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LUNG CANCER AND OCCUPATIONAL EXPOSURE TO COMBUSTION PRODUCTS

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"Indeed, nearly half of all recognized human carcinogens are occupational carcinogens. Although it is important to discover occupational carcinogens for the sake of preventing occupational cancer, the potential benefit of such discoveries goes beyond the factory walls since most occupational exposures find their way into the general environment, sometimes at higher concentrations than in the workplace."

Jack Siemiatycki, Lesley Richardson and Paolo Boffetta

ABSTRACT

Lung cancer, the most common cause of cancer death, is predominantly attributable to tobacco smoking. One of the many carcinogenic components of tobacco smoke are polycyclic aromatic hydrocarbons (PAH). Several occupational exposures containing high levels of PAHs are classified as carcinogenic to humans (Group 1) by the International Agency for Research on Cancer (IARC). Bitumen fumes and diesel motor exhaust (DME) which are complex mixtures of agents containing small quantities of PAHs, are classified as possibly (Group 2B) and probably carcinogenic (Group 2A) to humans, respectively.

The main goals of this thesis were to explore 1) the role of occupational exposures overall, and in particular combustion products in Central and Eastern Europe, a region with the world's highest lung cancer incidence rate in men; 2) whether occupational DME exposure in a population-based study and 3) exposure to bitumen fume among asphalt workers were associated with increased lung cancer risk.

The aims were addressed using three data sources; 1) the IARC multicenter case-control study on lung cancer conducted in six countries in Central and Eastern Europe (CEE) and the United Kingdom (2852 cases, 2923 controls); 2) the SYNERGY pooling project of eleven case-control studies of lung cancer from Europe and Canada (13479 cases, 16510 controls); and 3) a case-control study of lung cancer nested within a cohort of European asphalt workers (433 cases, 1253 controls). All three studies allowed careful adjustment for lifetime cumulative tobacco smoking.

The attributable fraction (AF) of lung cancer to occupational exposure overall in CEE was 7.9% (95% CI: 1.9 to 13.5%) in men. Silica and metals had the greatest AF contributions, and there was some suggestion that the AFs were higher among current- than among ex- or never-smokers. Among women, AFs were small or close to zero, except for small cell carcinoma lung cancers (AF 7.1%, 95% CI: 0 to 14.4%), an observation which needs further investigation and confirmation. We found no evidence of an association between occupational PAH exposure and lung cancer risk in CEE after adjusting for relevant occupational exposures and smoking.

Occupational DME exposure was associated with an increased lung cancer risk. Exposed subjects in the highest quartile of cumulative exposure had a 1.31-fold higher lung cancer risk (95% CI 1.19-1.43) than never exposed subjects. This association held in workers never employed in occupations known to have excess lung cancer risks, in women and in never-smokers. This result is in line with previous research, though most previous studies could not control for major potential confounders and have not had as large sample sizes as ours.

Amongst European asphalt workers, there was no evidence that lung cancer risk was related to indicators of inhalation or dermal exposure to bitumen fume, nor to other known or suspected occupational lung carcinogens present in this industry, with the exception of coal tar.

This thesis demonstrates (i) that both community-based and industry-based studies are important to identify and quantify risks in occupational cancer epidemiology; (ii) the significance of international collaborations to establish large-scale studies examining exposures and risks which cannot otherwise be adequately studied; and (iii) the necessity to consider the joint effect of exposures with each other and with smoking as agents commonly confer stronger effects when acting together.

SAMMANFATTNING

Lungcancer, den vanligaste dödliga cancerformen, är till största delen orsakad av tobaksrökning. En av de många cancerframkallande ämnen som finns i tobaksrök är polycykliska aromatiska kolväten (PAH). Yrkesmässig exponering för höga halter av PAH är i många fall klassifisserad som cancerframkallande (Grupp 1) av WHO's internationella cancerforskningsinstitut (IARC). Bitumenrök och dieselavgaser, som är komplexa blandningar och innehåller små mängder PAH, är klassificerade som möjligen cancerframkallande (Grupp 2B) respektive troligen cancerframkallande (Grupp 2A) för människor.

Det övergripande syftet med denna avhandling var att undersöka 1) hur stor roll yrkesexponeringar spelar övergripande för lungcancerrisken, och hur stor betydelse förbränningsprodukter har för lungcancerrisken i Cental- och ÖstEuropa, som är den region som har världens högsta lungcancerfrekvens bland män; 2) om yrkesexponering för dieselavgaser i arbetsmiljön och 3) exponering för bitumenrök bland asfaltsarbetare var förenat med en ökad lungcancerrisk. I samtliga fall var det möjligt att noggrannt justera för rökvanor.

För att kunna svara på dessa frågor användes tre källmaterial: 1) IARC's multi-center fall-kontroll studie av lungcancer i 6 länder i Cental- och ÖstEuropa och Storbritannien (2852 fall, 2923 kontroller); 2) SYNERGY projektet som utgör en sammanslagning av data från 11 befolkningsbaserade fall-kontrollstudier i Europa och Kanada (13479 fall, 16510 kontroller); och 3) en fall-kontroll studie av lungcancer inom en kohort av Europeiska asfaltarbetare (433 fall, 1253 kontroller).

Den etiologiska fraktionen (EF) för yrkesexponering sammantaget var 7.9% (95%CI: 1.9-13.5%) bland män i Cental- och ÖstEuropa. Kvarts och metallexponering bidrog mest till denna etiologiska fraktion, och vi fann att EF var större bland rökare än bland ex- och icke rökare. Den etiologiska fraktionen för yrkesexponeringar bland kvinnor var nära noll, utom för små-cellig lungcancer (EF 7.1%, 95% CI: 0-14.4%), denna observation behöver undersökas vidare i andra studier. Vi fann inga belägg för att förbränningsprodukter påverkar lungcancerrisken i Cental- och ÖstEuropa, efter att vi kontrollerat för effekten av tobaks rökning och andra relevanta yrkesexponeringar.

Vi fann ett samband mellan yrkesexponering för dieselavgaser och lungcancerrisk; kvartilen med den högsta kumulativa exponeringen gav oddskvoten 1.31 (95% 1.19-1.43) i jämförelse med de icke exponerade. Detta samband förelåg även om materialet begränsades till personer som aldrig haft ett arbete som medför ökad lungcancerrisk, samt bland kvinnor och icke-rökare. Resultat är i linje med tidigare forskning, skillnaden är att de flesta tidigare studier inte har kunnat justera för viktiga confounders och inte har varit lika stora som denna.

Bland asfalt arbetare fann vi inget säkert samband mellan ökad lungcancerrisk och exponering av inhalerad bitumen rök eller hudkontakt med kondenserad asfaltrök, vi fann heller ingen effekt för andra misstänkta- eller konfirmerade yrkesexponeringar som orsakar lung cancer, utom for stenkols tjära som tidigare använts inom denna industri.

Denna avhandling visar (i) att både populationsbaserade- och industribaserade studier är viktiga för att identifiera och kvantifiera risker inom yrkesrelaterad cancerepidemiologi; (ii) den signifikanta betydelsen av internationella samarbeten i att etablera storskaliga studier för att undersöka exponeringar och risker som annars inte skulle kunna studeras adekvat; och (iii) nödvändigheten av att väga in samfällda effekter av exponeringar med varandra och med rökning eftersom många substanser ofta innefattar en förstärkt effekt när de verkar tillsammans.

LIST OF PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text by their Roman numerals (I-IV). Published manuscripts are reprinted with permission of the BMJ Publishing Ltd (Paper I), Environmental Health Perspectives (Paper II), and the American Thoracic Society (Paper III).

I. Olsson AC, Fevotte J, Fletcher T, Cassidy A, 't Mannetje A, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, Lissowska J, Fabianova E, Mates D, Bencko V, Foretova L, Janout V, Brennan P, Boffetta P. Occupational exposure to polycyclic aromatic hydrocarbons and lung cancer risk: a multicenter study in Europe. *Occup Environ Med.* 2010 Feb;67(2):98-103. Epub 2009 Sep 22.

II. Olsson A, Kromhout H, Agostini M, Hansen J, Funch Lassen C, Johansen C, Kjaerheim K, Langård S, Stücker I, Ahrens W, Behrens T, Lindbohm ML, Heikkilä P, Heederik D, Portengen L, Shaham J, Ferro G, de Vocht F, Burstyn I, Boffetta P. A Case-Control Study of Lung Cancer Nested in a Cohort of European Asphalt Workers. *Environ Health Persp*ect. 2010 Oct;118(10):1418-1424. Epub 2010 Jun 9.

III. Olsson AC, Gustavsson P, Kromhout H, Peters S, Vermeulen R, Brüske I, Pesch B, Siemiatycki J, Pintos J, Brüning T, Cassidy A, Wichmann H-E, Consonni D, Landi MT, Caporaso N, Plato N, Merletti F, Mirabelli D, Richiardi L, Jöckel K-H, Ahrens W, Pohlabeln H, Lissowska J, Szeszenia-Dabrowska N, Zaridze D, Stücker I, Benhamou S, Bencko V, Foretova L, Janout V, Rudnai P, Fabianova, Stanescu Dumitru R, Gross I, Kendzia B, Forastiere F, Bueno-de-Mesquita B, Brennan P, Boffetta P, Straif K. Exposure to Diesel Motor Exhaust and Lung Cancer Risk in a Pooled Analysis from Case-Control Studies in Europe and Canada. *Am. J. Respir. Crit. Care Med.* Epub ahead of print 2010 Oct 29. as doi:10.1164/rccm.201006-0940OC

IV. Olsson AC, Gustavsson P, Zaridze D, Mukeriya A, Szeszenia-Dabrowska N, Rudnai P, Lissowska J, Fabianova E, Mates D, Bencko V, Foretova L, Janout V, Fevotte J, ‘t Mannetje A, Fletcher T, Brennan P, Boffetta P. Lung cancer risk attributable to occupational exposures in a multi-centre case-control study in Central & Eastern Europe, *Manuscript*

LIST OF ABBREVIATIONS

AF	Attributable fraction
AWE	Asphalt worker exposure database
B(a)P	Benzo(a)pyrene
CEE	Central and Eastern Europe
CI	Confidence intervals
COPD	Chronic obstructive pulmonary disease
COR	Confounding odds ratio
DME	Diesel motor exhaust
DOM-JEM	General population job-exposure matrix on DME from IRAS
DREAM	Method for structured semi quantitative dermal exposure assessment
IARC	International Agency for Research on Cancer
ICD-9	International classification of diseases, 9th Revision
ICD-O	International classification of diseases for oncology
INCO	IARC multi-centre case-control study of occupation, environment, and lung cancer in CEE
IRAS	The Institute of Risk Assessment Sciences, Utrecht University
ISCO-68	International standard classification of occupational from 1968
ISIC	International standard industrial classification
JEM	Job exposure matrix
List A	List of jobs with known excess risk of lung cancer
NACE Rev.1	Statistical classification of economic activities in the European community, revision 1.
NOK	Next-of-kin, associated person or relative of deceased case or control
NSCLC	Non-small cell lung cancer
NYK-83	Nordic standard occupational classification
OR	Odds ratio
PAH	Polycyclic aromatic hydrocarbons
SCLC	Small call lung cancer
SNPs	Single nucleotide polymorphisms
WHO	World Health Organization

BACKGROUND

LUNG CANCER EPIDEMIOLOGY

Lung cancer is the most frequent malignant tumour in humans after non-melanoma skin cancer and the most important cause of cancer-related death worldwide, with an estimated 1.6 million new cases and 1.38 million deaths per year in 2008. The majority of cases now occur in developing countries (55%).[1,2] The highest incidence rates in men are found in Central and Eastern Europe (57/100,000 person years) and in women in North America (35.8/100,000 person years), while the lowest rates in both genders occur in Middle Africa (1.7/100,000 person years). Among men, lung cancer incidence is now declining in most Western countries, but is still rising among women.[3] Despite having a declining incidence trend, men in Hungary and Poland have the highest lung cancer rates worldwide, 79.3 and 70.6 per 100,000 person years respectively.[2]

The two main types of lung cancer are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC most often arises in primary and secondary bronchi and develops quickly and therefore patients often seek care with a more advanced stage of disease which results in a worse prognosis.[4] NSCLC includes the histological sub-types squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Squamous cell carcinoma is the most common lung cancer among men, and also usually originates near a central bronchus. Adenocarcinoma is the most common lung cancer type among women and starts most often in peripheral lung tissue. Figure 1 shows the distribution of lung cancer types by sex in the SYNERGY project, one of the three studies included in this thesis.

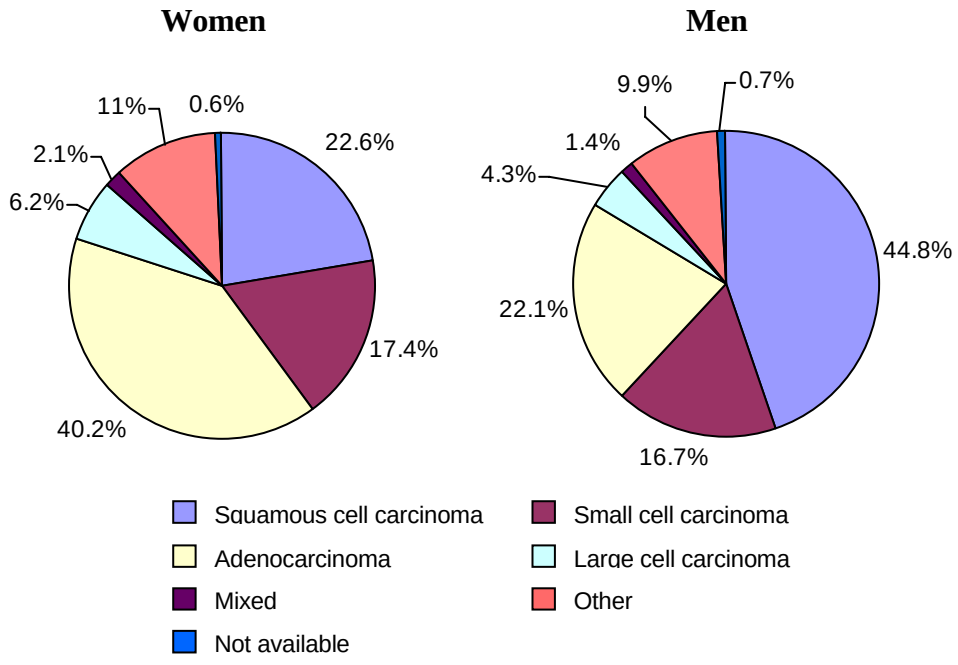


Figure 1. The distribution of different lung cancer types in the SYNERGY project, by sex (n=2563 women and n=10916 men).

RISK AND PROTECTIVE FACTORS

Tobacco smoking

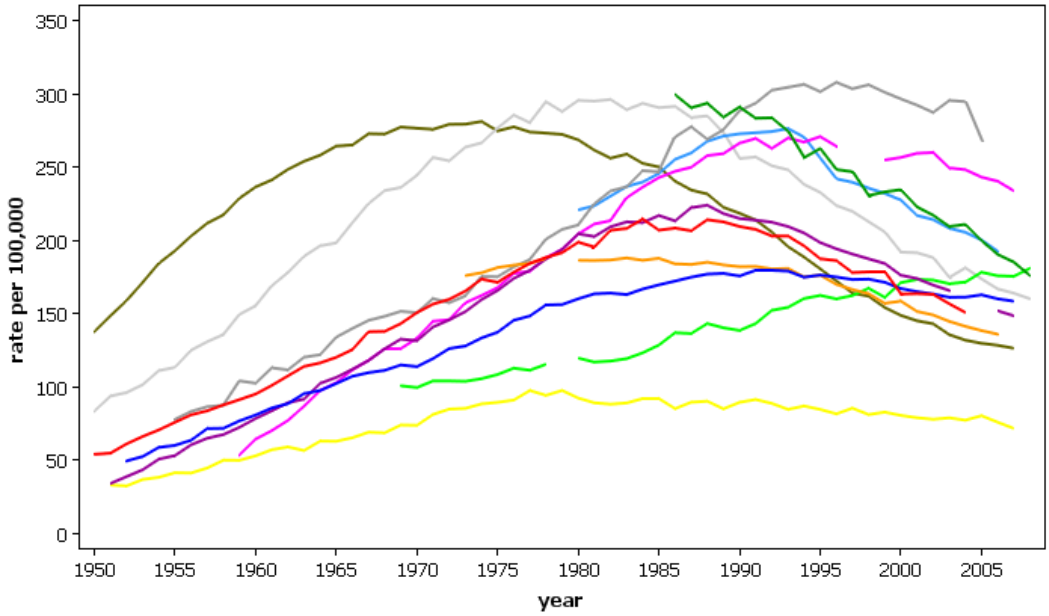
Tobacco smoking is the strongest risk factor for lung cancer. The current geographical and temporal patterns of lung cancer mortality rates, as seen in Figure 2, are largely determined by the earlier tobacco consumption in the different regions. A population change in tobacco consumption results in a corresponding change in lung cancer incidence and mortality after about 2 decades.[5] All types of lung carcinoma are strongly associated with tobacco smoking, the risk being the highest for squamous cell carcinoma, followed by small cell carcinoma and adenocarcinoma.[6] Amongst smokers, the strongest determinant of increased lung cancer risk is duration of smoking, but also the number of cigarettes and at what age the person started to smoke.[7] The risk may be altered by the type of cigarettes (e.g. low tar content, presence of a filter) and how deeply the smoker inhaled the tobacco.[8] Lung cancer risk associated with pipe and cigar smoking is similar to that of light cigarette smoking.[9] The relative risk of lung cancer associated with smoking appears to be similar in men and women.[10] Due to different frequencies of smoking in men and women, it is estimated that 85% of lung cancer in men and 47% of lung cancer in women is attributable to tobacco smoking.[6] Lung cancer rates are expected to rise in the decades to come in many parts of the world, particularly China, as a result of increased tobacco consumption.[11]

Involuntary smoking, resulting from living with a smoker (spouse) or working in a building with smokers, is associated with an increased risk of lung cancer of the order of 1.2 to 1.3-fold higher rates.[12,13] Passive smoking during childhood has also been shown to be associated with increased lung cancer risk in adulthood.[14]

Tobacco smoke contains numerous known and suspected carcinogens such as volatile aldehydes, *N*-nitrosamines, tobacco-specific nitrosamines, metals and polycyclic aromatic hydrocarbons (PAH), as well as agents that cause inflammation.[10] Some of these chemicals damage the cilia in the respiratory tract and make smokers' lungs more sensitive to cancer-causing chemicals because their cilia do not clear dust and mucus effectively. Smokers also absorb carcinogenic chemicals through their lungs, which may contribute to cancer in other parts of the body such as the bladder, kidney and pancreas.[13]

Carcinogens in tobacco smoke also induce gene mutations. For example, benzo(a)pyrene binds chemically to DNA. Chemicals that bind to DNA and form adducts cause DNA damage by impeding the correct and complete replication and repair of DNA. This DNA damage starts a process of mutagenesis which can lead to carcinogenesis. For example *TP53* and *KRAS* mutations are observed more frequently in lung cancers of smokers than in those of non-smokers.[15]

Mortality for lung cancer in various geographical regions, age standardised rates (world) in men aged 45+



Mortality for lung cancer in various geographical regions, age standardised rates (world) in females aged 45+

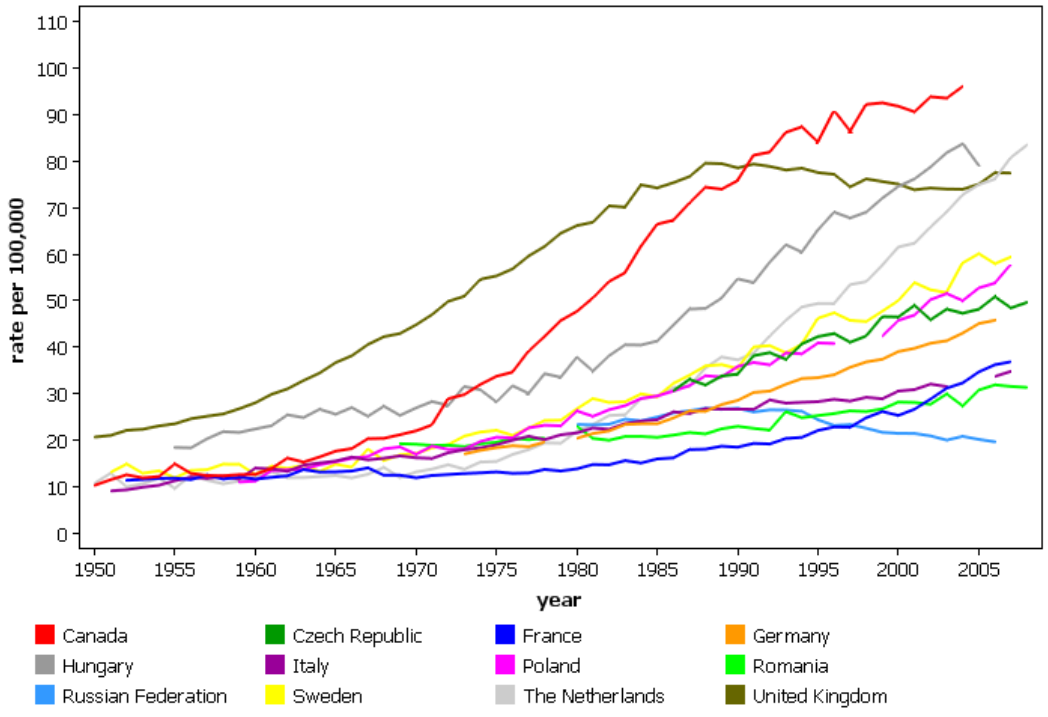


Figure 2. Time trends in lung cancer mortality rates (age-standardised rates) between 1950 and 2005 for a selection of countries participating in the SYNERGY project (http://synergy.iarc.fr). Source: World Health Organization mortality database http://www.who.int/whosis/whosis/

Alcohol

There is evidence that alcohol may constitute a risk factor for lung cancer among very high consumption groups but it is still difficult to exclude potential residual confounding from smoking.[16,17]

Contamination in drinking water

Studies conducted in the areas of the Gulf of Bengal, South America and Taiwan have shown increased lung cancer risk among people exposed to high arsenic levels in ground water.[18,19] It is currently not known what proportion of the European population is exposed to levels exceeding WHO guidelines.[19] Radon in drinking water is also associated with increased lung cancer risk.[20] With regard to water chlorination by-products, there is no consistent evidence of an effect on lung cancer risk.[19]

Diet

High serum levels of vitamin B6 and methionine are associated with a marked decrease in risk of developing lung cancer.[21] Much of the research on diet and lung cancer has been motivated by the hypothesis that diets high in antioxidant nutrients may reduce oxidative DNA damage and thereby protect against cancer.[22] In general, fruits and vegetables, in particular cruciferous vegetables, appear to confer a protective effect against lung cancer, while cured meat (e.g. sausage) and deep-fried cooking have been associated with an increased lung cancer risk.[4,23,24] Use of vitamin supplements has been repeatedly associated with increased lung cancer risk.[25-27]

Exercise and Physical activity

Several studies have reported that more physically active individuals have a lower risk for lung cancer than those who are more sedentary, even after adjustment for cigarette smoking. Yet, until today it has been difficult to exclude residual confounding from cigarette smoking.[28,29]

Indoor air pollution

Two of the most important indoor air pollutants in western countries that increase lung cancer risk in never-smokers are passive smoking and residential radon exposure. [13,30] Additionally of major concern in developing countries is indoor air contamination resulting from the use of unprocessed solid fuels, notably coal, for cooking and space heating.[31] Indoor air pollution is thought to be responsible for the elevated risk of lung cancer experienced by non-smoking women in several regions of China and other Asian countries.[32]

Outdoor air pollution

Constituents of "air pollution" vary by geographic region and over time depending on the pollution sources. Consequently, epidemiologic investigations of air pollution and lung cancer have been limited by the difficulty of estimating exposure.[33]. Yet, there is evidence that lung cancer rates are higher in cities than in rural settings and on the basis of large cohort studies in the United States and Europe there are grounds for concern

that air pollution may increase the risk of lung cancer, especially in combination with smoking and occupational exposures.[34-36]

Lung cancer susceptibility genes

Mutations that exist in more than 2% of individuals in a population are called polymorphisms. Large scale efforts have been made to discover single nucleotide polymorphisms (SNPs) and identify variant alleles in candidate cancer susceptibility genes to predict lung cancer risk.[37] In 2008, 3 independent studies found a locus in chromosome region 15q25 that was strongly associated with lung cancer.[38-40] An international genetic association study of lung cancer has subsequently confirmed the association with this and other SNPs in white populations; this study additionally found further SNPs in Asian populations.[41,42] Genetic susceptibility may provide mechanistic insight into the aetiology of a disease and help to identify susceptible subpopulations with respect to different exposures.[43]

Prior respiratory disease

Associations between chronic obstructive pulmonary disease (COPD) and lung cancer are complex to study because both COPD and lung cancer are strongly associated with smoking, which can lead to residual confounding from smoking. Nevertheless, a substantial body of evidence suggests that COPD or impaired lung function is associated with the occurrence of lung cancer.[44-49]

Occupational risk factors

A total of 20 occupational agents and complex mixtures of exposures are established human lung carcinogens as classified in the International Agency for Research on Cancer (IARC) monographs on the evaluation of carcinogenic risks in humans, as listed below:[30,50-51]

PAH-related exposures
- Soot (chimney sweeping)
- Coal gasification
- Coke production
- Coal-tar pitches (roofing)
- Aluminium production

Other chemicals
- Bis(chloromethyl)ether/chloromethyl methylether
- Sulfur mustard

Radiation exposures
- Radon-222
- Plutonium
- X-radiation or gamma-radiation

Metals
- Arsenic and inorganic arsenic compounds
- Beryllium and beryllium compounds
- Cadmium and cadmium compounds

- Chromium [VI] compounds
- Nickel compounds

Fibers and dusts

- Asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite
- Silica dust (quarts or crystobalite)

Other complex exposures

- Iron and steel founding
- Occupational exposure as a painter
- Rubber-manufacturing industry

Asbestos, metals, crystalline silica, and mixtures of PAHs are the most important occupational lung carcinogens in terms of numbers exposed.[1] Their contribution to the global burden of lung cancer overall is relatively small but they are responsible for an important proportion of lung tumours among exposed workers.[18] Asbestos exposure occurs in proximity to asbestos mining, processing, and distribution facilities, and in the removal or disintegration of asbestos insulation, brake linings and other products and was the first occupational agent to be shown to interact with smoking.[52]

Occupational exposure to chromium-VI occurs primarily through inhalation of contaminated dust and is thought to be the agent responsible for the carcinogenic potential of metals.[53] An increased incidence of lung cancer has been observed among chromate production workers, chromate-pigment manufacturers, chromium platers and chromium alloy workers.[54]

Nickel is mainly used in alloys such as stainless steel and in the manufacture of batteries, but the principle studies of its health effects have been carried out in workers in mining and processing industries. Nickel refineries also imply exposure to arsenic, sulphuric acid mists, cobalt, and sometimes asbestos, which makes it difficult to disentangle the independent effects of each agent in this context. The lung cancer risk associated with nickel is also greater in smokers than in non smokers, which indicates a joint effect.[55,56]

Inorganic arsenic exposure occurs in hot smelting; other exposed workers are fur handlers, manufacturers of sheep-dip compounds and pesticides, and wine yard workers.[1] However, the predominant general route of exposure to arsenic is by ingestion of contaminated drinking water.[53]

Silica exposure occurs in a wide range of industries and occupations such as mining and quarrying, potteries or ceramics, foundries, and various tasks in construction and manufacturing. Most epidemiologic studies on silica exposure and lung cancer risk have been industry-based.[57]

Hereafter follows a description of the agents that are particularly relevant for this thesis.

Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) represent a group of chemicals made up of two or more benzene rings interlinked in various arrangements affecting their toxicological and carcinogenic properties. The carcinogenic potential of PAHs increases with the number of benzene rings, and depending on their metabolic activation to reactive diol epoxide intermediates and their capacity of binding to targets in DNA. Benzo(a)pyrene (B(a)P) is often used as an indicator of carcinogenic PAHs.[58] PAHs are naturally present in fossil fuels and can be formed during incomplete combustion of any organic material, making them common in the environment. They are usually adsorbed onto fine particles in the air or appear as solids in soil or sediment and can enter the body by inhalation, ingestion or through the skin.[59]

PAHs represent a major group of lung carcinogens in tobacco smoke. In addition, they are present in industrial emissions and motor exhaust, and therefore imply occupational exposures for significant groups of workers, as well as contribute to urban air pollution.[60] The highest B(a)P levels have been measured in the aluminium-production industry when the Söderberg process is used.[61]

Several individual PAHs and mixtures including PAHs (e.g. B(a)P, soot, coal-tars) are classified as carcinogenic to humans by IARC.[62] Many PAHs are considered to be both tumour initiators and promoters/progressors.[58] In addition, occupational exposures during coal gasification, coke production, coal-tar distillation, paving and roofing, aluminium production and chimney sweeping, all entailing exposure to PAH mixtures, are classified as carcinogenic to humans.[61] PAH exposure increases the risk of lung, skin and bladder cancer.[63]

Bitumen

Bitumen is the residual product left after distillation of crude oil and is mainly used as a binder in asphalt mixes and in roofing applications. Workers are exposed to fume or gas as it evaporates at laying temperature and by contact with contaminated surfaces.[64]

The chemical composition of bitumen is influenced by characteristics of the original petroleum and by subsequent processing steps implemented to meet specific requirements, for example related to geographical conditions and traffic density. Consequently bitumen varies from one place to another and between manufacturers.[65] These differences make it difficult to study the effects of bitumen exposure in epidemiological studies. Exposure assessment becomes even more complex because a significant proportion of workers are seasonal workers, being employed in a variety of other occupations during their off season. The cover of this thesis shows members of a paving crew performing distinct tasks: a paver operator, rakermen, and screed men. Workers in larger companies are often more specialized and conduct fewer tasks, while workers in smaller companies are involved in many different tasks, which influence the precision of the exposure assessment. Road construction is dominated by one or just a few large companies in Denmark and France, whilst in Germany and the Netherlands this industry is shared between a large numbers of smaller companies.

Exposure levels for workers in the asphalt industry have decreased since the 1960s, but not in a constant manner as paving and roofing techniques and materials have changed over time.[66] For example coal tar was used in paving and roofing applications in many countries in the past but was phased out in Europe during the 1970s due to adverse health effects. Nonetheless, the problem of coal tar was then re-introduced by recycling asphalt contaminated by coal tar. In general, lowering of temperature of the bitumen mix at the paving sites has led to decreased exposure levels, and has changed the composition of exposure to PAHs.[67]

A large number of epidemiological studies have described cancer risk in asphalt workers and roofers in various countries.[68,69] In particular, lung cancer excesses have been observed in roofers. Roofers and mastic layers work with material at high operating temperatures and are therefore exposed to high concentrations of fumes.[70] In addition, the work is done manually, which implies that roofers and mastic layers may experience higher levels of exposure than road pavers for example.

The IARC monograph program classified extracts of steam-refined and air-refined bitumen as possibly carcinogenic to humans (Group 2B) in both 1985 and 1987, while other forms of bitumen were not considered classifiable as to their carcinogenicity to humans. Bitumen is now a priority agent for evaluation at future IARC monographs.[71,72]

Diesel engine emissions

Approximately three million workers in Europe have daily exposure to diesel motor exhaust (DME) at their workplace.[73] DME is also a public health concern because the general public is exposed to some diesel exhaust in most urban areas.[74]

DME consists of a complex mixture of components in gas or particulate form. The particulates are mainly composed of cores of elemental carbon, traces of metallic compounds, and adsorbed organic materials including aromatic hydrocarbons, polycyclic aromatic hydrocarbons, aldehydes, and nitrogen oxides.[75,76] The composition of DME has changed over time as a result of improvements in engine technology and type of fuels. The highest levels of occupational DME exposure have been reported among underground mining-, tunnel construction-, and underground mine maintenance workers.[77]

A large number of individual cohort and case-control studies have suggested an association between DME exposure and increased lung cancer risk.[78-82] Nevertheless, lack of dose-response within and across occupations, and incomplete adjustment for smoking and other confounders have hindered reaching a conclusion regarding the presence of a casual relationship.[83,84]

The IARC monograph program classified DME as probably carcinogenic to humans (in Group 2A) in 1989. DME is also selected among the priority agents for future IARC monographs.[71,85]

AIM OF THE THESIS

The main goal of this thesis was to increase our knowledge of the relationship between occupational exposure to combustion products and lung cancer risk in different epidemiological settings.

The specific goals were:

- To assess the association of occupational PAH exposure and lung cancer risk in a case-control study in Central and Eastern Europe and the UK, while controlling for potential confounders.

- To investigate the role of bitumen exposure in the development of lung cancer, while controlling for other occupational exposures and tobacco smoking in a case-control study nested in a cohort of European asphalt workers.

- To determine if there was an effect of occupational exposure to diesel engine emissions on the lung cancer risk among men and women in a pooled data set including detailed data on smoking and complete occupational histories from case-control studies in Europe and Canada.

- To estimate the lung cancer risk attributable to occupational exposures in Central and Eastern Europe, this being the region with the world's highest lung cancer incidence rates among men.

MATERIALS AND METHODS

The manuscripts that form this thesis are based on three sources of data; 1) the IARC multicenter case-control study on lung cancer conducted in six countries in Central and Eastern Europe and the United Kingdom (INCO); 2) a case-control study on lung cancer nested in a cohort of European asphalt workers; and 3) the SYNERGY project where eleven case-control studies from Europe and Canada have been pooled together to study joints effects of occupational exposures and smoking in the development of lung cancer.

IARC MULTICENTER CASE-CONTROL STUDY OF OCCUPATION, ENVIRONMENT AND LUNG CANCER IN CENTRAL AND EASTERN EUROPE (PAPER I & IV)

Study design

This multicenter case-control study on lung cancer was initiated to clarify why Central and Eastern Europe has the highest lung cancer rate in the world. The INCO study was conducted in seven European countries during the period 1998-2002. Sixteen centres were included : Borsod, Heves, Szabolcs, Szolnok, Budapest (Hungary), Lodz, Warsaw (Poland), Banska Bystrica, Bratislava, Nitra (Slovakia), Brno, Olomouc, Prague (Czech Republic), Bucharest (Romania), Moscow (Russia), and Liverpool (United Kingdom). IARC was responsible for the coordination of the study and ensured that each centre followed an identical protocol.

Study subjects

Cases were patients at the participating hospitals with newly diagnosed lung cancer, aged 74 years or less, and had resided in the study area for a minimum of one year before diagnosis. Confirmation of diagnose and histology specification (ICD-O) was obtained from local pathologists in each centre. Two centres recruited population controls; in Warsaw population controls were selected from the electronic register of residents and in Liverpool from the general practitioner registry. In the other centres, control subjects were randomly selected among eligible patients, i.e. with a condition occurring on a list of acceptable (non-smoking related) diseases (Figure 3), who were admitted to the same hospitals as the cases or from general hospitals serving the same population. Cases and controls were frequency matched on centre and referral (or residence) area, age (+/- 3 years) and gender.

The target was to interview cases within one month of initial diagnosis and no later than 3 months after confirmed diagnosis. Consents for participation were obtained from the patients and their physician; trained interviewers then approached the subjects who had agreed to participate. A total of 2861 cases and 2936 controls were recruited. The participation rate of eligible cases ranged between 44.7% in Liverpool to 98.9% in Olomouc, with an average of 84.1%. The participation rate of eligible controls was overall 83.6%. The most common reason for non-participation was refusal (13.0% in cases and 14.4% in controls). Patients too ill to be interviewed represented 1.6% among

cases and 0.6% among controls, and patients that had been discharged from the hospital before the interview comprised 0.8% of cases and 0.4% of controls. Death before interview was an uncommon reason for non-participation, occurring in only 0.4% of cases and 0.1% of controls.

Eligible diseases for hospital controls

- Malignant neoplasms: None
- Benign disorders: Any
- Endocrine and metabolic: Thyrotoxicosis, goitre, thyroiditis, hypothyroidism, adrenal gland disorders
- Blood disorders: Aplastic anaemia
- Circulatory disorders: Varicose veins
- Musculoskeletal disorders: Rheumatoid arthritis, osteoarthritis, backache, lumbago, sciatica (exclude fractures and osteoporosis)
- Gastro-intestinal: Appendicitis, anal fissure and fistula, perianal abscess, ischiorectal abscess, cholangitis
- Genito-urinary: Benign prostatic hyperplasia, renal infections, renal ureteric or bladder stone, cystitis, orchiitis or epididymitis
- Skin and subcutaneous tissue: Benign disorders of the breast (fibrocystic disease, benign mammary dysplasia), pilondal sinus, ingrowing nails, sebaceous cysts
- Respiratory system: None
- Ear and mastoid disorders: Any
- Eye conditions: Any, except cataract or diabetic retinopathy
- Plastic surgery cases: Any, except those from smoking related cancers
- Nervous system : Any, except stroke or Parkinson's disease

Figure 3. List of acceptable diseases for hospital controls in INCO

Exposure assessment

Interviews were conducted face to face with subjects and questionnaires included a structured part for demographic information including educational level, medical history, family history of cancer, tobacco smoking, environmental tobacco exposure in non-smokers, alcohol consumption, food frequency questionnaire, and a semi-structured part for occupational biography/history. Case and control subjects provided a list of all occupations held for at least one year. If the job included one of 16 specific activities the workers also completed a specialized questionnaire with more detailed questions about materials and processes they were involved in. The specialized questionnaires concerned: 1) iron and steel production, 2) coke production, 3) foundry workers, 4) glass factory, 5) garage, car mechanics, repairers, 6) wood workers/wood work, 7) painters, 8) welding, gas cutting, brazing or soldering, 9) chemical industry, 10) tannery workers, 11) tool makers, machinists, 12) miners, quarrymen, 13) insulation material or fibre panels, 14) printing, 15) meat workers/slaughterers, and 16) farmers and gardeners.

Industrial hygiene experts estimated the extent of occupational exposure to a group of agents that are known or suspected lung carcinogens (see Figure 4).

List of occupational exposures

10	INORGANIC INSULATION DUST	61	COAL COMBUSTION FUMES
11	ASBESTOS (general exposure)	62	COKE COMBUSTION FUMES
12	CHRYSOTILE ASBESTOS	63	PETROLEUM OIL COMBUSTION FUMES
13	AMPHIBOLE ASBESTOS	64	WOOD COMBUSTION FUMES
14	GLASS FIBRES	65	PETROL / GASOLINE ENGINE EMISSIONS
15	MINERAL WOOL FIBRES	66	DIESEL ENGINE EMISSIONS
16	CERAMIC FIBRES	67	PLASTICS OR RUBBER PYROLYSIS FUMES
18	EXTENDERS / FILLERS	68	ARC WELDING FUMES
19	ABRASIVES DUST	69	GAS WELDING FUMES
21	SAND	71	LUBRICATING OIL MIST
22	RESPIRABLE FREE CRYSTALLINE SILICA	72	CUTTING FLUIDS MIST
23	CONCRETE DUST	73	OTHER MINERAL OIL MIST
24	CEMENT DUST	74	GASOLINE / PETROLEUM
25	BRICK DUST	75	DIESEL / KEROSENE
31	COAL DUST	76	MINERAL SPIRITS (e.g. WHITE SPIRIT)
32	CARBON BLACK DUST	77	ASPHALT- BITUMEN FUMES
33	SOOT (from coal, coke, fuel oil, wood)	78	COAL TAR-PITCH FUMES
34	COKE DUST	79	CREOSOTES FUMES
35	GRAPHITE DUST	80	INORGANIC ACIDS
36	CHARCOAL DUST	81	FORMALDEHYDE
37	WOOD DUST (general exposure)	82	BCME (Bis Chloro Methyl Ether)
38	HARD WOOD DUST	83	VINYL CHLORIDE
39	SOFT WOOD DUST	84	ACRYLONITRILE
40	INORGANIC PIGMENTS DUST	85	STYRENE
41	CHROMATE DUST	86	PAH s - Poly Aromatic Hydrocarbons
42	CHROMATE FUMES	91	INORGANIC PESTICIDES
43	CHROMIUM & COMPOUNDS DUST	92	ORGANIC PESTICIDES (SYNTHETIC)
44	CHROMIUM & COMPOUNDS FUMES	93	WOOD PRESERVATIVES
45	NICKEL & COMPOUNDS DUST	101	ANIMAL VIRUSES
46	NICKEL & COMPOUNDS FUMES	102	ANIMAL FEEDING
47	CADMIUM & COMPOUNDS DUST	200	IONIZING RADIATIONS
48	CADMIUM & COMPOUNDS FUMES		
50	ASHES (from coal, coke or fuel oil combustion)		
51	ARSENIC & COMPOUNDS DUST		
52	ARSENIC & COMPOUNDS FUMES		
53	MILD STEEL DUST		
54	STAINLESS STEEL DUST		
55	HARD ALLOYS DUST		
56	IRON & COMPOUNDS FUMES		

Figure 4. List of occupational exposures assessed by the exposure experts in each centre in the INCO study

For each job in the subject's work history, the experts, blinded to the case-control status of the subjects, assigned job (International Standard Classification of Occupations (ISCO)-68) and industry codes (Statistical classification of economic activities in European community (NACE Rev. 1)) and evaluated whether any of the specific agents or groups of agents may have been present in the subject's work environment. For each

of the agents they considered to be present, the experts noted the degree of confidence that the exposure actually occurred (possible, probable, definite), and further evaluated the average level of concentration (low=1, medium=2 or high=3) based on agent specific categories, and the frequency of exposure during a normal working week (less than 5%, 5-30%, >30%). The definitions and cut-off levels for each exposure was provided in a coder's manual, and three workshops and additional meetings were organized for the occupational coding experts to ensure that the procedure was standardized and comparable across all centres.

Exposure to PAHs from soot and fumes from combustion of coal, coke, petroleum oil, wood, asphalt, coal tar and pitch, creosote fumes, diesel emissions, lubricating oil mist, cutting fluids and other mineral oil mist, carbon black dust, and plastics pyrolysis was automatically added via an algorithm when the experts coded any of these exposures. If the PAH exposure originated from a different source than from those exposures included in the algorithm, the experts were able to code PAHs directly. In brief, all exposures derived from combustion of coal or coal compounds contributed high levels of PAHs, exposures derived from combustion of wood and petroleum products contained medium levels of PAHs and the remaining exposures contributed low levels of PAHs, see an example in Figure 5.

Exposure as assessed by experts		**Automatically assessed by algorithm**
. COAL COMBUSTION FUMES	➔	**PAH**
intensity 3, freq. (x), conf. (y)		intensity 3, freq. (x), conf. (y)
intensity 2, freq. (x), conf. (y)		intensity 2, freq. (x), conf. (y)
intensity 1, freq. (x), conf. (y)		intensity 1, freq. (x), conf. (y)
. WOOD COMBUSTION FUMES	➔	**PAH**
intensity 3, freq. (x), conf. (y)		intensity 2, freq. (x-1), conf. (y)
intensity 2, freq. (x), conf. (y)		intensity 1, freq. (x-1), conf. (y)
intensity 1, freq. (x), conf. (y)		intensity 1, freq. (x-2), conf. (y-1)
. COKE COMBUSTION FUMES	➔	**PAH**
intensity 3, freq. (x), conf. (y)		intensity 1, freq. (x-2), conf. (y-2)
intensity 1 or 2, freq. (x), conf. (y)		0

Figure 5. Example on how occupational exposure to coal-, wood- and coke combustion fumes as assessed by the experts transformed to levels of PAH exposure with regards to intensity, frequency and confidence level using the algorithm.

Coke combustion fumes reflect exposures encountered when coke is used as a heat or energy source, which contains low levels of PAHs. Workers involved in the manufacture of coke were exposed to and assigned coal combustion fumes.

Statistical analyses

In paper I, we estimated the odds ratios (OR) of lung cancer and 95% confidence intervals (CI) by unconditional logistic regression, adjusted for age groups (<45, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75+), sex, centre, tobacco pack-years ((average number of cigarettes per day * years)/20) as a continuous variable, and occupational exposure (ever/never) to silica, asbestos, and metals (arsenic, chromium VI, cadmium).

Test for linear trends were calculated using the log likelihood ratio test, comparing the model without the variable of interest with the model including the variable fitted as a continuous variable by using the mid interval value for each stratum.

Test for heterogeneity across countries and between Central and Eastern Europe (CEE) and the UK was calculated using the log likelihood ratio test, i.e. we compared the model including the interaction term of exposure with an indicator for CEE or the UK, to that of a model without this term.

Analyses were repeated excluding exposures occurring in the 20 years prior to lung cancer diagnosis in cases/interview in controls, but results were not reported in paper I because the patterns of results did not change either in the CEE countries or in the UK.

In paper IV, we estimated OR for lung cancer and 95% CI by unconditional logistic regression, including terms for age group (8 categories), sex, centre, education (high, medium, low, unknown), tobacco smoking (log(tobacco pack-years+1)) and time-since-quitting smoking (current smokers, stopping smoking 2-7 years, 8-15 years, 16-25, 26+ years before interview/diagnosis, never smokers). Tobacco pack-years were calculated as average number of cigarettes per day multiplied by years of smoking and divided by 20. We applied a multinomial logistic regression when estimating the OR associated with the occupational exposures for different types of lung cancer, i.e. allowing the association of an exposure with each type of lung cancer to differ.

We estimated the attributable fraction (AF) of lung cancer using Miettienen's formula allowing adjustment for confounders: $AF = p(OR-1)/OR$, where OR was the adjusted odds ratio and p the proportion of cases exposed.[86] The confidence intervals for the attributable fraction were calculated using the method described by Greenland which accounts for the variability in the exposure prevalence estimates and the risk ratio estimates.[87]

THE IARC CASE-CONTROL STUDY OF LUNG CANCER NESTED IN A COHORT OF EUROPEAN ASPHALT WORKERS (PAPER II)

Study design

A historical cohort study was conducted to investigate the mortality of workers employed in road paving, asphalt mixing, water-proofing and roofing (jobs entailing exposure to bitumen fume and condensate). Road pavers represented the largest proportion of the study population. The workers were identified from companies in Denmark, Finland, France, Germany, Israel, the Netherlands and Norway, and from a nationwide health surveillance program in Sweden. The mortality follow-up was conducted from 1953 to 2000.

This initial cohort study of road pavers found higher lung cancer mortality with increasing average exposure to bitumen fumes, whilst no associations were observed with duration of exposure or cumulative exposure to bitumen fumes.[88-90] These results did not allow conclusions about the potential carcinogenicity of bitumen fume because the assessment of bitumen exposure was too crude and confounding could not be ruled out – bitumen exposure was based on main job classes; no information was available on employment in companies other than those included in the study (both within the asphalt industry and in other industries); and very limited information was available on tobacco smoking.

Given the above limitations of the asphalt worker cohort, a nested case-control study of lung cancer was initiated within the cohort to disentangle the contributions of bitumen, other agents occurring in the asphalt industry, other occupational exposures, and tobacco smoking to the increased risk of lung cancer observed in the analysis of the whole cohort. This nested case-control study is the focus of results in this thesis. The expanded aims required the collection of more detailed information to better characterize exposure to bitumen and other agents in the asphalt industry, and for information to be collected on other occupational exposure and smoking history. In the nested case-control study we also took into consideration exposure to bitumen condensate (dermal exposure), since there is evidence that dermal uptake of bitumen condensate for tasks with high degrees of contact with contaminated surfaces might contribute substantially to total bitumen exposure.[91]

The main hypothesis to be tested in the case-control study was therefore whether the risk of lung cancer was increased among asphalt workers according to exposure to bitumen, while adjusting for tobacco smoking and exposure to other known and suspected occupational lung carcinogens. A feasibility study, conducted in 2000, confirmed that a case-control was feasible in all countries included in the cohort analysis, with the exception of Sweden because of constraints in contacting the companies and acquiring additional exposure data.

Study subjects

Cases were male workers aged less than 75 years, who were included in the cohort study in Denmark, Finland, France, Germany, the Netherlands, Norway, and Israel, had been employed at least two full seasons in the asphalt companies included in the cohort, and died from or were diagnosed with lung cancer between 1980 and the end of follow-up, which ranged from December 2002 in France to June 2005 in Finland. Controls were selected randomly among members of the study population who fulfilled the matching criteria (birth year ± 3 years, country) and were free from respiratory and ill-defined cancer (International Classification of Diseases, 9th Revision (ICD-9): 160-165, 195-199) at the age of diagnosis or death of the case.

A list of eight eligible controls was prepared for each case, with the goal of interviewing three of them. As a consequence of incidence-density sampling of controls within cohorts, some cohort members (n=184) were selected as potential controls for more than one case: if they were interviewed, they were treated as multiple individuals in the statistical analysis.[92]

A total of 433 cases and 1253 controls were included in the analysis. The response rate was 65% among cases and 58% among controls, see Table 1.

Table 1. Number of cases and controls eligible for the study, interviewed, and included in the analysis, by country

Study subjects	Denmark	Finland	France	Germany	Israel	Netherl.	Norway	Total
Cases								
Eligible	163	66	168	87	26	60	105	675
Interviewed	140	37	73	64	19	22	82	437
Incl. in analysis	139	37	73	63	18	21	82	433
*Response rate %**	*86*	*56*	*43*	*74*	*73*	*37*	*78*	*65*
Controls								
Eligible	995	778	1344	664	226	267	778	5052
Contact attempted	427	200	392	382	82	182	298	1963
Contacted	343	187	341	382	74	117	248	1692
Interviewed	291	97	243	189	61	38	212	1131
Incl. in analysis	393	111	218	198	47	58	228	1253
*Response rate %***	*68*	*49*	*62*	*49*	*74*	*21*	*71*	*58*

* Cases interviewed over eligible cases

** Controls interviewed over those for whom contact was attempted

Exposure assessment

Living workers or their next-of kin (NOK) were interviewed over the telephone by trained interviewers; and the responses were entered into a Microsoft Access database created for this project during or directly after the interview. The questionnaire consisted of four sections: 1) demographic information; 2) general occupational history

(including the occupational history within the asphalt industry); 3) tobacco smoking; and 4) information on quality of interview and identity of NOK. NOK interviews were used for 98% of cases and 34% of controls. The last spouse was the preferred NOK to be interviewed when an index person was deceased. If the last spouse was not available, a previous spouse, a child, a sibling, another relative, a neighbour or a friend was selected in decreasing order of preference. Spouses were the most frequent NOK among cases (56%) and children were the most common NOK among controls (49%).

Detailed information on jobs held within the asphalt industry was collected from living subjects and fellow-workers that had worked alongside the study subjects. Information collected from the companies during the cohort phase served as starting point, which the interviewed person could corroborate, refute or amend. Fellow-workers were identified through the occupational history collected in the main interview, through industry representatives, through matching of the cohort records, and by asking the NOK.

Semi-quantitative exposure estimates for bitumen fume, organic vapours, and 4-6 ring PAHs were obtained from the Asphalt Workers Exposure (AWE) database for 85 defined jobs in the asphalt-, building- and ground construction industry.[93,94] These exposure estimates were included in algorithms together with other parameters to calculate individual exposure levels.[95] For example the work time parameter was based on the median length of the paving season-, work week- and work day as reported for each job and time-period by the companies. A multiplier for coal tar use was applied in the algorithm for estimating exposure to PAH.[93] Information on coal tar use and oil gravel paving came from the original company questionnaires as a primary source. If this information was lacking we used information from fellow-worker interviews or country-specific local industry experts.

Estimates of dermal exposure to bitumen condensate were based on a relative ranking of the 85 jobs identified within the asphalt-, building- and ground construction industry. The information came from structured semi-quantitative dermal exposure assessment (DREAM) observations of paving and mastic crews in Germany, Denmark, France and The Netherlands,[96] and dermal exposure measurement surveys.[91,97-102] Two industrial hygienists independently estimated exposure for jobs without DREAM observations or measurements. The consensus score was used in the analysis.

Assessment for dermal coal tar exposure could not be performed due to absence of relevant data. Dermal exposure estimates were, like the inhalation exposure estimates, adjusted for actual work time within each calendar period. In addition, we applied a hygienic behaviour multiplier to the algorithms to take into account clothing patterns, personal protective devices use (e.g. gloves) and hygienic behaviour (e.g. showering, cleaning hands with solvents or fuels). Similarly, we estimated the hygienic behaviour modifier at company-, job class-, time period-level, based on reported information coming from living subjects and fellow workers. Optimal hygienic behaviour (wearing a coverall, no short sleeves, no shorts, not working with bare trunk, wearing gloves, showering/bathing directly after work and cleaning hands with water and soap) resulted

in a low score leading to a low multiplier (0.1), while seven "poor hygienic behaviour" scores resulted in no adjustment, because the hygienic behaviour multiplier would be 1. When no work time and hygienic behaviour information was available for a certain period we had to extrapolate data, see Figure 6. In instances where there were estimates for an earlier or later period we used the closest available estimate in time; otherwise we took the median of the values for other companies in the same country in the same time period for the same job class.

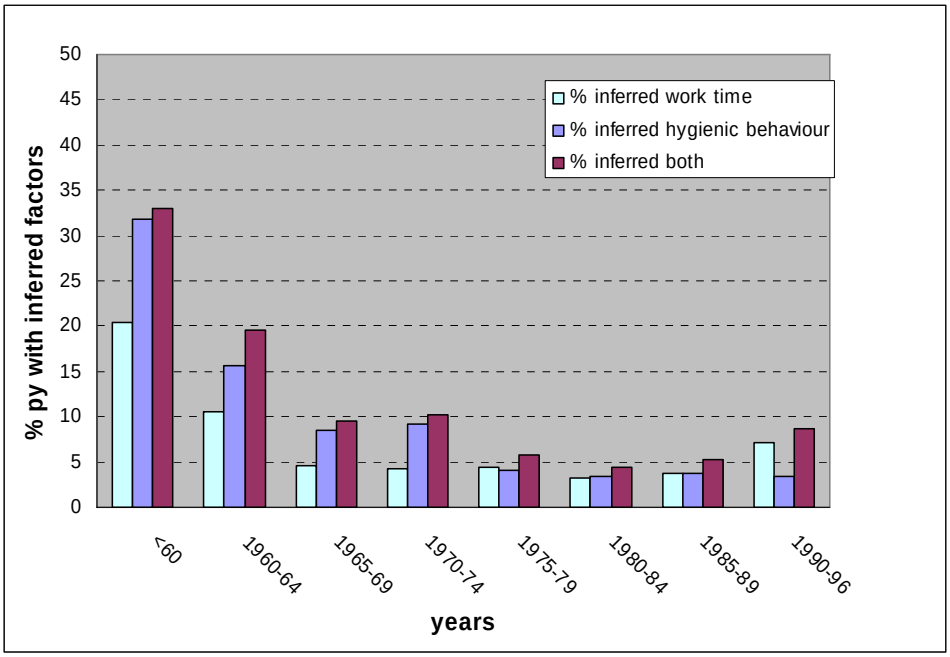


Figure 6. Percentage of work history years with extrapolated work time and hygienic behaviour.

We assumed asbestos, coal tar, crystalline silica, and diesel motor exhaust to be the exposures with the highest expected prevalence and potential for confounding the association with bitumen-related agents. Exposure to these agents was estimated by applying two exposure matrices; one for inside- and one for outside the asphalt-, building- and ground construction industry. Two industrial hygienists independently gave scores (0, 1, 2 referring to "no", "low", "high"), and the consensus score was kept. A similar approach was taken for jobs outside the asphalt/construction industry coded by ISCO and the International Standard Industry Classification (ISIC). A total of 1,297 job-industry combinations were evaluated in this way.

We linked the two job exposure matrices to each individual and squared the intensity scores to take into account the lognormal nature of exposure concentrations, and then multiplied by duration to get an indicator expressed as "cumulative exposure-years". Using the same scale for intensity in both matrices allowed us to sum the exposures to these agents across the full job history for each individual.

Statistical analyses

In preliminary analyses, the results of conditional and unconditional logistic regression models were compared, and no differences were found. Thus, in the analysis unconditional logistic regression models were fitted to calculate OR with 95% CI of lung cancer for each agent, adjusted for matching set, age group (<60, 60-64, 65-69, 70-74), country, cumulative tobacco smoking (<10, 10-19, 20-39, 40+ pack-years) and coal tar exposure.

In preliminary analyses 15-year lagged cumulative exposure and 15-year lagged average exposure were also considered. Since these variables did not provide additional insight into the results as compared to the respective un-lagged variables, they were not considered further.

For continuous variables, exposed subjects were categorized into quartiles with cut-off points based on the distribution among controls and unexposed subjects forming the reference category.

Tests for linear trends (across all subjects and across exposed subjects only) were calculated by comparing the log likelihood ratio of a model without the variable of interest to that of a model including the variable on a continuous scale; with values corresponding to the mid-interval of exposure score values in each category.

Heterogeneity across countries was tested comparing the log likelihood ratio of a model with an interaction term between the variable of interest and country to that of a model without it.

The possible confounding effect exerted by tobacco smoking in the analysis of the cohort based on national mortality rates was assessed by calculating country-specific confounding odds ratio (COR) according to the following formula:[103]

$$COR = \sum_i \frac{w_i \left(d_i' + OR' e_i' + OR'' f_i' \right)}{d_i'' + OR' e_i'' + OR'' f_i''} \qquad [1]$$

where, in the two age groups (45-64 and 65+, subscript *i*), *d'*, *e'* and *f'* are the proportions of non-smokers, ex smokers and current smokers among living controls belonging to the same birth cohorts as the participants of the surveys, *d''*, *e''* and *f''* are the corresponding proportions in national surveys, and *w* are the weights (based on the distribution of person-years in the cohort in the two age groups). The odds ratios of lung cancer for ex smokers (*OR'*) and current smokers (*OR''*) were set to 4 and 9, respectively.[104] National survey data on prevalence of smoking were obtained from the 'Closing the Gap' project,[105] with the exception of Norway[106] and Israel.[107]

SYNERGY - POOLED ANALYSIS OF CASE-CONTROL STUDIES ON THE JOINT EFFECTS OF OCCUPATIONAL CARCINOGENS (PAPER III)

The SYNERGY project started in 2007 and represents a pooling of data from lung cancer case-control studies where the primary objective is to study joint effects of exposure to concurrent occupational lung carcinogens (asbestos, PAH, nickel, chromium and silica) and smoking. The studies included in SYNERGY are well designed population- or hospital based case-control studies that have collected life time tobacco history and occupational data. The inclusion of studies in SYNERGY was also determined by the availability of exposure data for the selected agents in respective country or region. Several side-projects aside of the core objectives have been initiated in the SYNERGY project, the analyses on diesel is one such project.

Study design

The studies that have contributed data to the diesel analysis are described in Table 2. The LUCAS and LUCA studies were restricted to men and the PARIS study included only regular smokers. MORGEN is a case-control study nested in the prospective EPIC cohort in the Netherlands and the subjects filled in a questionnaire at recruitment. Besides MORGEN, all studies provided data on life time smoking habits and complete occupational history.

Table 2. Description of the studies included in the pooled analyses on occupational DME exposure and lung cancer

Study Acronym	Country	Cases	Controls	Data collection	Source of controls
		n=13304	n=16282	between years	P=population H=hospital
AUT-Munich	Germany	3180	3249	1990-1995	P
EAGLE	Italy	1921	2089	2002-2005	P
HdA	Germany	1004	1002	1988-1993	P
INCO_Cz. Rep.	Czech Rep.	304	452	1998-2002	H
INCO_Hungary	Hungary	391	305	1998-2001	H
INCO_Poland	Poland	793	835	1999-2002	H&P
INCO_Romania	Romania	179	225	1998-2001	H
INCO_Russia	Russia	599	580	1998-2000	H
INCO_Slovakia	Slovakia	345	285	1998-2002	H
INCO_UK	UK	442	917	1998-2005	P
LUCA	France	294	292	1989-1992	H
LUCAS	Sweden	1014	2307	1985-1990	P
MONTREAL	Canada	1176	1505	1996-2002	P
MORGEN	Netherlands	64	187	1993-1997	P
PARIS	France	169	227	1988-1992	H
ROME	Italy	329	324	1993-1996	H
TURIN/ VENETO	Italy	1100	1501	1990-1994	P

In most studies, cases and controls were frequency-matched for variables such as sex and age. The majority of interviews (84%) were conducted face to face with the subjects.

Study subjects

The original study sample comprised 13479 cases and 16510 controls. However, subjects providing incomplete information for calculating duration of jobs or cumulative smoking were omitted (175 cases and 228 controls), leaving 13304 cases and 16282 controls for these analyses.

The data was collected in 41 centers in 13 countries between 1985 and 2005. The response rates ranged between 68% (HdA) and 98% (LUCA) among cases, and 41% (AUT-Munich) and 100% (INCO-Hungary) among controls. The hospital based case-control studies generally achieved a higher response rate. The overall response rate weighted by the size of the study population was 82% among cases and 67% among controls. The MORGEN study is derived from a prospective cohort study conducted in the Netherlands. Following invitation by letter 45% agreed to participate in the cohort study; participants filled in a baseline questionnaire and were followed for a mean duration of 5.3 years (SD 2.7) up to lung cancer diagnosis in cases.

Exposure assessment

Occupational data were originally mostly coded according to national classifications, and therefore had to be recoded to ISCO-68.[108] A conversion table from the Nordic occupational classification (NYK-83) codes to ISCO-68 was created and validated at Karolinska Institutet and thereafter applied to the Swedish data. The countries participating in the INCO study were included as individual studies in these analyses.

DME exposure was estimated by using a general population job-exposure matrix (DOM-JEM) based on 5-digit ISCO-68 codes. The DOM-JEM for DME was created by three occupational exposure experts at the Institute of Risk Assessment Sciences (IRAS), at Utrecht University, and assigned scores of no exposure=0, low=1 or high=4 exposure levels of DME to each ISCO code. The assignment of DME exposure to each ISCO code was initially performed independently, and for conflicting scores a consensus was achieved. Initial agreement for the three experts was 92%.[109] Out of 1840 job codes in ISCO-68, 202 (11.0%) e.g. drivers, engineers, technicians and farmers were assigned low DME levels and 27 (1.5%) e.g. miners, mechanics for agricultural machinery and diesel engines, railway and road vehicle loaders were assigned high levels of DME exposure (more information about the DOM-JEM is available upon request). Linkage of the job histories with the DOM-JEM assigned a DME exposure level to each job period.

Statistical analyses

Logistic regression models were fitted to calculate OR and 95% CI of lung cancer associated with indices of DME exposure. We adjusted for age group (<45, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75+), sex, study, ever employment in a "List A" job (yes/no), tobacco smoking (log(cigarette pack-years+1)) and time-since-quitting smoking cigarettes (current smokers, stopping smoking 2-7 years, 8-15 years, 16-25, 26+ years before interview/diagnosis, never smokers). A "List A" job represents a list of occupations and industries known to present an excess risk of lung cancer, which was identified by Ahrens and Merletti in 1998 and updated by Mirabelli et al. in 2001.[110,111] Current smokers were persons that had smoked >1 cigarette per day for >1 year, and included those that had stopped smoking in the last 2 years before diagnose/interview. The cigarette pack-year was calculated: ∑duration × average intensity per day / 20. The subjects unexposed to DME were the reference category in each of the analyses.

P-values for linear trend were obtained by applying a logistic regression model including respective continuous variable.

Meta regression models were used to explore study-specific ORs as well as extent and sources of heterogeneity. We compared the DME effect in small vs. large studies (>/< 1500 subjects), old vs. recent studies (end of data collection before or after 1995), hospital-based vs. population-based case-control studies, and by study and region according to Globocan for: Western-, Northern-, Central and Eastern-, Southern Europe and Northern America.[2] The heterogeneity was assessed using a chi-squared test with inverse variance weights. The extent of heterogeneity between odds ratio estimates was assessed as a percentage (I^2).[112]

ETHICAL APPROVALS

The IARC multicenter study (paper I and IV) was approved by the IARC ethical review committee on March 19th 1999, and by local- or national ethic's committees in respective country between October 1997 and May 2002.

The IARC nested case-control study on lung cancer among European asphalt workers (paper II) was approved by the IARC ethical review committee on July 28th 2005, and by personal data protection authorities in Denmark, France, and Germany; the Ministry of Health in Finland, and national ethic's committees in Norway and the Netherlands between November 2004 and November 2005. Israel received ethical approval for the nested case-control study already during the cohort study in 1996.

The SYNERGY project (paper III) was reviewed and approved by the IARC Institutional Review Board on April 1st 2009; after we had collected ethical approvals or statements from an authorized authority that such an approval was not required. The original studies were, when required, approved by local or national ethical review committees at the time when they were conducted.

RESULTS AND COMMENTS

Below is a summary of the main results from each study. More detailed results are provided in the papers I-IV.

OCCUPATIONAL EXPOSURE TO POLYCYCLIC AROMATIC HYDROCARBONS AND LUNG CANCER RISK (PAPER I)

Approximately 16% of men and 4% of women had been exposed to PAHs at work. This prevalence varied substantially between the countries (p-value <0.001). The majority of exposed men (57%) and almost all exposed women (92%) had been exposed only to low levels of PAH. Ten percent of exposed men had experienced high PAH levels.

Among the subjects exposed to PAH, 34% were also exposed to silica, 28% were also exposed to metals (arsenic, chromium [VI] and cadmium) and 28% were also exposed to asbestos. Consequently, we included occupational exposure to asbestos, silica, and metals as covariates in the analyses. The ORs for PAH exposure decreased by approximately 15% after adjustment for concomitant occupational exposures.

The lung cancer risk following exposure to PAH differed across countries (p-value 0.05), this heterogeneity was explained by a stronger effect in the UK as compared to in the CEE countries (p-value 0.002). We found no evidence of heterogeneity within the CEE countries (p-value 0.73). The main analyses were therefore conducted separately for the CEE countries and the UK, see Table 3.

Table 3. Occupational exposure to PAH and relative risk of lung cancer

PAH exposure	Exposure category	Central and Eastern Europe Cases	Cont.	**OR***	95% CI	United Kingdom Cases	Cont.	**OR***	95% CI
Occupational exposure	Never **	2274	2391	1	Reference	166	192	1	Reference
	Ever	350	299	0.93	0.77-1.14	62	41	1.97	1.16-3.35
Max intensity PAH (µg/m^3)	0.05-0.1	194	197	0.82	0.65-1.04	37	23	2.12	1.12-4.00
	0.1-1	116	83	1.17	0.84-1.64	14	14	1.42	0.57-3.52
	1-5	40	19	1.11	0.60-2.05	11	4	2.68	0.74-9.77
Test for linear trend, p-value				*0.54*				*0.15*	
Cumulative exposure	<0.04	68	78	0.73	0.50-1.06	23	15	1.79	0.82-3.90
	<0.15	82	68	0.99	0.69-1.44	14	11	1.68	0.67-4.20
	<0.77	79	73	0.89	0.62-1.29	11	8	2.14	0.75-6.11
	>=0.77	121	80	1.13	0.80-1.58	14	7	2.77	0.94-8.11
Test for linear trend, p-value				*0.93*				*0.01*	
Years exposed	<6	96	83	0.9	0.64-1.26	20	18	1.30	0.60-2.82
	6-10	66	54	1.12	0.75-1.68	13	11	1.40	0.55-3.58
	11-20	63	66	0.76	0.51-1.13	18	2	15.11	3.05-74.89
	21-30	59	48	0.94	0.60-1.47	5	7	1.18	0.32-4.23
	>30	66	48	1.02	0.66-1.57	6	3	3.60	0.73-17.80
Test for linear trend, p-value				*0.61*				*<0.01*	

* Odds ratios are adjusted for centre (in CEE), sex, age, tobacco pack-years, silica, asbestos, and metals

** Referent group for all analyses shown in the table

In Central and Eastern Europe ever high-intensity exposure resulted in an OR for lung cancer of 1.11 (95% CI 0.60-2.05). PAH exposure for 30 or more years was associated with an OR of 1.02 (95% CI 0.66-1.57) and the highest quartile of cumulative exposure was associated with an OR of 1.13 (95% CI 0.80-1.58). In the UK ever high-intensity exposure resulted in an OR of 2.68 (95% CI 0.74-9.77), and a linear trend was present for duration of exposure and cumulative exposure.

This pattern of results did not change when studying those above the 90th percentile (>3.8 μg/m3-years) separately, and applying a 20-year lag did not modify the results either in the CEE countries or in the UK. Also, the risk estimates did not change markedly with regard to the time of exposure, i.e. years since first exposure.

The apparently stronger effect of PAH in the UK warranted further analyses. We suspected residual confounding from exposure to asbestos because a large proportion of the UK subjects had been exposed to asbestos, 47% among men and 4% among women compared to 11% in men and 2% in women in the Central and Eastern European countries, but the risk estimates did not change when introducing a 5-level variable to adjust for asbestos exposure in the regression model. The effect of PAH is present also in people unexposed to asbestos in the UK, which also points against confounding by asbestos. In contrast, asbestos exposure and smoking seemed to slightly modify the effect of PAH (Table 4).

Table 4. Lung cancer relative risk (ORs) following combined exposure to PAH and asbestos or tobacco smoking

Exposure		Central and Eastern Europe				United Kingdom			
PAH	**Asbestos**	Cases	Controls	**OR***	95% CI	Cases	Controls	**OR***	95% CI
No	No	2105	2221	1.0	Reference	115	156	1.0	Reference
Yes	No	277	224	1.0	0.84-1.29	23	20	2.1	0.99-4.27
No	Yes	169	170	1.1	0.86-1.41	51	36	2.3	1.29-4.26
Yes	Yes	73	75	1.4	0.96-2.02	39	21	4.4	2.17-8.94
PAH	**Tobacco Smoking**			**OR****				**OR****	
No	No	199	830	1.0	Reference	8	50	1.0	Reference
Yes	No	13	78	1.4	0.74-2.53	3	10	1.8	0.39-8.40
No	Yes	2075	1561	7.3	6.03-8.78	158	142	8.5	3.80-19.21
Yes	Yes	337	221	8.0	6.16-10.29	59	31	14.1	5.58-35.85

*ORs are adjusted for sex, age, tobacco, silica, arsenic, chromium, cadmium and centre in CEE
**OR are adjusted for sex, age, silica, asbestos, arsenic, chromium, cadmium and centre in CEE

A number of experimental studies have demonstrated a synergistic effect of PAH and asbestos.[113-116] The mechanism may be linked to the strong ability of asbestos fibres to effectively bind PAHs and to deliver them to cells of the lung.[117-119] However, our results concerning a synergistic effect were not statistically significant and therefore need to be replicated in other populations before a conclusion can be reached.

LUNG CANCER RISK ATTRIBUTABLE TO OCCUPATIONAL EXPOSURES IN CENTRAL & EASTERN EUROPE (PAPER IV)

Table 5 shows the OR for lung cancer following occupational exposure to individual agents, groups of agents, and for the group of agents overall in men. Unexposed subjects formed the reference group in all analyses. The attributable fraction for an agent, groups of agents or overall was calculated when the OR was larger than 1. It was mainly occupational exposure to silica and metals that contributed to the AF, with 4.9% and 5.0% respectively; and overall by 7.9% (95% CL 1.9%-13.5%). Individual metals were associated with increased risk estimates but the prevalence of exposure was low and did not clearly influence the AF. Exposure to silica and metals seemed to marginally affect the lung cancer risk in women, but the overall AF was 1.4% and not significantly different from 0%. Excluding subjects exposed to suspected lung carcinogens in the reference group did only marginally change these results.

Table 5. Lung cancer relative risk (OR) and attributable fraction (AF) for ORs >1, associated with individual occupational lung carcinogens and in groups among men

Occupational Exposure	Cases	Controls	**OR***	95% CI	AF %	95% CL
Overall						
(≥1 of the agents)	928	758	1.21	1.04-1.40	7.9	1.9-13.5%
Asbestos (all)	233	228	0.94	0.75-1.18		
Chrysotile only	99	111	0.81	0.60-1.11		
Metals (all)	371	275	1.38	1.13-1.67	5.0	2.1-7.8%
Arsenic & comp.	58	33	1.92	1.15-3.20	1.4	0.4-2.3%
Cadmium & comp.	108	73	1.48	1.04-2.10	1.7	0.3-3.1%
Chromium & comp.	312	237	1.27	1.03-1.56	3.2	0.5-5.9%
Nickel & comp.	157	125	1.14	0.86-1.50	0.9	0-2.9%
PAH	327	283	0.94	0.77-1.15		
Coal comb. fumes	156	136	0.98	0.74-1.30		
Coal tar pitch fumes	75	72	0.68	0.47-1.00		
Soot	231	182	1.04	0.82-1.33	0.4	0-3.1%
Ionizing radiation	64	56	1.04	0.68-1.58	0.1	0-1.4%
Free crystalline Silica	424	287	1.31	1.08-1.58	4.9	1.6-8.1%

*OR adjusted for age, centre, education, tobacco pack-years, time-since-quitting smoking

The OR associated with exposure to one or several of the agents ranged between 1.10 (95% CI 0.73-1.67) in Slovakia and 1.51 (95% CI 1.01-2.25) in the Czech Republic, but were not statistically different (test for heterogeneity, p-value 0.31). The prevalence of ever exposure in the different countries was lowest in Poland (24.5% in cases, 20.7 in controls) and highest in Hungary (51.1% in cases, 45.8% in controls). The results based on these ORs and proportions of cases exposed lead to a substantial variation in the AF estimates between the countries; 3.2% (95% CI 0-9.2%) in Poland and 15.7% (95% CI 1.1-28.1%) in the Czech Republic.

When stratifying on tobacco status, we observed no effect of occupational lung carcinogens among never- and former smoking men, but an increased OR among current smokers 1.36 (95% CI 1.13-1.63), while the effect of occupational exposures among women was similar in ever- (OR 1.16, 95% CI 0.64-2.11) and never smokers (OR 1.08, 95% CI 0.55-2.15).

The lack of effect in never- and former smoking men warranted further analyses to try to understand if the damaged lungs from current smoking lead to an effect of occupational exposures, or if the increased risk that we observe in smokers was due to residual confounding from smoking. Our assumption was that we would not observe any difference in the OR related to time-since-first exposure of occupational lung carcinogens if the effect in current smokers was only due to residual confounding from smoking. Table 6 shows that there was a small difference between long and short time-since-first exposure in never- and former smokers, and that the difference in current smokers was statistically significant (p-value <0.01).

Table 6. Lung cancer relative risk (OR) associated with time-since-first exposure to a confirmed lung carcinogen, by tobacco status

Tobacco status	Time-since-first exposure	Cases	Controls	**OR***	95% CI
Never smoker	Never exp.	175	699	1.00	Reference
	1-39 years	12	99	0.81	0.41-1.61
	>39 years	25	110	1.33	0.77-2.30
Test for heterogeneity, p-value				*0.44*	
Former smoker	Never exp.	325	494	1.00	Reference
	1-39 years	54	121	0.76	0.51-1.14
	>39 years	123	157	1.03	0.75-1.42
Test for heterogeneity, p-value				*0.37*	
Current smoker	Never exp.	1140	676	1.00	Reference
	1-39 years	412	239	1.17	0.95-1.44
	>39 years	357	92	1.87	1.42-2.46
Test for heterogeneity, p-value				*<0.01*	

*OR adjusted for age, sex, centre, education, tobacco pack-years and time-since-quitting smoking when appropriate

In men, squamous cell carcinoma was associated with occupational exposure to lung carcinogens, OR 1.32 (95% CI 1.10-1.58) resulting in an AF of 11.4% (95% CI 4.1-18.1%). The OR for small cell carcinoma and adenocarcinoma were slightly elevated but not statistically significant. In women, exposure to occupational lung carcinogens was associated with occupational exposures, OR 1.27 (95% CI 0.74-2.20) for adenocarcinoma, and 2.04 (95% CI 0.99-4.20) for small cell carcinoma. The AF for exposure to occupational lung carcinogens in women was 7.1% (95% CI 0-14.4%) for small cell carcinoma.

LUNG CANCER RISK AMONG EUROPEAN ASPHALT WORKERS (PAPER II)

Overall, 303 cases (70.0%) and 841 controls (67.1%) were exposed to bitumen fume with a median duration of 13 and 15.5 years, respectively. The prevalence of exposure to bitumen condensate was 71.4% among cases and 67.8% among controls. The overall prevalence of coal tar was 32.7%, ranging between 0% in Israel to 54% in Denmark.

The results of models without adjustment for tobacco smoking and coal tar exposure were comparable to results with adjustment, suggesting that these factors, as measured in this study, exerted little confounding effect on the association between bitumen exposure and lung cancer risk. Similarly, the inclusion of terms for exposure to other occupational agents, one by one and all together, suggested that none of these agents exerted a confounding effect on the association between lung cancer risk and occupational exposures to bitumen fumes.

The OR for ever exposure to bitumen fume was 1.12 (95% CI 0.84-1.49), and there was no relation between lung cancer risk and duration of exposure, cumulative exposure or average exposure (Table 7). Results for exposure to organic vapour and PAH were similar to those for exposure to bitumen fume.

Table 7. Inhalation exposure to bitumen fume and lung cancer risk

Exposure category	Cases	Controls	**OR***	95% CI
Never[c]	130	412	1.00	Reference
Duration of exposure (years)				
0.33-7.99	85	208	1.19	0.84-1.69
8.00-15.49	82	208	1.26	0.87-1.83
15.50-25.99	81	205	1.23	0.84-1.79
26.00-54.00	55	220	0.74	0.49-1.11
Test for linear trend, p-value			*0.37*	
Cumulative bitumen exposure (unit-years)				
0.18-9.55	88	211	1.31	0.93-1.85
9.56-28.17	73	210	0.99	0.68-1.45
28.18-68.00	82	208	1.16	0.78-1.72
68.01-620.48	60	212	0.77	0.50-1.19
Test for linear trend, p-value			*0.39*	
Average exposure to bitumen fume (units)				
0.08-0.97	78	209	1.20	0.84-1.71
0.98-2.20	75	211	1.15	0.78-1.70
2.21-3.61	65	209	0.90	0.60-1.34
3.62-16.67	85	212	1.16	0.78-1.73
Test for linear trend, p-value			*0.80*	

* OR is adjusted for set, country, age, tobacco pack-years and coal tar exposure

** Referent group for all analyses shown in the table

The OR for ever exposure to bitumen condensate was 1.17 (95% CI 0.88-1.56), and again no association with duration of exposure, cumulative or average exposure to this agent: the OR in the category at highest average exposure to bitumen condensate was 1.23 (95% CI 0.81-1.88), see Table 8.

Table 8. Dermal exposure to bitumen condensate and lung cancer risk

Exposure category	Cases	Controls	**OR***	95% CI
Never**[c]	124	403	1.00	Reference
Duration of exposure (years)				
0.33-7.99	85	211	1.22	0.86-1.74
8.00-15.49	84	209	1.34	0.93-1.94
15.50-26.49	89	218	1.35	0.93-1.96
26.50-54.00	51	212	0.72	0.47-1.10
Test for linear trend, p-value			*0.50*	
Cumulative bitumen condensate exposure (unit-years)				
0.59-61.54	79	213	1.21	0.85-1.72
61.55-185.25	81	212	1.22	0.84-1.76
185.26-407.07	66	213	0.99	0.66-1.49
407.08-4003.76	83	212	1.21	0.79-1.84
Test for linear trend, p-value			*0.58*	
Average exposure to bitumen condensate (unit)				
0.29-6.62	70	223	1.10	0.77-1.57
6.63-13.44	74	212	1.21	0.83-1.76
13.45-23.06	80	212	1.25	0.84-1.87
23.07-94.11	85	213	1.23	0.81-1.88
Test for linear trend, p-value			*0.26*	

*OR is adjusted for set, country, age, tobacco pack-years and coal tar exposure

** Referent group for all analyses shown in the table

To better explore the possible confounding effect of coal tar exposure, the analysis of bitumen fume and bitumen condensate was stratified by coal tar exposure. The results for ever-exposure are reported in Figure 7 and show no heterogeneity. Exclusion of workers ever employed as roofers (28 cases, 54 controls; Figure 7) and workers ever employed in mastic asphalt paving (4 cases, 8 controls; not shown in detail) had no material impact on risk estimates.

The robustness of these results was further assessed by excluding interviews of medium or low quality, by restricting the analysis to subjects with 5 or more years of employment in the asphalt industry, and by restricting the analysis to NOK interviews for deceased cases and controls (Figure 7). The unexposed subjects were the reference category in each of the analyses. These exclusions did not provide evidence of selection or information bias, although restriction of the analysis to high quality interviews resulted in slightly higher risk estimates.

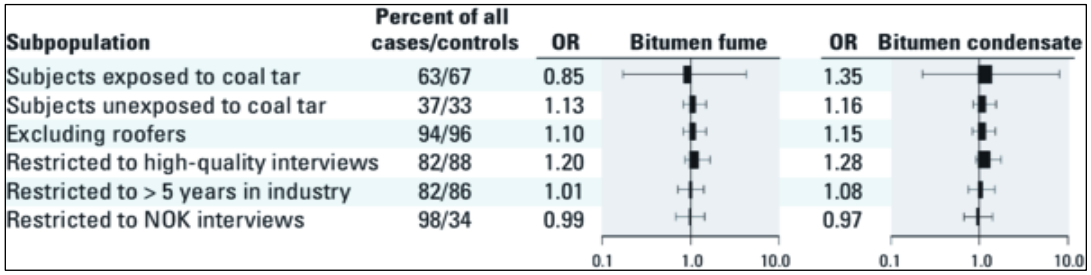


Figure 7. Results of selected sensitivity analyses. Lung cancer OR and 95% CI for ever exposure to bitumen fume (inhalation) and bitumen condensate (dermal)

The contribution of individual countries to the overall result was assessed by excluding one country at a time. The OR for ever-exposure to bitumen fume ranged from 1.06 (exclusion of France, 95% CI 0.78-1.45) to 1.21 (exclusion of Norway, 95% CI 0.87-1.68). The corresponding OR for ever-exposure to bitumen condensate ranged from 1.13 (exclusion of Finland, 95% CI 0.83-1.53) to 1.26 (exclusion of Norway, 95% CI 0.90-1.76).

One should be watchful in comparing the results of the cohort and the nested case-control study because not all cases identified in the cohort analysis were included in the case-control study as a result of exclusion of 1) one country (Sweden), 2) workers with less than two seasons of employment, 3) subjects who died before 1980, 4) workers employed in the job classes representing administrative and office work, and 5) subjects who were not reached or did not want to participate in the case-control study. In addition, the case-control analysis included additional cases of lung cancer identified after the end of the follow-up in the cohort analysis; 217 (50%) of the current cases were included after the cohort study was completed. Occupational exposure levels of bitumen fume have decreased during recent decades; therefore cases from earlier time periods included only in the cohort study might have been exposed on average to higher levels of bitumen fume and other agents compared to the cases included in the nested case-control study.[66] The results of the present study therefore reflect the effects of exposure circumstances prevalent in recent decades.

We compared the distribution of smoking among living controls in our study with the distributions of smoking from national surveys and calculated confounding odds ratio. The COR by smoking ranged from 1.07 in the Netherlands to 1.28 in Finland and Denmark, suggesting that a sizable proportion of the excess mortality from lung cancer observed when the cohort of asphalt workers was compared to national mortality rates could be explained by the higher prevalence of smoking among cohort members. However, the comparison of smoking prevalence between the case-control study and the national surveys is limited by several factors, including possible lack of correspondence of definition of smokers in the surveys and in the nested case-control study, and the suboptimal response rate among controls. The COR should therefore be interpreted only in qualitative terms.

OCCUPATIONAL EXPOSURE TO DIESEL MOTOR EXHAUST AND LUNG CANCER RISK (PAPER III)

The lifetime prevalence of occupational DME exposure among control subjects was 13.6% in women and 42.4% in men. Among control subjects, very few women (<1%) had experienced high levels of occupational DME exposure, vs. 8.3% among men. The proportion of highly exposed men among control subjects was particularly high in the UK (20.6%), Germany (11.5%), Hungary (10.6%) and Canada (9.7%).

Table 9 shows the OR for lung cancer associated with cumulative DME exposure. We observed a significant dose-response trend (p-value=<0.01). In the analysis by exposure category the confidence interval of the OR for the highest exposure category excluded unity (OR 1.31; 95% CI 1.19-1.43).

Table 9. Odds ratios for lung cancer associated with cumulative DME exposure

Subjects	Cumulative DME exposure	Cases	Controls	OR*	95% CI
All	Never	7676	10320	1.00	Reference
	1st Quartile	1269	1513	0.98	0.89-1.08
	2nd Quartile	1325	1497	1.04	0.95-1.14
	3rd Quartile	1440	1502	1.06	0.97-1.16
	4th Quartile	1594	1450	1.31	1.19-1.43
	***Test for trend, p-value*			*<0.01*	
Women	Never	2144	2810	1.00	Reference
	1st Quartile	146	198	0.83	0.64-1.08
	2nd Quartile	116	127	1.27	0.94-1.71
	3rd Quartile	51	71	0.94	0.62-1.42
	4th Quartile	35	45	1.58	0.96-2.59
	***Test for trend, p-value*			*0.20*	
Never smokers	Never	614	3486	1.00	Reference
	1st Quartile	44	334	0.74	0.52-1.05
	2nd Quartile	63	328	1.22	0.90-1.65
	3rd Quartile	33	305	0.85	0.57-1.26
	4th Quartile	47	320	1.26	0.90-1.78
	***Test for trend, p-value*			*0.28*	
Workers never employed in a "List A" job	Never	6954	9764	1.00	Reference
	1st Quartile	1034	1320	0.98	0.89-1.09
	2nd Quartile	1091	1309	1.07	0.97-1.18
	3rd Quartile	1223	1324	1.10	1.00-1.21
	4th Quartile	1412	1301	1.35	1.23-1.49
	**Test for trend, p-value*			*<0.01*	

***** OR is adjusted for age, sex, study, ever employment in a "List A" job, and cigarette pack-years and time-since-quitting smoking when appropriate.

**Test for trend, p-value obtained using the continuous variable for cumulative exposure

A random effects meta regression rendered essentially similar results (OR=1.26; 95% CI 1.14-1.40), see Figure 8. The OR for the highest quartile of DME exposure, when only adjusted for age, sex, and study was 1.42 (95% CI 1.31-1.54).

Figure 8 illustrates the study-specific odds ratios for the highest quartile of cumulative DME exposure vs. never exposed to DME. INCO-Romania, INCO-UK, LUCA, EAGLE and MORGEN had odds ratios point estimates below 1, while ORs in the other studies ranged between 1.16 (INCO-Czech Republic) and 1.77 (INCO-Poland). The odds ratios were attenuated by 10-20% in most countries, and the heterogeneity between the studies expressed as I^2 decreased from 32.5% to 13.8%, when adjusting for smoking (pack-years and time-since-quitting smoking).

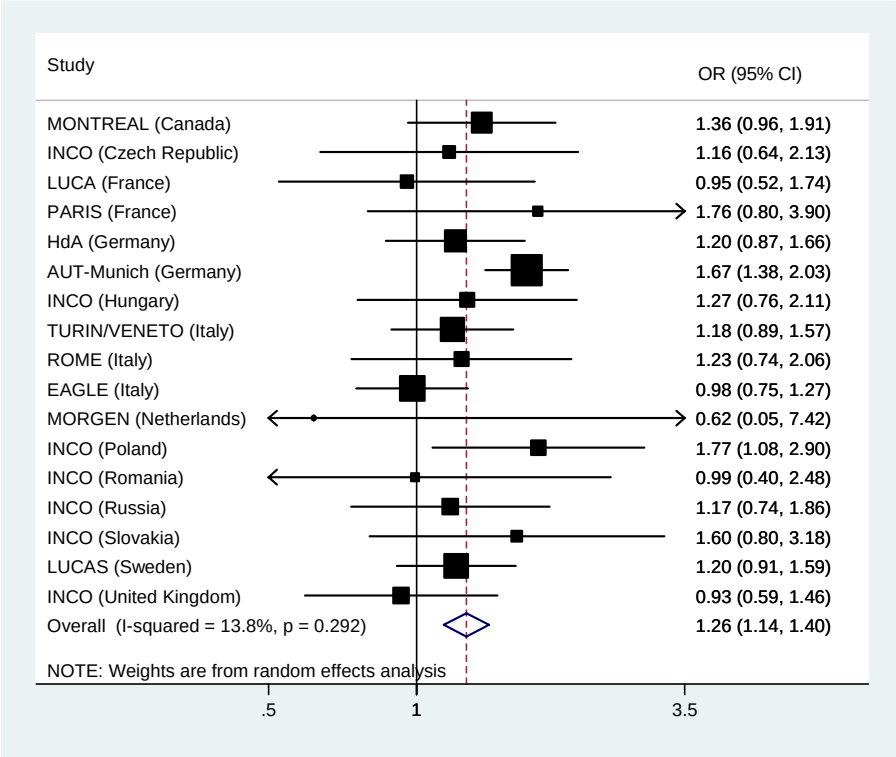


Figure 8. Study specific ORs for the highest quartile of cumulative DME exposure compared to never exposed, adjusted for age, sex, cigarette pack-years, time-since-quitting smoking, and ever employment in a "List A" job

In subgroups analyses, the OR for lung cancer among never smokers was 1.26 (95% CI 0.90-1.78) in the highest exposure category of cumulative DME exposure; no trend was observed (p-value= 0.28). The results in workers never employed in “List A” jobs were comparable with the overall results, i.e. an increased OR for lung cancer in the highest exposure category (OR 1.35, 95% CI 1.23-1.49), with a significant exposure-response trend (p-value=<0.01). Among women, the OR for lung cancer in the highest DME exposure category was 1.58 (95% CI 0.96-2.59). In men, we observed an OR of 1.28 (95% CI 1.17-1.41) for the fourth quartile, with a significant exposure-response trend (p-value=<0.01).

The effect of cumulative DME exposure was similar for different types of lung cancer. The OR for NSCLC among men was 1.27 (95% CI 1.14-1.40) in the highest exposure category of cumulative DME exposure, while 1.44 (95% CI 0.83-2.50) among women. For SCLC, the OR in the highest exposure category was 1.31 (95% CI 1.10-1.55) in men and 3.82 (95% CI 1.51-9.67) in women.

When estimating relative lung cancer risk in relation to duration of exposure we observed an OR close to 1 for exposure only to low levels of DME, for exposure durations of less than 30 years. The OR associated with > 30 years of exposure to low levels of DME exposure vs. never exposed was 1.17 (95% CI 1.07-1.29). Workers ever exposed to high levels of DME exposure experienced an increased risk of lung cancer within a short period of high exposure (<10 years), with an OR of 1.28 (95% CI 1.14-1.45). The highest increased risk was observed after 21-30 years of high level exposure, OR 1.52 (95% CI 1.15-2.02).

There was no evidence of heterogeneity across studies for the effect of DME in the highest quartile of cumulative exposure vs. the never exposed across studies (I^2 13.8%, p-value=0.29). However, when exploring other potential sources of heterogeneity we found a difference in the effect of DME in the studies completed before 1995 (OR 1.49, 95% CI 1.32-1.68) compared to in the more recent studies (OR 1.19, 95% CI 1.04-1.36); with a pooled OR 1.34 (95% CI 1.07-1.67), I^2 = 83.9% and p-value 0.01. Geographical region was also associated with significant heterogeneity; with the highest risk estimate in Western Europe (OR 1.51, 95% CI 1.30-1.76) and the lowest in Southern Europe (OR 1.07, 95% CI 0.90-1.28). The pooled OR for the highest quartile of cumulative DME exposure across regions was 1.29 (95% CI 1.11-1.50), I^2 = 59.8% and p-value 0.04. The effect of DME in large and small studies was not significantly different (p-value=0.13) with the pooled OR 1.33 (95% CI 1.14-1.54). Odds ratios were very similar for population-based and hospital-based case-control studies; for the highest quartile of cumulative DME exposure OR 1.30 (95% CI 1.17-1.44) vs. 1.31 (95% CI 1.09-1.59) respectively.

The prevalence of DME exposure was higher in the current analysis compared to the original studies that had estimated diesel exposure using expert case-by-case assessment, and/or specific project job exposure matrices (JEMs). This is a consequence of the ratings in the DOM-JEM, e.g. farmers are assigned low DME exposure and represent a relatively large proportion of the exposed population in some of the studies. In the INCO-Hungary study the prevalence of DME exposure decreased by 19% when farmers were excluded, while the decrease was only 1% in INCO-UK. The high prevalence of exposure is also a consequence of the nature of a JEM – namely to assign everybody in a given job code the same exposure, whereas individual assessments give the opportunity for attributing exposure to some people in a job but not others, and to take into account other particularities e.g. an increasing trend of diesel engines over time. This may contribute to multiple dimensions of exposure misclassification, but is not related to disease status and thus would most often lead to an attenuation of the OR estimates.

DISCUSSION

MAIN RESULTS

Occupational PAH exposure and lung cancer risk

We found no evidence of an association between occupational PAH exposure and lung cancer risk in the countries in Central and Eastern Europe after adjusting for relevant occupational exposures, but a significantly increased risk in the UK study centre in Liverpool. A greater proportion of the workers in the UK were exposed to high PAH levels and greater cumulative doses than other workers.

Studies in Germany, Sweden and Canada have shown an increased lung cancer risk among workers exposed to high levels of PAH in the general population (German, Sweden, Canada), and Armstrong et al. conducted a review and meta-analysis of 39 cohort studies and reported a relative risk of 1.20 (95% CI 1.11-1.29) at 100 μg/m^3 unit years of B(a)P exposure.[68,120-122] These studies had a more stringent definition of PAH, while in the current study we included PAH exposure also from mixtures containing low levels of PAHs, such as diesel emissions and oil mists. Thus, the ensemble of these studies are broadly in agreement with our results, the differences in relative risks estimated may be explained by choice of PAH definition, exposure assessment method and adjustment variables in the analyses.

We observed a suggestive joint effect of PAH and asbestos in the UK with an OR 4.4 for concurrent exposure, 2.1 for only PAH and 2.3 for only asbestos, indicating a supra-additive interaction. A synergistic effect of occupational PAH- and asbestos exposure has to our knowledge not been reported in epidemiological studies before but appears biologically plausible. Several epidemiological studies show evidence of a joint effect of smoking and asbestos exposure and a number of experimental studies have demonstrated a synergistic effect of PAH and asbestos.[113-116,123-125] The mechanism may be linked to the ability of asbestos fibres to effectively bind PAHs and to deliver them to cells of the lung.[117-119] However, our results concerning a synergistic effect are not statistically significant and therefore need to be replicated in other populations before a conclusion can be reached.

Role of bitumen exposure in the development of lung cancer

The main results of the case-control study of lung cancer nested in the cohort of European asphalt workers study were (i) no significant association between indicators of inhalation and dermal exposure to bitumen and lung cancer, (ii) the lack of an effect of other known or suspected occupational lung carcinogens in the asphalt industry or in other jobs, with the possible exception of exposure to coal tar, and (iii) a higher prevalence of tobacco smoking in the study population as compared to national surveys, which might have biased the results of the cohort study away from the null.

The results on the carcinogenic effect of tobacco smoking were consistent with the expected relationship and allowed fair adjustment for smoking.[104] The consistency of

results among countries, and the robustness with respect to indicators of quality of data are further arguments in favour of the credibility of our results. The results of this study are consistent with the recent evaluation of the IARC Monograph program of an increased risk of lung cancer among pavers and roofers who were exposed to coal-tar.[62] They also contribute to the interpretation of results of previous cohort studies of workers exposed to bitumen with no or limited exposure to coal tar.[64,68,69]

Occupational exposure to diesel motor exhaust and lung cancer risk

We used the recently established database from the SYNERGY project to explore the possible association between occupational DME exposure and lung cancer and found an exposure-response relationship between occupational DME exposure, measured by a semi-quantitative score of cumulative exposure, and lung cancer. In the analysis by categories of the cumulative dose score, the conventional limit for statistical significance of the OR was reached in the fourth quartile of cumulative dose. The results were similar in women, in never smokers, and in workers never employed in jobs known to entail increased lung cancer risk, although the odds ratios in the highest quartile did not attain statistical significance in all subgroup analyses. When we distinguished workers with low intensity exposure from those with high exposure, the latter showed excess risks with as low as 10 years duration, while those with low intensity exposure showed elevated risks only after 30 years and more of exposure. Our results are to a large extent in line with previous research, though most previous studies could not control for major potential confounders such as cigarette smoking and occupational exposures and have not had as large sample sizes as ours to assess risks in different subgroups.[78,82,83,126]

It is important to remember that our results reflect the effects of the DME exposure present before and up to the time when the studies were conducted. Modern engine emissions have become cleaner in the last 20 years, e.g. by the use of low-sulfur fuel and particle traps on vehicles.[127] However, the number of emitted particles may still be high and the consequences on the potential carcinogenicity are not clear. In addition, old types of engines and other sources of DME (e.g. ships, generators, diesel powered tools, paving equipment, etc.) continue to lead to DME exposure; our results suggest that DME exposure may contribute to the current lung cancer burden.

Lung cancer risk attributable to occupational exposures in Central and Eastern Europe

We studied to what extent occupational lung carcinogens overall may have contributed to the high lung cancer burden in Central and Eastern Europe in a multi-center case-control study. The attributable fraction for occupational exposure to one or more lung carcinogens was 7.9% in men; silica and metals contributing the most to the AF. Occupational lung carcinogens did not seem to substantially contribute to lung cancer in women. The largest effects were observed among current smokers. The AF was highest for squamous cell carcinoma among men (11.4%), and for small cell carcinoma among women (7.1%).

We expect our AF estimates to be underestimated because we restricted our selection of agents to confirmed lung carcinogens that were assessed in our study, for example beryllium is a confirmed lung carcinogen but was not assessed in our study.[50] In this case the impact would be small because the prevalence of beryllium in the general population would be very low. We also excluded exposure circumstances that have been classified as carcinogenic to humans such as "occupational exposure as a painter", confirmed carcinogens with limited evidence for lung carcinogenicity such as strong inorganic-acid mists and wood dust, and agents classified as probable carcinogens for the lung such as diesel motor exhaust.[51,85]

Our results show a stronger effect of occupational exposures among current smokers suggesting that smoking modifies the effect of occupational exposures. Several authors have demonstrated a joint effect of asbestos and smoking that lies between additivity and multiplicativity,[123,125,128] and there is evidence that the effect of some metals and radon is stronger in smokers. [56,129-131] We have previously suggested when including the centre from the UK, that occupational PAH and asbestos exposure may involve a joint effect. [132] Thus, the fact that we see a stronger effect of occupational exposures among current smokers in this study is not surprising.

METHODOLOGICAL CONSIDERATIONS

Cancer risks associated with occupational exposures that are still to be identified are expected to be small; therefore, they may be easily obscured by exposure misclassification, particularly when exposure levels are low. The main determinants of informative occupational cancer epidemiology studies are high quality exposure assessment, sufficient study sizes, and well-addressed bias. Small study size and misclassification can lead to null results even if a true effect exists. Three main types of bias are recognized in epidemiology, including selection bias, information bias, and confounding. Bias may distort the magnitude and direction of associations. Depending on the research question it is also important to choose the appropriate study design to ensure a sufficient exposure variation in the study population; otherwise, elevated risks may not be detectable. It is also important to investigate sources of heterogeneity in results.

Exposure assessment

This thesis involves three studies applying different methods for retrospective occupational exposure assessment. The multi-centre case-control study in Central and Eastern Europe (paper I & IV) used local experts to assess approximately 70 occupational exposures on a case-by-case basis based on the information obtained during interviews. The assessment of PAH exposure was in addition supported by an automatic assignment of PAH exposure via an algorithm when the experts coded any of 16 exposures mixtures containing PAHs, see page 17. In the asphalt nested case-control study (paper II) individual job histories, industry-specific JEMs, and information from detailed occupational questionnaires from companies were combined in algorithms that yielded semi-quantitative estimates of the relevant exposures for each subject. In the SYNERGY project (paper III), we used a general population job-exposure matrix based

on 5-digit ISCO-68 codes (DOM-JEM) to estimate exposure to diesel motor exhaust (0=no, 1=low, 2=high). Each of these methods, and other methods frequently used, is accompanied with pros and cons in terms of price tag, time and training requirements.

Self reporting of exposures is almost always inaccurate, because study participants are often not aware of what chemicals they have used.[133] In addition, extensive recall bias is likely to occur. Individual exposure assessment estimated by local experts is generally considered the most accurate method for assessing occupational exposures in population-based case-control studies, inducing less misclassification as experts can take into account differences in exposure between individuals with similar job-titles, local use of materials, production processes and personal protection equipment use.[134-137] However, even with expert assessment measurements are prone to recall and reporting bias as study participants are likely to have difficulties remembering details about work conditions decades ago, the level of knowledge of each expert varies as does the degree of standardizing work between experts who work independently in the same study. Job-exposure matrices translate jobs into specific exposures, and are more objective and standardized compared to other methods.[138] JEMs can have additional dimensions beside a job code, for example industry, time-period and/or country. Caution should be used in applying a JEM to populations and studies different from those for which it was initially designed.[139]

The studies included in this thesis have in my view used the most appropriate method for assessing exposures in their respective situations. The case-by-case expert assessment method was chosen in the INCO study (paper I & IV) because of a broad variety of natural resources, industries and technologies across Central and Eastern Europe, multiple agents of interest, and the lack of suitable JEMs at the time when the study was conducted. The asphalt nested case-control study (paper II) used a very detailed and elaborated exposure assessment method in comparison with previous studies among asphalt workers and included dermal exposure, which is particularly relevant in this industry. Here it would have been difficult to use case-by-case expert assessment, especially to try to harmonize the experts in this highly technical and heterogeneous industry. In addition, the majority of case subjects were deceased, so it would have been difficult to attain sufficient details for individual case-by-case expert assessment. The SYNERGY study (paper III) involves large numbers of subjects from different countries and from different jobs. In that study, occupational DME exposure was frequent at population level. Therefore, it was appropriate to first study the effect of occupational DME exposure using a general population JEM. It is a quick and cheap method and can well precede the development of a more sophisticated JEM.

Study size and power

Random error is the variability in the data that arises due to chance rather than to any systematic bias/confounding factors. The most effective way of reducing the effects of random error on odds ratio point estimates is to increase study size, so that the confidence intervals will become narrower and the effect estimate thus more precise. The relative size of the control group in a case-control study also influences the precision of the effect estimates. It is most often sufficient to use a case control ratio of 1:2, but a larger ratio may be needed in order to ensure an adequate ratio in specific

sub-group analyses. It is therefore necessary to calculate what study size is needed to be informative. Very large study sizes are required when the expected relative risk is small and prevalence of the exposure in the study population is low or very high. Multi-centre studies or pooled studies offer a solution. Besides increasing power, well-conducted multi-centre studies provide additional advantages, including a greater exposure contrast in the study population which is advantageous for exposure-response analyses, and the opportunity to investigate differences in exposure and disease patterns among countries. Pooling data from different studies offer similar advantages, but because of potential heterogeneity in study design and conduct, they may introduce more unexplained heterogeneity.

In the asphalt study (paper II), the assessment of occupational exposures to agents other than those related to bitumen was rather crude, which is reflected by lack of effect for most of them. This can be explained by exposure misclassification, but can also be attributed to the narrow range of exposure experienced by asphalt and construction workers, and low exposure levels as a result of declining exposure levels in the worksites.[66] In addition, the power to detect small effects is limited when the prevalence of co-exposures are as frequent as in this study, e.g. the prevalence of diesel motor exhaust exposure among the controls was 95% resulting in a power ~25% to detect an OR of 1.5.

Selection bias

Selection bias arises when cases and controls are recruited from different study bases and can occur if participation differs by subgroups of cases and controls with different probability of exposure. In the asphalt study (paper II) we were able to analyze whether determinants in the previous cohort study were associated with non-response in the nested case-control study. Long duration of employment was associated with participation, while cumulative exposure to bitumen was not. In the SYNERGY project (paper III) we excluded farmers in sensitivity analyses assuming that farmers living in rural areas may belong to specialized cancer hospitals with a larger catchments area than the region from which hospital controls were enrolled, which could result in a selection bias as has been shown in a previous small case-control study.[140] We further excluded the AUT-Munich study (the largest individual study with low response rate among controls) to explore its impact on the relative risk estimate; the odds ratios decreased slightly but did not change the overall results. Thus, a strong selection bias as a result of differences in non-participation among cases and controls was unlikely.

Information bias

Retrospective occupational exposure assessment using any method is always complex and associated with at least some degree of exposure misclassification. However, this type of information bias will be non-differential if it is unrelated to disease status, and would most often lead to an attenuation of the relative risk estimates. Simulations in a validation study of the occupational exposure assessment in the INCO study confirmed that the likely effect of misclassification on risk estimates was an attenuation towards the null, in particular for exposures with low prevalence in the study population.[141]

High exposure prevalence may thus result in less severe attenuation due to non-differential exposure misclassification. On the other hand, differential misclassification is related to disease status and can bias the estimates of the association in either direction, and consequently, raise spurious associations.

Recall and reporting bias may lead to differential misclassification. For example, self-reported information might differ systematically between cases and controls, leading to differential misclassification of exposure.[142] We tried to limit differential exposure misclassification by separating participant contact from the exposure assessment procedure, so that the latter would be conducted without knowledge of and thus independent of case/control status. Standardised tools for assessing exposures generally lead to reduced risk of recall bias. Not revealing any specific hypotheses to the study population for example by covering different topics during an interview (residential history, smoking, alcohol and diet) also tends to reduce recall bias. Bias may have been introduced through the use of next-of-kin interviews. For example in the asphalt nested case-control study (paper II), the data related to personal hygiene were too sparse to allow the modulation of job-history-based exposure estimates at the individual level. Thus, we used information provided by living control subjects to estimate exposures by company, job, and time-period; then we assigned these exposure estimates to all subjects in respective company, job, and time-period. Using the information at the individual level could have introduced a differential bias, as the information related to cases more often came from a next-of-kin, while the controls subjects were able to provide information in person.

Confounding and residual confounding

Confounding occurs when an exposure-outcome association is observed, but is not real and is due to a correlation between the exposure and another exposure that is a true causal risk factor for the outcome. The major potential confounding factor for all exposures of interest considered in this thesis was tobacco smoking, a major and very strong risk factor for lung cancer. It is likely that individuals with certain occupations smoke more than the other participants. Therefore, the excess risk related to higher exposure to tobacco must be carefully addressed when the association between occupational exposures and lung cancer is investigated.

Within stratum of the confounder, confounding is often referred to as residual confounding. One solution to limit residual confounding is to conduct sub-group analyses, e.g. among never-smokers. However, this approach may lead to substantial loss of power because of relatively small numbers of participants in the sub-groups, making the risk estimates unstable. Therefore, interpretation of the confidence intervals in the individual categories of exposure can be difficult. In order to achieve sufficient power in sub-group analyses, it may be necessary to weight the sampling to ensure enough participants in each category, e.g. lifetime non-smoking cases and controls, to assess the effect of occupational exposures in those sub-groups.

We have collected detailed data on smoking in all three studies, and have been able to adjust for different aspects of smoking. Thus, confounding and residual confounding from smoking should not be a major problem in the analyses presented in this thesis.

Study design

Both community-based and industry-based studies can contribute to our understanding of occupational carcinogenesis, but neither is without limitations. Valid and precise exposure information is seldom available in community-based studies while industry-based studies frequently cannot take into account individual smoking patterns and life-time occupational histories of the subjects. In addition, exposure assessment in industry-based studies is often based on job titles and employment records.[143-145] In the past 50 years, many asphalt companies have been purchased by or dispatched and merged with other companies, sometimes even on more than one occasion. This has contributed to incompleteness of records related to employees and the materials used by the companies.

Control subjects recruited from the population are theoretically preferable in community based case-control studies, although they often suffer from a low response rate and differential recall in cases and controls. Usually, hospital controls have the advantage of higher participation rate and more similarity to cases in recall of past lifestyle habits. Nevertheless hospital controls may not represent a random sample of the source population that generated the cases. A potential disadvantage is that the diseases of the controls may be associated with the exposure of interest, which then would provide a biased control group. We compared the effects of DME exposure in hospital based vs. population based case-control studies in the SYNERGY project (paper III), and observed no difference in relative risk estimates.

Heterogeneity

In the SYNERGY project (paper III) we observed significant heterogeneity of relative risk estimates of DME by country. This may result from variation in many factors, including the background risks of lung cancer. The most influential risk factor for lung cancer is the smoking pattern in respective country. Indeed the lung cancer mortality varies largely in the countries included in the analyses and has changed dramatically over the last 50 years; lung cancer mortality peaked around 1970 in the UK, while as late as around 2000 in Poland and Hungary, see Figure 2. According to the level of industrialization in each local setting, exposure to other lung carcinogens may also have differed. The frequency of employment in jobs known to entail increased lung cancer risk among the controls in the SYNERGY study, ranged from 3% in MORGEN (the Netherlands) to 16% in HdA (Germany), was approximately controlled for in the analyses.

In the asphalt study (paper II) we made considerable efforts to deal with the country differences in exposures in the best possible way. For example oil gravel paving was only used in some companies in one country, coal tar- and asbestos use stopped at different times in different countries, and the length of the paving season varied by

country. These aspects were integrated in the exposure assessment, which was specific to the country, company, job and time-period.

GENERAL DISCUSSION AND FUTURE RESEARCH

The first step towards prevention of cancers arising from occupational exposures is to identify specific carcinogenic agents. Reaching for this goal, it is imperative to clarify the role of the many agents that are suspected occupational carcinogens today. For those found to be carcinogenic, knowledge of the doses associated with increased risk and whether certain groups of people are more susceptible than others are needed to ensure that safe-threshold levels protect the most sensitive groups whenever possible.

Our results contribute to the clarification of the potential for bitumen fume and diesel motor exhaust (DME) to be carcinogenic to the lung. For bitumen fume, we did not observe an association with lung cancer risk, an inference made from studies of asphalt workers. If these results are valid, exposure to bitumen fume in exposure circumstances with means of protection and at levels currently experienced by workers in the asphalt industry does not increase lung cancer risk. This does not, however, rule out the possibility that exposure to bitumen under different circumstances may still be hazardous for lung cancer – such as among workers who re-cycle old asphalt containing coal tar or those using old paving techniques with higher laying temperatures. Furthermore, our results only contribute to lung cancer and cannot inform whether there is a bitumen-associated risk for other cancers.

Recent epidemiological studies have supported the carcinogenicity of DME for lung cancer. However, questions remained regarding potential residual confounding by smoking, the nature of the dose-response relationship and the possibility that findings arose by chance. Using combined data from 11 lung cancer studies with complete occupational histories and detailed information on smoking habits, we found a statistically significant exposure-response relationship and consistent results in various subgroups including women and among workers never employed in occupations with established lung cancer risk, and after careful adjustment for smoking habits as well as among never smokers. Yet, assessment of exposure to DME in our study did not take into account the changes in the use of diesel engines over time and it was not possible to estimate absolute concentration levels for DME. Thus, cohort studies among heavily exposed occupations with quantitative exposure measurements may shed further light on this association. Results from one prospective study led by the US NCI and NIOSH in underground miners will become available soon.

Risk assessment and occupational epidemiology studies need to be undertaken in developing countries where exposures are likely to be different, exposure levels higher and regulatory systems weaker. Demonstrating that a health hazard is relevant in a local setting would help encourage national authorities to react and enforce protection of workers.

CONCLUSION

- We found no evidence of an association between occupational PAH exposure and risk of lung cancer in the Central and Eastern European countries after adjusting for relevant occupational exposures and smoking, but a significantly increased risk of lung cancer associated with PAH, possibly acting jointly with asbestos in the UK. A greater proportion of the workers in the UK were exposed to high PAH levels and greater cumulative doses than the workers in CEE.

- Indicators of inhalation or dermal exposure to bitumen among asphalt workers were not associated with increased lung cancer risk. Our data suggest that a sizable proportion of the excess mortality from lung cancer in the cohort study of asphalt workers, relative to the general population, was attributable to their higher tobacco consumption, and possibly to coal tar exposure, while other occupational agents did not appear to play important roles.

- Occupational exposure to diesel motor exhaust was associated with an increased lung cancer risk in the pooled data from case-control studies in Europe and Canada. Our results revealed a small raised risk, consistent across studies and with a significant exposure-response trend. This association was unlikely to be explained by bias or confounding which we addressed by adjusted models and analyses in sub-groups not exposed to potential confounders.

- Occupational exposures, in particular silica and metal exposure, contributed moderately to the lung cancer risk among men in the Central and Eastern European countries; the effect of occupational lung carcinogens was stronger among current smokers. We observed almost no effect of occupational exposures on the lung cancer risk among women, except for a contribution to small cell carcinoma lung cancers (AF 7.1%, 95% CI: 0 to 14.4%), an observation which needs further investigation and confirmation.

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