Performance of Different Exposure Assessment Approaches in a Study of Bitumen Fume Exposure and Lung Cancer Mortality

Igor Burstyn, PhD,[1,2] Paolo Boffetta, MD, MPH,[2] Timo Kauppinen, PhD,[3] Pirjo Heikkilä, PhD,[3] Ole Svane, PhD,[4] Timo Partanen, PhD,[3] Isabelle Stücker, PhD,[5] Rainer Frentzel-Beyme, PhD,[6] Wolfgang Ahrens, PhD,[6] Hiltrud Merzenich, PhD,[6] Dick Heederik, PhD,[1] Mariette Hooiveld, MSc,[1] Bert Brunekreef, PhD,[1] Sverre Langård, PhD,[7] Britt G. Randem, MD, MPH,[7] Bengt Järvholm, PhD,[8] Ingvar A. Bergdahl, PhD,[8] Judith Shaham, PhD,[9] Gilles Ferro,[2] and Hans Kromhout, PhD[1]*

Background *We compared performance of different exposure assessment approaches in a cohort study of cancer risk among European asphalt workers.*
Methods *Three bitumen fume exposure indices (duration of exposure (years), average exposure (mg/m^3) and cumulative exposure (mg/m^3*years)) and two latency models (with and without a 15 year lag) were considered for an association between lung cancer mortality and bitumen fume.*
Results *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) improved model fit, albeit to the same extent.*
Conclusions *Constructing quantitative indices of exposure intensity was justified because they produced the greatest improvement in fit of models that explored possible relationship between bitumen fume exposure and lung cancer risk. The identified associations require further investigation.* Am. J. Ind. Med. 43:40–48, 2003. © *2003 Wiley-Liss, Inc.*

KEY WORDS: cohort study; quantitative exposure assessment; exposure reconstruction methodology; model fit

INTRODUCTION

This study of cancer risk in the European asphalt industry, coordinated by the International Agency for Research on Cancer (IARC), was prompted by an ongoing controversy over the carcinogenicity, especially to the lung, of emissions derived from bitumen, a customary binder in

[1]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands
[2]Unit of Environmental Cancer Epidemiology, International Agency for Research on Cancer, Lyon, France
[3]Finnish Institute of Occupational Health, Helsinki, Finland
[4]Danish Working Environment Service, Copenhagen, Denmark
[5]INSERM U.170, Villejuif, France
[6]Bremen Institute for Prevention Research and Social Medicine (BIPS), Bremen, Germany
[7]Centre for Occupational and Environmental Medicine, The National Hospital University of Oslo, Oslo, Norway
[8]Occupational Medicine, Department of Public Health and Clinical Medicine, Umea University Hospital, Umea, Sweden
[9]Occupational Cancer Unit, Occupational Health and Rehabilitation Institute, Raanana, Israel

Contract grant sponsor: IARC Special Training Award (to Igor Burstyn); Contract grant sponsor: European Commission, Directorate-Generale-XII (DG-XII), Biomed-2 programme ; Contract grant number: BMH4-CT95-1100; Contract grant sponsor: European industrial associations: EAPA (European Asphalt Pavement Association), Eurobitume and CONCAWE (the oil companies' European organization for environment, health and safety). Full Acknowledgments cited in Boffetta et al., 2003a, this issue

*Correspondence to: Hans Kromhout, Institute for Risk Assessment Sciences, Utrecht University; PO Box 80176, 3508 TD Utrecht, The Netherlands. E-mail: H.Kromhout@iras.uu.nl

Accepted 30 September 2002
DOI 10.1002/ajim.10168. Published online in Wiley InterScience (www.interscience.wiley.com)

asphalt mix [IARC, 1985, 1987; Hansen, 1989a, 1989b, 1991, 1992; Wong et al., 1992; Partanen and Boffetta, 1994; Cole et al., 1999].[1] This paper explores some of the methodological issues in exposure assessment highlighted by the IARC study of asphalt workers.

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 [Seixas and Checkoway, 1995; Stewart et al., 1996; Stewart, 1999]. 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 employees exposed to bitumen [Boffetta et al., 2003a,b], we constructed a large database of exposure measurements [Burstyn et al., 2000a] that was used to build statistical models of exposure intensity to bitumen fume [Burstyn et al., 2000b], the main exposure agent of interest. The elaborated model was shown to be reasonably valid [Burstyn et al., 2002] and was applied to construct a study-specific exposure matrix with quantitative bitumen fume exposure estimates for workers in asphalt paving [Burstyn et al., 2003]. 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 to depend only on exposure duration. Yet another approach would be to consider only the average exposure intensity, and not take exposure duration into account. In this study, we set out to compare the performance of these 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 employees involved in handling asphalt, from its manufacture at an asphalt plant to its application in 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 exposed to bitumen fumes 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. The Swedish cohort was also excluded from the current analysis because duration of exposure could not be accurately estimated for its members. This was a consequence of the fact that the job histories in Sweden did not contain information about jobs held after the entry into the cohort. 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.

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.

Employment histories were coded according to a classification of jobs, which was constructed for the study [Burstyn et al., 2003]. 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) [Burstyn et al., 2003].

A detailed description of the cohort can be found elsewhere [Boffetta et al., 2001, 2003a,b (this issue)].

Exposure Assessment

Details of exposure assessment were presented elsewhere [Burstyn et al., 2000a,b, 2002, 2003], and will only be briefly reviewed here. Exposure measurements collected by European asphalt companies and various agencies in the countries represented in the cohort, were assembled into a single database [Burstyn et al., 2000a]. The exposure data primarily was comprised of industrial hygiene measurements of exposure levels for a variety of agents among asphalt paving workers, and supplementary information. The supplementary information allowed linkage of exposure measurements with information on production conditions in firms recruited for the study. The earliest samples originated

[1] Throughout this study 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.'

from the late 1960's, and the majority were collected in the late 1970's and between 1985 and 1997.

Exposure measurement data were used to construct a predictive model of bitumen fume exposure [Burstyn et al., 2000b]. 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. The bitumen fume exposure model was validated by comparing predicted values with those measured in the USA [Burstyn et al., 2002]. The validity of bitumen fume exposure models was assessed as satisfactory, given the available exposure data.

The statistical model of bitumen fume exposure and the answers to the company questionnaires were linked to produce a study-specific exposure matrix [Burstyn et al., 2003]. 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 model [Burstyn et al., 2000b] 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 hr work-shift. The resulting exposure matrix was time period and company specific. According to the exposure matrix, road pavers were not exposed to asbestos and there was no variability across time periods and companies, in the levels of exposure to respirable silica and asbestos. Estimates of bitumen fume, organic vapor, and 4–6 ring polycyclic aromatic hydrocarbons (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). We corrected the duration of exposure for the seasonal nature of work in the asphalt industry. 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. 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.

Statistical Analysis

Correlation between different indices of bitumen fume exposure among cohort members was examined using the Spearman rank correlation coefficient.

Relative risks and associated 95% confidence intervals were estimated using Poisson regression [Breslow and Day, 1987]. All Poisson regression models included age (0–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, and 80 + years), calendar period of exit from cohort (pre-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.

The performance of an exposure index was judged by the extent to which it improved model fit, not on the basis of whether it produced positive associations [Loomis et al., 1999]. An improvement in model fit, upon addition of bitumen fume exposure index, was evaluated using a profile log-likelihood ratio test [Clayton and Hills, 1998]. Degrees of freedom for the log likelihood (LL) ratio 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 $-2 \times$ (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 (STATA Corporation, College Station, Texas). Person-

year allocation was carried out in SAS 6.12 (SAS Institute, Cary, North Carolina), 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 subjects 10,060 persons belonged to the inception cohort. In the entire cohort selected for analysis, a total of 1,636 persons were reported to have died at the end of the follow-up. Among these, there were 135 deaths due to lung cancer.

Cumulative and duration exposure indices were highly correlated ($r = 0.83$). However, cumulative and average exposure indices were not correlated ($r = 0.07$). Likewise, average and duration exposure indices were not correlated ($r = -0.20$). Lagged exposure variables showed a similar pattern: $r = 0.93$ between cumulative and duration exposure indices, $r = 0.63$ between cumulative and average exposure indices, and $r = 0.56$ between average and duration exposure indices. All *P*-values for Spearman rank correlation coefficients were below 0.00001.

Table I presents relative risk estimates quantified through Poisson regression models. There appears to be no association between duration of exposure to bitumen fume 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. Average bitumen fume exposure above the lowest exposure category was associated with a statistically significant rise in risk of lung cancer mortality,

TABLE I. Various Estimates of Bitumen Fume Exposure Among Persons Employed Only in Asphalt Paving and Risk of Lung Cancer Mortality*

			All subjects				Inception cohort only			
Lag	**Exposure index (units)**	**Exposure group**	**N**	**py**	**RR**	**95% CI**	**N**	**py**	**RR**	**95% CI**
15 years	Duration (years)	0	53	125461	1.00	—	43	114473	1.00	—
		0.003– < 1.45	22	21666	0.71	0.41–1.24	11	17311	0.57	0.27–1.18
		1.45– < 3.90	24	17846	0.72	0.41–1.26	14	13108	0.67	0.34–1.32
		3.90– < 8.05	17	14113	0.54	0.29–1.01	7	9426	0.33	0.14–0.79
		8.05–30.30	19	10556	0.62	0.31–1.24	4	4380	0.26	0.08–0.82
	Average (mg/m^3)	0	53	125461	1.00	—	43	114473	1.00	—
		0.71– < 1.21	22	36989	0.37	0.21–0.66	16	33970	0.29	0.15–0.58
		1.21– < 1.32	20	8689	0.78	0.42–1.47	8	4298	0.94	0.40–2.22
		1.32– < 1.47	21	7134	1.01	0.54–1.90	4	2464	0.90	0.30–2.68
		1.47–6.46	19	11369	1.58	0.79–3.13	8	3492	1.30	0.55–3.07
	Cumulative (mg/m^3 years)	0	53	125461	1.00	—	43	114473	1.00	—
		0.004– < 1.61	20	21144	0.71	0.40–1.26	10	17765	0.52	0.24–1.10
		1.61– < 3.71	20	14415	0.77	0.43–1.37	12	10865	0.71	0.35–1.45
		3.71– < 9.57	19	16888	0.50	0.27–0.91	9	11079	0.38	0.17–0.85
		9.57–47.04	23	11735	0.74	0.38–1.45	5	4514	0.33	0.11–0.96
0 years	Duration (years)	0.41– < 1.75	35	60355	1.00	—	23	54461	1.00	—
		1.75– < 4.59	37	54534	0.91	0.57–1.44	21	47062	0.82	0.45–1.49
		4.59– < 9.87	36	41522	0.85	0.53–1.37	25	34955	0.86	0.48–1.55
		9.87–41.53	27	33073	0.51	0.29–0.90	10	22062	0.34	0.15–0.76
	Average (mg/m^3)	0.31– < 1.03	32	122395	1.00	—	31	119144	1.00	—
		1.03– < 1.23	37	26382	2.72	1.64–4.53	24	21632	2.17	1.22–3.85
		1.23– < 1.37	33	18835	2.22	1.22–4.07	8	7537	1.69	0.71–4.02
		1.37–5.38	33	21872	3.02	1.69–5.39	16	10225	3.30	1.69–6.46
	Cumulative (mg/m^3 years)	0.33– < 2.16	34	81380	1.00	—	23	75823	1.00	—
		2.16– < 4.61	31	39403	1.14	0.70–1.87	23	34487	1.27	0.70–2.28
		4.61– < 9.66	33	35704	0.97	0.60–1.59	20	28701	0.94	0.50–1.74
		9.66–71.96	37	32997	0.85	0.50–1.44	13	19529	0.58	0.27–1.24

N, number of lung cancer deaths; py, person-years; RR, relative risk estimates; 95% CI, 95 percent confidence interval for RR.
*In Poisson regression all models are adjusted for age, calendar period, country, and coal tar exposure. Sweden is excluded.

although no exposure-response was evident. Lagged average bitumen fume exposure followed an unusual pattern. Subjects exposed only within 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.

Only average exposure indices (lagged or not) improved model fit (Table II). 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.

DISCUSSION

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 survivor 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 [Checkoway et al., 1989a]. A healthy worker survivor effect, influencing the relationship between duration of exposure and lung cancer mortality, is likely to confound any 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, which is reflected in the correlation coefficients between the three indicators of exposure.

Models with the average exposure indices better explained lung cancer mortality risk. They showed a strong 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 [Checkoway and Rice, 1992; Cherry et al., 1998]. 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 [Conolly, 1995]), 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 the argument further. Furthermore, possible uncontrolled confounding in our analyses (see below) precludes us from exploring the issue of threshold further through more sophisticated exposure indices, such as cumulative exposure above a certain threshold. The difficulty in interpreting a model that shows an association between risk of lung cancer mortality and average but not cumulative 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

TABLE II. Comparison of Fit (Via Log Likelihood Ratio Test*) 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 index	ν	− 2LLR	*P*	ν	− 2LLR	*P*
15 years	Duration	4	4.11	0.4	4	9.96	0.04
	Average	4	20.14	0.0005	4	18.84	0.0008
	Cumulative	4	5.58	0.2	4	8.45	0.08
0 years	Duration	3	6.45	0.09	3	8.57	0.04
	Average	3	19.49	0.0002	3	13.74	0.003
	Cumulative	3	1.25	0.7	3	4.52	0.2

ν, degrees of freedom for log likelihood (LL) ratio test; − 2LLR, $-2 \times (LL_{type\ A} - LL_{type\ B})$; *P*, *P*-value for the log-likelihood ratio test: *P* (chi-squared(− 2LLR)), one-sided because we expected model fit to either improve or remain unchanged.

*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).

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 bitumen-related health problems. Data on differences in lifestyle factors between long- and short-term workers may be helpful in this regard. Furthermore, we are aware that several modeling approaches have been proposed for adjustment of cumulative exposure's association with risk for the healthy worker survivor effect [Steenland et al., 1995, 1996; Arrighi and Hertz-Picciotto, 1996], but we chose not to pursue them pending ascertainment of data on potential confounders that we were not able to collect in the cohort phase of the investigation (see below).

Due to declining trends in bitumen fume exposure, subjects with the highest average bitumen fume exposure were likely to have been employed further in the past. Work performed in the past was also more likely to have been associated with use of coal tar, an established carcinogen. Although we did correct for coal tar use in our analyses, the coal tar exposure estimates were quite crude, being based exclusively on self-report by companies. Therefore, unrecognized coal tar exposure in earlier periods may have confounded associations between average bitumen fume exposure and lung cancer risk. This issue can only be resolved through obtained better exposure history data through a nested case-control study.

Latency Model

As indicated by the model fit tests, neither latency model (zero and 15 years) considered in this investigation appeared to outperform the other. In order to develop a better latency model, we may need to perform time-window analysis, to explore the possibility that exposures in different time windows may confound one another [Checkoway et al., 1989b]. 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. Such analyses can be complicated by low relative risks in the cohort and by complex underlying latency patterns. The validity of the use of the strength of exposure-response association *per se* in selecting optimal time-window model has recently been called into question [Salvan et al., 1995; Loomis et al., 1999] amid suggestions that in latency analysis an incorrectly specified model may lead to differential bias in exposure estimates [Loomis et al., 1999]. Thus, given the declining time trend in exposure intensity [Burstyn et al., 2003], 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 [Salvan et al., 1995], but more research is needed to develop practical guidelines for resolving these difficulties [Loomis et al., 1999].

Exposure Misclassification: Job Histories and Exposure Matrix

Job histories for some cohort members did not represent their entire working life. 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. This may mean that we captured the major periods of occupational bitumen exposure also in the ''non-inception'' segment of the cohort, which was based on cross-sectional enrollment.

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 model was demonstrated to be imprecise, but reasonably valid: relative bias-70% [Burstyn et al., 2002]. 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 [Burstyn et al., 2002, 2003]. 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 model [Burstyn et al., 2000b]. 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 [Burstyn et al., 2003]. The first two levels of grouping were analogous to exposure assessment conducted in a study of pig farmers [Preller et al., 1995; Kromhout et al., 1996]. If group-level estimates were unbiased, we would expect that when applied in exposure-response modeling they would produce unbiased exposure-response slopes with inflated errors [Berkson, 1950; Tielemans et al., 1998]. However, if group-level means were biased, exposure-response

relationships would be attenuated [Berkson, 1950]. Such attenuation due to grouping may also occur under certain relative magnitudes of variance components, but such conditions are likely to be uncommon in occupational epidemiology [Tielemans et al., 1998].

On the third and final level, individual exposure estimates obtained from application of the exposure matrix to job histories (e.g., by calculating cumulative and average exposures) were grouped to form exposure categories for epidemiological analyses. Grouping was based on allocating the same number of lung cancer cases to each non-zero exposed exposure category. This served to satisfy the requirements of the statistical technique used to model exposure-response relationships (Poisson regression) [Breslow and Day, 1987; Clayton and Hills, 1998]. Exposure assignment carried out at this level and subsequent grouping does not reduce attenuation in an exposure-response relationship [Kromhout et al., 1999], because it does not produce a Berkson-type error structure that aggregates exposure estimates around an *a priori* identified unbiased mean value [Berkson, 1950].[2] Instead, on this third level, groups were formed from values that may well have belonged to different underlying distributions, thereby producing biased group means that carry the same error structure (and exposure misclassification) as individually assigned exposure estimates. However, in presence of clear multi-modality, such as exposed and unexposed groups, appropriate grouping of assigned exposure estimates reduces non-differential exposure misclassification. Thus, opportunities to reduce attenuation of exposure-response association by producing Berkson-type error structure appear to lie in exposure *assessment*, not in the subsequent exposure *assignment* and exposure-response modeling [Kromhout et al., 1999].

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 company. 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.

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.

[2] Pre-defined means in the theorem proven by Dr. J. Berkson.

Confounding

Inadequate control for confounders could have affected our comparison of the performance of different exposure assessment indices, if some exposure indices are more affected by an uncontrolled confounder than others. The issue of confounding in overall cohort analysis and its implication for assessment of the strength of evidence for causal link between bitumen fume and lung cancer is explored more fully elsewhere [Boffetta et al., 2001; Randem et al., 2003; Boffetta et al., 2003a,b; Hooiveld et al., 2003.

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 [Burstyn et al., 2003] and (b) smoking prevalence has declined among asphalt workers over time [Randem et al., 2003]. Inclusion of age and calendar period at exit may have partially adjusted for such ''birth cohort'' effects in our analysis. 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 [Boffetta et al., 2003b].

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 that the tar content of asphalt may vary considerably, producing a wide range of PAH exposures [Burstyn and Kromhout, 2000]. This issue is explored further in analysis of a tar-free sub-cohort, presented in a companion paper [Boffetta et al., 2003b].

Bitumen fume effects observed in our analyses can also be attributed to organic vapor or PAH, since exposures to these three agents were strongly correlated [Burstyn et al., 2003]. Thus, our results implicate exposure to asphalt emissions as a whole, and not bitumen in particular, as a risk factor for lung cancer.

CONCLUSION

The results do not allow us to conclusively establish the presence or absence of a causal link between exposure to bitumen fume and lung cancer. Nonetheless, the construction of quantitative indices of exposure intensity was justified because they produced the greatest improvement in fit of models that explored possible relationship between bitumen fume exposure and lung cancer risk. The identified associations 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 [Kromhout and Vermeulen, 2000]). 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 [Doll, 1996].

REFERENCES

Arrighi HM, Hertz-Picciotto I. 1996. Controlling the healthy worker survivor effect: An example of arsenic exposure and respiratory cancer. Occup Environ Med 53:455–462.

Berkson J. 1950. Are there two regressions? Am Stat Asso J June:164–180.

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

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

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

Breslow NE, Day NE. 1987. 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.

Burstyn I, Boffetta P, Burr GA, Cenni A, Knecht U, Sciarra G, Kromhout H. 2002. Validity of empirical models of exposure in asphalt paving. Occup Environ Med 59:620–624.

Burstyn I, Kromhout H. 2000. Are all the members of a paving crew uniformly exposed to bitumen fume, organic vapor, and benzo(a)pyrene? Risk Anal 20(5):653–664.

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

Burstyn I, Kromhout H, Cruise PJ, Brennan P. 2000a. Designing an international industrial hygiene database of exposures among workers in the asphalt industry. Ann Occup Hyg 44(1):57–66.

Burstyn I, Kromhout H, Kauppinen T, Heikkilä P, Boffetta P. 2000b. Statistical modeling of determinants of historical exposure to bitumen and polycyclic aromatic hydrocarbons among paving workers. Ann Occup Hyg 44(1):43–56.

Checkoway H, Pearce N, Crawford-Brown DJ. 1989a. Research methods in occupational epidemiology, New York: Oxford University Press Inc.

Checkoway H, Pearce N, Crawford-Brown DJ. 1989b. Special applications of occupational epidemiology data. In: Checkoway H, Pearce N, Crawford-Brown DJ, editors. Research methods in occupational epidemiology. New York: Oxford University Press Inc., pp302–304.

Checkoway H, Rice CH. 1992. Time-weighted averages, peaks and other indices of exposure in occupational epidemiology. Am J Ind Med 21:25–33.

Cherry NM, Burgess GL, Turner S, McDonald JC. 1998. Crystalline silica and risk of lung cancer in the potteries. Occup Environ Med 55:779–785.

Clayton D, Hills M. 1998. Statistical models in epidemiology, Oxford: Oxford University Press Inc.

Cole P, Green LC, Lash TL. 1999. Lifestyle determinants of cancer among Danish mastic asphalt workers. Reg Toxicol Pharmacol 30:1–8.

Conolly RB. 1995. Cancer and non-cancer risk assessment: Not so different if you consider mechanisms. Toxicol 102(1–2):179–188.

Doll RS. 1996. Weak associations in epidemiology: Importance, detection, and interpretation. J Epidemiol 6(4):S11–S20.

Hansen ES. 1989a. Cancer incidence in an occupational cohort exposed to bitumen fumes. Scand J Work Environ Health 15:101–105.

Hansen ES. 1989b. Cancer mortality in the asphalt industry: A ten year follow up of an occupational cohort. Br J Ind Med 46:582–585.

Hansen ES. 1991. Mortality of mastic asphalt workers. Scand J Work Environ Health 17:20–24.

Hansen ES. 1992. Reply: Cancer mortality and incidence in mastic asphalt workers. Scand J Work Environ Health 18:133–141.

Hooiveld M, Spee T, Burstyn I, Kromhout H, Heederik D. 2003. Lung cancer mortality in a Dutch cohort of asphalt workers: evaluation of possible confounding by smoking. Am J Ind Med 43:79–87 [this issue].

IARC. 1985. 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.

IARC. 1987. Overall evaluations of carcinogenicity: An updating of IARC monographs volumes 1–42. IARC Monographs on the evaluation

of carcinogenic risks to humans, supplement 7, Lyon: International Agency for Research on Cancer.

Kromhout H, Vermeulen R. 2000. Long-term trends in occupational exposure: Are they real? What causes them? What shall we do with them? Ann Occup Hyg 44(5):325–327.

Kromhout H, Tielemans E, Preller E, Heederik D. 1996. Estimates of individual dose from current measurements of exposure. Occup Hyg 3:23–39.

Kromhout H, Loomis D, Kleckner RC. 1999. Uncertainty in the relation between exposure to magnetic fields and brain cancer due to assessment and assignment of exposure and analytical methods in dose-response modeling. Ann NY Acad Sciences 895:141–155.

Loomis D, Salvan A, Kromhout H, Kriebel D. 1999. Selecting indices of occupational exposure for epidemiologic studies. Occup Hyg 5(1): 73–91.

Partanen T, Boffetta P. 1994. Cancer risk in asphalt workers and roofers: Review and meta-analysis of epidemiologic studies. Am J Ind Med 26:721–740.

Preller L, Kromhout H, Heederik D, Tielen MJ. 1995. Modeling long-term average exposure in occupational exposure-response analysis. Scand J Work Environ Health 12(6):504–512.

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

Salvan A, Stayner L, Steenland K, Smith R. 1995. Selecting an exposure lag period. Epidemiology 6:387–390.

Seixas NS, Checkoway H. 1995. Exposure assessment in industry specific retrospective occupational epidemiology studies. Occup Environ Med 52:625–633.

Steenland K, Deddens J, Salvan A, Stayner L. 1995. Healthy worker effect and cumulative exposure. Epidemiology 6:339–340.

Steenland K, Deddens J, Salvan A, Stayner L. 1996. Negative bias in exposure-response trends in occupational studies: Modeling the healthy worker survivor effect. Am J Epidemiol 143:202–210.

Stewart PA. 1999. Challenges to retrospective exposure assessment. Scand J Work Environ Health 25(6, special issue):505–510.

Stewart PA, Lees PSJ, Francis M. 1996. Quantification of historical exposures in occupational cohort studies. Scand J Work Environ Health 22:405–414.

Tielemans E, Kupper LL, Kromhout H, Heederik D, Houba R. 1998. Individual-based and group-based occupational exposure assessment: Some equations to evaluate different strategies. Ann Occup Hyg 42(2): 115–119.

Wong O, Bailey WJ, Amsel J. 1992. Cancer mortality and incidence in mastic asphalt workers: Letter to the editor and author's reply. Scand J Work Environ Health 18:133–141.