assuming constant differences between exposure categories.

The association between semi-quantitative exposure to bitumen fume and smoking habits was evaluated through multiple regression analysis, using dummy variables for smoking status (never, former, or current smoker) and for four age classes (< 30, 30–39, 40–49, and 50 + years).

We assumed that the distribution of smoking habits for the different job classes or exposure categories in the subcohort with smoking information could be applied to the corresponding job class or exposure category of the entire cohort. This made it possible to estimate the RR for lung cancer due to smoking (assuming a fivefold increased risk for former smokers and a 15-fold increased risk for current smokers), and adjust the observed association between lung cancer and exposure (based either on job classes or semi-quantitative exposure information) for differences in smoking habits. The method of correction has been described earlier [Axelson and Steenland, 1988] by the following equations.

The hazard (incidence or mortality) rate (I) is:

$$I = (\%\text{never}) \times 1 + (\%\text{former}) \times 5 + (\%\text{current}) \times 15 \quad (1)$$

Then the RR for lung cancer due to smoking is:

$$RR_{\text{smoking}} = I_{\text{exposed}} / I_{\text{non-exposed}} \quad (2)$$

And the RR for bitumen exposure, adjusted for smoking is:

$$RR_{\text{exposure, smoking adjusted}} = RR_{\text{exposure}} / RR_{\text{smoking}} \quad (3)$$

RESULTS

Smoking Habits

Compared to the 2,576 workers without smoking information, the mean age at first employment of the 1,138 workers with known smoking habits was lower (28 vs. 32 years) and the mean date of first employment was later (1983 vs. 1976). However, these differences were smaller for asphalt workers (1980 vs. 1977) than for workers in building and ground construction (1983 vs. 1977).

Of workers with known smoking habits, 75% ever smoked. The percentage of ever smokers was higher among asphalt workers (79% ever smoked) and unspecified workers (77% ever smoked) compared to building and ground construction workers (72% ever smoked). This was mainly due to differences in number of current smokers. Among workers in other job classes 69% ever smoked.

These differences in smoking habits were evaluated by logistic regression with building and ground construction workers as reference group. For asphalt workers, the odds ratio (OR) for ever smoking was 1.5 (95% CI = 1.0–2.3). After adjusting for age, the OR_{adjusted} was 1.7 (95% CI = 1.1–2.6). Therefore, age (and therefore birth cohort) did not explain smoking differences between asphalt workers and building/ground construction workers.

Mortality of Smoking-Related Diseases for Different Job Classes

Total mortality for the entire cohort was slightly lower than expected (SMR = 0.98; 95% CI: 0.89–1.07), as is usual in occupational cohorts. The overall SMR for lung cancer was elevated, with borderline statistical significance (SMR = 1.26; 95% CI: 1.00–1.58).

Asphalt workers had a slightly higher increased risk for lung cancer (SMR = 1.24; 95% CI: 0.57–2.36) than building and ground construction workers (SMR = 1.13; 95% CI: 0.54–2.08) (Table III). Unspecified workers had a statistically significant increased risk for lung cancer (SMR = 1.46; 95% CI: 1.00–2.05).

It could be argued that if the increased risk for lung cancer among asphalt workers was due to smoking rather than to exposure to bitumen, mortality ratios for other smoking-related diseases, such as other types of cancer of the airways, non-malignant respiratory diseases, and cardiovascular diseases, would also be elevated. We found elevated risks for cancer of the esophagus (SMR = 3.62; 95% CI: 0.44–13.06), pancreas cancer (SMR = 1.17; 95% CI: 0.03–6.54), bladder cancer (SMR = 1.67; 95% CI: 0.04–9.29), and non-malignant respiratory diseases (SMR = 2.27; 95% CI: 0.98–4.48). However, the risk for diseases of the circulatory system was statistically significantly decreased (SMR = 0.50; 95% CI: 0.25–0.90). There were no cases of cancer of the larynx.

An internal comparison group is preferred to the national population, because of potential confounding by socio-economic status, which is often related to smoking habits [Steenland et al., 1984]. When comparing asphalt workers to building and ground construction workers, they showed lower risks for total mortality (RR = 0.84; 95% CI: 0.56–1.25), and cancer mortality (RR = 0.95; 95% CI: 0.51–1.78). The RR for lung cancer mortality was increased (RR = 1.04; 95% CI: 0.41–2.61). Using the information on smoking habits in Table II, the estimated RR for lung cancer among

TABLE III. Standardized Mortality Ratio's for Selected Causes of Death by Job Class for 3,714 Subjects With at Least One Season of Employment, in a Dutch Cohort of Workers From Road-Construction Companies, 1969–1999

Cause of death	Ever asphalt				Only building/ground construction				Only unspecified				Other			
(ICD codes)	Obs	Exp	SMR	(95%-CI)	Obs	Exp	SMR	(95%-CI)	Obs	Exp	SMR	(95%-CI)	Obs	Exp	SMR	(95%-CI)
All causes	49	57.87	0.84	(0.63–1.12)	67	71.12	0.94	(0.73–1.20)	178	177.77	1.00	(0.86–1.16)	176	173.16	1.02	(0.87–1.18)
All malignant neoplasms (140–208)	22	19.18	1.15	(0.72–1.73)	25	23.54	1.06	(0.69–1.57)	67	59.26	1.13	(0.88–1.44)	61	57.17	1.07	(0.82–1.37)
Esophagus (150)	2	0.55	3.62	(0.44–13.06)	0	0.69	0.00	—	2	1.67	1.20	(0.14–4.32)	1	1.47	0.68	(0.02–3.79)
Pancreas (157)	1	0.85	1.17	(0.03–6.54)	4	1.06	3.78	(1.03–9.68)	4	2.64	1.52	(0.41–3.88)	3	2.54	1.18	(0.24–3.45)
Larynx (161)	0	0.20	0.00	—	1	0.25	4.03	(0.10–22.45)	2	0.60	3.31	(0.40–11.96)	0	0.56	0.00	—
Trachea, bronchus, and lung (162)	9	7.24	1.24	(0.57–2.36)	10	8.84	1.13	(0.54–2.08)	33	22.65	1.46	(1.00–2.05)	25	22.23	1.12	(0.73–1.66)
Bladder (188)	1	0.60	1.67	(0.04–9.29)	1	0.72	1.39	(0.04–7.72)	1	1.89	0.53	(0.01–2.95)	5	1.97	2.53	(0.82–5.91)
Diseases of circulatory system (390–459)	11	21.88	0.50	(0.25–0.90)	20	27.05	0.74	(0.45–1.14)	69	68.21	1.01	(0.79–1.28)	74	69.57	1.06	(0.84–1.34)
Diseases of respiratory system (460–519)	8	3.52	2.27	(0.98–4.48)	3	4.15	0.72	(0.15–2.11)	7	11.15	0.63	(0.25–1.29)	10	12.73	0.79	(0.38–1.45)

asphalt workers was adjusted for smoking and became smaller ($RR_{smoking\ adjusted} = 0.92$) (Table IV).

Modeled Semi-Quantitative Exposures

The distribution of non-smokers, former smokers, and current smokers was more or less equally distributed among non-exposed subjects (Table II). Figure 1 shows the plotted values of semi-quantitative cumulative exposure to bitumen fume by smoking categories. For current smokers, distinction was made for amount of smoking. Mean log (ln) transformed cumulative exposures for former smokers ($\beta = 0.68$, $P < 0.01$) and for current smokers ($\beta = 0.38$, $P < 0.01$) were statistically significantly higher compared to non-smokers. After adjusting for age, former smokers had still statistically significant higher exposure levels ($\beta = 0.35$, $P = 0.01$). For current smokers, the regression coefficient was still positive but without statistical significance ($\beta = 0.19$, $P = 0.12$). It suggests that smoking status is positively associated with cumulative exposure, and, therefore, confounding by smoking cannot be excluded. There was also positive association between cigarette consumption and semi-quantitative cumulative exposure. Light smokers ($\beta = 0.30$, $P = 0.09$), moderate smokers ($\beta = 0.45$, $P < 0.01$), and heavy smokers ($\beta = 0.60$, $P < 0.01$) had higher mean exposures compared to never smokers. After adjusting for age, exposure levels were still higher but without statistical significance (light smokers, $\beta = 0.09$, $P = 0.62$; moderate smokers, $\beta = 0.22$, $P = 0.11$; heavy smokers, $\beta = 0.28$, $P = 0.17$). Average exposure indices yielded similar results.

Internal analyses using the non-exposed subjects as reference category showed a positive statistically non-significant association between (semi-quantitative) cumulative bitumen fume exposure and lung cancer risk (Table IV), although the RR for medium exposed subjects was below one. After adjusting for differences in smoking habits, all RRs decreased, but a weak positive association could still be observed. With average exposure, there were no observed cases in the highest exposure category. There was a positive statistically significant ($P = 0.02$) association with mortality from lung cancer. This positive association remained visible after adjusting for smoking, with borderline statistical significance ($P = 0.06$). The RRs for both cumulative and average exposures had wide CIs.

DISCUSSION

We have described results from a Dutch cohort study of workers in asphalt production and road paving, road construction, and building and ground construction. For a sample of the cohort, information on smoking habits was available and it appeared that smoking habits differed slightly between occupational classes. The observed higher mortality from lung cancer among asphalt workers compared

TABLE IV. Relative Risks for Lung Cancer (ICD-9 = 162), With and Without Adjustment for Smoking, for Different Exposure Categories, in a Dutch Cohort of 3,714 Workers With at Least One Season of Employment, 1969–1999

	Obs	RR[a]	(95%-CI)	$RR_{smoking\ adjusted}$[b]
Job class				
Only building or ground construction	10	1.00		1.00
Ever asphalt road paving or mixing	9	1.04	(0.41–2.61)	0.92
Only unspecified blue/white collar	33	1.25	(0.61–2.55)	1.13
Other	25	1.01	(0.47–2.17)	1.05
Duration of bitumen exposure (years)				
Non-exposed	3	1.00		1.00
$>$ 0–1.8	9	1.02	(0.26–4.09)	0.78
$\geq$ 1.8–4.6	18	1.40	(0.37–5.27)	1.16
$\geq$ 4.6–9.9	9	0.64	(0.15–2.77)	0.54
$\geq$9.9	33	2.53	(0.65–9.81)	2.23
(*Test for linear trend*)[c]		(*0.30*)		(*0.35*)
Semi-quantitative cumulative bitumen exposure (units × years)				
Non-exposed	3	1.00		1.00
$>$ 0–3.87	18	1.32	(0.37–4.66)	1.10
$\geq$ 3.87–10.05	18	1.72	(0.48–6.18)	1.46
$\geq$ 10.05–26.83	10	0.82	(0.21–3.13)	0.74
$\geq$ 26.83	23	2.06	(0.59–7.25)	1.57
(*Test for linear trend*)		(*0.39*)		(*0.55*)
Semi-quantitative average bitumen exposure (units)				
Non-exposed	3	1.00		1.00
$>$ 0–1.29	13	1.15	(0.32–4.10)	0.99
$\geq$ 1.29–3.21	52	1.67	(0.51–5.45)	1.36
$\geq$ 3.21–4.76	4	2.12	(0.47–9.64)	1.57
$\geq$ 4.76	0	0.00	(0.00–0.00)	0.00
(*Test for linear trend*)		(*0.02*)		(*0.06*)

[a]Adjusted for age at risk, calendar period, and duration of employment.
[b]Using formulas described under Methods.
[c]*P* value for a test for linear trend.

to other job classes within this industry is therefore somewhat confounded by tobacco smoking. However, the absence of an association with mortality from cardiovascular diseases suggests otherwise. Because the SMR is below one, confounding by smoking seems unlikely or small in magnitude. To evaluate potential confounding more quantitatively, we performed a more detailed analysis using an internal reference group of building and ground construction workers. We found a statistically non-significant increased RR for lung cancer among asphalt workers of 1.04. After adjusting for smoking, this estimate became below 1 ($RR_{smoking\ adjusted} = 0.92$).

The association between modeled semi-quantitative cumulative exposure to bitumen fume and lung cancer mortality is to some extent confounded by smoking as well. The cumulative exposure could be strongly related with years of consumption of cigarettes. These data suggest that a positive association between cumulative exposure and smoking was present. Therefore, part of the increased risk for bitumen fume exposure could be explained by smoking. When ad hoc corrections were applied (using information about the strength of the association between smoking and lung cancer mortality from external studies), the RRs compared to non-exposed workers were reduced, but the positive association remained. These findings suggest that a nested case-control study seeking information on smoking status may be warranted.

To adjust for smoking, assumptions were made on estimates of risks of smoking for lung cancer for former and current smokers. Especially for former smokers, the risk for lung cancer strongly depends on age when quitting smoking, how much smoked before quitting, and how long ago they quit. However, applying higher risk estimates for the association between smoking and lung cancer (tenfold increased risk for former smokers or 20-fold increased risk for current smokers) did not significantly change the results.

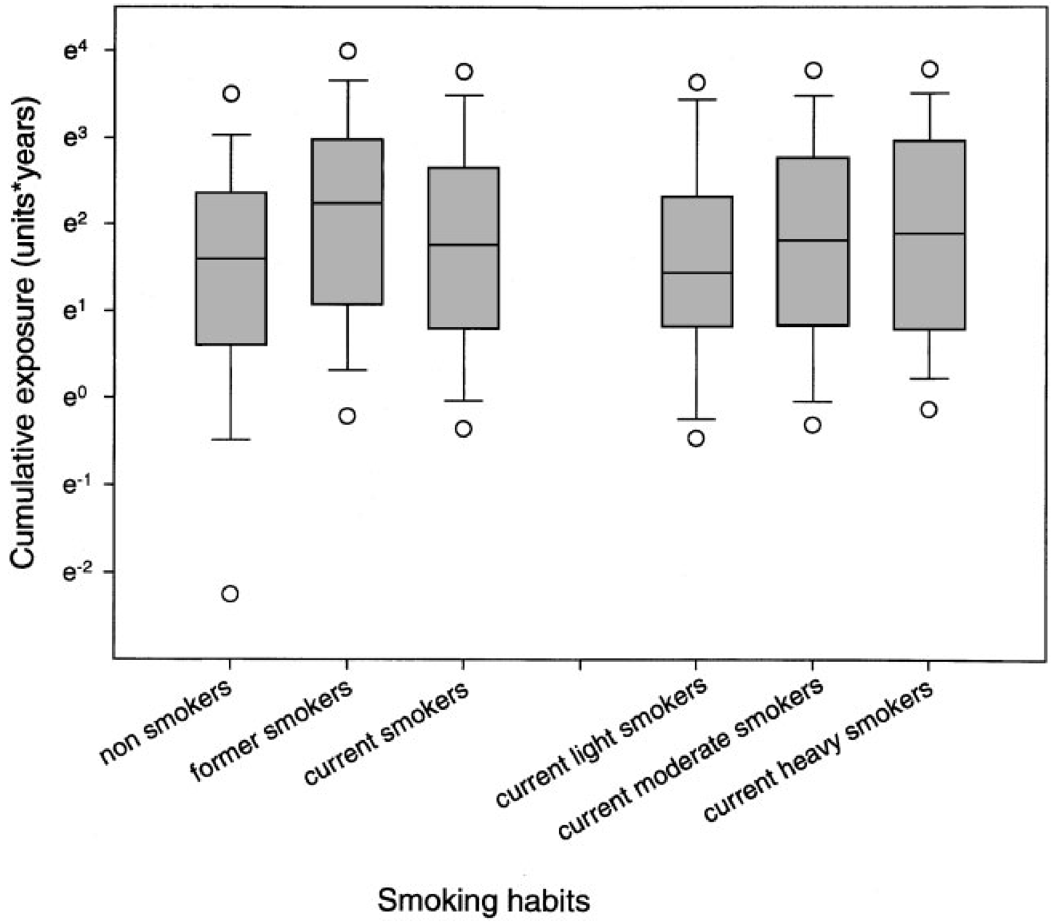

FIGURE 1. Box-plots for modeled semi-quantitative cumulative exposure to bitumen fume by smoking, for 803 exposed subjects with known smoking habit, in a Dutch cohort of workers from road-construction companies, 1969–1999.

The mean semi-quantitative cumulative exposure of former smokers was higher than mean exposure of non-smokers and (although not statistically significant) of current smokers. This could be a time-effect of higher exposures in the past [Burstyn et al., 2003]. However, after adjusting for age, the positive association between smoking habits and cumulative exposure remained.

The sub-cohort of workers for whom smoking habits could be retrieved only included workers employed in 1993 and later. Therefore, when applying distribution of smoking habits to the entire cohort with workers since 1927, bias may have been introduced. We analyzed the complete database of all available medical records of workers from all asphalt road construction and production companies in The Netherlands (9,773 workers). It appeared that 339 workers (3.5%) were classified as non-smoker or unknown smoker according to the information on their last questionnaire, while information at earlier questionnaires showed that they did smoke. This indicates that the number of smokers is probably underestimated. When stratified by year of birth, the number of subjects who ever smoked decreased in time (born before 1940: 85%, 1940–1949: 82%, 1950–1959: 76%, 1960–1969: 81%, and born 1970 or later: 54%). Since older workers were underrepresented in the sub-cohort with smoking habits, this also indicates an underestimation of the number of smokers. Selection bias could also have been introduced since the overall response for the medical survey was only 50%. Only the nested case-control study may allow proper treatment of potential confounding by smoking in this population.

CONCLUSION

Within the Dutch cohort, smoking habits differed between job classes. Therefore, smoking confounded the observed higher mortality from lung cancer for asphalt workers compared to building and ground construction workers, and the association of bitumen fume exposure with lung cancer mortality. However, after adjusting for smoking, the suggested positive association was still present, for cumulative and average (semi-quantitative) exposure.

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REFERENCES

Axelson O, Steenland K. 1988. Indirect methods of assessing the effects of tobacco use in occupational studies. Am J Ind Med 13:105–118.

Boffetta P, Burstyn I, Partanen T, Kromhout H, Svane O, Langård S, Järvholm B, Frentzel-Beyme R, Kauppinen T, Stücker I, Shaham J, Heederik D, Ahrens W, Bergdahl I, Cenée S, Ferro G, Heikkilä P, Hooiveld M, Johansen C, Randem B, Schill W. 2001. IARC epidemiological study of cancer mortality among European asphalt workers (IARC Internal Report No. 01/003). Lyon: International Agency for Research on Cancer.

Boffetta P, Burstyn I, Partanen T, Kromhout H, Svane O, Langård S, Järvholm B, Frentzel-Beyme R, Kauppinen T, Stücker I, Shaham J, Heederik D, Ahrens W, Bergdahl I, Cenée S, Ferro G, Heikkilä P, Hooiveld M, Johansen C, Randem B, Schill W. 2003a. Cancer mortality among European asphalt workers: An international epidemiological study. I. Results of the analysis based on job titles. Am J Ind Med 43:18–27 [this issue].

Boffetta P, Burstyn I, Partanen T, Kromhout H, Svane O, Langård S, Järvholm B, Frentzel-Beyme R, Kauppinen T, Stücker I, Shaham J, Heederik D, Ahrens W, Bergdahl I, Cenée S, Ferro G, Heikkilä P, Hooiveld M, Johansen C, Randem B, Schill W. 2003b. Cancer mortality among European asphalt workers: An international epidemiological study. II. Results on exposure to bitumen fume and other agents. Am J Ind Med 43:28–39 [this issue].

Breslow NE, Day NE, editors. 1987. Statistical methods in cancer research. Vol. II—The design and analysis of cohort studies. Lyon, France: International Agency for Research on Cancer.

Burstyn I, Kromhout H, Kauppinen T, Heikkilä P, Boffetta P. 2000. Statistical modeling of the determinants of historical exposure to bitumen and polycyclic aromatic hydrocarbons among paving workers. Ann Occup Hyg 44:43–56.

Burstyn I, Boffetta P, Kauppinen T, Heikkilä P, Svane O, Partanen T, Stücker I, Frentzel-Beyme R, Ahrens W, Merzenich H, Heederik D, Hooiveld M, Langård S, Randem B, Järvholm B, Bergdahl I, Shaham J, Ribak J, Kromhout H. 2003. Estimating exposures in asphalt industry for an international epidemiological cohort study of cancer risk. Am J Ind Med 43:3–17 [this issue].

Kauppinen T, Heikkilä P, Partanen T, Virtanen SV, Pukkala E, Ylöstalo P. 2003. Mortality of workers in Finnish road paving companies. Am J Ind Med 43:49–57 [this issue].

Randem BG, Langård S, Dale I, Kongerud J, Martinsen JI, Andersen A. 2003. Cancer incidence among male Norwegian asphalt workers. Am J Ind Med 43:88–95 [this issue].

Royal Statistical Society. 1987. The GLIM system release 3.77. Oxford, United Kingdom: Numerical Algorithms Group Limited.

SAS Institute, Inc. 1996. SAS Version 6.12. Cary, NC: SAS Institute, Inc.

Steenland K, Beaumont J, Halperin W. 1984. Methods of control for smoking in occupational cohort mortality studies. Scand J Work Environ Health 10:143–149.