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Cancer Mortality Among European Asphalt Workers: An International Epidemiological Study. II. Exposure to Bitumen Fume and Other Agents

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Background *An increased risk of lung cancers among asphalt workers has been suggested in epidemiological studies based on large scale statistical analyses.*

Methods *In a multi-country study of 29,820 male workers employed in road paving, asphalt mixing and roofing, 32,245 ground and building construction workers and 17,757 other workers from Denmark, Finland, France, Germany, Israel, the Netherlands, Norway, and Sweden, with mortality that was documented from 1953–2000. Exposures to bitumen fume, coal tar, 4–6 ring polycyclic aromatic hydrocarbons, organic vapor, diesel exhaust, asbestos, and silica dust were assessed via a job-exposure matrix. Standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) based on national mortality rates, as well as relative risks (RRs) based on Poisson regression models were calculated.*

Results *The SMR of lung cancer among workers exposed to bitumen fume (1.08, 95% CI 0.99–1.18) was comparable to that of non-exposed workers (SMR 1.05, 95% CI 0.92–1.19). In a sub-cohort of bitumen-exposed workers without exposure to coal tar, the SMR of lung cancer was 1.23 (95% CI 1.02–1.48). The analysis based on the semi-quantitative, matrix-based exposures in the whole cohort did not suggest an increased lung cancer risk following exposure to bitumen fume. However, in an analysis restricted to road pavers, based on quantitative estimate of bitumen fume exposure, a dose-response was suggested for average level of exposure, applying a 15-year lag, which was marginally reduced after adjustment for co-exposure to coal tar. The results for cancer of the head and neck were similar to those of lung cancer, although they were based on a smaller number of deaths. There was no clear suggestion of an association with bitumen fume for any other neoplasm.*

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Conclusions *The results of the analysis by bitumen fume exposure do not allow us to conclude on the presence or absence of a causal link between exposure to bitumen fume and risk of cancer of the lung and the head and neck.* Am. J. Ind. Med. 43:28–39, 2003.

KEY WORDS: asphalt; bitumen fume; coal tar; epidemiology; lung neoplasms; mortality; road paving; roofing

INTRODUCTION

An increased risk of lung cancer among asphalt workers has been suggested in epidemiological studies largely based on routine statistics and record linkages [Partanen and Boffetta, 1994]. Given the importance of bitumen and its fume as occupational and environmental exposures, it is important to clarify whether (i) asphalt workers are at increased risk of cancer of the lung, and possibly other organs, and (ii) whether any excess risk can be attributed to exposure to bitumen fume or other agents, such as coal tar. The International Agency for Research on Cancer (IARC) and its collaborators assembled a retrospective cohort of asphalt workers from the asphalt industry (road paving, asphalt mixing, and roofing) in seven European countries (Denmark, Finland, France, Germany, the Netherlands, Norway, and Sweden) and Israel. The primary goal of the study was to assess whether an increased risk of lung cancer is associated with bitumen fume exposure. Details on the study design and the detailed results of the mortality analysis have been reported [Boffetta et al., 2001]. In a companion paper, we report the results of the analysis of mortality based on employment in specific job groups [Boffetta et al., 2003]. In this article, we report results based on assessment of exposure to bitumen fume and other agents.

MATERIALS AND METHODS

Study Population

The study population has been described in detail in Boffetta et al. [2001, 2003]. The study cohort included workers first employed during 1913–1999 in road paving and asphalt mixing companies in seven participating countries (Denmark, Finland, France, Germany, Israel, the Netherlands, and Norway) and in a nationwide health surveillance program in Sweden. The period of employment varied among countries: the first year was in the 1910s–1930s in all countries but Denmark (1953) and Germany (1965); the last year varied from 1992 in Sweden to 1999 in Germany and the Netherlands. In all countries except for Sweden, personal identifiers and employment histories of workers were abstracted from company records. Enrollment of the cohort in Sweden was based on a nationwide out-patient medical service program provided by the Swedish Construction Industry's Organization for Working Environment Safety and Health to construction workers during 1969–1992 [Engholm and Englund, 1995]. Full employment histories were coded according to a classification of jobs which included bitumen workers, building construction workers, ground construction workers, other and unspecified blue collar workers, and white collar workers. In all countries, except for Sweden, the entire occupational history in the target companies was available. In Sweden, information was available only on the jobs held up to the time of the last health examination. For this reason, we were able to assess duration of employment for the members of the Swedish cohort with less precision than for other workers.

We excluded women from the data analysis and workers with less than one full season of employment in the target companies. Out of the 124,871 workers originally included in the cohort, 79,822 were retained in the analysis. They contributed 1,216,443 person-years of observation: Table I reports the distribution of person-years by country contributed by workers exposure to bitumen fume and other agents. A total of 736,327 person-years (60.5% of the total) were contributed by workers classified as exposed to bitumen fume: cohorts from Denmark, France, and Norway contributed 27.1%, 22.1% and 16.0% of bitumen-exposed person-years, respectively. The proportion of exposed person-years was 27.5% for coal tar, 35.3% for asbestos, 65.1% for silica dust, and 89.6% for diesel exhaust.

In order to assess the influence of truncated job histories and follow-up times, some analyses were repeated on the 'inception cohort,' comprising only workers who entered employment in the participating companies at or after the beginning of the period for which full employment records are available. Furthermore, a coal tar-free sub-cohort was identified, which included workers employed in companies or periods in which exposure to coal tar was estimated not to have occurred. This sub-cohort included 17,444 workers employed in bitumen-exposed jobs, who contributed 243,554 person-years of observation.

A follow-up for mortality was conducted in all participating countries. The date of beginning of follow-up spanned from 1953 in Norway to 1979 in France, the end of follow-up was between 1995 and 2000. Mean duration of follow-up was 16.7 years in the whole cohort, with no

TABLE I. Distribution of Person-Years by Country and Exposure to Selected Agents

Country	Bitumen fume	Coal tar	Asbestos	Silica dust	Diesel exhaust	Total
Denmark	199192	117986	136709	143039	196793	212300
Norway	117852	20431	15431	42218	120013	177205
Sweden	66145	47220	215979	311607	375843	375875
Finland	50324	15568	41860	62668	90199	97529
Netherlands	49483	28478	14641	44662	48982	55020
Germany	67811	7781	4438	32801	66349	82240
France	162854	97047	0	155212	162234	170870
Israel	22666	0	0	150	29565	45404
Total	736327	334509	429057	792358	1089979	1216443

difference between bitumen workers and building or ground construction workers; it varied from 11.7 years in France and Germany to 21.9 years in Norway. A total of 10,096 cohort members were reported to be dead at the end of the follow-up. The overall proportion of cohort members lost to follow-up was 0.7%; an additional 0.5% of cohort members emigrated during the follow-up period.

Exposure Assessment

The first step of the exposure assessment was a review of literature on determinants of exposure in asphalt paving, the largest bitumen-exposed subgroup in the cohort [Burstyn et al., 2000a]. We concluded that published reports were inadequate for exposure reconstruction. Therefore, we sought additional data, including unpublished results, by establishing a database of industrial hygiene measurements, called the asphalt worker exposure (AWE) database [Burstyn et al., 2000b]. The data comprised a total of 2007 industrial hygiene measurements of exposure levels for a variety of agents among asphalt workers, and supplementary information. The earliest samples originated from the late 1960s; most samples were collected in the late 1970s and between 1985 and 1997. An analysis of the AWE database identified determinants of exposure to be used to reconstruct exposures experienced by cohort members [Burstyn and Kromhout, 2000; Burstyn et al., 2000c]. Concentrations of bitumen fume, organic vapor, and benzo(a)pyrene steadily declined over the last 20 years at a rate of 6% to 14% per year. Mastic laying, re-paving, surface dressing, oil gravel paving, and asphalt temperature were significant determinants of bitumen fume and organic vapor exposure. Benzo(a)pyrene levels depended primarily on the use of coal tar in paving (a practice discontinued in recent decades in Western Europe). These models were found to be suitable for group-based exposure assessment [Burstyn et al., 2002].

In addition, we gathered information about companies enrolled in the study through a company questionnaire that ascertained temporal changes in production characteristics and work organization, which can be used to reconstruct exposures. Among production characteristics, the questionnaire ascertained the type of materials used (e.g., coal tar, asbestos), asphalt application methods (e.g., mastic laying, hot mix paving), and average time spent handling these materials or utilizing given paving methods. The questionnaire was administered to knowledgeable company representatives. Questionnaires were checked for errors, omissions, and inconsistencies and were entered into a common database. Company questionnaire information was compared with data about production characteristics derived from the exposure measurement reports in the AWE database. Experts from each country checked the quality of company questionnaires and supplemented it, when required.

The road construction workers' exposure matrix (ROCEM) was constructed on the basis of data from company questionnaires, analyses of the AWE database, and expert evaluations [Burstyn et al., 2003]. It consists of semi-quantitative estimates of exposure to six agents and groups of agents and of quantitative estimates of exposure to three of them (Table II). Quantitative estimates of exposure were derived by applying mixed-effects models [Burstyn et al., 2000c] to company questionnaire data. The statistical models were used to calculate predicted median values of average exposure for a group of workers employed under production conditions indicated in the company questionnaires. Then, frequency-weighted sums of predicted exposures under these production conditions were calculated for each time period and company. This was carried out only for road pavers since it was not possible to obtain sufficient data to construct predictive models of exposure for other job classes. Details of the application of regression models to the company questionnaires have been reported elsewhere [Burstyn et al., 2003]. For all jobs and agents considered in the study, semi-quantitative exposure estimates were also derived on the basis of (i) expert evaluation of relative exposure intensities between working conditions, (ii) patterns of exposure observed in both the statistical models and AWE database, and

TABLE II. Agents Included in the Exposure Assessment

Agent	Definition	Assessment[a]
Bitumen fume	Occupational exposure to solid-phase inhalable organic matter of bitumen origin	SQ + Q
Organic vapor	Occupational exposure to phase−phase organic matter of bitumen, tar or solvent origin	SQ + Q
PAH[b]	Occupational exposure to inhalable 4−6 ring polycyclic aromatic hydrocarbons emitted from bitumen- and tar-containing materials	SQ + Q
Diesel exhaust	Occupational exposure to inhalable diesel exhaust from road paving and construction machinery, excluding road traffic	SQ
Asbestos	Occupational exposure to asbestos fibers	SQ
Silica	Occupational exposure to respirable crystalline silica dust	SQ
Coal tar	Occupational exposure to coal tar	SQ

[a]SQ, semi-quantitative; Q, quantitative (only jobs exposed to bitumen).
[b]Benzo[a]pyrene was used as a representative of polycyclic aromatic hydrocarbon (PAH) exposure in quantitative assessment.

(iii) data gathered by company questionnaires [Burstyn et al., 2003]. To account for differences in work-shift duration between companies and time periods, both quantitative and semi-quantitative estimates of exposure intensity were further standardized to 8-hour shifts.

For a number of entries in job histories, semi-quantitative exposure estimates could not be calculated from company questionnaire data. Therefore, semi-quantitative assessment of exposures in jobs other than road paving, asphalt mixing, waterproofing and roofing, and building and ground construction followed an approach analogous to the one employed by Macaluso et al. [1996] in assessing exposures for poorly specified jobs. The overall procedure for these job classes involved reconstructing their exposures as a weighted average of exposures for cells in the exposure matrix that were based on primary data. Details on the country- and job class-specific exposure assessment algorithms can be found in previous reports [Boffetta et al., 2001; Burstyn et al., 2003].

Exposure indices were derived by linking ROCEM to job histories of cohort members. We derived for each worker the following indices of exposure to the agents included in ROCEM: (i) never/ever exposed; (ii) duration of exposure (years exposed to a given agent); (iii) cumulative exposure (product of exposure duration and intensity, integrated over work-history); (iv) average level of exposure over work history (ratio of cumulative and duration exposure indices). In order to model latency associated with lung cancer, additional indices of duration of exposure, average level of exposure and cumulative exposure were created, after allocating the first 15 person-years of exposure to the non-exposed group and ignoring exposure during the last 15 years before death or end of follow-up.

Exposure groups for epidemiological analyses were derived on the basis of exposure indices. For each quantitative or semi-quantitative exposure index, non-exposed subjects formed a separate category, and exposed subjects were divided in quartiles, each including approximately one fourth of lung cancer deaths. Workers belonging to job groups with unknown exposure formed a separate category.

For the estimate of exposure duration we had to correct for the seasonal nature of work in the asphalt industry, given that working seasons in any given year varied between companies and countries. This was achieved by weighting duration of exposure for each full calendar year employed in paving by the ratio of working season duration (in months) to 12 months. Incomplete calendar years of employment were not weighted by season duration because it was assumed that in such cases job histories reflected actual duration of work. Working season duration estimates were derived from company questionnaires, and were specific to each company and job class combination.

Statistical Analysis

In preliminary analyses and in analyses based on job classes [Boffetta et al., 2001, 2003], there was no suggestion of an increased risk of any neoplasms except for lung and head and neck cancers. Therefore, we restrict this report to results of these two neoplasms, in addition to mortality from all causes and mortality from all neoplasms.

Age-, calendar period- and sex-specific national mortality reference rates, derived from the mortality data bank of the World Health Organization, were used to derive the expected numbers of deaths. Standardized mortality ratios (SMRs) were calculated as ratios of observed and expected numbers of deaths, using ad-hoc SAS programs [Sas Institute, 1990]; 95% confidence intervals (CIs) based on the Poisson distribution of observed numbers of deaths.

Country-specific results are not systematically reported: they can be found in the study report [Boffetta et al., 2001] and in companion papers [Bergdahl and Järvholm, Hooiveld et al., Kauppinen et al., Randem et al., Shaham et al., and Stücker et al., 2003]. However, country-specific results for

lung cancer and other important causes of death are discussed when there is evidence of heterogeneity.

In order to overcome some of the limitations of indirect standardization, relative risks (RRs) and associated 95% CIs were estimated using multivariate Poisson regression analysis [Breslow and Day, 1987]. In the regression models, we included age (10 five-year groups), calendar period (≤ 1974, 1975–1979, 1980–1984, 1985–1989, 1990 and later), country and total duration of employment (<1, 1–4, 5–9, 10–14, 15–19, 20+ years) as covariates. Coal tar exposure was adjusted for by lagged (15 years) cumulative coal tar exposure index.

Linear trends in SMRs and log (RRs) were estimated assuming constant differences in the exposure metric between exposure categories. Only *P*-values indicating a trend are reported.

Among road pavers, there was a very strong correlation between both semi-quantitative and quantitative estimates of exposure to bitumen fume, 4–6 ring polycyclic aromatic hydrocarbons and organic vapor (correlation coefficients 0.83–1.00, depending on exposure index): results according to the two latter agents therefore parallel closely those of exposure to the former and are not reported in detail.

The Poisson regression analysis was carried out using the statistical package STATA 6.0 [Stata Corporation, 1997]. Person-years were allocated in SAS 6.12 [Sas Institute, 1990], using an in-house computer program developed at IARC.

RESULTS

The overall mortality was similar among workers exposed to bitumen fume (SMR 0.93, 95% CI 0.91–0.96) and non-exposed workers (SMR 0.90, 95% CI 0.87–0.93) (Table III). Results for mortality from all cancers were similar to those for all causes. The SMR of lung cancer among workers ever exposed to bitumen fume was similar to that among non-exposed workers: 1.08 (95% CI 0.99–1.18) and 1.05 (95% CI 0.92–1.19). No differences in lung cancer mortality were observed for coal tar, asbestos, silica, and diesel exposures. The SMR of head and neck cancer (i.e., cancers of the oral cavity, pharynx, and larynx) among workers exposed to bitumen fume, coal tar or asbestos was higher than that among workers not exposed these agents. For the remaining neoplasms, there was no evidence of a possible association with exposure to bitumen fume. A more detailed analysis has been conducted on mortality from lung and head and neck cancer and indicators of bitumen exposure.

Results for mortality from all causes and from all cancers, and other causes of death have been reported in detail elsewhere [Boffetta et al., 2001]. In summary, an increased all-cause mortality was shown according to lagged duration of exposure, but not to other indices; no increase in overall cancer mortality was found for any index of exposure.

When we analyzed mortality from lung cancer according to indices of semi-quantitative lagged exposure to bitumen fume based on 757 deaths, we found no evidence of a

TABLE III. Standardized Mortality Ratios of Selected Causes of Death by Exposure to Occupational Agents

Cause of death	Bitumen fume		Coal tar		Asbestos		Silica		Diesel	
(ICD-9 codes)	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed
PY	480117	736327	861102	334509	787387	429057	396042	792358	126465	1089979
All causes (001–999)										
SMR	0.90	0.93	0.91	0.95	0.90	0.95	0.91	0.93	0.89	0.93
95% CI	0.87–0.93	0.91–0.96	0.89–0.94	0.92–0.98	0.88–0.93	0.92–0.98	0.88–0.95	0.90–0.95	0.84–0.95	0.91–0.95
Obs	3711	5925	6100	3358	5438	4198	3339	6176	1085	8551
All malignant neoplasms (140–208)										
SMR	0.95	0.96	0.93	1.00	0.92	1.00	0.92	0.97	0.93	0.96
95% CI	0.89–1.01	0.91–1.00	0.89–0.98	0.94–1.06	0.87–0.97	0.95–1.06	0.85–0.98	0.92–1.02	0.83–1.05	0.92–1.00
Obs	945	1663	1548	1012	1469	1139	821	1749	277	2331
Head and neck cancer (140–149, 161)										
SMR	0.90	1.10	1.00	1.11	1.00	1.18	1.19	1.00	1.16	1.04
95% CI	0.66–1.19	0.95–1.28	0.82–1.20	0.91–1.34	0.84–1.17	0.93–1.48	0.92–1.52	0.85–1.17	0.72–1.77	0.90–1.20
Obs	48	173	113	104	148	73	64	154	21	200
Trachea, bronchus, and lung (162)										
SMR	1.05	1.08	1.08	1.05	1.09	1.05	1.19	1.01	1.31	1.05
95% CI	0.92–1.19	0.99–1.18	0.98–1.19	0.93–1.17	0.99–1.19	0.94–1.17	1.05–1.34	0.92–1.11	1.05–1.60	0.97–1.13
Obs	232	524	431	308	444	312	260	484	93	663

PY, person-years; SMR, standardized mortality ratio; CI, confidence interval; Obs, observed deaths.

positive dose-response relationship (Fig. 1). Similar results were found (not shown in detail) when using indices of unlagged exposure and excluding data from Sweden, where duration of exposure could be estimated with less precision than in other sub-cohorts.

Figure 2 shows the results of the analysis of lung cancer mortality according to quantitative indices of lagged exposure to bitumen fume for workers only employed in jobs entailing exposure to bitumen during paving [see Boffetta et al., 2003], and was based on 153 lung cancer deaths. A positive association was present for lagged average level of exposure, but not with lagged cumulative exposure. Corresponding indices of unlagged average and cumulative exposure showed a positive dose-response with lung cancer risk: RRs were 1.43 (CI 0.87–2.33), 1.77 (0.99–3.19) and 3.53 (1.58–7.89) for 2.2–4.6, 4.7–9.6 and 9.7+ mg/m^3-years of cumulative exposure, and 2.77 (CI 1.69–4.53), 2.43 (1.38–4.29) and 3.16 (1.83–5.47) for 1.03–1.23, 1.24–1.36 and 1.37+ mg/m^3 average exposure (P-value of test for trend < 0.01 for both variables).

All indices of quantitative exposure to bitumen fume were positively associated with mortality from all cancers (not shown in detail). An association was suggested with mortality from oral and pharyngeal cancer (based on 16 deaths), although the trend approached statistical significance only for lagged cumulative exposure (P-value 0.05).

In Figure 3, we report the results of the analysis of lung cancer mortality by lagged cumulative exposure to agents other than bitumen fume. No association was suggested according to exposure to coal tar (although a positive relationship was present for all cause mortality). Lung cancer mortality did not increase according to cumulative exposure to asbestos; although a small increase in RRs was suggested for increasing average level of lagged exposure (P-value of test for trend 0.3). Similarly, cumulative lagged exposure to silica dust was not clearly associated with lung cancer mortality, although an association was suggested with average level of lagged exposure (P-value of test for trend 0.4). No association was present between lung cancer mortality and cumulative exposure to diesel exhaust.

The results on exposure to bitumen fume presented in Figures 1 and 2 are not adjusted for the possible confounding effect of other occupational agents. We therefore fitted regression models similar to those reported in Figures 1 and 2, including additional terms for cumulative exposure to coal tar, diesel exhaust, and silica dust. The inclusion of terms for diesel exhaust and silica dust suggested no confounding effect of these agents. Although the effect of the additional adjustment factors on the risk estimates for bitumen fume was modest, adjustment for tar exposure tended to reduce the RR for bitumen fume exposure. For example, in the case of lagged quantitative cumulative exposure to bitumen fume, the RR in the highest quartile for the total cohort was reduced to 1.45 (95% CI 0.60–3.48), and the P-value of the test for linear trend increased to 0.9.

Residual confounding by coal tar may have occurred because semi-quantitative coal tar exposure indices were probably subject to considerable error. Therefore we also restricted the analysis of mortality to bitumen-exposed workers who were never exposed to coal tar. Overall mortality was decreased (SMR 0.91, 95% CI 0.86–0.96), as was cancer mortality (SMR 0.87, 95% CI 0.78–0.96).

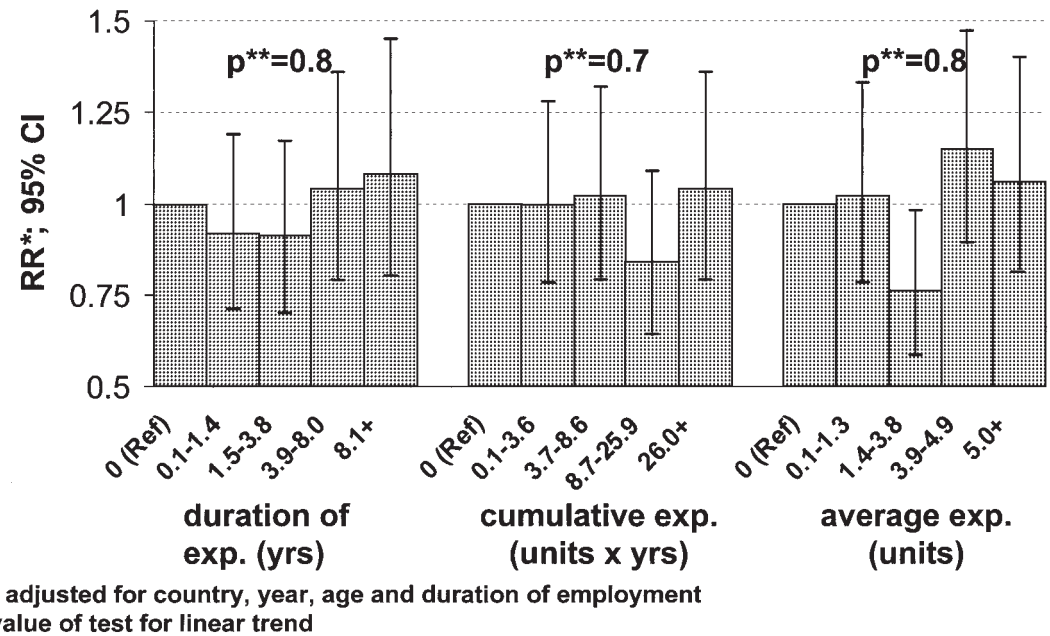

FIGURE 1. Relative risk (RR) of lung cancer by semi-quantitative exposure to bitumen fume (15-year lag).

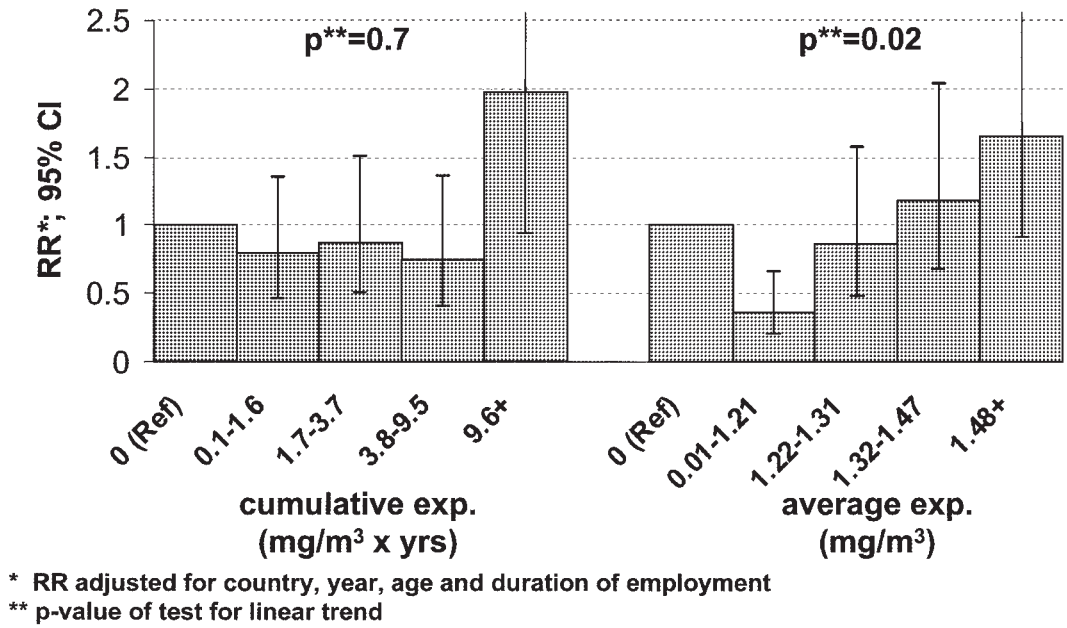

FIGURE 2. RR of lung cancer by quantitative exposure to bitumen fume (15-year lag).

There was no excess of mortality from head and neck cancer (SMR 1.06, 95% CI 0.68–1.56); lung cancer mortality was significantly increased (SMR 1.23, 95% CI 1.02–1.48). Figure 4 presents the results of the analysis of mortality from lung cancer in the tar-free cohort, replicating the results reported in Figure 1. Although the results were fairly imprecise due to the small number of deaths, there was no suggestion of an association with any index of exposure. In the analysis based on quantitative exposure indices, in which a total of 63 deaths from lung cancer were observed, there was no association with cumulative exposure, but a positive association with indices of average exposure was suggested by the data (not shown in detail).

The association between mortality from lung cancer and exposure to bitumen fume was further assessed in the inception cohort, that is, among workers first employed in the companies included in the study after the beginning of the period of enumeration of the cohort (inception cohort). These

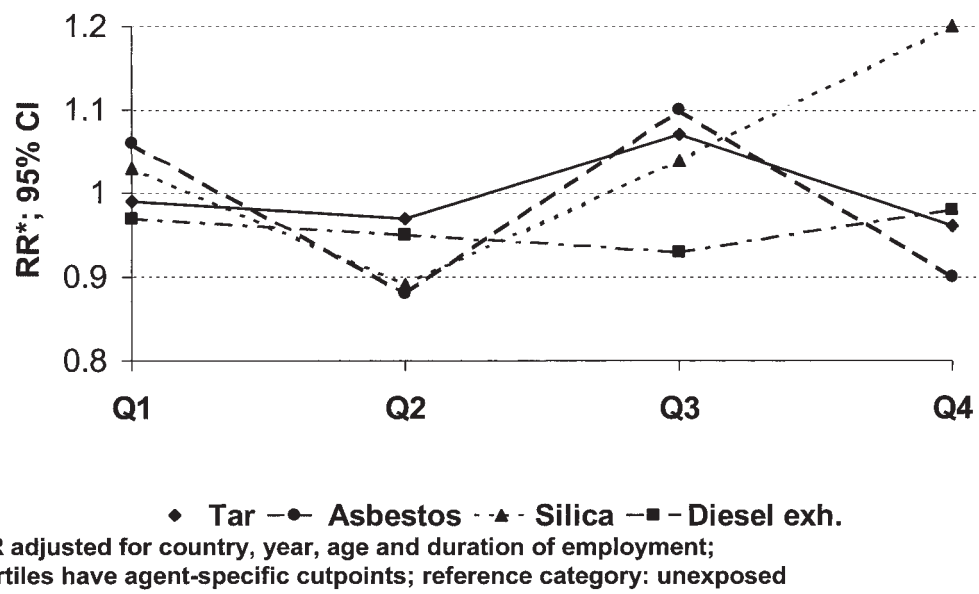

FIGURE 3. RR of lung cancer by quartiles of semi-quantitative cumulative exposure to agents other than bitumen fume (15-year lag).

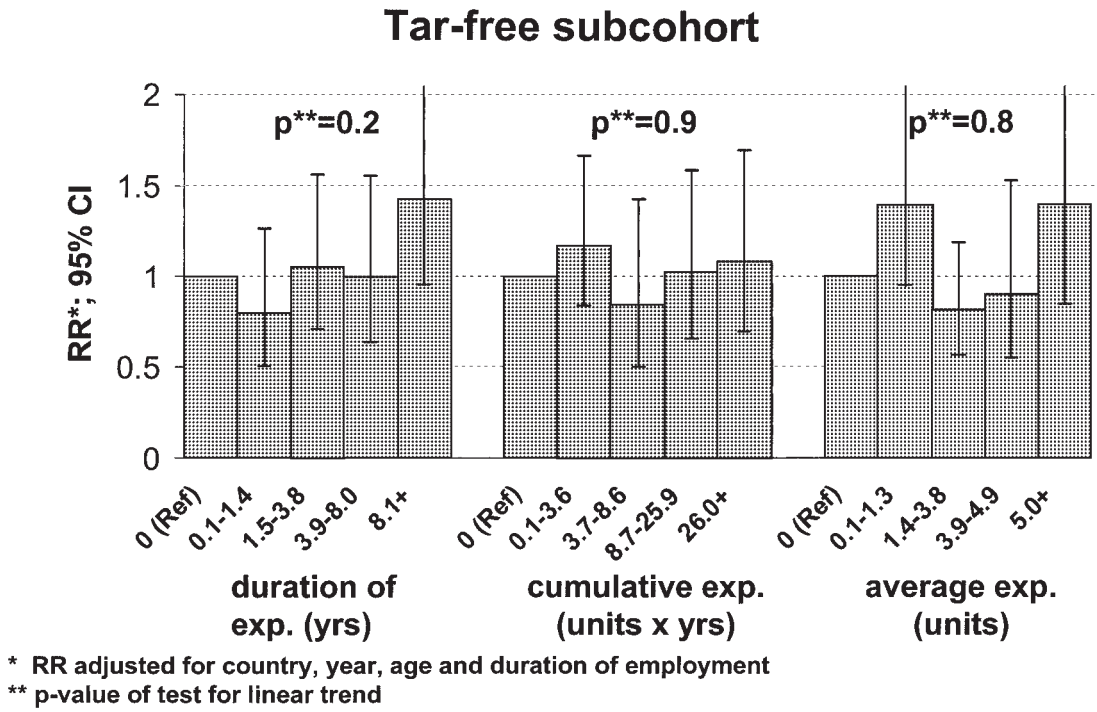

FIGURE 4. RR of lung cancer by semi-quantitative exposure to bitumen fume (15-year lag).

results were based on 276 deaths from lung cancer, and were very similar to those based on the entire cohort.

The analysis of mortality from head and neck cancer was hampered by small numbers. In Figure 5, we report the results according to unlagged semi-quantitative and quantitative cumulative exposure to bitumen fume, based on 221 and 42 deaths, respectively. A dose-response relationship was suggested for the quantitative indicator of exposure. The application of a 15-year lag resulted in higher RRs for quantitative cumulative exposure (*P*-value of test for linear

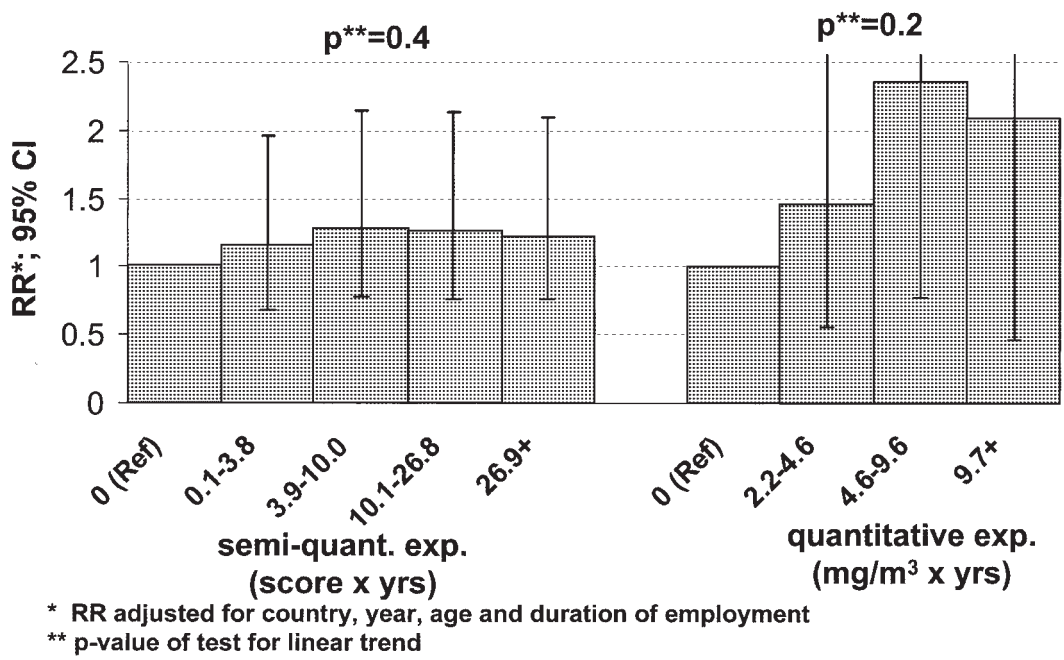

FIGURE 5. RR of head and neck cancer by cumulative exposure to bitumen fume (no lag).

trend 0.01), but not for semi-quantitative cumulative exposure. The analyses by various indicators of average exposure were also suggestive of a dose-response relationship, e.g., RR 0.93 (95% CI 0.30–2.84), 2.27 (0.91–6.38) and 1.81 (0.70–4.67) for increasing quartiles of unlagged average exposure, *P*-value of test for trend 0.15. These results were strongly dependent on the findings in the German component of the study.

DISCUSSION

Our analysis by semi-quantitative indices of exposure to agents estimated via ROCEM did not suggest an association between lung cancer risk and estimated semi-quantitative exposure to bitumen fumes. However, a dose-response was suggested with quantitative average exposure. A comparable association with quantitative cumulative exposure was no longer present when a 15-year lag was applied. Quantitative estimates were available only for subjects who were employed exclusively in asphalt paving. The exposure-response with average indices of exposure to bitumen fume was also suggested when we restricted the analysis to workers never exposed to tar, but it was not present for lagged quantitative cumulative exposure. However, the tar-free sub-cohort contained too few deaths for precise risk estimation across exposure groups. When lung cancer risk estimates due to quantitative bitumen fume exposure indices were adjusted for coal tar exposure in Poisson regression models, the strength of exposure-response weakened without dissipating.

The results of cancer of the buccal cavity and the pharynx were similar to those of lung cancer, although they were based on a small number of deaths.

As in all historical occupational cohort studies, misclassification of exposure is a matter of serious concern. The exposure estimates used in the study depended on many factors, the most important being (i) the validity of measurements included in the AWE database, (ii) the adequacy and validity of the models used to predict exposure, in particular the many assumptions made to assess exposures when empirical data were scanty, (iii) the quality of company questionnaires, and (iv) the completeness and validity of job history information and job classification.

We have attempted to address issues (i) and (ii) in the development of the AWE database and of ROCEM [Burstyn et al., 2000b,c, 2002, 2003]; involvement of industry representatives in the finalization of ROCEM was an additional step to improve its validity. We are aware that, notwithstanding our efforts, ROCEM exposure estimates likely contain a great deal of misclassification, in particular for job groups other than bitumen workers. Errors and inaccuracies may have occurred in the company questionnaires (issue iii). To minimize this problem, all company questionnaires were reviewed for logical inconsistencies and re-evaluated in collaboration with experts from each country. Issue (iv) is even more problematic, since it is largely out of our control. Although, through the feasibility study [Partanen et al., 1995] we aimed to select, countries and companies with good information on employment history, the final cohort included a large number of workers with poor employment information, who were either excluded from the analysis or classified in unspecific job groups, in which exposure misclassification is the greatest. For example, in the Norwegian cohort, 11 cases of lung cancer occurred among 141 individuals, who were excluded from the database due to unknown date of hiring.

However, it should be stressed that, given the prospective nature of the investigation, the sources of information bias discussed above can only result in exposure misclassification that is non-differential with respect to outcome. This type of misclassification leads to under-estimation of true risk in the case of binary exposure variables and tends to attenuate exposure-response relationships in the case of multilevel exposure variables, with a decrease in the risk estimate in the category at highest exposure, but not necessarily in the other categories [Dosemeci et al., 1990]. Therefore, exposure misclassification can generate null results such as those found for lung cancer mortality with semi-quantitative indices of exposure to bitumen fume and coal tar, but not positive associations, such as those found for lung cancer with quantitative indices of exposure to bitumen fume. However, given that exposure assessment was based on job titles, misclassification of workers employed in a job entailing an increased risk would result in an overestimate of the risk among workers employed in jobs in which high-risk workers are misclassified.

The positive associations observed between mortality from lung cancer and some indicators of exposure to bitumen fume, coal tar, and other agents may be due to confounding. Other exposures within the asphalt industry are potential confounders. We targeted our exposure assessment towards the main candidates of a possible carcinogenic effect, in particular in the lung. In the statistical analysis, we have fitted regression models including terms for exposure to several agents. In particular, inclusion of terms for cumulative exposure to coal tar (lagged by 15 years) reduced most RR estimates of lung cancer associated with indices of exposure to bitumen fume. This result suggests a confounding effect of coal tar exposure which, however, does not completely explain the positive association between lung cancer risk and quantitative indices of exposure to bitumen fume. However, the misclassification of the assessment of coal tar is likely to be greater than that of bitumen fume, resulting in incomplete adjustment. As a consequence, the effect of the 'adjustment' should be interpreted more as providing evidence of a confounding effect (and its likely direction) than as generating fully 'unconfounded' results.

The second group of potential confounders consists of occupational carcinogens to which cohort members might

have been exposed in jobs held in companies other than those included in the study (both within and outside the asphalt industry). Many members of the cohort had a rather short duration of employment in the cohort (the overall average duration of employment was 6.2 years, adjusted for length of season), and it is plausible (i) that they have been employed in other companies of the asphalt industry, and (ii) that they have been exposed to occupational carcinogens in jobs held in other industries (the first possibility is less likely in the Swedish cohort, which was enumerated on the basis of a nationwide health surveillance system instead of company records). The lack of information on employment in other companies in the asphalt industry would bias the risk estimates in an unpredictable direction: it is however plausible that bias would be more important for indices of duration of exposure (and consequently cumulative exposure) than of average level of exposure (assuming stability in jobs for the same worker and comparable working conditions across companies).

The lack of information on other jobs is a potential source of information bias, since it is possible that workers employed within our cohort in jobs with higher levels of bitumen fume exposure have also been more frequently exposed to carcinogens in other industries. Again, this phenomenon would contribute to an increase of relative risk for indices of average level of exposure, and less so for indices of cumulative exposure. Some evidence of exposure of cohort members to carcinogens outside the asphalt industry has been provided from interviews of surviving members of the Finnish cohort [Kauppinen et al., 2003]. However, there was no evidence that the effect was differential with respect to bitumen exposure level.

A third group of potential confounders includes non-occupational factors. Given the emphasis of this study on the risk of lung cancer, tobacco smoking is the main candidate for an important confounding effect. It was not possible to systematically collect information on smoking among workers included in this cohort. In studies from the USA, workers in jobs comparable to those included in this cohort (roofers, heavy equipment operators, etc.) reported a higher consumption of tobacco than other workers [Brackbill et al., 1988; Stellman et al., 1988; Nelson et al., 1994]. The presence of a stronger association with indices of average level of exposure than with indices of cumulative exposure might provide some evidence in favor of a confounding effect of smoking. The average levels of exposure in ROCEM decrease with time, as did the prevalence of smoking among blue collar workers in many of the countries included in the study [Nicholaides-Bouman et al., 1993]. As a consequence, workers in the highest categories of average level of exposure (but not necessarily of cumulative exposure) might have smoked more than workers in other categories. The elevated mortality from chronic non-neoplastic respiratory diseases is also compatible with a confounding effect of tobacco smoking, but reduced cardiovascular mortality in the overall cohort argues against this interpretation [Boffetta et al., 2001]. Furthermore, analyses of smoking patterns in the Dutch sub-cohort suggest that confounding by smoking can explain differences in lung cancer morality risk between different jobs, but not ROCEM-based exposure groups [Hooiveld et al., 2003]. A similar conclusion of confounding of comparison between lung cancer risk in different jobs by smoking was reached for the Finnish and Norwegian sub-cohorts [Kauppinen et al., 2003; Randem et al., 2003].

Other possible lifestyle-related confounders include a diet poor in fruits and vegetables, exposure to environmental lung carcinogens and factors associated with low social class [Blot and Fraumeni, 1996]. Since these factors tend to be positively correlated with tobacco smoking, their effect on risk estimates for the agents under study—if any—is likely to have been similar to that of tobacco smoking. However, since the association of lung cancer risk with diet, environmental exposures, and other social class-related factors is much weaker than that with tobacco smoking, the potential confounding effect of these other factors—if present—would be of a smaller magnitude than that of smoking.

In conclusion, our exposure-response analysis of ROCEM-derived exposure estimates suggests an association between lung cancer mortality and indices of average level of exposure to bitumen fume, while the results based on indices of duration of exposure and cumulative exposure do not consistently suggest a positive association. There are three plausible explanations for these results: (i) exposure to bitumen fume, as experienced by workers in this cohort, could be carcinogenic; (ii) the results could be due to confounding by other agents present in the asphalt industry; (iii) the results could be due to confounding by agents other than those present in the asphalt industry.

In favor of the first hypothesis, misclassification might have been greater for duration of exposure and cumulative exposure than for average level of exposure, because of the incomplete ascertainment of job histories and the limited ability to correct for the seasonal nature of the work. In addition, adjustment for other ROCEM-assessed agents and restriction of the analysis to the tar-free sub-cohort did not completely cancel the increases in RRs, and the RRs in the categories at highest average level of exposure are too high to be explained solely by confounding form tobacco smoking [Siemiatycki et al., 1988].

Coal tar is the main candidate as a confounder of the association between bitumen fume exposure and lung cancer risk. The fact that adjustment for coal tar exposure and restriction of the analysis to a coal tar-free subcohort reduced the RRs of lung cancer associated with bitumen fume exposure speaks in favor of a confounding effect. As mentioned above, it is likely that coal tar exposure assessment suffered from a greater degree of misclassification than bitumen fume exposure, resulting in imperfect adjustment of an underlying

confounding effect. We have no empirical evidence within our cohort of a confounding effect played by tobacco smoking, other occupational exposures, and other factors external to the asphalt industry. There are indirect pieces of evidence that make such a confounding effect possible. However, tobacco smoking appears to be a more likely confounder in job-level comparisons, such as that carried out in the companion paper [Boffetta et al., 2002], than in analyses based on modeled quantitative exposure indices.

Arguments similar to those applied to lung cancer can be used to discuss the increased risk of cancer of the buccal cavity and the pharynx following exposure to bitumen fume. However, some additional considerations apply to these findings. Cancers of the buccal cavity and pharynx are not consistently reported at increased risk in occupational settings in which elevated polycyclic aromatic hydrocarbon exposure occurs and lung cancer risk is increased [Boffetta et al., 1997]. The fact that the results in the total cohort are largely dependent on the contribution of the German component detracts from a causal interpretation. Alcohol drinking, in addition to tobacco smoking, is an important cause of oral and pharyngeal cancer and should be considered as a potential confounder.

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