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Mortality from Obstructive Lung Diseases and Exposure to Polycyclic Aromatic Hydrocarbons among Asphalt Workers

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Work in the asphalt industry has been associated with nonmalignant respiratory morbidity and mortality, but the evidence is not consistent. A historical cohort of asphalt workers included 58,862 men (911,209 person-years) first employed between 1913 and 1999 in companies applying and mixing asphalt in Denmark, Finland, France, Germany, Israel, the Netherlands, and Norway. The relations between mortality from nonmalignant respiratory diseases (including the obstructive lung diseases: chronic bronchitis, emphysema, and asthma) and specific chemical agents and mixtures were evaluated using a study-specific exposure matrix. Mortality from obstructive lung diseases was associated with the estimated cumulative and average exposures to polycyclic aromatic hydrocarbons and coal tar (p values of the test for linear trend = 0.06 and 0.01, respectively). The positive association between bitumen fume exposure and mortality from obstructive lung diseases was weak and not statistically significant; confounding by simultaneous exposure to coal tar could not be excluded. The authors lacked data on smoking and full occupational histories. In conclusion, exposures to polycyclic aromatic hydrocarbons, originating from coal tar and possibly from bitumen fume, may have contributed to mortality from obstructive lung diseases among asphalt workers, but confounding and bias cannot be ruled out as an explanation for the observed associations.

asthma; benzo(a)pyrene; bronchitis; coal tar; cohort studies; emphysema; polycyclic hydrocarbons, aromatic

Abbreviations: ICD-9, *International Classification of Diseases,* Ninth Revision; PAH, polycyclic aromatic hydrocarbon; ROCEM, Road Construction Workers' Exposure Matrix.

There is a concern about past and present health risks posed by occupational exposures in the asphalt industry, but the evidence for specific exposure-disease associations in the industry is equivocal. The primary chemical mixture of interest in the studies of health hazards in the industry is bitumen, a distillation product of crude oil. Bitumen can be combined with coal tar to form a binder for asphalt (binder plus filler of sand and/or gravel). In Western Europe, coal tar use has largely been discontinued in the asphalt industry. A more in-depth description of the asphalt industry and associated patterns of exposure can be found elsewhere (1, 2).

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Fumes are emitted when hot asphalt is applied to surfaces during paving. During that process, exposures to small particles (3–5) containing polycyclic aromatic hydrocarbons (PAHs) occur (1, 5). Such particle-bound PAH exposure has been associated with increases in respiratory morbidity and mortality in several different environments: diesel exhaust (6), coke oven fumes (7, 8), and environmental air pollution (9, 10). Nonetheless, the agents responsible for these health effects have not been identified, because in these environments persons are exposed to different complex mixtures rather than to pure substances. At the same time, particle-bound PAHs and their oxygenated derivatives have been shown to exert proinflammatory and tissue-damaging effects, possibly contributing to respiratory morbidity and mortality (11, 12). These toxic effects are thought to be mediated by macrophages and epithelial cells in the respiratory tract, and they arise through the generation of reactive oxygen species (12–14). Exposures to both PAHs and their oxygenated derivatives occur in work with coal tar (15) and, to a lesser extent, pure bitumen (16).

There is some prior indication that exposures in the asphalt industry may contribute to mortality and morbidity from nonmalignant respiratory diseases. A nonsignificant excess of mortality from bronchitis, emphysema, and asthma was reported among 679 Danish mastic asphalt workers heavily exposed to bitumen fumes and PAHs (17). However, the study (17) suffered from serious limitations and revealed elevated standardized mortality ratios for causes of death not likely to be related to PAHs (18). Highway maintenance workers in California were reported to have an excess mortality from emphysema (eight cases observed vs. 3.2 expected (19)), but this excess could not be attributed to any specific exposure. Registry-based studies showed for US roofers, who have been exposed to both coal tar and bitumen fumes, a twofold increase in risk of death from nonmalignant respiratory diseases (20, 21). Other studies of mortality among asphalt workers did not uncover elevated risks for obstructive lung diseases (2). Respiratory symptoms, including those indicative of chronic bronchitis, have been associated with exposure to bitumen fume in several cross-sectional studies (22–25), but these studies did not adequately control for confounding by smoking and tended to have low power. Overall, evidence to date does not consistently link work in the asphalt industry to elevated risk of nonmalignant respiratory diseases.

The International Agency for Research on Cancer assembled a historical international cohort of employees from the asphalt industry. The analysis presented in this paper investigates mortality from nonmalignant respiratory diseases and its relation with occupational PAH exposure. (The issue of bitumen fume exposure and cancer mortality in the cohort has been addressed elsewhere (26, 27).)

MATERIALS AND METHODS

Study population

A detailed description of the cohort can be found elsewhere (26, 28). In the current analysis, we included 58,862 male workers first employed between 1913 and 1999 in 217 companies applying and mixing asphalt in seven countries: Denmark, Finland, France, Germany, Israel, the Netherlands, and Norway. Oil refineries, sites where bitumen is distilled from crude oil, were excluded from the study. In comparison with the previous report (26), the study population in this report excluded workers in the asphalt industry from Sweden, for whom quantitative exposure estimates for PAHs were much less precise than for other national cohorts. In this study population, there were 12,367 persons who were employed only in asphalt paving and for whom quantitative exposure estimates for PAH and bitumen fume were available (analyzed separately, see below). There were 36,831 persons in a subcohort never exposed to coal tar. The procedures for identification of suitable companies varied in the participating countries, as did the number and average size of the companies included in the study. The basic requirement for the inclusion of a company in the study was the availability of a complete retrospective employee roster during the enrollment period. Personal identifiers and employment histories of workers were abstracted from company records. A minimal duration of employment for inclusion in the cohort was one work season, as reported by companies in a questionnaire that described production characteristics (see below). The inclusion criterion was applied because short-term workers may differ in their occupational and nonoccupational risk factors from long-term employees (29). Once a company had been selected for the study, efforts were made to enroll all manual workers.

Occupational histories were coded on the basis of information from personnel records according to classifications of jobs constructed for the study. A "job" in this classification scheme represented the primary activity of a worker in a given time period (e.g., asphalt paving or employment at an asphalt-mixing plant), but it does not reflect the specific tasks performed. These job classes formed the basis for the linkage between employment histories and the study-specific exposure matrix: the Road Construction Workers' Exposure Matrix (ROCEM, see below). Complete individual occupational histories in the target companies were available for all cohort members.

Mortality follow-up

A follow-up for mortality, in which data were obtained on the primary causes of death, was conducted in all the participating countries (26, 30–36). Subjects were followed beyond the period of employment in the companies studied. Data on the contributing or underlying causes of death were not available. The earliest follow-up started in 1953, and the latest ended in 2000. The average duration of follow-up was 17 years (standard deviation, 8 years). These data were similar for all the groups of workers and all the countries. The cohort accumulated 911,209 person-years of observation. Persons who were employed only in asphalt paving accumulated 189,484 person-years of observations. The subcohort never exposed to coal tar in the companies studied accumulated 529,067 person-years of observation. The loss to follow-up was 0.9 percent; an additional 0.3 percent of the total cohort members emigrated during the follow-up.

Causes of death were coded according to the *International Classification of Diseases*, Ninth Revision (ICD-9). Mortality from nonmalignant respiratory diseases was identified by ICD-9 codes 460–519. Mortality from chronic bronchitis, emphysema, and asthma (ICD-9 codes 490–493) was collectively classified as arising from obstructive lung diseases. Because of the poor ability of death certification in Europe to discriminate between asthma (ICD-9 code 493) and chronic obstructive pulmonary disease (chronic bronchitis and/or emphysema, ICD-9 codes 490–492) (37, 38), no distinction was made in the current analysis between mortality from asthma and chronic obstructive pulmonary disease.

Exposure assessment

We estimated exposures to bitumen fume, coal tar, benzo[*a*]pyrene (marker for four- to six-ring PAHs), diesel exhaust, respirable silica, and asbestos in the cohort (39). These agents cover the major occupationally occurring chemicals and mixtures to which asphalt workers can be exposed (1). Exposures were reconstructed by using 1) information about changes in the production characteristics in each company over time, 2) the relations between production characteristics and exposure levels, and 3) job histories.

We gathered information about the companies enrolled in the study through a company questionnaire that ascertained temporal changes in the production characteristics and work organization. Among the production characteristics, the questionnaire ascertained the type of materials used (e.g., coal tar, asbestos), the asphalt application methods (e.g., mastic laying, hot mix paving), and the average time spent handling these materials or utilizing existing paving methods. The questionnaire was administered to knowledgeable company representatives. Questionnaires were checked for errors, omissions, and inconsistencies, and responses were entered into a common database. Experts from each country checked the quality of the company questionnaires and supplemented them, when required.

Quantitative estimates of exposure to bitumen fume and benzo[*a*]pyrene were obtained only for workers employed in road paving. Most of the personal exposure measurements from asphalt companies (in countries enrolled in the cohort), collected between the late 1960s and 1997, were assembled into a single database (40). The following contextual information was coded for each exposure measurement: job (using a classification similar to what was used in the company questionnaire), production characteristics within a job (using a classification similar to what was used in the company questionnaire), repeated measurements for a worker, and country. Quantitative exposure assessment was restricted to one job (road paving), and we attempted to correct for between-country differences but discovered that there were no systematic differences among countries that cannot be explained by the time period, type of paving, materials used, and exposure monitoring methods.

Analyzing the relations between measured exposure concentrations and contextual information identified determinants of exposure. Thus, we constructed mixed-effects models, with production characteristics as fixed effects and repeated measurements on a worker as random effects, to support quantitative exposure assessment to bitumen fume and benzo[*a*]pyrene among road pavers (41, 42). Use of coal tar was the strongest determinant of exposure to PAHs and benzo[*a*]pyrene. We demonstrated that, although the use of coal tar (yes/no) accounted for 20 percent of the variability in benzo[*a*]pyrene concentrations, there was still an independent relation between the total organic fume levels and benzo[*a*]pyrene concentrations (41). The time period, mastic laying, repaving, surface dressing, and oil-gravel paving were significant determinants of exposures to both bitumen fume and benzo[*a*]pyrene. The models were judged to be sufficiently valid for relative ranking of exposures in the epidemiologic study (43). We used the mixed-effects models of exposure to predict exposure levels for production conditions described by the company questionnaires, thereby producing modeled quantitative exposure intensity estimates in ROCEM (39).

A similar algorithm was developed for semiquantitative exposure assessment for all workers and agents (39). Semiquantitative exposure estimates were calculated on the basis of assumptions about the relative exposure intensities between different jobs for each agent (e.g., the same bitumen fume exposure intensity during hot mix paving and asphalt mixing) that were developed by the authors in consultation with industry representatives. Company questionnaires provided information on whether a given job was performed and what materials were used in a particular time period. Some of the elements of the statistical models described above, such as declining time trends, were incorporated into the semiquantitative exposure assessment. However, in their simplest form, semiquantitative exposure estimates simply reflected the proportion of time that such materials as coal tar and asbestos were reported to have been used or the proportion of vehicles that were powered by diesel (diesel exhaust exposure index).

All exposure estimates in ROCEM were standardized to an 8-hour work shift, using information on the average work shift duration reported in company questionnaires. The resulting exposure matrix was time period, company, and job class specific. According to the exposure matrix, asphalt pavers were not exposed to asbestos; subgroups of asphalt pavers possibly exposed to different concentrations of respirable silica could not be identified. In ROCEM, jobs with a high PAH exposure also tended to have a high bitumen fume exposure ($r = 0.96$, $p < 0.0001$, semiquantitative exposure scores; $r = 0.93$, $p < 0.0001$, quantitative exposure estimates). The second main source of PAH exposure was coal tar, as witnessed by the correlation ($r = 0.46$, $p < 0.0001$) of semiquantitative exposure scores for PAHs and coal tar in ROCEM, the strongest correlation of coal tar exposure estimates to that of any other agent. For example, the correlation between exposure scores for coal tar and bitumen fume in ROCEM was 0.34 ($p < 0.0001$).

Exposure indices

In the analyses with ROCEM-based estimates of exposure, we derived the following indices of exposure: 1) duration, 2) cumulative exposure (product of exposure duration and

TABLE 1. Exposure to four- to six-ring polycyclic aromatic hydrocarbons and mortality from nonmalignant respiratory disease in an International Agency for Research on Cancer-assembled cohort of asphalt workers first employed between 1913 and 1999

Exposure index, population	Exposure metric	Exposure group	Diseases of the respiratory system (ICD-9* codes 460–519)			Bronchitis, emphysema, and asthma (ICD-9 codes 490–493)		
			Observed deaths	RR*,†	95% CI*	Observed deaths	RR†	95% CI
Semiquantitative indices‡	Exposure duration§	Not exposed	80	1.00		34	1.00	
		>0–<1.59	88	1.33	0.89, 1.97	55	1.69	0.93, 3.08
		1.59–<3.84	92	1.19	0.80, 1.77	48	1.26	0.68, 2.32
		3.84–<8.45	90	1.32	0.90, 1.92	57	2.05	1.13, 3.70
		≥8.45	93	1.23	0.86, 1.75	27	0.61	0.33, 1.13
		p value, trend		0.24			0.67	
	Cumulative exposure¶	Not exposed	80	1.00		34	1.00	
		>0–<18.00	97	0.94	0.67, 1.33	46	0.77	0.46, 1.28
		18.00–<47.86	91	1.32	0.94, 1.85	51	1.18	0.72, 1.94
		47.86–<99.02	89	1.77	1.26, 2.48	42	1.32	0.79, 2.20
		≥99.02	86	1.25	0.90, 1.76	48	1.23	0.74, 2.02
		p value, trend		0.01			0.06	
	Average exposure#	Not exposed	80	1.00		34	1.00	
		>0–<6.01	106	0.94	0.67, 1.32	41	0.70	0.42, 1.19
		6.01–<10.20	79	1.48	1.06, 2.06	39	1.35	0.82, 2.23
		10.20–<28.39	94	1.33	0.95, 1.85	50	1.14	0.69, 1.88
		≥28.39	84	1.87	1.27, 2.76	57	1.64	0.96, 2.81
		p value, trend		<0.001			<0.001	
Quantitative indices, pavers only	Cumulative exposure**	>0–<233	27	1.00		11	1.00	
		233–<624	28	1.36	0.78, 2.38	14	1.55	0.68, 3.54
		624–<1,414	29	2.24	1.20, 4.17	16	2.97	1.25, 7.07
		≥1,414	28	2.94	1.32, 6.55	12	4.06	1.35, 12.19
		p value, trend		<0.001			<0.001	
	Average exposure††	>0–<90	32	1.00		8	1.00	
		90–<128	25	1.43	0.82, 2.48	12	2.68	1.05, 6.81
		128–<254	27	1.27	0.70, 2.30	12	1.77	0.66, 4.73
		≥254	28	1.52	0.80, 2.88	21	2.67	1.01, 7.03
		p value, trend		0.22			0.08	

* ICD-9, *International Classification of Diseases*, Ninth Revision; RR, relative risk; CI, confidence interval; PAH, polycyclic aromatic exposure.
† Model adjusted for country, calendar period, age, and duration of employment.
‡ All workers.
§ Years.
¶ PAH units × years.
# PAH units.
** Benzo[*a*]pyrene (ng/m^3) × years.
†† Benzo[*a*]pyrene (ng/m^3).

intensity, integrated over work history), and 3) average exposure over the work history (ratio of cumulative exposure to duration of exposure). The estimates of duration of exposure were corrected for differences in duration of the working season between companies and countries. For each semiquantitative exposure index, unexposed subjects formed a separate reference category, and exposed subjects were divided into quartiles, each including approximately one fourth of the deaths from all nonmalignant respiratory diseases. Quantitative exposure indices were available for workers employed only in asphalt paving, all of whom were exposed to bitumen fume, and PAHs. Therefore, for quantitative exposure indices, there was no nonexposed group for bitumen fume and PAHs; the lowest exposure group was used as a reference in exposure response analyses. (Workers not exposed to PAH and bitumen fume were not used as a reference in the analyses with quantitative exposure indices, because we wanted to increase the chance that the reference groups did not differ in terms of confounders from exposed subjects. The majority of workers not exposed to these agents were employed in building or ground construction, where exposures to respirable silica, asbestos, and diesel exhaust were likely to be higher than those observed in asphalt paving.)

Exposure-response analyses

Relative risks and their associated 95% confidence intervals were estimated using Poisson regression (44). All Poisson regression models included an exposure index for

TABLE 2. Exposure to coal tar in all jobs and mortality from nonmalignant respiratory diseases in an International Agency for Research on Cancer-assembled cohort of asphalt workers first employed between 1913 and 1999

Exposure index	Exposure group	Diseases of the respiratory system (ICD-9* codes 460–519)			Bronchitis, emphysema, and asthma (ICD-9 codes 490–493)		
		Observed deaths	RR*,†	95% CI*	Observed deaths	RR†	95% CI
Exposure duration (years)	Not exposed	216	1.00		87	1.00	
	>0–<1.25	52	1.48	1.04, 2.10	34	1.62	1.02, 2.56
	1.25–<2.36	51	1.51	1.06, 2.15	32	1.60	1.00, 2.54
	2.36–<4.51	52	1.36	0.96, 1.93	30	1.38	0.86, 2.22
	≥4.51	58	0.98	0.69, 1.38	34	1.32	0.81, 2.14
	p value, trend		0.58			0.19	
Cumulative exposure (coal tar units × years)	Not exposed	216	1.00		87	1.00	
	>0–<0.48	64	0.94	0.69, 1.30	34	1.10	0.70, 1.71
	0.48–<0.83	49	2.00	1.39, 2.87	29	1.97	1.22, 3.20
	0.83–<1.91	51	1.50	1.04, 2.14	33	1.63	1.02, 2.61
	≥1.91	49	1.41	0.97, 2.04	34	1.77	1.09, 2.87
	p value, trend		0.01			0.01	
Average exposure (coal tar units)	Not exposed	216	1.00		87	1.00	
	>0–<0.20	63	0.95	0.69, 1.30	34	1.20	0.77, 1.86
	0.20–<0.51	52	1.48	1.01, 2.16	29	1.33	0.80, 2.19
	0.51–<0.66	49	1.50	1.01, 2.21	35	1.70	1.05, 2.75
	≥0.66	49	2.52	1.70, 3.73	32	2.52	1.53, 4.15
	p value, trend		<0.001			<0.001	

* ICD-9, *International Classification of Diseases,* Ninth Revision; RR, relative risk; CI, confidence interval.
† Model adjusted for country, calendar period, age, and duration of employment.

each agent of interest, age (0–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, ≥70 years), calendar period of exit from the cohort (pre-1974, 1975–1979, 1980–1984, 1985–1989, ≥1990), total duration of employment (<1, 1–4, 5–9, 10–14, 15–19, ≥20 years), and country. Linear trends in log(relative risk) were estimated, assuming constant differences between exposure categories. Only the *p* values for these tests are reported. Poisson regression analyses were carried out in Stata version 6.0 software (Stata Corporation, College Station, Texas). Person-years were allocated in SAS version 6.12 software (SAS Institute, Cary, North Carolina), using an in-house computer program developed at the International Agency for Research on Cancer.

RESULTS

Table 1 presents the results of the models that were used to examine associations between mortality from nonmalignant respiratory diseases and estimated inhalation exposure to four- to six-ring PAHs (including benzo[*a*]pyrene). Although the duration of PAH exposure was not associated with elevated mortality from nonmalignant respiratory disease and obstructive lung diseases, we observed positive associations between cumulative and average PAH exposures and nonmalignant respiratory mortality. These positive associations were even stronger in the subgroup of pavers for whom quantitative exposure estimates were available. The relative risk of mortality from obstructive lung diseases was most strongly associated with quantitative cumulative exposure to PAH: For the most highly exposed group (>1,414 ng of benzo[*a*]pyrene per $m^3 \times$ years), the relative risk was estimated to be 4.06 (95 percent confidence interval: 1.35, 12.19).

As seen in table 2, the analysis for coal tar exposure yielded similar results. Cumulative and average exposures to coal tar were positively associated with mortality from all the nonmalignant respiratory diseases and obstructive lung diseases. There was evidence of an exposure-response relation, as indicated by a significant trend toward higher relative risks with increasing estimated semiquantitative exposures. As with PAHs, these trends were stronger for obstructive lung diseases and average exposure indices. A work-history average exposure above 0.51 coal tar units was associated with a statistically significant increase in the risk of mortality from obstructive lung diseases. This corresponds approximately to using coal tar-containing materials for one half of each 8-hour work shift throughout one's career. Adjustment of the relative risks associated with cumulative coal tar exposure for simultaneous exposure to average and cumulative bitumen fume exposure resulted in negligible changes to the risk estimates (data not shown).

Table 3 shows that mortality from nonmalignant respiratory diseases was positively associated with cumulative and average bitumen fume exposure indices, as was indicated by significant trends and elevated relative risks. (The results for duration of exposure were indeed identical to those shown

TABLE 3. Exposure to bitumen fume and mortality from nonmalignant respiratory diseases in an International Agency for Research on Cancer-assembled cohort of asphalt workers first employed between 1913 and 1999

Exposure index, population	Exposure metric	Exposure group	Diseases of the respiratory system (ICD-9* codes 460–519)			Bronchitis, emphysema, and asthma (ICD-9 codes 490–493)		
			Observed deaths	RR*,†	95% CI*	Observed deaths	RR†	95% CI
Semiquantitative indices‡	Exposure duration§	Not exposed	80	1.00		34	1.00	
		>0–<1.59	88	1.33	0.89, 1.97	55	1.69	0.93, 3.08
		1.59–<3.84	92	1.19	0.80, 1.77	48	1.26	0.68, 2.32
		3.84–<8.45	90	1.32	0.90, 1.92	57	2.05	1.13, 3.70
		≥8.45	93	1.23	0.86, 1.75	27	0.61	0.33, 1.13
		p value, trend		0.24			0.67	
	Cumulative exposure¶	Not exposed	80	1.00		34	1.00	
		>0–<5.25	97	1.02	0.72, 1.45	50	0.85	0.51, 1.44
		5.25–<10.68	88	1.48	1.04, 2.11	51	1.36	0.81, 2.27
		10.68–<28.69	90	1.27	0.90, 1.78	47	1.08	0.65, 1.79
		≥28.69	88	1.29	0.93, 1.80	39	1.13	0.67, 1.90
		p value, trend		0.04			0.31	
	Average exposure#	Not exposed	80	1.00		34	1.00	
		>0–<1.57	90	1.05	0.75, 1.49	42	0.87	0.51, 1.47
		1.57–<3.89	108	1.19	0.87, 1.63	46	0.98	0.60, 1.60
		3.89–<5.10	81	1.36	0.96, 1.91	48	1.28	0.77, 2.14
		≥5.10	84	1.52	1.07, 2.16	51	1.37	0.82, 2.29
		p value, trend		<0.001			0.04	
Quantitative indices, pavers only	Cumulative exposure**	>0–<1.65	28	1.00		15	1.00	
		1.65–<3.73	27	1.16	0.68, 1.98	12	0.91	0.42, 1.96
		3.73–<8.52	28	1.08	0.58, 2.00	18	1.48	0.69, 3.17
		≥8.52	29	1.22	0.45, 3.34	8	1.24	0.26, 5.94
		p value, trend		0.70			0.39	
	Average exposure††	>0–<0.95	29	1.00		9	1.00	
		0.95–<1.16	26	1.23	0.71, 2.15	10	1.46	0.57, 3.73
		1.16–<1.29	30	1.52	0.83, 2.78	18	1.98	0.79, 5.00
		≥1.29	27	0.89	0.47, 1.70	16	1.33	0.51, 3.42
		p value, trend		0.83			0.64	

* ICD-9, *International Classification of Diseases,* Ninth Revision; RR, relative risk; CI, confidence interval.
† Model adjusted for country, calendar period, age, and duration of employment.
‡ All workers.
§ Years.
¶ Bitumen units × years.
# Bitumen units.
** $mg/m^3 \times$ years.
†† mg/m^3.

for PAH in table 1 because there was no PAH exposure in the absence of exposure to bitumen and vice versa.) However, the risk of obstructive lung diseases appeared to be positively, but not significantly, associated with average bitumen fume exposure: The elevated relative risk in the highest exposure group was 1.37 (95 percent confidence interval: 0.82, 2.29) with a significant *p* value for the trend ($p = 0.04$). This significant trend appears to be due, at least in part, to lower mortality in the lowest exposed group as compared with the nonexposed group. Bitumen fume exposure was also assessed quantitatively for persons employed only in paving. There was no indication that quantitative bitumen fume exposure was associated with mortality from all nonmalignant respiratory diseases. Evidence for an association between exposure to bitumen fume and mortality from obstructive lung diseases among pavers was weak: Relative risks were elevated but not to a statistically significant extent. The associations between bitumen fume and nonmalignant respiratory diseases were confounded by simultaneous exposure to coal tar, because the inclusion of the cumulative coal tar exposure variable into the models eliminated elevated relative risks for bitumen fume and left no evidence of an exposure-response trend with bitumen fume exposure. For example, in the highest exposure category for the semiquantitative index of average bitumen fume exposure, the relative risk for mortality from obstructive lung diseases decreased to 1.05 (95 percent confidence interval: 0.57, 1.92; *p* value for trend = 0.56) after adjust-

TABLE 4. Exposure to bitumen fume and mortality from nonmalignant respiratory diseases in the International Agency for Research on Cancer-assembled subcohort of asphalt workers who were not exposed to coal tar and first employed between 1913 and 1999

Exposure index, population	Exposure metric	Exposure group	Diseases of the respiratory system (ICD-9* codes 460–519)			Bronchitis, emphysema, and asthma (ICD-9 codes 490–493)		
			Observed deaths	RR*,†	95% CI*	Observed deaths	RR†	95% CI
Semiquantitative indices‡	Cumulative exposure§	Not exposed	80	1.00		34	1.00	
		>0–<5.25	51	1.14	0.73, 1.79	25	1.19	0.60, 2.37
		5.25–<10.68	24	1.32	0.80, 2.19	8	0.91	0.39, 2.14
		10.68–<28.69	24	1.08	0.67, 1.77	8	0.96	0.44, 2.16
		≥28.69	37	1.54	1.02, 2.34	11	1.35	0.65, 2.80
		p value, trend		0.06			0.65	
	Average exposure¶	Not exposed	80	1.00		34	1.00	
		>0–<1.57	44	1.15	0.73, 1.80	17	0.95	0.46, 1.94
		1.57–<3.89	59	1.32	0.91, 1.92	23	1.10	0.60, 2.00
		3.89–<5.10	22	1.57	0.97, 2.55	9	1.78	0.83, 3.82
		≥5.10	11	1.08	0.56, 2.06	4	0.94	0.32, 2.73
		p value, trend		0.12			0.44	
Quantitative indices, pavers only	Cumulative exposure#	>0–<1.65	17	1.00		7	1.00	
		1.65–<3.73	12	1.04	0.49, 2.21	3	0.65	0.17, 2.52
		3.73–<8.52	11	1.02	0.39, 2.69	6	2.04	0.57, 7.31
		≥8.52	14	1.67	0.38, 7.23	3	2.22	0.18, 27.2
		p value, trend		0.71			0.43	
	Average exposure**	>0–<0.95	21	1.00		6	1.00	
		0.95–<1.16	18	1.51	0.76, 3.01	7	2.08	0.63, 6.85
		1.16–<1.29	6	1.55	0.59, 4.07	3	2.78	0.63, 12.3
		≥1.29	9	0.68	0.22, 2.12	3	1.63	0.31, 8.54
		p value, trend		0.88			0.35	

* ICD-9, *International Classification of Diseases,* Ninth Revision; RR, relative risk; CI, confidence interval.
† Model adjusted for country, calendar period, age, and duration of employment.
‡ All workers.
§ Bitumen units × years.
¶ Bitumen units.
# mg/m^3 × years.
** mg/m^3.

ment for cumulative coal tar exposure. As seen in table 4, these results were confirmed by analyses of the subcohort not exposed to coal tar. We observed that nonmalignant respiratory disease mortality was associated with bitumen fume exposure in the entire cohort but not in the subgroup of pavers. Among persons never exposed to coal tar, only in the subcohort of pavers was there a tendency, albeit weak, for the risk of mortality from obstructive lung diseases to be positively associated with bitumen fume exposure. For example, the relative risk of mortality from obstructive lung diseases doubled in the highest cumulative exposure group for bitumen fume (relative risk = 2.22, 95 percent confidence interval: 0.18, 27.2), but it was not statistically significant. The risk estimates for obstructive lung diseases had broad confidence intervals in the tar-free cohort because of the limited number of deaths.

Cumulative (table 5) and average (data not shown) exposures to silica, diesel exhaust, and asbestos were not positively associated with mortality from obstructive respiratory diseases, after adjustment for country, age, calendar period, and duration of employment. Therefore, there was no reason to consider them to be confounders of associations with PAH, coal tar, or bitumen fume.

DISCUSSION

Summary of findings

We observed that mortality from obstructive lung diseases was positively associated with cumulative and average exposures to PAHs. Exposure to bitumen fume was positively, but not significantly, associated with mortality from obstructive lung diseases. However, this association could have been confounded by simultaneous exposure to coal tar.

Our findings provide additional evidence in support of hypotheses generated in previous studies, which linked elevated mortality from obstructive lung diseases to a high exposure to particle-bound PAHs (6, 10, 12), bitumen fume, and/or coal tar (7, 8, 17, 19–21). This evidence is least convincing for pure bitumen fume, possibly because of the relatively low levels of PAHs in pure bitumen fume and the low power of the analysis of the tar-free cohort.

TABLE 5. Exposures to silica, diesel exhaust, and asbestos in relation to mortality from bronchitis, emphysema, and asthma (ICD-9* codes 490–493) in an International Agency for Research on Cancer-assembled cohort of asphalt workers first employed between 1913 and 1999

Agent	Exposure group (agent unit × years)	Observed deaths	RR*,†	95% CI*
Silica	Not exposed	81	1.00	
	>0–<0.28	40	0.80	0.52, 1.22
	0.28–<0.52	33	1.00	0.65, 1.56
	0.52–<1.06	30	0.99	0.63, 1.56
	≥1.06	33	1.01	0.64, 1.60
	p value, trend		0.79	
Diesel exhaust	Not exposed	25	1.00	
	>0–<0.94	52	0.79	0.42, 1.47
	0.94–<2.03	52	0.94	0.51, 1.75
	2.03–<5.91	53	0.85	0.47, 1.53
	≥5.91	39	0.88	0.51, 1.51
	p value, trend		0.90	
Asbestos	Not exposed	120	1.00	
	>0–<0.01	26	1.07	0.68, 1.68
	0.01–<0.03	26	0.69	0.43, 1.08
	0.03–<0.13	25	0.88	0.55, 1.42
	≥0.13	24	0.66	0.41, 1.05
	p value, trend		0.06	

* ICD-9, *International Classification of Diseases,* Ninth Revision; RR, relative risk; CI, confidence interval.
† Model adjusted for country, calendar period, age, and duration of employment.

Etiologic agents

One of the difficulties of attributing the observed increased risk of obstructive lung disease to PAHs in bitumen and coal tar lies in the fact that fumes emitted during asphalt work are a complex mixture of both aliphatic and aromatic hydrocarbons. Based on our analyses, the main argument in favor of four- to six-ring PAHs as causative agents in the observed exposure-response relations is that the associations with measures of total organic fume (i.e., bitumen fume) are weaker than those observed for PAHs. In our earlier work, we explored the variability in types of PAHs present in fumes emitted during paving. We found little evidence of difference in PAH exposure profiles between different paving operations, except when coal tar was used, which increased the proportion of four- to six-ring PAHs, such as benzo[*a*]pyrene, in fumes (41). Nonetheless, we must accept the possibility that heterogeneity in the composition of fumes emitted during paving (e.g., differences in particle size distributions and chemical compositions) complicates the attribution of our findings to particle-bound PAHs.

Diesel exhaust is yet another source of PAH exposure among asphalt workers, but we observed no associations with diesel exhaust indices. Nevertheless, if different diesel exhaust levels were associated with specific types of paving, coal tar use, and time period, then it would be possible for PAH exposure indices to reflect changes in diesel exhaust exposure levels. The available data are not sufficient to test this supposition, because 1) we know little about the patterns of diesel engine use in the asphalt industry and 2) diesel exhaust exposure was not systematically monitored in asphalt companies in the countries studied.

Confounding

Tobacco smoking, a major cause of obstructive lung disease (45), is the principal uncontrolled potential confounder in our study. Analyses based on average exposure indices are most prone to confounding by smoking. The average levels of exposure in ROCEM decreased with time, as did the prevalence of smoking in many of the countries included in the study (46). As a consequence, workers in the highest categories of average level of exposure (but not necessarily of cumulative exposure) may have smoked more than workers in other categories, as suggested by analyses of the Dutch subcohort (34).

The weak positive association of bitumen fume with mortality from nonmalignant respiratory diseases and obstructive lung diseases could be an artifact of simultaneous exposure to coal tar. Cumulative exposure to coal tar was weakly yet positively correlated with both semiquantitative and quantitative bitumen fume exposure indices (Spearman's rank correlation coefficients in the range of 0.2–0.4). Adjustment for simultaneous exposure to coal tar reduced the association with exposure to bitumen fume. In the analysis of the subcohort not exposed to coal tar, relative risk estimates for obstructive lung diseases (table 4) were

imprecise, being based on less than 10 deaths per exposure group. Overall, our data did not allow us to exclude the possibility that exposure to bitumen fume contributes to mortality from obstructive lung diseases.

Exposures to silica, diesel exhaust, and asbestos were not associated with mortality from obstructive lung diseases. This was due to low exposures to these agents, similar levels of exposure across the industry, or nondifferential exposure misclassification. Occupational exposures outside the asphalt industry were not assessed because we lacked complete occupational histories. Thus, the possibility remains that our findings were confounded by other occupational exposures from employment both within and outside the asphalt industry.

Bias

The methods used to assess occupational exposures may also have biased the outcome of this study. First, bias may have arisen in the sampling strategy used to collect exposure data that were the basis of the quantitative exposure models. This factor, however, was adjusted for in the statistical exposure models (41), which were deemed reasonably valid for application in the epidemiologic study (43). Second, information about production conditions in the companies recruited for the study could have been incomplete, inaccurate, or biased. In particular, company-reported use of coal tar may contain substantial errors. We attempted to limit this source of error by asking a panel of experts from each country to evaluate again the data collected via the company questionnaires. Nonetheless, it was impossible to validate most of the company questionnaire data. Company questionnaires were also used to estimate exposure duration, through corrections for workday and working season duration. The reported duration of workdays and working seasons was not validated. Duration of exposure was a key factor in the estimation of cumulative, rather than average, exposure indices. Therefore, the average exposure indices were the least prone to this source of error. Third, there may have been coding errors in job histories for cohort members. However, we are confident that such coding errors were the least likely in the subcohort of persons identified as having been employed only in paving (for whom quantitative exposure estimates were available).

The problem of inaccurate death certification of obstructive lung diseases is widespread in the European Community (37). Thus, one of the weaknesses of our study was lack of information on contributing causes of death. This leaves open the possibility of nondifferential misclassification of cases of obstructive lung disease, which could have resulted in biased risk estimates (47, 48). However, obtaining such data was not feasible within the framework of the current cohort study. Furthermore, information on the contributing causes of death would still not address the issue of the incidence of nonfatal obstructive lung disease in the cohort.

Occupational hygiene intervention

Although the global burden of obstructive lung diseases is projected to grow, a reduction in occupational exposures could contribute to reducing this trend in industrialized countries (49). Our results suggest that mortality rates from obstructive lung diseases may have been effectively reduced in asphalt companies that discontinued use of coal tar in the binder. However, we cannot exclude the possibility that a small risk of mortality due to obstructive lung disease from bitumen fume exposure is still present. If so, it is probably attributable to the PAH content of bitumen fume (1, 42, 50–52). Bitumen is a relatively minor source of PAH exposure when a mixture of coal tar and bitumen is used as binder in asphalt being paved. However, there are PAHs in bitumen fume, and their concentrations can be high (comparable to coal tar) in some paving operations (41, 42). Thus, it is not surprising that PAH exposures occurred in the absence of coal tar. The role of other additives to asphalt in respiratory disease cannot be excluded (53).

Conclusions

Our results support the notion that exposures to PAHs, derived primarily from coal tar and possibly bitumen fume, are risk factors for mortality from obstructive lung diseases among asphalt workers. However, confounding and bias cannot be definitely ruled out as an explanation for the observed associations. Nonetheless, our findings provide additional evidence that exposure to particle-bound PAHs contributes to mortality from obstructive lung diseases.

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REFERENCES

1. Burstyn I, Kromhout H, Boffetta P. Literature review of levels and determinants of exposure to potential carcinogens and other agents in the road construction industry. AIHAJ 2000;61:715–26.
2. Butler M, Burr G, Dankovic D, et al. Hazard review: health effects of occupational exposure to asphalt. Cincinnati, OH: US Department of Health and Human Services and National Institute for Occupational Safety and Health, 2000. (DHHS publication no. (NIOSH) 2001110).
3. Hicks JB. Asphalt industry cross-sectional exposure assessment study. Appl Occup Environ Hyg 1995;10:840–8.
4. Watts RR, Wallingford KM, Williams RW, et al. Airborne exposures to PAH and $PM_{2.5}$ particles for road paving workers applying conventional asphalt and crumb rubber modified asphalt. J Expo Anal Environ Epidemiol 1998;8:213–29.
5. Binet S, Bonnet P, Brandt H, et al. Development and validation of a new bitumen fume generation system which generates polycyclic aromatic hydrocarbon concentrations proportional to fume concentrations. Ann Occup Hyg 2002;46:617–28.
6. Sydbom A, Blomberg A, Parnia S, et al. Health effects of diesel exhaust emissions. Eur Res J 2001;17:733–46.
7. Swaen GM, Slangen JJ, Volovics A, et al. Mortality of coke plant workers in the Netherlands. Br J Ind Med 1991;48:130–5.
8. Corhay JL, Bury T, Louis R, et al. Bronchial responsiveness in active steelworkers. Eur Res J 1998;11:272–7.
9. Pope CA 3rd, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 2002;287:1132–41.
10. Dockery DW, Pope CA 3rd, Xu X, et al. An association between air pollution and mortality in six U.S. cities. N Engl J Med 1993;329:1753–9.
11. Nel AE, Diaz-Sanchez D, Li N. The role of particulate pollutants in pulmonary inflamation and asthma: evidence for the involvement of organic chemicals and oxidative stress. Curr Opin Pulm Med 2001;7:20–6.
12. Nel AE, Diaz-Sanchez D, Ng D, et al. Enhancement of allergic inflammation by the interaction between diesel exhaust particles and the immune system. J Allergy Clin Immunol 1998;102:539–54.
13. Li N, Venkatesan MI, Miguel A, et al. Induction of heme oxygenase-1 expression in macrophages by diesel exhaust particle chemicals and quinones via the antioxidant-responsive element. J Immunol 2000;165:3393–401.
14. Bonvallot V, Baeza-Squiban A, Baulig A, et al. Organic compounds from diesel exhaust particles elicit a proinflammatory response in human airway epithelial cells and induce cytochrome p450 1a1 expression. Am J Respir Cell Mol Biol 2001;25:515–21.
15. McNeil D. Tar and pitch. In: Kirk RE, Othmer DF, eds. Encyclopedia of chemical technology. New York, NY: John Wiley & Sons, Inc, 1983:564–600.
16. Broome DC. Bitumen. In: Hobson GD, ed. Modern petroleum technology. New York, NY: John Willey & Sons, Inc, 1973:804–15.
17. Hansen ES. Mortality of mastic asphalt workers. Scand J Work Environ Health 1991;17:20–4.
18. Cole P, Green LC, Lash TL. Lifestyle determinants of cancer among Danish mastic asphalt workers. Regul Toxicol Pharmacol 1999;30:1–8.
19. Maizlish N, Beaumont J, Singleton J. Mortality among California highway workers. Am J Ind Med 1988;13:363–79.
20. Milham S. Occupational mortality in Washington State: 1950–1989. Cincinnati, OH: US Department of Health and Human Services and National Institute for Occupational Safety and Health, 1997. (DHHS publication no. (NIOSH) 96133).
21. Stern FB, Ruder AM, Chen G. Proportional mortality among unionized roofers and waterproofers. Am J Ind Med 2000;37:478–92.
22. Baylor CH, Weaver NK. A health survey of petroleum asphalt workers. Arch Environ Health 1968;17:210–14.
23. Nyqvist B. Respiratory tract symptoms of asphalt workers. Another occupational bronchitis? Lakartidningen 1978;75:1173–5.
24. Maintz G, Schneider WD, Maczek P. Chronic obstructive lung disease caused by long lasting occupational exposure to asphalt fumes. Z Erkrank Atm Org 1987;168:71–6.
25. Krasniuk EP, Cherniuk VI, Rossinskaia LN, et al. The effect of manufacturing factors in asphalt-bitumen plants on the health of the workers. (In Russian). Lik Sprava 2000;(2):106–12.
26. Boffetta P, Burstyn I, Partanen T, et al. Cancer mortality among European asphalt workers: an international epidemiological study. I. Results of the analysis based on job titles. Am J Ind Med 2003;43:18–27.
27. Boffetta P, Burstyn I, Partanen T, et al. Cancer mortality among European asphalt workers: an international epidemiological

study. II. Exposure to bitumen fume and other agents. Am J Ind Med 2003;43:28–39.
28. Boffetta P, Burstyn T, Partanen T, et al. IARC epidemiological study of cancer mortality among European asphalt workers. Final report. Lyon, France: International Agency for Research on Cancer, 2001. (IARC internal report no. 01/003).
29. Boffetta P, Sali D, Kolstad H, et al. Mortality of short-term workers in two international cohorts. J Occup Environ Med 1998;40:1120–6.
30. Kauppinen T, Heikkila P, Partanen T, et al. Mortality and cancer incidence of workers in Finnish road paving companies. Am J Ind Med 2003;43:49–57.
31. Shaham J, Knecht Y, Burstyn I, et al. Epidemiologic study of cancer mortality among Israeli asphalt workers. Am J Ind Med 2003;43:69–78.
32. Stucker I, Meguellati D, Boffetta P, et al. Cohort mortality study among French asphalt workers. Am J Ind Med 2003;43: 58–68.
33. Bergdahl IA, Jarvholm B. Cancer morbidity in Swedish asphalt workers. Am J Ind Med 2003;43:104–8.
34. Hooiveld M, Spee T, Burstyn I, et al. Lung cancer mortality in a Dutch cohort of asphalt workers: evaluation of possible confounding by smoking. Am J Ind Med 2003;43:79–87.
35. Randem BG, Langard S, Kongerud J, et al. Mortality from nonmalignant diseases among male Norwegian asphalt workers. Am J Ind Med 2003;43:96–103.
36. Randem BG, Langard S, Dale I, et al. Cancer incidence among male Norwegian asphalt workers. Am J Ind Med 2003;43:88–95.
37. Mackenbach JP, Van Duyne WM, Kelson MC. Certification and coding of two underlying causes of death in the Netherlands and other countries of the European Community. J Epidemiol Community Health 1987;41:156–60.
38. Sidenius KE, Munch EP, Madsen F, et al. Accuracy of recorded asthma deaths in Denmark in a 12-months period in 1994/95. Respir Med 2000;94:373–7.
39. Burstyn I, Boffetta P, Kauppinen T, et al. Estimating exposures in the asphalt industry for an international epidemiological cohort study of cancer risk. Am J Ind Med 2003;43:3–17.
40. Burstyn I, Kromhout H, Cruise PJ, et al. Designing an international industrial hygiene database of exposures among workers in the asphalt industry. Ann Occup Hyg 2000;44:57–66.
41. Burstyn I, Kromhout H, Kauppinen T, et al. Statistical modelling of the determinants of historical exposure to bitumen and polycyclic aromatic hydrocarbons among paving workers. Ann Occup Hyg 2000;44:43–56.
42. Burstyn I, Kromhout H. Are the members of a paving crew uniformly exposed to bitumen fume, organic vapor, and benzo(*a*)pyrene? Risk Anal 2000;20:653–63.
43. Burstyn I, Boffetta P, Burr GA, et al. Validity of empirical models of exposure in asphalt paving. Occup Environ Med 2002;59:620–4.
44. Breslow NE, Day NE. Statistical methods in cancer research. Vol II. The design and analysis of cohort studies. Lyon, France: International Agency for Research on Cancer, 1987. (IARC scientific publication no. 82).
45. Farzan S. Tobacco smoking. In: Farzan S, ed. A concise handbook of respiratory diseases. Norwalk, CT: Appelton & Lange, 1992:224.
46. Nicolaides-Bouman A, Forey B, Lee P, et al. International smoking statistics: a collection of historical data from 22 economically developed countries. Oxford, UK: Oxford University Press, 1993.
47. Brenner H, Loomis D. Varied forms of bias due to nondifferential error in measuring exposure. Epidemiology 1994;5:510–17.
48. Brenner H, Savitz D, Gefeller O. The effects of joint misclassification of exposure and disease on epidemiologic measures of association. J Clin Epidemiol 1993;46:1195–202.
49. Gulsvik A. The global burden and impact of chronic obstructive pulmonary disease worldwide. Monaldi Arch Chest Dis 2001; 56:261–4.
50. Lindstedt G, Sollenberg J. Polycyclic aromatic hydrocarbons in the occupational environment. Scand J Work Environ Health 1982;8:1–19.
51. Brandt HC, de Groot PC, Molyneux MK, et al. Sampling and analysis of bitumen fumes. Ann Occup Hyg 1985;29:27–80.
52. Machado ML, Beatty PW, Fetzer JC, et al. Evaluation of the relationship between PAH content and mutagenic activity of fumes from roofing and paving asphalts and coal tar pitch. Fundam Appl Toxicol 1993;21:492–9.
53. Miller AB, Feng A, Hanley K, et al. Acute health effects of conventional and crumb rubber modified asphalt among road pavers. (Abstract 67). Fairfax, VA: American Industrial Hygiene Association, 1999.