european epidemiology studies of asphalt workers

a review of the cohort study and its results

Prepared by:

Dr. Gerard M.H. Swaen
Department of Epidemiology
Maastricht University

Reviewed for CONCAWE by:

R. Ahlberg
A.J. Riley

J.H. Urbanus (Technical Coordinator)

ABSTRACT

An overview is provided of the first set of results of an epidemiology study program on asphalt workers in selected European countries. This report contains a brief description of the study, its methodology and results.

KEYWORDS

Asphalt; asphalt fumes; bitumen; bitumen fumes; epidemiology

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SUMMARY

The International Agency for Research on Cancer (IARC), in close collaboration with CONCAWE, Eurobitume (representing bitumen producers) and the European Asphalt Paving Association (representing the main users), has conducted an international epidemiologic investigation to study the possible long-term health effects in European asphalt workers. This report contains a brief description of the study, its methodology and results. For more extensive information the reader is referred to the main IARC report and the scientific articles that have been published by the research group in Volume 43 of the American Journal of Industrial Medicine. This review has been prepared to provide managers and scientists from other disciplines than epidemiology in the bitumen producing and user or related industries with an easily accessible summary document about the IARC investigation.

IARC has investigated the mortality patterns of a cohort of 29820 employees in the road paving, asphalt mixing, waterproofing and roofing industry. The workers were employed in one of these industries for at least one season between 1953 and 2000 and were followed for mortality until 1 January 2000. The mortality patterns of the asphalt workers exposed to bitumen fume were compared with the mortality patterns of a group of non-exposed construction workers and with the general population.

A small but statistically significant excess of lung cancer mortality was observed in the bitumen fume exposed workers. It is difficult to attribute this excess specifically to exposure to bitumen fume since concomitant exposure to coal tar and other chemicals may also have played a role. In addition, a small difference in smoking habits between the exposed and non-exposed workers may have caused this small excess of lung cancer mortality. IARC has recommended to conduct a case-control study, nested in the cohort, to further investigate the possible reasons for the observed excess.

1. INTRODUCTION

On request from industry associations CONCAWE, Eurobitume and the European Asphalt Paving Association, the International Agency for Research on Cancer (IARC) prepared a research proposal for an epidemiologic study of asphalt workers in Europe. First a feasibility study was performed to evaluate whether or not a retrospective cohort study could be carried out with sufficient quality to yield relevant results. Later the actual retrospective cohort study was conducted.

The main background of this request was that bitumen and its fumes contain small amounts of chemicals that are known to induce cancer in animals and possibly in humans, but under different exposure conditions and in different exposure intensities. For instance, it is generally accepted that certain polycyclic aromatic hydrocarbons can induce cancer. However, this does not mean that exposure to mixtures that contain relatively low concentrations of these chemicals are also capable of increasing the lung cancer risk in humans.

Basically there are two research designs available to investigate a specific association between an exposure and a long-term effect, in this case between occupational exposure to bitumen emissions and the risk of lung cancer. The most obvious design is that of a cohort study. In a cohort study a population, consisting of persons with exposure to the agent under investigation, is followed through time to observe the incidence of a disease, which is then compared with the incidence in a non-exposed population. This can be done either in a prospective or in a retrospective manner. The advantage of a retrospective design is that the investigator does not have to wait a long time to observe a sufficient number of cases with the disease to draw conclusions. The main disadvantage of a retrospective cohort study is that detailed information on exposure and co-exposures may be limited. In retrospective cohort studies the effects of exposures that occurred a long time ago are studied. The availability of exposure measurements and information on changes in production processes vary greatly from industry to industry. If past exposures cannot be well characterized, in terms of quantitative dimensions, no dose response analyses can be investigated and the results are difficult to use for setting occupational exposure standards.

It should be recognised however that these shortcomings are also encountered in prospective cohort studies. Generally currently exposed individuals carry with them a long history of past exposures to both material in question and other confounding factors and thus the same problems will be encountered.

A second disadvantage of retrospective cohort studies is that they usually do not identify information on other risk factors that may also influence the incidence of the disease under investigation. With respect to the possible increased risk of lung cancer associated with exposure to bitumen fumes it is very important to take into account the possible confounding effect of cigarette smoking and historical use of coal tar derived materials. Cigarette smoking is known to be a very potent cause of lung cancer. It is estimated that over 90% of all cases of lung cancer are caused by cigarette smoking.

A small difference in smoking habits between exposed and non-exposed persons can already result in substantial differences in lung cancer rates, not at all related to occupational exposures. Cohort studies usually have large sample sizes and it would be a major undertaking to collect data on smoking habits from all the study subjects. Case-control studies on the other hand have smaller sample sizes and usually cases and controls (or next of kin if deceased) are contacted to collect data on exposure, so that it becomes feasible to collect information on other risk factors for the disease under investigation.

In epidemiology, a very efficient research design has emerged by combining a retrospective cohort study with a case-control study. First a retrospective cohort study is conducted. Next the observed cases of the disease of interest are taken as the cases for a case-control study. Then, from all original cohort members free of the disease, a comparison (control) group is sampled, with which the cases can be compared. This is called a nested case-control design and it effectively combines the advantages of both research designs into one.

This line of reasoning has been applied by IARC and associated investigators in their research efforts in the field of occupational exposure to bitumen emissions. First a retrospective cohort study of asphalt workers has been conducted. Now a nested case-control study is planned.

The purpose of this report is to review the study results that have so far been reported from the IARC cohort study on asphalt workers. First the study design will be described in greater detail. Next, the results will be reviewed.

Full details of the study results can be found in the IARC Internal Report 01/003 [1] and also in extensive peer review publications by the collaborating authors.

2. RESEARCH DESIGN

The feasibility of an international retrospective cohort mortality study of asphalt workers was examined by an international group of epidemiologists from a number of countries, brought together by IARC. The feasibility of conducting a retrospective cohort mortality study is dependent upon three conditions.

1. Is it possible to compile a complete list of asphalt workers who have been involved in jobs with exposure to bitumen in the past?
2. Is it possible to follow these persons through time to observe the incidence or mortality and disease?
3. Is it possible to compare the observed incidence or mortality and disease in the exposed group with that of a non-exposed group?

All researchers from the participating countries were asked to investigate these matters, before embarking on the research project itself.

From the feasibility study it was learned that the study would be feasible in the following countries: France, Sweden, Israel, the Netherlands, Norway, Finland, Denmark and Germany. The results of the feasibility study have been previously reported by Partanen et al [2].

There are basically three types of comparison groups that can be applied in occupational retrospective cohort studies. First a non-exposed group of other workers can be retrospectively assembled and followed for the incidence of disease. Second the age-, time period- and cause specific mortality rates of the total population can be used to calculate an expected number of deaths, which then can be compared with the observed number. A third option consists of making internal comparisons between workers who have only been exposed for a short period and longer term employees.

The IARC epidemiological study of cancer mortality among European asphalt workers can be divided into four different phases:

1. The cohort enumeration phase, including exposure assessment.
2. The mortality follow-up of the enumerated cohort.
3. The statistical analysis.
4. Presentation and interpretation of the results.

This report will deal with these four phases consecutively.

3. THE COHORT ENUMERATION PHASE

First, in each participating country (except Sweden) suitable road paving and asphalt mixing companies were identified. Suitability depended on the availability of a complete employee roster, and the quality of the employee data. The number of companies included per country varied from 1 in Israel to 138 in Germany.

The personnel files of the companies were searched to identify the names of employees and former employees eligible to be included in the study. Several eligibility criteria were used for the cohort enumeration, which were not applied uniformly in all countries. First a minimal employment period was used in several countries, varying from 1 week to three months. The time interval from which employees were eligible for the study also varied from country to country.

From the personnel files, personal identifiers, date of birth, last known address and job history were abstracted. For each included company an effort was made to include all manual workers eligible for the study. All workers with one or more of the following job titles: paver, roofer, waterproofer or asphalt mixer were included in the "asphalt fumes exposed group" referred to as bitumen workers. All other manual workers were included in the non-exposed comparison group. In Sweden a different approach was taken. Here the cohort enumeration was based on the national construction workers survey that existed between 1969 and 1992 and information derived from this on job titles was used to identify bitumen workers or workers for the comparison group.

The total study population used for the statistical analysis consisted of 79822 workers employed at some point in time, either in a job designated as bitumen fume exposed or in another, non-exposed job in the asphalt industry or construction business.

The number of study subjects in several specific exposure groups is given in **Table 1**:

Table 1: Distribution of workers over the specific exposure categories in the IARC study (ref. Boffetta et al 2003 [5])

Country	Bitumen workers	Building or ground construction workers	Other workers
Denmark	9652	1129	4366
Norway	5687	2467	1033
Sweden	4381	16518	61
Finland	2642	2652	382
Netherlands	541	702	2437
Germany	3223	2486	2271
France	2513	5789	6714
Israel	1181	502	493
TOTAL	**29820**	**32245**	**17757**

3.1. JOB TITLE AND EXPOSURE CHARACTERISATION

In epidemiology studies aimed at investigating the possible health effects of occupational exposure to substances or mixtures it is important to characterize the type of exposure present in the study population as completely as possible. Job title is an important aspect of describing exposure.

The exposure characterization serves several purposes:

1. First, exposed workers must be distinguished from non-exposed workers.
2. Second, a quantitative or semi-quantitative estimate of the magnitude of exposure to the specific agent under investigation may allow the researchers to investigate the existence of dose-response relationships. In epidemiology, the presence of a dose-response relationship is considered an important criterion for a causal association between exposure and the risk of the health effect.
3. Third, exposure to other compounds that may also cause health effects in the workers should be taken into account. These co-exposures may confound the relationship between the exposure to the specific compound and the specific health effect under investigation. In this respect it is noteworthy that a co-exposure can only have a confounding effect if it is related to the health effect of interest as well as to the exposure to the compound under investigation.

Ad 1. Workers exposed to bitumen fumes and workers not exposed to bitumen fumes were distinguished by means of their job titles or the type of company they worked for together with an assessment of whether they have a blue collar job or not. A worker was classified as exposed to bitumen fumes if he had ever held a blue collar job in the road paving industry, in the asphalt mixing industry or in the roofing industry. 29,820 workers were categorised as ‘ever held a job’, and considered as bitumen workers.

Ad 2. A considerable effort was made to further characterize the exposure to bitumen fumes in a more quantitative manner. This basically was done for all 29,820 workers who were designated as bitumen exposed workers. Exposure assessments were based on actual exposure measurements that were available from the industry. The researchers had access to 2007 industrial hygiene measurements for a variety of agents among asphalt workers that had been collected since the late 1960’s, and these were used to compile the Asphalt Worker Exposure (AWE) database. About 70% of the measurements came from the Scandinavian countries. The exposure measurements were considered to be sufficiently extensive and balanced to permit statistical modelling with respect to bitumen fume, organic vapour and PAH exposures in paving operations. For the other jobs, e.g. mastic worker, the data were used to infer exposure rankings on what was called a semi-quantitative scale.

In addition, information on temporal changes in production characteristics, work practices and work organization was collected from the companies by means of questionnaires. These questionnaires were either mailed to representatives of the companies or were filled in by representatives of the companies during a meeting.

The exposure measurements and the company questionnaire data were used as the basis to derive exposure assessments covering the total exposure period under investigation, for each job title and for each country in the study. This formed the basis of the “Road Construction Workers Exposure Matrix” (ROCEM). From the ROCEM quantitative or semi-quantitative exposure estimates were made for all job titles in the study, for all time intervals in the study and for each company specifically. The key to linking the ROCEM data to the individual workers included in the study was the job title. Each job was regarded to result in the same exposure, taking account of the time period and company. For workers with unspecified jobs a weighted average was taken of the exposure estimates for the jobs that particular worker could have had. The ROCEM data set was used to perform three types of dose characteristic-response analyses. These were by duration of exposure, by cumulative exposure and by average level of exposure over work history. The ROCEM included exposure estimates of bitumen fume, organic vapour, PAH, diesel exhaust, asbestos, silica and coal tar.

Ad 3. Workers included in the cohort study, as part of the exposed group or of the group not exposed to bitumen fumes, may have been exposed to other chemicals or agents that by themselves could have an effect on the lung cancer risk. Thus, if exposure to these agents is related to exposure to bitumen fumes, either positively or negatively, these co-exposures can have a confounding effect on the study outcome. Therefore a considerable effort was made to evaluate these co-exposures. This was basically done in a similar manner to the assessment of exposure to bitumen. Again the company questionnaires and the job title and time interval formed the basic parameters that were fed into the exposure assessment model. The co-exposures considered in the study were exposure to asbestos, silica dust, diesel exhaust and exposure to coal tar. Since a major concern was a possible confounding effect of historical exposure to coal tar, this possible confounding factor was handled with caution. This was done by constructing a so-called coal tar free subgroup in the bitumen exposed workers, a subgroup of bitumen workers consisting of workers for whom exposure to coal tar at any time in their work history could be excluded, based on the data provided in the company questionnaires. The estimates for co-exposures were also handled in a semi-quantitative manner.

Another factor taken into account with respect to exposure assessment was differences in shift work and work season. Differences in shift duration and work season were noted between companies and time periods. These were taken into account by introducing appropriate weights.

Missing data for individual workers were estimated based on the available data for their colleagues. Cross validation analyses were performed by estimating the model parameters on half of the cohort and applying the parameters to the remaining half. An external validation was performed by comparison with predicted exposures for an external exposed group, for which actual exposure measurements were available. This external validation turned out to be satisfactory.

Four exposure metrics were used in the analysis. First, the total cohort was divided into exposed and non-exposed workers. Next, analyses were made by duration of exposure, on the assumption that if bitumen exposure increased the risk the lung cancer rate would be greater in workers with a long duration of exposure. Similar analyses under similar assumptions were made for cumulative exposure and average level of exposure.

4. FOLLOW-UP

The second phase of a retrospective cohort study consists of confirmation of the current health status of the study subjects. In most retrospective cohort studies information on the current health status is restricted to vital status and cause of death (being the underlying disease that has resulted in the death of the person). In most, if not all European countries, death is a well-recorded item and information on death and the cause of death is readily available for scientific research, subject to a number of privacy considerations. Because of the accurate recording of death and the cause of death it is widely used as the central health effect parameter in retrospective cohort studies. In most European countries follow-up can be conducted by means of population registries or mortality registrations.

The end date of the follow-up in the European Asphalt Worker Study varied from country to country. In Finland for instance the end date of the follow-up was 1994, whereas the end date in Germany was 2000. The completeness of the follow-up in the European Asphalt Workers was quite good. Only 545 workers out of the 79822 were lost to follow-up (0.7%).

5. STATISTICAL ANALYSIS

One of the most important aims of the statistical analysis is to investigate if a proportion of the mortality observed in the cohort is attributable to exposure to the chemical under investigation. In any cohort followed for some time there will be deaths. The larger the cohort, the more deaths will occur. The older the cohort under investigation, the more deaths can be expected and thirdly, the longer the cohort is followed the more deaths can be expected. These phenomena occur independently of the effect on mortality of the chemical under investigation.

In summary, the observed death rates in a cohort are strongly influenced by:

1. The age distribution of the cohort
2. The duration of follow-up
3. The time interval covered by the follow-up
4. The working conditions of the subjects
5. Other risk factors

The possible effect of the first three factors must be taken into account before the fourth condition can be properly investigated. This is done in the statistical analysis and there are two different ways to achieve these adjustments or standardisation. Firstly, there is the indirect method of standardisation and secondly there is a direct method of standardisation. Both approaches have been followed by IARC.

In the indirect method the observed number of deaths is compared to an expected number of deaths that has been calculated by applying age, calendar time and cause specific rates from the general population to the person-years of observation. The Standardized Mortality Ratio (SMR) is calculated by dividing the observed number of deaths by the expected number of deaths. An SMR of 1 reflects the situation in which the observed number of deaths is equal to the expected number, a situation is which the exposure factors under investigation appear not to have had an effect on mortality rates. An SMR of two depicts that the risk has doubled, possibly as the result of the exposure situation. If the SMR is smaller than unity the observed mortality seems to be lower than expected. For the calculation of SMRs the national mortality rates serve as a reference.

The second method of standardisation utilises cause-, age- and interval specific mortality rates from another cohort or from the same cohort but for a specific non-exposed group of workers. This direct standardisation can be carried out by means of a Poisson regression analysis in which the mortality rates of non-exposed workers act as the reference. Therefore the relative risk (RR) for the non-exposed group, or lowest exposed group in this type of analyses is always one.

A number of dose-response analyses have also been conducted in which specific exposure indices have been studied in relation to the risks of mortality from specific diseases. Three exposure indices have been used: duration of exposure, average exposure and cumulative exposure.

From other studies it is known that some time interval must elapse before a given exposure can induce cancer and certainly cancer mortality. Therefore an additional analysis was performed, the so-called lagged analysis. In this analysis a first time interval (for example 15 years, as in this study) is not regarded as being a risk period for developing the health effect under investigation. If an exposure can cause cancer, the introduction of a time lag should increase the observed excess mortality risk.

6. RESULTS OF THE SMR ANALYSES

A large number of statistical analyses on the data have been carried out and have been published in the extensive report written by the study group and have been presented in the form of nine sets of tables (IARC report). Table numbers as they appear in the IARC Internal Report [1] are indicated between brackets in italic characters in the text here below and in Section 7.

From these tables the following results emerge:

The total mortality in the overall group of bitumen workers (job class 1) was very close to the expected number. In the asphalt workers 3987 deaths were observed, compared to an expected number of 4162.8 (SMR=0.96 95% CI: 0.93-0.99). In this group of asphalt workers, a small but statistically significant excess of lung cancer mortality was observed. 330 Deaths from lung cancer were observed compared to an expected number of 283.08, giving an SMR of 1.17 (95% CI: 1.04-1.30). In the total group of asphalt workers there were also small excesses of laryngeal and oesophagus cancer mortality but these were not statistically significant.

Similar small excesses for lung cancer mortality were seen in the jobs included in the category of asphalt worker: for road pavers (SMR=1.17, 95% CI: 1.01-1.35, based on 189 cases), asphalt pavers (SMR=1.15 95% CI: 0.93-1.40, based on 100 cases), asphalt mixers (SMR=1.12 95% CI: 0.73-1.66, based on 25 cases), unspecified pavers/mixers (SMR=1.18 95% CI: 0.61-2.07, based on 12 cases), roofers (SMR=1.33 95% CI:0.73-2.23, based on 14 cases) and unspecified bitumen workers (SMR=1.13 95% CI: 0.92-1.37, based on 99 cases). Asphalt workers in some countries had elevated SMRs for lung cancer mortality (Germany, Norway, Denmark, The Netherlands, Finland, and Israel) while in some other countries the lung cancer mortality was lower than expected (France and Sweden).

A number of more specific analyses were performed to investigate in more detail the association between exposure and the risk for diseases, including lung cancer (see **Table 2**). Here only the analyses with respect to lung cancer mortality are discussed since that is the main outcome of interest.

First an analysis of the risk for lung cancer was made by duration of exposure to bitumen fume (*Table 5.1.1*). This analysis revealed an inverse association between the duration of exposure to bitumen fumes and the risk for lung cancer. The SMR for lung cancer was 1.25 (95% CI: 1.04-1.49, based on 124 cases) in the group exposed less than 1.75 years and 0.95 (95% CI: 0.80-1.12, based on 145 cases) in the group with over 9.87 years of exposure. After the inclusion of a lag time period of 15 years the inverse relationship essentially disappeared and the SMRs for lung cancer were comparable across the four exposure duration groups (*Table 5.2.1*). Lagged analyses are performed to investigate the possible time window in which an adverse effect may occur. A lag period of 15 years indicates that the researchers disregard the first 15 years after beginning of exposure, which is a plausible assumption.

Next an analysis was made of the risk for lung cancer mortality by cumulative exposure to bitumen fumes (*Table 5.3.1*). The quantitative exposure estimates by job title, time interval and country were multiplied by the duration of exposure to derive the cumulative exposure metric. The bitumen cohort was divided into four groups of cumulative exposure and SMRs were calculated for each group. No increase in risk was observed with increasing cumulative exposure to bitumen. In fact the SMR for lung cancer was highest in the group with the lowest cumulative exposure to bitumen fumes (SMR=1.16 95% CI: 0.97-1.38 based on 132 cases) and lowest in the subgroup with the highest cumulative exposure (SMR=1.02 95% CI: 0.85-1.20, based on 136 cases). This trend however was not statistically significant. Again the introduction of a 15-year lag essentially eliminated the inverse trend and there was no difference between the cumulative does groups with respect to lung cancer risk.

The lung cancer mortality risk within the bitumen workers was also analysed by average exposure to bitumen fumes over the job career. For this analysis a new exposure metric was calculated by dividing cumulative exposure by duration of exposure. In this analysis a statistically significant trend between average exposure and the risk for lung cancer was noted (p<0.03, *Table 5.5.1*) and even for all cause mortality. The introduction of a 15-year time lag produced a similar finding.

These analyses were repeated after excluding all workers with less than one season of employment. Similar results were obtained.

Since there were other potentially confounding exposures in the cohort, the cause specific mortality was studied with respect to other occupational exposures. Since coal tar is a well-recognized exposure that can increase the risk of lung cancer and since exposure to bitumen fumes is correlated to coal tar exposure, special emphasis was given to this analysis. The workers were categorized by the duration of exposure to coal tar, into four groups, and the lung cancer mortality was analysed for each group. The SMR for lung cancer in the coal tar exposed group was 1.05 (95% CI: 0.93-1.17) compared to an SMR of 1.08 (95% CI: 0.98-1.18) in the non-exposed group. Thus no association was found between duration of exposure to coal tar and the risk of lung cancer mortality (*Table 6.1.1*). The introduction of a 15-year lag did not change these results. In addition, no association was found between cumulative exposure to coal tar and the risk for lung cancer mortality (*Table 6.3.1*). Again, a 15-lag period did not alter the results (*Table 6.4.1*). Similar analyses were performed for the association between average exposure to coal tar and the risk for cause specific mortality. Basically no association was found between average exposure to coal tar and the risk for lung cancer, with or without a 15-year time lag.

The data were then analysed to see if there was a relationship between cumulative asbestos exposure and cause specific mortality (*Table 7.1.1*). The data did not indicate that there was a relationship between asbestos exposure and any of the investigated cause specific mortality including lung cancer mortality.

The relationship between cumulative exposure to silica dust and lung cancer mortality was also investigated. These analyses did not show such a relationship.

The SMRs for lung cancer mortality were marginally elevated in the workers with cumulative exposure to Polycyclic Aromatic Hydrocarbons (SMR 1.08 95% CI:0.99-1.18, based on 525 cases). A similar marginal association was found between cumulative diesel exhaust and lung cancer mortality (SMR=1.08 95% CI:0.99-1.18, based on 535 cases) and for cumulative exposure to organic vapour (SMR=1.08 95% CI: 0.99-1.18, based on 524 cases.

7. RESULTS OF THE RR ANALYSES

In addition to the indirect analyses a series of direct analyses were performed. In these analyses the age, time interval and cause specific mortality rates of the non-exposed population are used as a reference. The advantage of this approach is that the mortality risks of non-exposed workers are compared to mortality risks of exposed workers, essentially eliminating the occurrence of the 'healthy worker effect'. The healthy worker effect in occupational epidemiology studies is related to the phenomenon that mortality and health in general are more favourable in workers than in the general population. Sometimes workers are screened with respect to their health status before hire and invalidated individuals are not likely to apply for jobs with high physical demands. The healthy worker effect can arise if incidence or mortality rates from the general population are used for reference rates for working populations.

The major disadvantage of this approach is that the mortality rates per cell in the non-exposed group can be relatively unstable. The SMR and RR analyses should yield the same results, but in practice there may be small differences. No results are given for the total exposed cohort, but only the more sophisticated dose response analyses.

The RR analyses generally yielded lower risk estimates than the SMR analyses. In the dose response analyses, independent of whether duration of exposure, cumulative exposure or average exposure were used, no evidence was found for an increased risk for lung cancer (*Table 8.1.4*). The data provided some support for an association between other diseases of the respiratory system and exposure to bitumen fume (*Table 8.1.6*). This was also true for the association between tar exposure and the risk for non-malignant diseases of the respiratory system (*Table 8.2.6*). In addition an association was found between exposure to polycyclic aromatic hydrocarbons and the relative risk for buccal cavity cancer, which was statistically significant for average exposure (*Table 8.5.3*). The direct analysis of the association between quantitative exposure estimates to bitumen fume and lung cancer also resulted in a statistically significant increase (*Table 8.8.4*).

Table 2 Lung cancer mortality risks in the asphalt cohort, by job title, duration of exposure, cumulative exposure and average exposure* with respect to bitumen fume

Job title (number of cases)	SMR	(95% CI)	RR	(95% CI)
Bitumen worker (330)	1.17	(1.04-1.30)	1.09	(0.89-1.34)
Road pavers (189)	1.17	(1.01-1.35)	1.08	(0.87-1.34)
Asphalt paver (100)	1.15	(0.93-1.40)	0.99	(0.77-1.27)
Asphalt mixers (25)	1.12	(0.73-1.66)	1.18	(0.75-1.84)
Unspecified paver/mixer (12)	1.18	(0.61-2.07)	1.07	(0.55-2.10)
Roofers (14)	1.33	(0.73-2.23)	1.34	(0.71-2.53)
Unspecified bitumen worker (99)	1.13	(0.92-1.37)	1.53	(0.92-2.57)
Duration of exposure, 15 year lag				
0<-<1.4456 years (82)	1.10	(0.88-1.37)	0.92	(0.71-1.19)
1.4456<-<3.8987 (87)	1.06	(0.85-1.31)	0.91	(0.70-1.17)
3.897<-<8.0548 (85)	1.08	(0.86-1.34)	1.04	(0.79-1.36)
8.0548+ (95)	1.14	(0.93-1.40)	1.08	(0.80-1.45)
Cumulative exposure**, 15 year lag				
0<-<3.6463 (93)	1.09	(0.88-1.34)	1.00	(0.78-1.28)
3.6463<-<8.6099 (80)	1.21	(0.96-1.50)	1.02	(0.79-1.32)
8.6099<-<25.9110 (82)	0.96	(0.76-1.19)	0.84	(0.64-1.09)
25.9110 + (94)	1.16	(0.94-1.42)	1.04	(0.79-1.36)
Average exposure***, 15 year lag				
0<-<1.3823 (87)	1.08	(0.86-1.33)	1.02	(0.78-1.33)
1.3823<-<3.8173 (99)	0.92	(0.75-1.13)	0.76	(0.59-0.98)
3.8173<-<4.9678 (88)	1.30	(1.04-1.60)	1.15	(0.89-1.47)
4.9678 + (75)	1.21	(0.95-1.51)	1.06	(0.81-1.40)

* decimal figures as presented in IARC report [1]
** [semi-quantitative exposure units]x[years]
*** [semi-quantitative exposure units]

8. RESULTS REPORTED IN VOLUME 43 OF THE AMERICAN JOURNAL OF INDUSTRIAL MEDICINE

Most of the results of the main study and a number of additional analyses have been published in peer-reviewed publications, particularly in one volume of the American Journal of Industrial Medicine (volume 43, 2003). These articles were preceded by an introduction written by Boffetta and Burstyn [3]. In that introduction a brief review of earlier studies on the carcinogenicity of bitumen fume is presented. The authors concluded that the main uncertainty in the assessment of previous epidemiological data arises from the ability to exclude the possibility of confounded results by concurrent or historical use of coal tar.

However, based on the results of the cohort study a second uncertainty lies in the estimation of the lung cancer risk experienced by asphalt workers. It remains unclear whether or not road pavers as a group have or have not experienced an excess of lung cancer. Thirdly, since cigarette smoking is a potent risk factor for lung cancer and since smoking is a common habit, small differences in smoking can have a significant confounding effect on lung cancer risk. Following the introduction, nine full articles on the European cohort study on bitumen workers were published in that same volume of the American Journal of Industrial Medicine. These are briefly described here below in the order in which they appear in the Journal.

1. Burstyn et al: **Estimating exposures in the asphalt industry for an international epidemiological cohort study of cancer risk [4].**

   This article describes in detail the procedures that were used in the exposure assessment component of the cohort study. In short, data on production process and work practices were collected by means of the company questionnaire, which were linked to available industrial hygiene measurements and the specific job titles of the workers. By means of expert judgement and statistical modelling exposure estimates were derived for specific job titles, specific time periods and for all 217 participating companies. The exposure matrix covered exposures to coal tar, bitumen fume, organic vapour, polycyclic aromatic hydrocarbons, diesel exhaust, silica and asbestos.

2. Boffetta et al: **Cancer mortality among European asphalt workers: An international epidemiological study. I. Results of the analysis based on job titles [5].**

   In this article the results of the cohort study are presented for specific jobs that have been identified. With respect to lung cancer the main conclusions are:

   1. A small excess of lung cancer in the bitumen workers: An SMR of 1.17 (95% CI: 1.04-1.30) for bitumen workers, but a relative risk of 1.09 (95% CI: 0.89-1.34) based on an internal analysis.

   2. These conclusions were consistent across the specific jobs included in the bitumen exposed worker group, being road paver, asphalt paver, asphalt mixer, unspecified paver/mixer, and they were somewhat higher for roofers/waterproofers and unspecified bitumen exposed workers. A cross-country comparison revealed that the excess in the SMR analysis was mainly confined to Germany, but the smaller excess in the internal analysis was mainly confined to Denmark.

3. Boffetta et al: **Cancer mortality among European asphalt workers: An international epidemiological study. II Exposure to bitumen fume and other agents [6].**

   In this article the data have been analysed based on exposure to bitumen fume, coal tar, asbestos, silica, and diesel exhaust as assessed by the constructed exposure matrix. The main conclusions were:

   1. Workers exposed to bitumen fume had experienced an SMR for lung cancer of 1.08 (95% CI: 0.99-1.18).

   2. Workers exposed to bitumen fume but not to coal tar were reported to have experienced an SMR for lung cancer of 1.23 (95% CI:1.02-1.48).

   3. Using the semi-quantitative exposure assessments did not suggest an increased lung cancer risk following exposure to bitumen fume.

   4. If the semi-quantitative exposure assessments were applied to the road pavers only, a dose response was suggested with average exposure, but not with cumulative exposure or duration of exposure. However the tests for trend for all three dose-response curves were not statistically significant.

   5. If quantitative exposure assessments were used a positive dose-response was found with average exposure but not with cumulative exposure.

   6. Similar patterns were found for cancer of the head and neck, but based on small numbers of individual cases.

   7. No noteworthy associations were found between lung cancer and exposure to coal tar, asbestos, silica or diesel exhaust.

4. Igor Burstyn et al: **Performance of different exposure assessment approaches in a study of bitumen fume exposure and lung cancer mortality [7].**

   In the European Bitumen study several exposure indices or metrics were used, i.e. duration of exposure, average exposure and cumulative exposure. In addition, two latency models were used, one without a latency period and another with 15 years of exposure. It was concluded that the construction of quantitative exposure indices was justified, and that the possible relationship between bitumen exposure and lung cancer requires further investigation.

5. Kauppinen et al: **Mortality and cancer incidence of workers in Finnish road paving companies [8].**

   The results of the Finnish component of the European bitumen workers study was reported. The mortality data were already included in the overall analysis presented earlier. A small, but not statistically significant excess in lung cancer mortality risk was found, which was in line with the overall findings.

A stronger excess risk for lung cancer mortality was found for the construction workers and other workers (Table II article). Some data on smoking habits of the workers were presented. 77% of the workers exposed to bitumen fume were ever smokers compared with 68% in the non-exposed workers. There appeared to be relatively heavy smokers among the bitumen workers: 22% smoked or had ever smoked twenty cigarettes or more per day compared with 13% in the non-exposed workers (Table V article).

6. Stücker et al: **Cohort mortality study among French asphalt workers [9].**

   In this article the results of the French component of the IARC study were presented. In addition to some indication for an excess of lung cancer risk in the internal analysis but not in the SMR analysis, there was evidence for an excess on stomach cancer mortality in French asphalt workers.

7. Shaman et al: **Epidemiologic study of cancer mortality among Israeli asphalt workers [10].**

   This article presents the results of the Israeli component to the IARC study. In the Israeli component a marginal excess of lung cancer mortality was found (SMR=1.05 95% CI: 0.62-1.66). Eighteen observed deaths from lung cancer were noted compared to an expected number of 17.14. The investigators concluded that these data do not provide evidence of a causal link between lung cancer risk and exposure to bitumen fumes.

8. Hooiveld et al: **Lung cancer mortality in a Dutch cohort of asphalt worker: Evaluation of possible confounding by smoking [11].**

   In this article the results of the Dutch component of the IARC study are presented. Since some data on smoking were available an attempt was made to assess the possibility that the association between bitumen exposure and lung cancer mortality could have been confounded by differences in smoking habits. A factor can only act as a confounder if that factor is associated to the risk factor under investigation as well as to the disease under investigation. For 31% of the Dutch cohort information on the smoking habits was available. The percentage of ever smokers was higher among asphalt workers (79%). and unspecified workers (77%) compared to building and ground construction workers (72% ever smokers). After adjustment for smoking with the available smoking data the relative risk for lung cancer in the asphalt workers decreased from 1.04 to 0.92. Some indication for a trend between semi-quantitative exposure to bitumen and lung cancer remained.

9. Randem et al: **Cancer incidence among male Norwegian asphalt workers [12].**

   In this article the results of the Norwegian component of the IARC study, based on cancer incidence are presented. Cases of cancer were traced with the aid of the Norwegian Cancer Registry. Seventy-five observed cases of lung cancer in the exposed cohort were compared to an expected number of 55.9 giving a Standardized Incidence Ratio of 1.3 (95% CI: 1.1-1.7). Small elevations for stomach cancer and non-Hodgkin's lymphoma and a decreased risk for malignant melanoma were also noted.

10. Randem et al: **Mortality from non-malignant diseases among male Norwegian asphalt workers [13].**

    Within the Norwegian cohort a separate analysis was made to investigate the risk for non-malignant respiratory diseases in Norwegian asphalt workers. The results of this separate analysis are presented in this article. The study population consisted of 8610 workers employed in the Norwegian asphalt industry, between 01-01-1970 and 12-31-1996. 67 Deaths from non-malignant respiratory diseases were noted compared to an expected number of 53.7 (SMR=1.25 95% CI:0.97-1.59).

11. Bergdahl et al: **Cancer morbidity in Swedish asphalt workers [14].**

    In this article Bergdahl and Järvholm report the results of the Swedish component of the IARC study with respect to cancer incidence. The cohort consisted of 6150 asphalt workers Thirty-two cases of cancer were observed and the Standardized Incidence Ratio (SIR) for lung cancer was 0.98 (95% CI: 0.67-1.39). Since smoking data were available from questionnaires undertaken at regular health examinations it was possible to adjust the results for differences in smoking habits between asphalt workers and construction workers. The relative risk for lung cancer in asphalt workers was 1.03 (95% CI: 0.70-1.45) as compared to construction workers. Because of the lack of historical data in the cohort the investigators reported to be unable to carry out any dose-response or exposure time response analyses.

9. GENERAL CONCLUSIONS AND REMARKS

The epidemiology study of asphalt workers conducted by IARC is a well-conducted study. Part of its strength lies in the fact that the participating countries adopted the same protocol, which has resulted in a more or less uniform approach and a much increased study population.

In general the results can be summarized as follows. The overall mortality of the asphalt worker cohort is below the expected number of deaths based on the age, and time interval specific mortality rates of the general national populations of the participating countries.

A small, but statistically significant excess for lung cancer mortality was found in the workers who had been employed in a job with exposure to bitumen fume. Dose-response analyses revealed an association between average exposure and the lung cancer risk, but not between duration of exposure or cumulative exposure and lung cancer risk. In the cohort there was substantial concomitant exposure to coal tar. When the possible effect of this concomitant exposure to coal tar was taken into account the excess for lung cancer mortality was further reduced. In addition to the possible association between bitumen fume and lung cancer a statistically significant association was reported between bitumen fume exposure and mortality from non-malignant respiratory diseases.

A weakness in the design of this study is that no information on cigarette smoking habits of the workers was collected, particularly since the possible health outcome is lung cancer. Although it is known that lung cancer is strongly related to cigarette smoking, it is generally recognized that collecting information on smoking habits from such a large population is a major undertaking and is almost impossible. Therefore the proposed nested case-control study will focus on collection of smoking data for lung cancer deaths and controls within the cohort under investigation. In addition, improved assessment of bitumen fume exposures will be pursued, as well as exposure information for known and suspect lung carcinogens in other industries where study subjects have been employed at some stage of their working lives.

Finally, the workers included in the current cohort came primarily from companies engaged in asphalt road paving which represents the main application of bitumen. There are only small, and consequently rather uninformative, numbers of workers from other user industries traditionally of interest with regard to asphalt fume health effects, such as mastic workers and roofers, as their industrial associations were not represented in the initial industry group responsible for stewarding the cohort study.

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