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Exposure Assessment for a Nested Case–Control Study of Lung Cancer among European Asphalt Workers

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Objective: Development of a method for retrospective assessment of exposure to bitumen fume, bitumen condensate, organic vapour, polycyclic aromatic hydrocarbons, and co-exposures to known or suspected lung carcinogens for a nested case–control study of lung cancer mortality among European asphalt workers.

Methods: Company questionnaires and structured questionnaires used in interviews and industry-specific job-exposure matrices (JEMs) were elaborated and applied. Three sources of information were eventually used for exposure assessment and assignment: (i) data obtained in cohort phase, (ii) data from living subjects, next-of-kin, and fellow-workers questionnaires, and (iii) JEMs for bitumen exposure by inhalation and via skin and co-exposures to known or suspected lung carcinogens within and outside cohort companies. Inhalation

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and dermal exposure estimates for bitumen were adjusted for time trends, time spent in a job, and other determinants of exposure (e.g. oil gravel paving). Clothing patterns, personal protective devices, and personal hygiene were taken into consideration while estimating dermal exposure.

Results: Occupational exposures could be assessed for 433 cases and 1253 controls for relevant time periods. Only 43% of work histories were spent inside original asphalt and construction companies. A total of 95.8% of job periods in cohort companies could be coded at a more detailed level. Imputation of work time and 'hygienic behaviour' multipliers was needed for <10% of work history years. Overall, downward trends in exposure were present and differences existed between countries and companies. As expected, correlations were strongest ($r > 0.7$) among bitumen-related agents, while correlations between coal tar, bitumen-related agents, and established lung carcinogens were weaker ($r < 0.4$).

Conclusions: A systematic and detailed approach was developed to estimate inhalation and dermal exposure for a nested case–control study among asphalt workers.

Keywords: asphalt industry; bitumen; case–control study; dermal exposure; epidemiology; exposure assessment; inhalation exposure; lung cancer

INTRODUCTION AND BACKGROUND

Historically, there has been concern about past and present lung cancer risks posed by occupational exposures among asphalt workers (e.g. Partanen and Boffetta, 1994; Boffetta *et al.*, 2003a; Anttila *et al.*, 2009). Among the agents with carcinogenic potential to which a substantial proportion of asphalt workers are likely to be exposed are bitumen-related agents [bitumen fume, organic vapour, 4–6 ring polycyclic aromatic hydrocarbons (PAH), and bitumen condensate (Boffetta *et al.*, 2003b)]. At present, there is only limited knowledge on environmental or other risk factors contributing to the incidence of lung cancer in the asphalt industry. Some data show that workers may have been exposed to other chemicals or agents (within and outside the asphalt industry) that by themselves could influence the risk of lung cancer (IARC, 1984, 1985, 2010). The most important one being exposure to coal tar (Burstyn *et al.*, 2003). Thus, if exposure to these agents is related to exposure to bitumen-related agents, either positively or negatively, these co-exposures can have a confounding effect on the study outcome.

In this paper, we describe an exposure assessment method developed for a multi-centre nested case–control study of lung cancer risk in the European asphalt industry. The study is an extension of a cohort study that suggested increased occurrences of lung cancer among workers employed in road paving, asphalt mixing, waterproofing, and roofing in the asphalt industry (Boffetta *et al.*, 2003a,b; Burstyn *et al.*, 2003). Epidemiological analyses that used the exposure estimates described in this paper are reported in Olsson *et al.* (2010).

METHODS

General approach

The occupational exposure assessment strategy within the nested case–control study started from information already obtained in the cohort phase of the study (e.g. company-based work histories, company questionnaires, and empirical exposure models) (Burstyn *et al.*, 2003). Our aim was to collect more detailed information on work history within the asphalt industry and construct detailed job-exposure matrices (JEMs) for the main exposure of interest (bitumen) and co-exposures inside and outside companies enrolled in the cohort.

We also introduced assessment of dermal exposure to bitumen condensate in the nested case–control study because recent evidence suggests that this route can contribute considerably to total exposure to bitumen for workers with high degrees of contact with contaminated surfaces (McClean *et al.*, 2004a,b). Quantifying the dermal exposure route is a challenge given the complexity of the process and because only very limited data are presently available for modelling this exposure route.

The job histories, JEMs, and information from detailed occupational questionnaires were combined in deterministic algorithms that yielded semi-quantitative estimates of the relevant exposures to bitumen fume, bitumen condensate, organic vapour, PAH, and co-exposure to known or suspected lung carcinogens (asbestos, crystalline silica, diesel motor exhaust, and coal tar) for each subject.

The study population, collected information, and all exposure assessment and assignment procedures are described in detail below for the exposures of primary interest (bitumen-related exposures) and for co-exposures to known and suspected occupational lung carcinogens.

Study population

In this multi-centre nested case–control study on lung cancer, we included male workers aged <75 years, who were included in the original cohort study among European asphalt workers conducted in Denmark, Finland, France, Germany, the Netherlands, Norway, and Israel and were alive and free from cancer on 1 January 1980 (Boffetta *et al.*, 2009). In contrast to the cohort study (Boffetta *et al.*, 2001; Boffetta *et al.*, 2003a,b; Burstyn *et al.*, 2003), we excluded workers in the asphalt and construction industry from Sweden because of constraints in contacting the companies and acquiring additional exposure data. The minimal duration of employment for inclusion in the study was employment for two full seasons in any of the companies included in the cohort. The end of follow-up period was country-specific and ranged from December 2002 in France to June 2005 in Finland. The number of companies included in the study varied from 1 in Israel to 39 in Norway. We enrolled 433 cases and 1253 controls (corresponding to an overall response rate of 65% and 58%, respectively) with year of diagnosis or death between 1980 and 2005.

Questionnaire

All participating centres used the same occupational questionnaires and protocol for exposure assessment. A structured questionnaire was used in telephone interviews conducted by trained interviewers to obtain employment (within and outside asphalt and construction companies from the cohort study). For deceased subjects, we contacted one or more next-of-kin (NOK) who were selected in the following decreasing order of preference: spouse, descendant, sibling, other relative, neighbour, or friend. In addition, for deceased subjects, we aimed to interview at least one ex-colleague in the asphalt companies (‘fellow-workers’) who could provide information on job tasks, personal protective devices use (e.g. gloves), personal hygiene (e.g. showering, bathing after work, cleaning hands with solvents and fuels), and clothing patterns (e.g. wearing shorts, coveralls) of the deceased. Living subjects provided all the necessary information by themselves.

The questionnaire was designed to elicit lifetime occupational history and additional information relevant to exposure assessment, such as job titles, tasks, industries, companies, start and stop dates, working environments, and specific exposures. A separate more specific questionnaire was completed for employment in any of the following job ‘classes’: road paving, asphalt mixing, waterproofing/roofing, building construction, and ground construction. Details gathered included duration of work (e.g. length of season, days/week, and hours/day), products handled, technology in use, and any changes of these factors that had taken place over the years of interest. The actual questionnaires can be found in the supplementary material (see supplementary material I, II, and III, living subject questionnaire, NOK questionnaire, and fellow-worker questionnaire, at *Annals of Occupational Hygiene* online for details).

Work history

We reconstructed the individual job history (inside and outside the original companies for the cohort phase) for each subject based on information obtained from three sources: (i) main interview (from a living subject or NOK); (ii) fellow-worker interview (from a living subject or fellow-worker); and (iii) information obtained from company records during the cohort study. These sources of information sometimes overlapped. The information from living subjects was given the highest priority followed by information obtained from fellow-workers and then NOK. If no information from these sources was available, we relied on original cohort information.

In the cohort study, occupational histories were coded on the basis of information from personnel records according to an *ad hoc* classification of road paving, roofing, waterproofing, and building and ground construction jobs (Burstyn *et al.*, 2003). In the cohort study, the classification could only be used at the two-digit level (10 job classes). Information from living subjects, fellow-workers, and/or NOK allowed coding of job histories at a more detailed job title level (85 job titles). A job title represented the primary activity of a worker in a given time period and job class (e.g. asphalt paving) and reflected specific tasks performed (e.g. foreman, paver operator, raker man). An overview of all 85 job titles (job codes) can be found in the supplementary material (see supplementary material IV and Table 1S, at *Annals of Occupational Hygiene* online, for details).

Most subjects had part of their work history outside the original cohort companies. Jobs and industries outside the cohort companies were coded by five-digit codes of the International Standard Classification of Occupations and four-digit codes of the

International Standard Industry Classification (ILO 1968; United Nations, 1971) and NACE Rev 1.1 Classification of Economical Activities (Eurostat, 2002). Cases and controls had been active in a total of 1297 job–industry combinations.

Exposure assessment and assignment

Assessment and assignment of occupational exposure were based on three sources of information: (i) information obtained in the cohort phase of the study [e.g. company questionnaires, the Asphalt workers exposure (AWE) database, and empirical exposure models] (Burstyn *et al.*, 2000a,b, 2003); (ii) questionnaires from living subjects, NOK, and fellow-workers collected during the case–control study; and (iii) JEMs with base estimates for bitumen-related exposure by inhalation, dermal exposure to bitumen condensate, and co-exposures to known or suspected lung carcinogens within and outside the original cohort companies. These JEMs considered the following exposures: inhalation of bitumen fume, organic vapour, PAH, asbestos, crystalline silica, diesel motor exhaust and coal tar, and dermal exposure to bitumen condensate.

Due to difficulties in obtaining enough and reliable information from fellow-workers for especially cases who were almost all deceased, we decided not to use the information on techniques and materials used, work time, and 'hygienic behaviour' collected in the case–control study at individual level. Instead, we either used original company questionnaire information (for techniques and materials used) collected during the cohort phase or estimated company-, job class-, and time period-specific median levels (for work time and hygienic behaviour) from reported data by living subjects and fellow-workers in the case–control study. An overview of the sources of information used in the strategy for exposure assessment and the type of metrics for assessed exposures is presented in Table 1 (discussed further below).

Bitumen-related agents

The intensity of exposure to bitumen fume within the asphalt industry for all 85 possible job titles was assessed independently by two experts and any differences of opinion were resolved by consensus (I.B. and H.K.). Distinctions were made in assessment of exposures for various routes of exposure (airborne and dermal).

Semi-quantitative base estimates for inhalation exposure to bitumen fume, organic vapour, and PAH emitted from bitumen- and tar-containing materials, excluding those originating from diesel motor exhaust, were estimated for job titles specifically created for the asphalt and construction industries. We started with the statistical models derived from the AWE database (Burstyn *et al.*, 2000b). Relative differences in exposure intensity between job titles ('base estimates') were predominantly based on a re-appraisal of measurements in the AWE database, where we took into account a maximum 4-fold difference in average exposure concentrations between workers within a paving crew (Burstyn and Kromhout, 2000). The list of base estimates was completed through reaching consensus after individual assessments by I.B. and H.K. The inhalation base estimates are presented in the supplementary material (see supplementary

Table 1. Overview of sources of information used and type of metrics for assessed exposures

Exposures	Route of exposure			
	Inhalation			Dermal
Main exposure	BF	OV	PAH	BC
Base estimate	mROCEM	mROCEM	mROCEM	ROCDEM
Time trend	ROCEM	ROCEM	ROCEM	ROCEM
Work time	LS/FW	LS/FW	LS/FW	LS/FW
Hygienic behaviour	N.A.	N.A.	N.A.	LS/FW
Oil gravel	CQ	CQ	CQ	N.A.
Coal tar	N.A.	N.A.	CQ	N.A.
Co-exposures	Asbestos	Silica	DME	Coal tar
Inside asphalt/constr	CQ SQ	SQ	SQ	CQ SQ
Outside asphalt/constr	ISCO/ISIC SQ	ISCO/ISIC SQ	ISCO/ISIC SQ	ISCO/ISIC SQ

BC, bitumen condensate; BF, bitumen fume; CQ, company questionnaire information; DME, diesel motor exhaust; FW, fellow-worker; ISCO/ISIC, five-digit codes International Standard Classification of Occupations and four-digit codes International Standard Industry Classification; LS, living subjects; mROCEM, modified-road construction workers' exposure matrix; N.A., not applicable; OV, organic vapour; ROCDEM, road construction workers' dermal exposure matrix; ROCEM, road construction workers' exposure matrix; SQ, semi-quantitative estimates (0, 1, and 2).

material IV and Table 1S, at *Annals of Occupational Hygiene* online, for details).

Semi-quantitative estimates of relative intensity of dermal exposure to bitumen condensate were assigned to the same 85 job codes. Information that was used for this purpose arose from six dermal exposure measurement surveys performed in The Netherlands (Jongeneelen *et al.*, 1988), USA (McClean *et al.*, 2004a,b, 2007), Finland (Väänänen *et al.*, 2005, 2006), and Italy (Cirla *et al.*, 2005) and from structured semi-quantitative dermal exposure assessment (DREAM) observations (van-Wendel-de-Joode *et al.*, 2003) of paving and mastic crews specifically performed as part of this study in Germany, Denmark, France, and The Netherlands.

These observations were done by the same ‘trained experts’ in all countries to mitigate inter-observer differences. Even though data from relatively few studies could be incorporated into common format, the number of data points available for the dermal exposure assessment exceeded 500 (444 measurements and 89 DREAM observations). The majority of these data were from paving and roofing crews.

For all dermal exposure measurement studies, the geometric mean exposure to pyrene (PAH in case of the Italian study) at the wrist pad was calculated and normalized against the dermal exposure at the wrist of a screed man (arbitrarily set to 100). The same procedure was used for the semi-quantitative estimates resulting from the DREAM observations. Consequently, an average exposure for dermal exposure at the hands was estimated by taking a weighted (by number of observations) geometric mean exposure across the studies. The resulting estimate was again normalized against the estimates for the lorry driver transporting asphalt, whose exposure was set to 1. This procedure resulted in semi-quantitative dermal exposure estimates for 13 job title codes out of 21 among road pavers, 1 job title code out of 7 among mixers, and 2 job title codes out of 12 among waterproofers and roofers. The job titles codes without estimates ($N = 24$) and other (ground and building construction) job title codes ($N = 45$) were independently assessed taking the estimates of the 16 job title codes with dermal exposure data into account by two occupational hygienists (I.B. and H.K.) and the consensus score was kept. The base estimates for dermal exposure to bitumen condensate are presented in detail in the supplementary material (see supplementary material IV and Table 1S at *Annals of Occupational Hygiene* online).

Algorithms for exposure assignment

The detailed work histories were linked to the JEM with base estimates and were adjusted for actual work time and hygienic behaviour to arrive at semi-quantitative exposure metrics for each subject for each year of follow-up. The actual algorithms for inhalation exposure (equations 1–6) and dermal exposure (equations 7–8) are given below.

Inhalation exposure base estimates (for the year 1997) for a given job were adjusted for time trend according to calendar year in which that specific job was performed. The same time trends as in the cohort study were applied to the inhalation exposure assuming absence of a time trend prior to 1970 but a continuing downward time trend after 1970 (Burstyn *et al.*, 2000b, 2003).

In addition, the estimates were adjusted for actual average job duration per year (algorithms 1–6). For each company, each job class and each time period the median length of fellow-worker/living subject reported paving season were multiplied by the reported median length of the work week and length of work day. This number was divided by 480 (12 months × 5 days × 8 h) to calculate the job duration modifier. In this calculation, a work week including work on Saturdays was set at 5.6 (rather than 6) days following discussion with country-specific experts.

Presence of oil gravel paving (only in Norway in specific companies) was also taken into account using the multipliers described by Burstyn *et al.*, (2000b). Oil gravel paving decreased exposure to bitumen fume by a factor 0.22 and exposure to PAH by a factor 0.52, while in contrast exposure to organic vapour increased by a factor 1.62 (algorithms 2 and 3 and 5 and 6).

A coal tar use multiplier was applied in the algorithm for exposure to PAH (Burstyn *et al.*, 2000b). The intensity score of exposure to PAH was multiplied by a factor 5.37 when coal tar was being used (algorithms 3 and 6). Information on use of coal tar and oil gravel paving came from the original company questionnaires obtained from the cohort study as a primary source. If the company questionnaires with this information was lacking or the company the subject had worked in was not part of the cohort study, information coming from the fellow-worker or living subject interview was used, taking into account the expertise of country-specific local industry experts. In two cases, external information was used as well, e.g. confounder study for roofers in Finland and Denmark (Priha *et al.*, 2008).

The algorithms used for the three inhalation exposure variables were as follows for the period 1970–2005:

$$\text{bitumen fume}_{x,y1,z1} = \text{base estimate}_{bf,y1,1997} \times \left(\exp^{((1997-z1)\times 0.062)}\right) \times \text{work time multiplier}_{x,y2,z2} \times \exp^{(-1.51)}\text{oil gravel}_{x,y2,z1}(1/0) \quad (1)$$

$$\text{organic vapour}_{x,y1,z1} = \text{base estimate}_{ov,y1,1997} \times \left(\exp^{((1997-z1)\times 0.135)}\right) \times \text{work time multiplier}_{x,y2,z2} \times \exp^{(0.48)}\text{oil gravel}_{x,y2,z1}(1/0) \quad (2)$$

$$\text{PAH}_{x,y1,z1} = \text{base estimate}_{PAH,y1,1997} \times \left(\exp^{((1997-z1)\times 0.107)}\right) \times \text{work time multiplier}_{x,y2,z2} \times \exp^{(-0.65)}\text{oil gravel}_{x,y2,z1}(1/0) \times \exp^{(1.68)}\text{coal tar use}_{x,y2,z1}(1/0) \quad (3)$$

where x = company, $y1$ = job title code, $y2$ = job class, $z1$ = calendar year, and $z2$ = calendar year period.

For each year prior to 1970, the algorithms were as follows:

$$\text{bitumen fume}_{x,y1,z1} = \text{base estimate}_{bf,y1,1997} \times \left(\exp^{((1997-1970)\times 0.062)}\right) \times \text{work time multiplier}_{x,y2,z2} \times \exp^{(-1.51)}\text{oil gravel}_{x,y2,z1}(1/0) \quad (4)$$

$$\text{organic vapour}_{x,y1,z1} = \text{base estimate}_{ov,y1,1997} \times \left(\exp^{((1997-1970)\times 0.135)}\right) \times \text{work time multiplier}_{x,y2,z2} \times \exp^{(0.48)}\text{oil gravel}_{x,y2,z1}(1/0) \quad (5)$$

$$\text{PAH}_{x,y1,z1} = \text{base estimate}_{PAH,y1,1997} \times \left(\exp^{((1997-1970)\times 0.107)}\right) \times \text{work time multiplier}_{x,y2,z2} \times \exp^{(-0.65)}\text{oil gravel}_{x,y2,z1}(1/0) \times \exp^{(1.68)}\text{coal tar use}_{x,y2,z1}(1/0) \quad (6)$$

We applied a similar time trend for dermal exposure to bitumen condensate as for inhalation to bitumen fume, despite the fact that we lacked historical dermal exposure data that should have been required to establish such a trend. The rationale for this was that the main routes of dermal exposure, 'direct deposition of bitumen fume' and 'contact with contaminated surfaces with bitumen condensate', would be affected in a similar way by temporal trends in bitumen fume concentrations in the air.

Dermal exposure estimates were, like the inhalation exposure estimates, adjusted for actual work time within each calendar year period. In addition, we applied a hygienic behaviour multiplier to take into account clothing patterns, personal protective devices use, and personal hygiene (algorithms 7 and 8).

As with the actual work time modifiers, we estimated hygienic behaviour modifiers at company, job class, and time period levels, based on reported information from living subjects and fellow-workers. Hygienic behaviour multiplier was estimated on the basis of seven items: wearing a coverall, short sleeves, shorts, gloves, working with bare trunk, showering/or bathing directly after work and cleaning hands with industrial surfactants, diesel fuel, or solvents. The overall (across countries, companies, job classes, and time periods) distribution of median percentages of time trends for each of these items was used to assign a score of 1, 3, or 10 to each item (van-Wendel-de-Joode *et al.*, 2003). The sum of these scores for each subject's job was divided by 70 to yield a summary hygienic behaviour multiplier. Optimal hygienic behaviour (wearing a coverall, no short sleeves, no shorts, not working with bare trunk, wearing gloves, showering/bathing directly after work, and cleaning hands with water and soap) resulted in a multiplier of 0.10 (7/70).

The algorithm for dermal exposure to bitumen condensate for the years 1970–2005 is described by:

$$\text{bitumen condensate}_{x,y1,z2} = \text{base estimate}_{bc,x,y1} \times \left(\exp^{((1997-z1)\times 0.062)}\right) \times \text{work time multiplier}_{x,y2,z2} \times \text{hygienic behaviour multiplier}_{x,y2,z2} \quad (7)$$

where x = company, $y1$ = job code, $y2$ = job class, $z1$ = calendar year, and $z2$ = calendar year period.

For each year prior to 1970, the algorithm was as follows:

$$\text{bitumen condensate}_{x,y1,z2} = \text{base estimate}_{bc,x,y1} \times \left(\exp^{((1997-1970)\times 0.062)}\right) \times \text{work time multiplier}_{x,y2,z2} \times \text{hygienic behaviour multiplier}_{x,y2,z2} \quad (8)$$

Co-exposures to known and suspected occupational lung carcinogens

Exposure to other known and suspected lung carcinogens was assessed separately for work years spent within and outside the original companies from the cohort study (Table 1). Exposure to coal tar, crystalline silica, diesel motor exhaust, and asbestos was assigned to each individual through a JEM for the asphalt and construction industry. Two hygienist (H.K. first and reviewed by I.B.) assessed a semi-quantitative intensity score (0, 1, and 2) for each of the job title codes and a consensus score was kept.

A similar approach was used for jobs outside the asphalt and construction industries (1297 job–industry combinations). In principle, time period-specific adjustments were only made for the asphalt and construction industries, in which exposure to asbestos or coal tar was only assigned when an individual worked during the time when these agents were still in use. The last year in which coal tar was used was mainly derived from the information provided from the companies in the original company questionnaires. For asbestos, a similar procedure was applied with the original company questionnaires again as primary source of information. If within the original company questionnaire, this information was lacking or a company was not part of the original cohort study, information coming from the fellow-worker interview was used, taking into account the appraisal of country-specific local industry experts.

The two JEMs were linked to each individual and intensity scores were raised to power of two before multiplying by duration of exposure to derive an indicator expressed in exposure years. Intensity was raised to the power of two to reflect the lognormal distribution of occupational exposures in the calculation of cumulative exposure, which otherwise would be purely dominated by the duration part of the equation (Sunyer *et al.*, 2005). Eventually, with both matrices using the same scale for intensity, it was possible to sum exposures to other lung carcinogens across the full job history for each individual.

Statistical analysis

For each agent, three dimensions of exposure were assessed: duration of exposure (years), cumulative exposure (semi-quantitative unit-years), and average exposure (semi-quantitative units). Assessed historical exposure patterns (average assigned intensity plotted versus time periods) were also examined graphically for each agent and type of exposure measure.

Descriptive statistics and Pearson correlations between cumulative exposures (estimates) for each of the assessed agents were calculated. Microsoft Access 2.0 facilitated data management and database applications development. All statistical analyses were carried out in SAS version 9.1 (SAS, 2003) and graphs were prepared in Sigma Plot version 10.0 (Systat, 2006).

RESULTS

Occupational exposures could be assessed for all 1686 subjects (433 cases and 1253 controls) for all relevant years.

Sources of information

Only 2% of cases and 66% of controls were interviewed in-person. Spouses and children were the most commonly interviewed NOK. Non-relative NOK was the source of information for 4% of cases and only 1% of controls.

Fellow-workers and NOK provided information for >94% of person-years of cases, while this percentage was <30% for controls, among whom >70% of person-years were covered by the subjects themselves. Company records collected during the cohort study were used for 3% of person-years of cases and 1% of person-years of controls. Country-specific percentages can be found in the supplementary material V and Table 2S, at *Annals of Occupational Hygiene* online.

Detail of job histories and imputation of multipliers

The number of work history years spent inside and outside of the asphalt and construction industries is shown in Fig. 1. Overall, the cases and controls spent 43% of their work history inside the asphalt and construction companies included in the cohort. Among cases and controls from Finland, this percentage was the lowest (36%), while it was the highest in The Netherlands (61%).

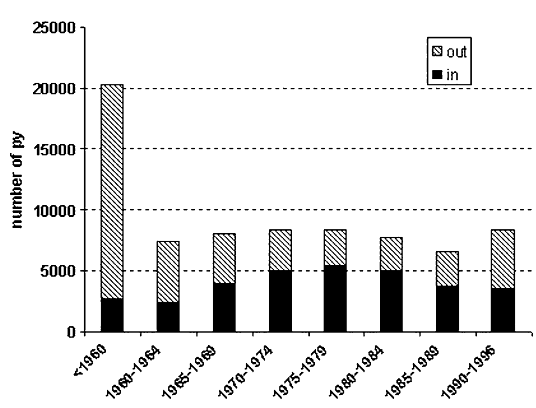

Fig. 1. Number of work history years spent inside and outside the original cohort companies by time period.

Within the companies that took part in the cohort study, jobs could be coded at job title level for 95.8% of all work-history years. Coding was done at the less specific (job class) codes only for <4% of all years of work histories.

Imputation of work time and hygienic behaviour multipliers was needed for, respectively, 18.6% and 8% of years of work histories. For 10% of work history years, either one or both multipliers had to be imputed. In Fig. 2, the distribution of work history years with extrapolated multipliers is shown by time period. The figure shows that for the period prior to 1960 for about one-third of all person-years imputation was needed. However, actual number of years spent in the asphalt industry during this time period was limited (Fig. 1).

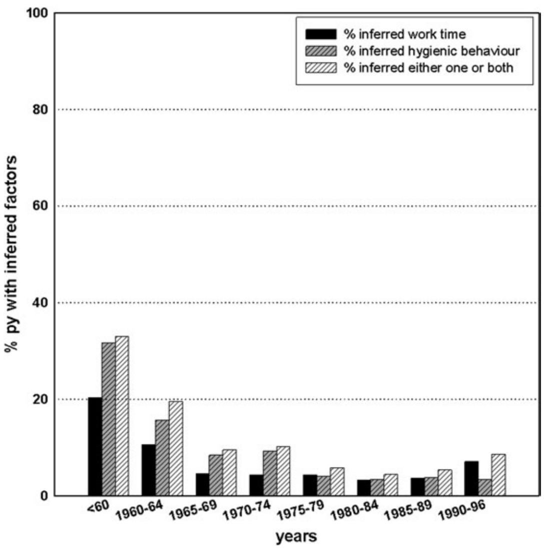

Fig. 2. Percentage of work history years with extrapoled work time and 'hygienic behaviour' multipliers.

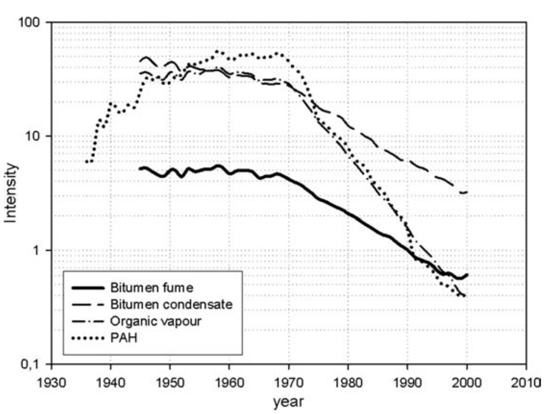

Fig. 3. Temporal trends in assigned exposure intensity for main exposure variables.

Trends in assigned exposure intensity

In Fig. 3, temporal trends in assigned exposure intensity are presented for the main exposure variables across all countries. Only for exposure to PAH, a clear upward trend is visible prior to 1970. The phasing out of coal tar subsequently resulted in a steep decline of average assigned PAH exposure intensity scores across countries. The trend in organic vapour intensity resembled that of PAH. Trends in inhalation to bitumen fume and dermal exposure to bitumen condensate were quite similar, but due to considerable differences in hygienic behaviour and actual work time, important differences of up to a factor of three in assigned bitumen condensate intensity between countries were present (see supplementary material V and Figure 1S, at *Annals of Occupational Hygiene* online, for details).

For inhalation exposures to bitumen fume, organic vapour, and PAH, differences among countries were considerable (see supplementary material V and Figures 2S–4S, at *Annals of Occupational Hygiene* online, for details) again due to differences in work time, in variability of end date for use of coal tar and time trends in predominant paving techniques (e.g. oil gravel paving).

Distribution of estimated occupational exposures

Overall, 841 controls (67.1%) were exposed to bitumen fume with a median duration of exposure of 15.5 years. Corresponding values for average exposure were 2.2 units (range 0.1–16.7) and for cumulative exposure 28.2 unit-years (range 0.2–620).

The prevalence of exposure to organic vapour was similar, but for PAH somewhat higher at 84.8%. In the case of dermal exposure to bitumen condensate, the proportion of exposed individuals was 67.8% with similar median duration of exposure of 15.5 years. Median cumulative exposure to bitumen condensate was 185 unit-years (range 0.6–4000) and median average exposure was 13.5 units (range 0.3–94).

The prevalence of exposure to asbestos was 73.6%, prevalence of exposure to crystalline silica was 76.8%, and prevalence of exposure to diesel motor exhaust 95.1%. The prevalence of exposure to coal tar was much lower at 32.7% and differed considerably between countries (Israel 0%–Denmark 54%). Country-specific estimates of estimated main exposures of interest and co-exposures can be found in the supplementary material VI and Table 3S, at *Annals of Occupational Hygiene* online.

Correlations between exposure variables

Correlation coefficients between cumulative exposure estimates are presented in Table 2. As expected, correlations were strongest ($r > 0.7$) between bitumen-related agents (bitumen fume, bitumen condensate, PAH, and organic vapour) and considerable ($0.4 < r < 0.7$) between coal tar and bitumen-related agents. Correlations were rather weak ($r < |0.4|$) for the remaining three co-exposures (asbestos, crystalline silica, and diesel motor exhaust) and measures of exposure to bitumen.

DISCUSSION AND CONCLUSIONS

We presented exposure assessment and assignment methodology that was used in a nested case–control study of lung cancer risk among asphalt workers. For the first time in an epidemiological study, we were able to assess exposure to bitumen via both inhalation as well as the dermal route. We obtained more comprehensive data on employment histories than in both the original cohort study (Boffetta *et al.*, 2003a,b) and any other study of cancer risk among asphalt workers (Partanen and Boffetta 1994). In particular, more detailed job histories in the asphalt industry were collected, at the level of specific jobs and tasks within an occupation. Additionally, we obtained insight into employment history during the considerable number of working years spent by cases and controls outside of the companies enrolled in the original cohort and even outside the asphalt industry. These more detailed employment histories allowed much more detailed inputs into assignment of inhalation exposures to the main agents of interest and co-exposures. For dermal exposure to bitumen condensate, a new model was created on the basis of available dermal measurements and observations (Jongeneelen *et al.*, 1988; McClean *et al.*, 2004a,b, 2007; Väänänen *et al.*, 2005, 2006; Cirla *et al.*, 2005) and using a recently developed dermal exposure observation method (van-Wendel-de-Joode *et al.*, 2003). The main limitations of the exposure assessment were lack of reliable information at the individual study subject level, and the semi-quantitative nature of the exposure estimation, as well as lack of understanding of the extent of error in the exposure estimates. This lack of understanding of measurement error structure and magnitude makes it very challenging to predict how uncertainty in exposure assessment may impact epidemiological analyses.

We are certain that the estimation of the main exposures of interest (e.g. inhalation exposure to bitumen fume, organic vapour and PAH as well as dermal exposure to bitumen condensate) has been less error prone than the co-exposures to coal tar, asbestos, crystalline silica, and diesel motor exhaust. The information available for the latter exposures was much more limited and was not available at company level outside the cohort companies. In addition within the asphalt industry, exposure intensity has been relatively low (diesel motor exhaust) or have occurred only during a very limited time period (e.g. asbestos in asphalt mixes).

Information from NOK on specific job details from deceased cases and controls lacks often necessary detail and accuracy (Boyle and Brann, 1992; Hansen *et al.*, 1997). As suggested by Hansen *et al.* (1997), we therefore in addition approached fellow-workers to provide details on jobs performed within the asphalt companies. However, contrary to initial plans, the data collected from fellow-workers were too sparse to allow the modulation of job history-based exposure estimates at individual study subject level, by factors such as hygienic behaviour and work time. In addition, living subjects providing this information were predominantly controls and using this information at the individual level would have led to a systematic bias in risk estimates between cases and controls. The use of this information

Table 2. Pearson correlation coefficients between cumulative exposure variables (exposed subjects only)

Agent	BF	OV	PAH	BC	Asbestos	Silica	DME	Coal tar
BF	1.00**	0.90**	0.86**	0.72**	−0.15**	−0.31**	0.29**	0.42**
OV		1.00**	0.86**	0.72**	−0.14**	−0.29**	0.31**	0.40**
PAH			1.00**	0.74**	−0.07*	−0.20**	0.29**	0.61**
BC				1.00*	−0.15**	−0.32**	0.39**	0.47**
Asbestos					1.00**	0.15**	0.13**	−0.16**
Silica						1.00**	0.02	−0.25**
DME							1.00**	0.25**

BF, bitumen fume; BC, bitumen condensate; DME, Diesel motor exhaust; OV, organic vapour.
* $p < 0.01$, ** $p < 0.0001$.

at company, job class, and time period levels instead will have led to some misclassification. We believe nevertheless, that company, job class and time period will be the most important determinants of work content, work time and availability of protective clothing, gloves, and facilities, such as presence of showers at the work site.

In conclusion, the present study used the most detailed and elaborated exposure assessment method in comparison with previous studies among asphalt workers. We developed a systematic and a detailed approach to estimate exposure to relevant known and suspected carcinogens within and outside the asphalt industry. This methodology can be adopted in other case–control studies of occupational exposures to achieve, at the very least detailed and explicit documentation of exposure assessment.

SUPPLEMENTARY DATA

Supplementary data can be found at http://annhyg.oxfordjournals.org/.

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