

Chapter 8: Evaluation of performance of different exposure assessment approaches and indices in analysis of an association between bitumen fume exposure and lung cancer mortality.

Burstyn I, Boffetta P, Kauppinen T, Heikkilä P, Svane O, Partanen T, Stücker I, Frentzel-Beyme R, Ahrens W, Merzenich H, Heederik D, Hooiveld M, Langård S, Randem B, Järholm B, Bergdahl I, Shaham J, Ribak J, Ferro G, Brunekreef B, Kromhout H: Evaluation of performance of different exposure assessment approaches and indices in analysis of an association between bitumen fume exposure and lung cancer mortality (in preparation).

Abstract

Objective: To evaluate performance of different exposure assessment approaches in cohort study of cancer risk among European asphalt workers.

Methods: Exposure to bitumen fume among pavers and lung cancer risk was the focus of this methodological investigation. Members of the cohort selected for analysis were males employed in asphalt paving only, for at least one paving season. An inception/entry sub-cohort was also identified among these persons. Three exposure indices were considered: duration of exposure (years), average exposure (mg/m^3) and cumulative exposure ($\text{mg}/\text{m}^3 \cdot \text{years}$). Two latency models were considered for an association between lung cancer and bitumen fume: with and without a 15-year lag. Standardized mortality ratios (SMRs) and 95% confidence intervals (CI) were computed. We examined rank correlations among bitumen fume exposure indices. Relative risk associated with bitumen fume exposure was estimated via Poisson regression. All models were adjusted for coal tar exposure (ever/never), age, calendar period and country. Competing exposure-response models were compared using a log-likelihood ratio test (measure of model fit).

Results: We selected 12,367 male workers employed only in asphalt paving for at least one paving season for analysis. In the cohort, there were 134 deaths due to lung cancer versus 106.91 expected (SMR=1.25; 95%CI: 1.05-1.48). Only exposure ranks based on strata of duration and cumulative exposure indices were correlated. There was no association between lung cancer risk and either duration or cumulative exposure. However, there was the suggestion of an increase in lung cancer risk accompanying rise in average exposure. Only models with average bitumen fume exposure (with or without lag) markedly improved model fit. Average bitumen fume exposure indices with and without 15-year lag improved model fit to the same extent.

Conclusions: We found a positive association between average bitumen fume exposure and lung cancer mortality risk. This association could be the result of confounding by other carcinogenic exposures and lifestyles. No clear latency model emerged from analysis. Constructing quantitative exposure indices appeared to have been justified because (a) the healthy worker effect confounded any associations between duration of exposure and lung cancer mortality risk and (b) we identified statistically significant associations between bitumen fume exposure and lung cancer risk that require further investigation.

Introduction

This study of cancer risk in the European asphalt industry was prompted by an ongoing controversy over the carcinogenicity of emissions derived from bitumen, a binder used in asphalt (1-8).¹ The controversy was prompted by results of previous studies of the health effects of emissions derived from bitumen (the current binder used in the asphalt mix in Western Europe) that suggested that asphalt workers were at elevated risk for lung cancer (1-9). The International Agency for Research on Cancer (IARC) coordinated the study. One of the components of the study was the assessment of occupational exposures to known and suspected lung carcinogens in the asphalt industry. There is a belief among some epidemiologists and exposure assessors that quantitative exposure assessment of exposure intensity, when possible, is preferable to semi-quantitative and qualitative methods of assessing exposure (10-12). This is driven, at least in part, by the need to conduct quantitative risk assessment on the basis of human exposure data. Nonetheless, quantitative exposure assessment has rarely been performed for large historical occupational cohorts, primarily due to lack of sufficient exposure monitoring data. For a multicentric epidemiological study of lung cancer among persons exposed to bitumen, we constructed a large database of exposure measurements (13) that was used to build statistical models of exposure intensity to bitumen fume (14), the main exposure agent of interest. The elaborated model was shown to be reasonably valid (15) and was applied to construct a study-specific exposure matrix with quantitative bitumen fume exposure estimates for workers in asphalt paving (16). Another approach to assessing exposure among asphalt paving workers would be to assume that they were all exposed to the same concentration of bitumen fume. This would lead to differences in cumulative bitumen fume exposure among asphalt pavers, depending only on exposure duration. In this report we set out to compare the performance of these two exposure assessment approaches, under different latency assumptions, in exposure-response modeling of bitumen fume and lung cancer for asphalt paving workers.

Methods

Cohort

IARC coordinated assembly of a retrospective cohort of asphalt workers from European companies in the asphalt industry (road paving, asphalt mixing and roofing) in eight countries (Denmark, Finland, France, Germany, the Netherlands, Norway, Sweden and Israel). Asphalt workers in the context of this study were defined as individuals involved in handling asphalt, from its manufacture at an asphalt plant to its application in road paving. In addition, a small number of roofers and waterproofers were enrolled in the study in some countries. There were also employees in the target companies that had been employed in ground and building construction. Employees of oil refineries who might be considered asphalt workers were excluded.

The current analysis focused on those members of the cohort who were employed only in asphalt paving, in order to enable quantitative exposure assessment and reduce the possibility of confounding due to exposures to carcinogens from outside the asphalt industry. Female subjects were excluded from analysis because they represented a small proportion of the cohort. Furthermore, the Swedish cohort was also excluded from the current analysis because duration of exposure could not be accurately estimated for the majority of its members. This

¹ Throughout this manuscript we will use the European convention of referring to the binder used in asphalt mixes as 'bitumen'. In the USA, the binder is referred to as 'asphalt'.

was a consequence of the fact that the job histories in Sweden consisted only of the job held at the time of entry into the cohort. Lastly, a minimal duration of employment of one paving season was applied for inclusion in the cohort. All subjects selected for analyses were exposed to bitumen fume because bitumen was always used in the binder during asphalt paving.

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. A basic requirement 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.

Employment histories were coded according to a classification of jobs, which was constructed for the study (chapter 7). These job classes formed the basis for the linkage between employment histories of individual workers and estimates of exposure derived from the Road Construction Workers' Exposure Matrix (ROCEM, see chapter 7).

Exposure assessment

Details of exposure assessment were presented in chapter 3 (construction of exposure measurement database), chapter 4 (statistical modeling of bitumen fume exposure among pavers), chapter 6 (validation of the bitumen fume exposure models) and chapter 7 (assembling the study-specific exposure matrix ROCEM). This process will only be briefly reviewed here. In chapter 3 we described how individual exposure measurements from European asphalt companies, in countries enrolled in the cohort, were assembled into a single database. The exposure data comprised industrial hygiene measurements of exposure levels for a variety of agents among asphalt workers, and supplementary information. The supplementary information allowed linkage of exposure measurements with information on production conditions in firms recruited for the study, collected via company questionnaires. Most of the available exposure data was collected in the participating countries as of February 1999 (N of measurements 2007). The major contributors (70% of samples) were the four Nordic countries, with 35% of samples collected in Norway. The earliest samples originated from the late 1960's, and the majority were collected in the late 1970's and between 1985 and 1997. The data set was judged to be sufficiently large and balanced to permit statistical modeling of the intensity of exposure to bitumen fume in paving operations.

In chapter 4, we presented how exposure measurement data was used to construct a predictive model of bitumen fume exposure. The model identified a declining time trend in exposure concentrations between 1970 and 1997. Mastic laying, re-paving, surface dressing, and oil gravel paving were significant determinants of bitumen fume exposure. It was concluded that for road paving workers, bitumen fume exposure intensity could be assessed on the basis of time period and production characteristics. In chapter 6 we described how bitumen fume exposure model was validated by comparing predicted values with those measured in the USA. The data used in this external validation was not used to construct the models described in chapter 4. Predicted bitumen fume exposures tended to be lower (average factor of 3) than concentrations found during paving in the USA. This apparent bias might be attributed to known differences between Western European and USA paving practices. In addition, the internal validity of the bitumen fume exposure model was evaluated by a modified cross-validation procedure. The bitumen fume exposure model appeared to be internally valid but imprecise. Overall, the validity of bitumen fume exposure models was assessed as satisfactory, given the available exposure data.

In chapter 7, we described the linkage of the statistical models of exposure to the company questionnaires to produce a study-specific exposure matrix, ROCEM. Production characteristics in the companies enrolled in the study were ascertained via a questionnaire and consultations with industry representatives and industrial hygienists. Quantitative exposure estimates for road paving workers were derived by applying regression models (based on monitoring data, chapter 4) to exposure scenarios identified by company questionnaires. Information on coal tar use was derived directly from the questionnaires. All estimates were standardized to an 8-hour work-shift. The resulting exposure matrix was time period-, company- and job class-specific. The exposure matrix showed a non-monotonic historical decrease in bitumen fume exposure, with exposure temporarily rising in the 1970's due to substitution of oil gravel paving (cold application) with hot mix asphalt paving. According to the exposure matrix, road pavers were not exposed to asbestos and there was no variability in their exposures to respirable silica and asbestos. Estimates of bitumen fume, organic vapour and PAH were strongly correlated, indicating that their health effects could not be assessed independently. On the other hand, there was little correlation between coal tar use and bitumen exposure concentrations, indicating that it might be possible in the cohort to adjust for potential confounding by coal tar exposure.

Exposure indices

In the analyses with ROCEM-based estimates of exposure, we derived for each worker the following indices of bitumen fume exposure: (a) duration of exposure, (b) cumulative exposure (product of exposure duration and intensity, integrated over work-history) and (c) average exposure over the work history (ratio of cumulative exposure and duration of exposure). In estimating duration of exposure we had to correct for the seasonal nature of work in the asphalt industry, given that the working season 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 (full calendar year). Each incomplete calendar year of employment was 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. In order to model the latency associated with lung cancer, additional indices were created of duration of exposure, average exposure and cumulative exposure, after ignoring the last 15 years before death or end of follow-up (15 year lag).

For each quantitative exposure index, unexposed subjects formed a separate category, and exposed subjects were divided into quartiles, each including approximately one fourth of lung cancer deaths (International Classification of Diseases (ICD) 9th revision: code 162). Subjects with unknown exposure were excluded from analysis. The same cut-points for the definition of quartiles were kept in analyses of subsets of the cohort (e.g., inception cohort) in order to permit a direct comparison across subsets.

To assess the influence of truncated job histories and follow-up times, analyses were also repeated on the “inception cohort”, comprising only subjects who entered employment in the participating firms after or at the start of follow-up.

Follow-up and statistical analysis

A follow-up for mortality was conducted in all participating countries. The earliest follow-up started in 1953, and the latest ended in 2000. The overall loss to follow-up was 0.6% and varied little between countries.

Standardized mortality ratios (SMRs) were computed for persons employed only as pavers, allowing comparison of risk to the general population. Age-, calendar period- and sex-specific national mortality reference rates were computed using the mortality data bank of the World Health Organization. The expected numbers of deaths were derived by multiplying the accumulated person-years by the national reference rates across sex, age, and calendar-year strata, and SMRs were calculated as ratios of observed and expected numbers of deaths. An in-house IARC computer program was used to estimate the individual contribution to each stratum and to calculate SMRs and 95% confidence intervals (95%CI) based on the Poisson distribution of observed numbers of deaths. SMRs were not calculated if the number of expected deaths was zero.

Rank correlation between different indices of bitumen exposure was examined using Spearman correlation coefficients.

Relative risks (RR) and associated 95% confidence intervals were estimated using Poisson regression (17). All Poisson regression models included age (0-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80+ years), calendar period of exit from cohort (\leq 1974, 1975-1979, 1980-1984, 1985-1989, 1990 and later), country and coal tar use (yes/no). The coal tar exposure variable was included in the models in order to test for potential confounding of an effect of bitumen fume exposure (if any) by coal tar exposure.

An improvement in model fit, upon addition of bitumen fume exposure index, was evaluated using a profile log-likelihood ratio test (18). Degrees of freedom for the log likelihood ratio (LL) test were equal to the number of levels of a categorical variable added to the model, minus one. The log-likelihood ratio test was computed as

$$-2 \times (\text{change in LL due to bitumen fume exposure variable}).$$

The log-likelihood ratio follows an approximately chi-squared distribution that can be used to evaluate the statistical significance of the test. A one-sided chi-squared p-value was used, because we expected model fit to either improve or remain unchanged.

Poisson regression analyses were carried out in STATA 6.0. Person-year allocation was carried out in SAS 6.12 (using an in-house computer program developed at IARC).

Results

We selected 12,367 male workers employed only in asphalt paving for one or more paving seasons for analysis. Among these persons, 8,472 belonged to the inception cohort. In the entire cohort selected for analysis, a total of 1,625 persons were reported to have died at the end of the follow-up versus 1,656.56 expected, yielding an SMR of 0.98 (95%CI: 0.93-1.03). The SMR for all malignant neoplasms (ICD-9, codes 140-208) was close to the expected value (SMR=0.99; 408 observed; 95%CI: 0.90-1.09). There were 134 deaths due to lung cancer versus 106.91 expected. This constituted a statistically significant increase in lung cancer risk compared to the general population (SMR=1.25; 95%CI: 1.05-1.48).

Duration and cumulative exposure indices were highly correlated ($r=0.82$). However, cumulative and average exposure indices were not correlated ($r=0.09$). Likewise, duration and average exposure indices were not correlated ($r=-0.19$). Lagged exposure variables showed a similar pattern: $r=0.92$ between lagged cumulative and duration exposure indices, $r=0.52$ between average and duration exposure indices, and $r=0.61$ between average and cumulative exposure indices. All p-values for Spearman rank correlation coefficients were less than 0.00001.

Table 8.1 presents relative risk estimates quantified through Poisson regression models. There appears to be no association between duration of bitumen fume exposure and lung cancer mortality, with some suggestion of a decrease in risk for persons with longer duration of exposure. Cumulative bitumen fume exposure was also not associated with lung cancer risk. These patterns persisted for the inception cohort and upon lagging duration and cumulative exposure variables. An increase in average bitumen fume exposure was associated with a statistically significant rise in risk of lung cancer mortality. Lagged average bitumen fume exposure followed an unusual pattern. Persons exposed 15 years prior to diagnosis (unexposed group in lagged analysis) were at a higher risk of lung cancer mortality than persons in the lowest quartile of lagged average bitumen fume exposure. However, as the level of lagged average bitumen fume exposure increased, so did the risk of lung cancer mortality. The highest quartiles of average lagged bitumen fume exposure were associated with a statistically significant higher risk of lung cancer mortality than the "unexposed" category.

Only average exposure indices (lagged or not) improved model fit (Table 8.2). Both lagged and non-lagged average bitumen fume exposure variables produce the same improvement in the fit of a model that included only age, calendar period, country and coal tar use. This implies that both lagged and un-lagged average bitumen fume exposure variables fit data equally well.

Table 8.1: Various estimates of bitumen fume exposure among persons employed only in asphalt paving and risk of lung cancer mortality; all models adjusted for age, calendar period, country, and coal tar exposure (Sweden excluded, one season of employment inclusion criteria applied).

Lag	Exposure metric (units)	Exposure group	All persons				Inception cohort only			
			N ^A	py ^B	RR ^C	95%CI ^D	N ^A	py ^B	RR ^C	95%CI ^D
15 years	Duration (years)	0	53	124543	1.00	--	25	33502	1.00	--
		0.003-<1.45	21	22112	0.75	0.43-1.31	15	6294	0.61	0.26-1.44
		1.45-<3.90	24	17512	0.86	0.50-1.47	12	6996	0.41	0.17-1.01
		3.90-<8.05	17	13838	0.67	0.36-1.23	10	6681	0.33	0.13-0.85
		8.05-30.30	19	10552	0.83	0.43-1.61	15	7089	0.39	0.14-1.12
	Average (mg/m ³)	0	53	124543	1.00	--	25	33502	1.00	--
		0.71-<1.21	22	37044	0.39	0.22-0.69	6	7879	0.16	0.05-0.47
		1.21-<1.32	20	8707	0.89	0.49-1.62	15	5493	0.35	0.14-0.88
		1.32-<1.47	20	6954	1.16	0.64-2.11	16	5113	0.43	0.17-1.10
		1.47-6.46	19	11309	1.92	1.00-3.68	15	8575	1.68	0.66-4.26
	Cumulative (mg/m ³ -years)	0	53	124543	1.00	--	25	33502	1.00	--
		0.004-<1.61	20	21840	0.76	0.43-1.33	13	5244	0.64	0.26-1.54
		1.61-<3.71	19	13935	0.86	0.49-1.55	10	5285	0.46	0.18-1.16
		3.71-<9.57	20	16567	0.63	0.35-1.12	12	8202	0.31	0.12-0.77
		9.57-47.04	22	11672	0.96	0.51-1.78	17	8329	0.41	0.15-1.12
0 years	Duration (years)	0.41-<1.75	34	59439	1.00	--	16	10875	1.00	--
		1.75-<4.59	38	54838	0.93	0.58-1.48	19	16757	0.87	0.45-1.70
		4.59-<9.87	35	41072	0.87	0.54-1.41	22	15286	0.87	0.45-1.70
		9.87-41.53	27	33051	0.59	0.88-1.06	20	17644	0.46	0.21-1.00
	Average (mg/m ³)	0.31-<1.03	32	121790	1.00	--	12	26290	1.00	--
		1.03-<1.23	36	26441	2.73	1.65-4.53	17	6904	2.86	1.25-6.55
		1.23-<1.37	33	18704	2.42	1.35-4.34	25	12912	1.91	0.79-4.59
		1.37-5.38	33	21465	3.38	1.95-5.86	23	14457	2.45	1.05-5.71
	Cumulative (mg/m ³ -years)	0.33-<2.16	33	81084	1.00	--	14	14089	1.00	--
		2.16-<4.61	32	38858	1.28	0.78-2.08	15	12366	1.19	0.57-2.49
		4.61-<9.66	33	35821	1.06	0.65-1.73	21	14550	1.03	0.52-2.05
		9.66-71.96	36	32637	1.02	0.87-1.04	27	19558	0.79	0.38-1.63

A = number of lung cancer deaths; B = person-years; C = relative risk estimates; D = 95 percent confidence interval for RR.

Table 8.2: Comparison of fit (via log likelihood ratio test ^A) of the bitumen fume - lung cancer mortality models in a cohort of persons who were only employed in asphalt paving.

Model		Population					
		All persons			Inception cohort only		
Lag	Exposure metric	v ^B	-2LLR ^C	p ^D	v ^B	-2LLR ^C	p ^D
15 years	Duration	4	2.084	0.72	4	6.610	0.16
	Average	4	22.557	0.0002	4	19.895	0.0005
	Cumulative	4	3.297	0.51	4	7.509	0.11
0 years	Duration	3	4.161	0.24	3	5.036	0.17
	Average	3	23.585	0.00003	3	7.345	0.06
	Cumulative	3	1.156	0.76	3	1.421	0.70

A = comparison of model that included age, calendar period, country, and coal tar exposure (type A) *versus* model that included age, calendar period, country, coal tar exposure and bitumen fume exposure variable (type B); B = degrees of freedom for log likelihood (LL) ratio test; C = $-2 \times (LL_{\text{type A}} - LL_{\text{type B}})$; D = p-value for the log-likelihood ratio test: $p(\text{chi-squared}(-2LLR))$, one-sided because we expected model fit to either improve or remain unchanged.

Discussion

Comparison to general population

Patterns of SMRs suggested that persons exposed to bitumen fume during paving, as a group, were at increased risk of lung cancer compared to the general population. However, this increase in lung cancer risk cannot be attributed to any specific agent on the basis of SMR analyses alone.

Duration, average and cumulative exposure indices

A downward trend, though not statistically significant, in risk of lung cancer mortality was observed with increased duration of employment as a paver and hence bitumen fume exposure. This is symptomatic of the "healthy worker effect" whereby healthier individuals remain employed longer. However, such an effect has been reported to be weaker for cancer than for any other cause of death (19). The healthy worker effect, governing the relationship between duration of exposure and lung cancer mortality, is likely to confound association between lung cancer mortality and cumulative exposure. This is probably at least in part due to the fact that average exposure intensity spanned a narrower range of values (factor of $17=5.38/0.31$) than duration of exposure (factor of $101=41.53/0.41$). Consequently, cumulative exposure was determined more by duration of exposure than by its intensity.

Models with an average exposure index better explained lung cancer mortality risk. They suggested a positive association between the risk of lung cancer mortality and average bitumen fume exposure. The other two indices were not associated positively with the risk of lung cancer mortality. Such patterns for chronic diseases, including cancer, have been observed in other occupational cohorts, but the cause of such patterns is poorly understood (20,21). If the mechanism of bitumen carcinogenesis involves either a threshold or non-linearity at lower doses in exposure-response curves (as has been suggested for other carcinogens (22)), then we may expect average bitumen exposure to be more closely associated with cancer risk than exposure duration. However, too little is known about the possible mechanism of bitumen carcinogenesis to develop with argument further. The difficulty in interpreting a model that shows an association between risk of lung cancer mortality and average exposure is that it implies, unrealistically, that exposure for any length of time (within the range of the data) at the same exposure level confers the same relative

risk. Better methods for controlling for the healthy worker effect may lead us to the ability to model a more biologically plausible relationship between lung cancer risk and cumulative exposure. Information on reasons for retirement from asphalt work may be helpful in this regard, since it may help us to identify the population of workers who left the industry because of health problems. Data on differences in lifestyle factors between long-term and short-term workers may be helpful in this regard. Furthermore, it has been suggested that adjustment for person-years in active employment may correct for confounding by the healthy worker survivor effect in studies of cumulative exposure (23).

Latency model

As indicated by model fit tests, neither latency model considered in this investigation appeared to outperform the other. In order to develop a better latency model, we may need to perform time-windows analysis, to explore the possibility that exposures in different time windows may confound one another (24). In such analyses, the contribution of lagged exposure (say, by 15 years) to change in risk of health outcome can be adjusted for an exposure that occurred 15 years prior to the outcome. The validity of the use of the strength of exposure-response association *per se* in an selecting optimal time-window model has recently been called into question (25,26) amid suggestions that in latency analysis an incorrectly specified model may lead to differential bias in exposure estimates (26). Thus, given the declining time trend in exposure intensity (chapter 7), for average exposure, if lag was too long, biologically effective exposure would be overestimated, and if lag was too short, biologically effective exposure would be underestimated. The opposite should hold for duration of exposure (and duration-driven cumulative exposure): if lag was too long, biologically effective exposure would be underestimated; if lag was too short, biologically effective exposure would be overestimated. Differential underestimation of exposure can be expected to produce overestimation of an exposure-response relationship. Conversely, differential overestimation of exposure can be expected to produce underestimation of an exposure-response relationship. In practice, as in our data, it might be very difficult to distinguish between a well-specified latency model and bias due to differential exposure misclassification produced by lagging. Model fit, measured by the log-likelihood ratio test, has been suggested to overcome these complications in differentiating between competing latency models (25), but more research is needed to develop practical guidelines for resolving these difficulties (26).

Exposure misclassification: job histories and exposure matrix

Truncated job histories may be another source of exposure misclassification in the study. If follow-up started after the date of first employment, we would underestimate a person's exposure. Such differential misclassification of exposure would tend to produce negative bias in exposure-response relationships. However, when we attempted to control for this factor by restricting analyses to the inception (entry) cohort we did not observe a stronger exposure-response relationship.

Non-differential misclassification of exposure could have arisen from imprecision in the exposure matrix. Errors in the exposure matrix may have originated either from the statistical model of exposure intensity or from the company questionnaires. Statistical models were demonstrated to be imprecise, but valid (chapter 6). This made them suitable for grouped model-based exposure assessment, such as we utilized, where non-differential

misclassification of exposure is reduced on group level (chapter 6 and 7). This grouping of exposure estimates occurred on three sequential levels. On the first level, exposure measurements were pooled to estimate exposures for a number of exposure scenarios by using mixed effects models (chapter 4). On the second level, exposures for an average/typical person described by a company questionnaire were estimated. This second level of grouping was achieved in construction of the exposure matrix (chapter 7). On the third and final level, individual exposure estimates obtained from application of the exposure matrix to job histories were grouped to form exposure groups for epidemiological analyses. These sequential levels of aggregating data can be expected to improve validity of risk parameter estimation at the expense of loss in precision if they result in Berkson-type error (27-29).

However, we cannot predict the direction and magnitude of errors due to the company questionnaires (the backbone of this exposure assessment), because validity of company questionnaire data was not evaluated systematically. One of the key factors in creating duration-driven exposure indices for the epidemiological analyses was adjustment of exposure duration for the length of the paving season. Length of paving season was assessed as a single value for all pavers in a given firm. This did not allow for the working season to vary from year to year and in response to changes in paving technology and weather. Thus, it is likely that our data did not adequately reflect the seasonal nature of work, introducing errors into duration-driven exposure indices used in exposure-response modeling.

As in many studies, we cannot predict with certainty either the direction or the magnitude of bias in exposure estimates and the resultant exposure-response associations. It would appear that the most immediate reduction in bias from exposure assessment procedure could be achieved by improving our knowledge of the job histories of study subjects. This can be most efficiently achieved in a nested case-control study design, in which we can focus our efforts on reconstructing exposure histories for individuals most informative for relative risk estimation.

Confounding

The main potential confounder that we did not take into account in the cohort phase of the study was cigarette smoking. As an established risk factor for lung cancer, if cigarette smoking was not equally frequent in all exposure groups (and time periods), it could produce a distortion in the observed relationship between bitumen fume and lung cancer mortality risk. This is particularly true for the observed positive association between average exposure and risk of lung cancer mortality because (a) the highest average exposures could only have been experienced due to employment before 1970 (chapter 7) and (b) smoking prevalence has declined among asphalt workers over time (30). Inclusion of age and calendar period at exit may have partially adjusted for such "birth cohort" effects in the study. Information on the cigarette smoking habits of cohort members was not readily available, but can, potentially, be obtained in a nested case-control study from the next-of-kin or medical records.

Other sources of confounding in the study may be due to incomplete occupational histories for cohort members. This would occur if (a) they were exposed to carcinogens while employed outside of the asphalt industry or asphalt companies not recruited for the cohort and (b) there was a correlation between exposures to carcinogens from outside of the asphalt industry and bitumen fume. As a result, in current analysis we may be attributing to bitumen fume risk incurred due to exposure to another carcinogen or carcinogens.

It is also possible that in our analyses we did not completely adjust for coal tar exposure, owing to the fact that coal tar exposure was assessed in a fairly crude manner, without taking into account the amount of coal tar added to the asphalt mix. We have demonstrated in chapter 5 that the tar content of asphalt may vary considerably, producing a wide range of PAH exposures. To explore this issue further we need to model the health risks of bitumen exposure on a tar-free sub-cohort. However, a coal tar-free sub-cohort may have too little power for comprehensive exposure-response modeling (60 lung cancer deaths and 134,063 person-years).

Bitumen fume effects observed in our analyses can also be attributed to organic vapour or PAH, since exposures to these three agents were strongly correlated (chapter 7). Thus, our results implicate exposure to asphalt emissions as a whole, and not bitumen in particular, as a risk factor for lung cancer.

Conclusion

We found a positive association between average quantitative bitumen fume exposure and lung cancer mortality risk, lending support to the hypothesis of the carcinogenicity of bitumen fume in absence of coal tar exposure. This association must be interpreted through further analyses and/or a case-control study nested within the cohort, since it may be the result of confounding by other carcinogenic exposures and lifestyles. Duration of exposure and cumulative exposure were not associated with lung cancer mortality risk, weakening the evidence for carcinogenicity of bitumen fume. No clear latency model emerged from the analysis. Constructing quantitative exposure indices appeared to have been justified because (a) the healthy worker effect confounded any associations between duration of exposure and lung cancer mortality risk and (b) we identified statistically significant associations between bitumen fume exposure and lung cancer risk that require further investigation. Valid assessment of average exposure gains particular significance for analyses in which duration of exposure is confounded by the healthy worker effect and/or those analyses for which exposure intensity range is narrow (as is expected to be the case in future studies because occupational exposures continue to decline (31)). This may be especially true for studies with low expected relative risks that are likely to dominate occupational and environmental epidemiology in developed countries in the future (32).

References

1. IARC. IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 35: Polynuclear aromatic compounds, part 4, bitumens, coal-tars and derived products, shale-oils and soots. Lyon: International Agency for Research on Cancer; 1985.
2. Partanen T, Boffetta P. Cancer risk in asphalt workers and roofers: review and meta-analysis of epidemiologic studies. *Am.J.Ind.Med.* 1994;26:721-40.
3. Hansen ES. Cancer mortality in the asphalt industry: a ten year follow up of an occupational cohort. *Br.J.Ind.Med.* 1989;46:582-5.
4. Hansen ES. Cancer incidence in an occupational cohort exposed to bitumen fumes. *Scand.J.Work Environ.Health* 1989;15:101-5.

5. Hansen ES. Mortality of mastic asphalt workers. *Scand.J.Work Environ.Health* 1991;17:20-4.
6. Hansen ES. Reply: cancer mortality and incidence in mastic asphalt workers. *Scand.J.Work Environ.Health* 1992;18:133-41.
7. Wong O, Bailey WJ, Amsel J. Cancer mortality and incidence in mastic asphalt workers: letter to the editor and author's reply. *Scand.J.Work Environ.Health* 1992;18:133-41.
8. Cole P, Green LC, Lash TL. Lifestyle determinants of cancer among Danish mastic asphalt workers. *Regulatory Toxicol.Pharmacol.* 1999;30:1-8.
9. IARC. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement 7. Lyon: International Agency for Research on Cancer; 1987.
10. Seixas NS, Checkoway H. Exposure assessment in industry specific retrospective occupational epidemiology studies. *Occup.Environ.Med.* 1995;52:625-33.
11. Stewart PA, Lees PSJ, Francis M. Quantification of historical exposures in occupational cohort studies. *Scand.J.Work Environ.Health* 1996;22:405-14.
12. Stewart PA. Challenges to retrospective exposure assessment. *Scand.J.Work Environ.Health* 1999;25(6, special issue):505-10.
13. Burstyn I, Kromhout H, Cruise PJ, Brennan P. Designing an international industrial hygiene database of exposures among workers in the asphalt industry. *Ann.Occup.Hyg.* 2000;44(1):57-66.
14. Burstyn I, Kromhout H, Kauppinen T, Heikkilä P, Boffetta P. Statistical modeling of determinants of historical exposure to bitumen and polycyclic aromatic hydrocarbons among paving workers. *Ann.Occup.Hyg.* 2000;44(1):43-56.
15. Burstyn I, Boffetta P, Burr GA, Cenni A, Knecht U, Sciarra G, Kromhout H. Validity of empirical models of exposure in asphalt paving. *Occup.Environ.Med.* 2000;submitted
16. Burstyn I, Boffetta P, Kauppinen T, Heikkilä P, Svane O, Partanen T, Stucker I, Frentzel-Beyme R, Arhens W, Merzenich H, et al. Estimating exposures in asphalt industry for an international epidemiological cohort study of cancer risk. *Occup.Environ.Med.* 2001;submitted
17. Breslow NE; Day NE. Statistical methods in cancer research. Vol.II - The design and analysis of cohort studies. Lyon: International Agency for Research on Cancer Scientific Publications no 82; 1987.
18. Clayton D; Hills M. Statistical Models in Epidemiology. Oxford: Oxford Univesity Press, Inc.; 1998.
19. Checkoway H; Pearce N; Crawford-Brown DJ. Research Methods in Occupational Epidemiology. 1 ed. New York: Oxford University Press, Inc.; 1989.

20. Checkoway H, Rice CH. Time-weighted averages, peaks and other indices of exposure in occupational epidemiology. *Am.J.Ind.Med.* 1992;21:25-33.
21. Cherry NM, Burgess GL, Turner S, McDonald JC. Crystalline silica and risk of lung cancer in the potteries. *Occup. Environ. Med.* 1998;55:779-85.
22. Conolly RB. Cancer and non-cancer risk assessment: not so different if you consider mechanisms. *Toxicol.* 1995;102 (1-2):179.-188
23. Steenland K, Deddens J, Salvan A, Stayner L. Negative bias in exposure-response trends in occupational studies: modeling the Healthy Worker Survivor Effect. *Am.J.Epidemiol.* 1996;143:202-10.
24. Checkoway H, Pearce N, Crawford-Brown DJ. Checkoway H, Pearce N, Crawford-Brown DJ, editors. *Research methods in occupational epidemiology.* 1 ed. New York: Oxford University Press, Inc.; 1989; 10, Special applications of occupational epidemiology data. p. 302-4.
25. Salvan A, Stayner L, Steenland K, Smith R. Selecting an exposure lag period. *Epidemiology* 1995;6:387-90.
26. Loomis D, Salvan A, Kromhout H, Kriebel D. Selecting indices of occupational exposure for epidemiologic studies. *Occupational Hygiene* 1999;5(1):73-91.
27. Berkson J. Are there two regressions? *American Statistical Association Journal* 1950;June:164-80.
28. Seixas NS, Sheppard L. Maximizing accuracy and precision using individual and grouped assessments. *Scand.J.Work Environ.Health* 1996;22:94-101.
29. Tielemans E, Kupper LL, Kromhout H, Heederik D, Houba R. Individual-based and group-based occupational exposure assessment: Some equations to evaluate different strategies. *Ann.Occup.Hyg.* 1998;42(2):115-9.
30. Randem B, Langård S, Dale I, Kongerud, ., Martinsen JI, Andersen A. Cancer incidence among male Norwegian asphalt workers. in preperation 2001.
31. Kromhout H, Vermeulen R. Long-term trends in occupational exposure: Are they real? What causes them? What shall we do with them? *Ann.Occup.Hyg.* 2000;44(5):325-7.
32. Doll RS. Weak associations in epidemiology: importance, detection, and interpretation. *J Epidemiol* 1996;6(4):S11-S20

