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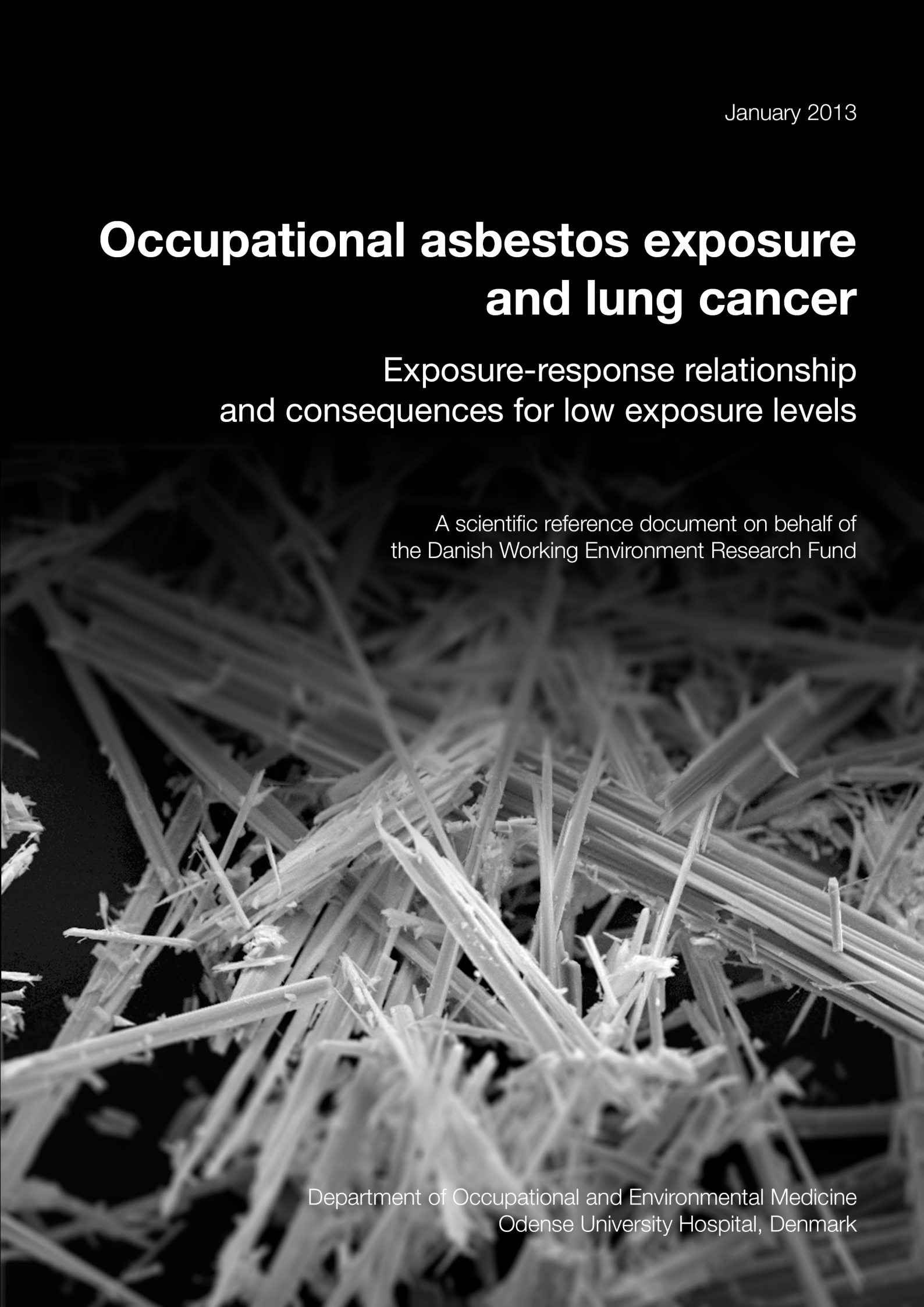
Occupational asbestos exposure and lung cancer

Exposure-response relationship and consequences for low exposure levels

A scientific reference document on behalf of the Danish Working Environment Research Fund



Department of Occupational and Environmental Medicine
Odense University Hospital, Denmark

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SUMMARY

INTRODUCTION

Lung cancer is the most commonly diagnosed cancer worldwide. In Denmark lung cancer accounts for about 13% of all new cancers in males and 12% in females. Lung cancer is now the leading cause of cancer death among both females and males. Since the 1950s the incidence of lung cancer has steadily increased among females while leveling off and declining for males after the 1980s. It has been estimated that about 4% to 8% of lung cancer cases may be related to asbestos exposure.

It is difficult to decide when asbestos exposure is sufficient to cause lung cancer in individual cases. Estimating previous asbestos exposure is uncertain. Many different methods have been used to measure asbestos fibers in the air, but results from differing measuring methods cannot be readily compared. Asbestos air measurements are seldom available when individual compensation cases are evaluated. The fiber potency to cause lung cancer probably varies with fiber type, fiber size and industry. However, these differences are still not disentangled and somewhat controversial. Most occupational exposures involve exposure to both chrysotile and amphiboles. In addition the majority of previously asbestos-exposed workers who contract lung cancer are also smokers. Thus the complex interaction between smoking asbestos should also be taken into consideration.

The aim of this project is to produce a stringent and critical review of the scientific literature concerning asbestos exposure and its causation of lung cancer. Particular emphasis has been placed on the exposure-response relationship at low-level asbestos exposure. This document provides updated evidence upon which guidelines concerning the identification and recognition of asbestos-related lung cancer can be based.

METHODS

Based on the posted grant proposal 19 search questions were extracted. These search questions corresponded directly to the requested information. Two broad systematic literature searches were performed with PubMed and EMBASE. They were combined and doublets removed resulting in 4,088

references. These references were systematically combined into 4 main groups: lung cancer, asbestos exposure, exposure-response as well as competing and predisposing factors. They were initially sorted by title then by abstracts. Thereafter specific "bottom up" PubMed searches were performed for each search question and integrated into the existing reference groups. References were further sorted according to inclusion and exclusion criteria.

A writing and an internal expert group each with 8 members were established. Key cohort and case-control studies (N=28) were read by 2 writing group members and evaluated using a data extraction sheet based on the extraction sheet developed by the Scottish Intercollegiate Guidelines Network (SIGN). Key review and meta-analyses articles (N=10) were evaluated likewise using the R-AMSTAR assessment sheet. Reviewed articles were described as narratives and in evidence tables.

A working seminar was held on November 22 and 23 in Odense for the writing and internal expert groups. The 4 seminar working groups thoroughly discussed and revised the manuscript draft. Twenty-one useful statements were discussed, edited and graded based on the quality of evidence: good evidence (+++), some evidence (++) or limited evidence (+). Consensus concerning the grading of the edited statements was obtained. The revised draft was sent to two external reviewers. The final version was redrafted in accordance with these 2 reviewers' comments and presented to the National Board of Industrial Injuries for approval.

RESULTS

Cell type and location of asbestos-related lung cancer does not differ from that of non-asbestos-related lung cancer. There is very little information concerning the prognosis of asbestos-related lung cancer. Our own data showed no differences in survival when comparing those with and without asbestos exposure. It is unlikely that the prognosis of asbestos-related lung cancer differs from non-asbestos-related lung cancer.

Asbestos exposure assessment should be based on a thorough occupational history. This should be supplemented with expert opinion, appropriate job exposure matrices and published air measurements that can be related to the exposure in question. The presence of pleural plaques, either on one or both sides, increases the likelihood of previous asbestos exposure with relevant lung cancer latency, when competing causes can be eliminated. However, they do not reflect the degree of such exposure. The presence of asbestos bodies or asbestos fibers in either lung tissue or lung washings increases the

likelihood of asbestos exposure. However, they do not reflect the degree or time window of exposure. The absence of pleural plaques, asbestos bodies or asbestos fibers does not rule out that there has been considerable asbestos exposure.

All forms of asbestos are associated with lung cancer. The evidence is not conclusive concerning differential lung cancer risks associated with fiber type and fiber dimensions, when other relevant aspects are taken into account in meta-analyses. For practical purposes most occupational exposures can be assumed to be of a mixed type. The exposure-response between asbestos exposure and lung cancer risk is basically linear. However, it levels off at very high exposures around 150 f-y/ml. The majority of studies demonstrate that the relative risk for lung cancer increases between 1 and 4% per f-y/ml. This corresponds to a doubling of risk at 25-100 f-y/ml. However, 1 high quality study has shown that a doubling of lung cancer risk was seen at about 4 f-y/ml. There is insufficient evidence that a no-effect threshold exists. No minimal latency time for asbestos-related lung cancer has been established. However, for practical purposes it can be assumed to be 10 years after the onset of exposure. Limited evidence suggests that lung cancer risk from asbestos decreases decades after exposure.

Although there is some tendency for lung cancer risk to run in families, there is not enough evidence to include age, sex or family lung cancer history when evaluating cases of potential asbestos-related lung cancer. Neither should most other diseases be taken into consideration when evaluating these cases. However, lung fibrosis from whatever cause is associated with an increased lung cancer risk. This is particularly true of lung fibrosis from asbestos (asbestosis). Asbestosis is caused by a considerable degree of asbestos exposure, which also embodies an increased lung cancer risk. Exposure to other acknowledged occupational lung cancer risks, such as welding and polycyclic aromatic hydrocarbons (PAH), should be taken into consideration. Exposure to environmental pollutants such as radon and air pollution in Denmark are generally low and thus should not be considered when evaluating individual cases of possible asbestos-related lung cancer. Asbestos-exposed smoking workers have a greater lung cancer risk than asbestos-exposed non-smokers. The increased risk is between additive and multiplicative. About 20 years after smoking cessation the relative risk from smoking is reduced by 90% or more.

CONCLUSION

The exposure-response between asbestos exposure and lung cancer risk is basically linear, but may level off at very high exposures. Many studies demonstrate that the relative risk for lung cancer increases between 1 and 4% per f-y/ml, corresponding to a doubling of risk at 25-100 f-y/ml. Cell type and location of lung cancer is not helpful in differentiating asbestos-related lung cancer from other lung cancers. The presence of pleural plaques, asbestos bodies or asbestos fibers is useful as markers of asbestos exposure and as such helpful in supporting previous asbestos exposure. The interaction between asbestos and smoking regarding lung cancer risk is between additive and multiplicative.

POPULAR DANISH SUMMARY

INTRODUKTION

På verdensplan er lungekræft den hyppigst diagnosticerede kræftform. I Danmark kan 13% af alle nye kræfttilfælde blandt mænd tilskrives lungekræft, mens det for kvinder er 12%. Ligeledes er lungekræft den førende årsag til kræftdød blandt mænd og kvinder. Siden 1950´erne har antallet af nye kræfttilfælde blandt kvinder været stadigt stigende, mens man blandt mænd har set en udjævning og et fald siden 1980´erne. Man regner med, at ca. 4-8% af alle lungekræfttilfælde skyldes asbestudsættelse.

Det er svært at afgøre, hvilket omfang af asbestudsættelse, der er tilstrækkeligt til at forårsage lungekræft i det enkelte individ. Dette skyldes flere ting, bl.a. usikkerheden omkring estimering af tidligere asbestudsættelse. Mange forskellige metoder har været anvendt til at måle asbestfibre i luften, men resultater med forskellige målemetoder kan ikke umiddelbart sammenlignes. Desuden er asbestmålinger i luften sjældent tilgængelige, når der føres erstatningssager. Den karcinogene effekt af asbest afhænger af fibertype, fiberstørrelse og industri, men disse forskelle er endnu ikke helt afklarede, ligesom erhvervsmæssig asbesteksponering ofte også betyder eksponering for både krysotil og amphibol asbest. Endvidere er en stor andel af de personer, der tidligere har været udsat for asbest, også rygere, hvilket betyder, at den komplekse interaktion mellem asbest og rygning, ligeledes skal tages i betragtning.

Formålet med dette projekt er at producere en stringent og kritisk gennemgang af den videnskabelige litteratur om asbest og dens årsagssammenhæng med lungekræft. Særlig vægt er lagt på eksposition-respons-forholdet i lavdosisområdet. Dette dokument bidrager således med en opdateret gennemgang af evidensen vedrørende asbestrelateret lungecancer. Retningslinjer for identifikation og anerkendelse af asbestrelateret lungekræft kan baseres på dette arbejde.

METODE

På baggrund af Arbejdstilsynets opslag blev der udarbejdet 19 spørgsmål. For at besvare disse spørgsmål, blev foretaget to brede, systematiske litteratursøgninger i henholdsvis PubMed og

EMBASE. Det gav 4.088 hits, når resultaterne blev kombineret og dubletter fjernet. Disse referencer blev systematisk sorteret, først i 4 hovedgrupper: lungekræft, asbest, eksposition-respons samt konkurrerende og prædisponerende faktorer på baggrund af titel, og sidenhen i 19 undergrupper (svarende til de 19 spørgsmål) på baggrund af resume. Herefter blev der udført specifikke søgninger i PubMed for hvert af de 19 spørgsmål (bottom-up søgning). Disse referencer blev ligeledes sorteret efter titel og resume og efterfølgende integreret i de eksisterende 19 undergrupper. Grupperne med referencer blev sorteret en sidste gang efter inklusions og eksklusionskriterier.

To arbejdsgrupper med hver 8 personer blev etableret: en skrive- og en intern ekspertgruppe. Hver enkelt kohorte- og case-kontrolstudie, der skulle indgå i besvarelsen af eksposition-respons sammenhængen mellem asbest og lungekræft (n=28), blev læst af 2 personer fra skrivegruppen og efterfølgende evalueret efter et SIGN-inspireret skema. Reviews og metaanalyser blev gennemgået på samme måde, men evalueret med et R-AMSTAR skema. Kohorte- og case-kontrolstudierne blev beskrevet tabellarisk såvel som narrativt.

Den 22.-23. november 2012 blev der i Odense afholdt et seminar for de to arbejdsgrupper, hvor det foreløbige manuskriptudkast blev drøftet og revideret. 21 statements blev ligeledes diskuteret, redigeret og bedømt på baggrund af kvaliteten af den foreliggende evidens: god evidens (+++), nogen evidens (++) eller begrænset evidens (+). Det reviderede manuskriptudkast blev sendt til to eksterne bedømmere. Efterfølgende blev deres kommentarer indarbejdet i teksten, og det endelige manuskript blev herefter sendt til godkendelse hos Arbejdsskadestyrelsen.

RESULTER

Celletype og placering for den asbestrelaterede lungekræft adskiller sig ikke fra den ikke-asbestrelaterede lungekræft. Det foreligger meget lidt viden om prognosen for asbestrelateret lungekræft. Egne data viste heller ingen forskelle i overlevelse ved sammenligning af lungekræfttilfælde med og uden asbestudsættelse. Det er derfor mindre sandsynligt, at prognosen for asbestrelateret lungekræft adskiller sig fra ikke-asbestrelateret lungekræft.

Vurdering af asbesteksponering bør baseres på en grundig gennemgang af erhvervsmæssig historik suppleret med eksponeringsmatricer og luftmålinger relateret til den aktuelle eksponering. Tilstedeværelsen af pleurale plaques, enten ensidigt- eller dobbeltsidigt, øger sandsynligheden for, at tidligere asbesteksponering med relevant latenstid for lungekræft har fundet sted. Dog er de ikke en

markør for omfanget af asbesteksponering. Asbestlegemer eller asbestfibre i enten lungevæv eller lungeskyllevask øger ligeledes sandsynligheden for asbesteksponering har fundet sted, men afspejler ikke omfanget eller tidsvinduet for eksponering. Samtidig udelukker fraværet af pleurale plaques, asbestlegemer eller asbestfibre ikke, at en betydelig asbesteksponering har fundet sted.

Alle former for asbest er forbundet med lungekræft, men evidensen for, at den karcinogene effekt afhænger af fibertype og -dimension, er stadig ikke tilstrækkelig, når metaanalyser gennemgås. Det kan bl.a. tilskrives, at erhvervsmæssig asbesteksponering sjældent kun afspejler eksponering for én type asbest. Eksposition-respons sammenhængen mellem asbest og lungekræft er tilnærmelsesvis lineær, men udjævnes ved meget høje eksponeringsniveauer på omkring 150 fiber-år/ml. De fleste studier viser, at den relative risiko for lungekræft stiger med 1-4% pr fiber-år/ml. Dette svarer til en fordobling af risikoen ved 25-100 fiber-år/ml asbestudsættelse. Dog har et studie af høj epidemiologisk kvalitet vist, at risikoen for lungekræft blev fordoblet allerede ved 4 fiber-år/ml. Der er ikke solid evidens for eksistensen af et no-effect tærskelniveau samt en nedre grænse for latenstiden for asbestrelateret lungecancer. Det kan antages at latenstid er ca. 10 år fra eksponeringens start. Begrænset data indikerer, at risikoen for lungekræft falder årtier efter eksponering.

Selv om der en vis tendens til familiær arvelighed for lungekræft, er der ikke evidens for at inkludere faktorer som alder, køn eller familiær lungekræft i vurderingen af potentiel asbestrelateret lungekræft hos individer. Ej heller bør de fleste andre sygdomme tages i betragtning i vurderingen af disse sager. Undtagelsesvis er lungefibrose, som er associeret med øget risiko for lungekræft, især hvis den kan tilskrives asbesteksponering (asbestose). Asbestose skyldes en betydelig grad af asbesteksponering, hvilket ligeledes er forbundet med øget risiko for lungekræft. Eksponering for andre anerkendte erhvervsbetingede risikofaktorer, såsom svejsning og polycykliske aromatiske kulbrinter (PAH), bør tages i betragtning. Eksponering for miljøforurenende stoffer som radon og luftforurening er generelt lavt i Danmark, og bør således ikke indgå i den individuelle vurdering af potential asbestrelateret lungekræft. Asbesteksponerede arbejdstagere, der samtidig ryger, har højere risiko for lungekræft end asbesteksponerede ikke-rygere. Den øgede risiko er et sted mellem additiv og multiplikativ. Omkring 20 år efter rygeophør er den relative risiko for lungekræft i forbindelse med rygning reduceret med minimum 90%.

KONKLUSION

Sammenhængen mellem asbest og lungekræft er tilnærmelsesvis lineær, men stabiliserer sig ved meget høje eksponeringsniveauer. Flere undersøgelser viser, at den relative risiko for lungekræft stiger mellem 1 og 4% pr. fiber-år/ml, svarende til en fordobling af risikoen ved 25-100 fiber-år/ml. Celletype og lokaliteten af asbestrelateret lungekræft adskiller sig ikke fra lungekræft udløst af andre faktorer. Tilstedeværelsen af pleurale plaques, asbestlegemer eller asbestfibre er anvendelige som markører for tidligere asbesteksponering. Samspillet mellem asbest og rygning for udviklingen af lungekræft er mellem additiv og multiplikativ.

MEMBERS OF THE WORKING GROUPS

WRITING GROUP

David Sherson (DS)	Denmark
Jesper Bælum (JB)	Denmark
Jesper Rasmussen (JR)	Denmark
Karen Ege Olsen	Denmark
Lene Snabe Nielsen (LSN)	Denmark
Maria Albin (MA)	Sweden
Niels Christian Hansen (NCH)	Denmark
Søren Dahl (SD)	Denmark

INTERNAL EXPERT GROUP

Christy Barlow	USA
Dick Heederik	the Netherlands
Johnni Hansen	Denmark
Jørgen Vestbo	Denmark
Mercello Lotti	Italy
Panu Oksa	Finland
Sverre Langård	Norway
Thomas Kraus	Germany

ABBREVIATIONS

AB	Asbestos bodies
AF	Asbestos fibers
AFE	Attributable fraction of exposed
ARLC	Asbestos-related lung cancer
Bq	Becquerel
COPD	Chronic obstructive pulmonary disease
DISCO	Danish version of the International Standard Classification of Occupations
EPA	U.S. Environmental Protection Agency
ETS	Environmental tobacco smoke
f/cc	Fibers per cubic centimeter identical with f/ml
f/ml	Fiber/milliliter
f-y/ml	F-ys per milliliter
GST	Glutathione S-transferase
GWAS	Gene-wide association studies
HEI	Health Effects Institute (UK)
HR	Hazard ratio
HSE	Health and Safety Executive (UK)
IARC	International Agency for Research on Cancer
ILD	Interstitial lung disease
IPF	Idiopathic lung fibrosis
IRR	Incidence rate ratio
K	Potency factor
K_L	Potency factor for lung cancer
K_M	Potency factor for mesothelioma
mppcf	Million particles per cubic foot
NARLC	Non-asbestos related lung cancer
NSCLC	Non-small cell lung cancer
O_L	Observed lung cancer mortality
OR	Odds ratio
OSHA	Occupational Safety and Health Administration (US)
OSWER	Office of Solid Waste and Emergency Response (EPA, US)
PAF	Population attributable fraction
PAH	Polycyclic aromatic hydrocarbons
PCM	Phase contrast microscope
PP	Pleural plaques
R_L	Excess lung cancer mortality $R = 100\ (O_L\text{-}E_L)/(E_L x X)$
RR	Relative risk

SCLC	Small cell lung cancer
SEM	Scanning electron microscope
SIR	Standard incidence ratio
SSc	Systemic sclerosis
SMR	Standard mortality ratio
TEM	Transmission electron microscope

1. INTRODUCTION

It is often very difficult to decide when previous asbestos exposure is sufficient to cause lung cancer in individual cases. Estimating previous asbestos exposure is often extremely uncertain. The vast majority of asbestos-exposed workers are also smokers. Thus, the interaction between smoking and asbestos must also be taken into consideration. On this background the National Board of Industrial Injuries in Denmark has requested a scientific reference document concerning low-dose asbestos exposure and lung cancer. The Department of Occupational and Environmental Medicine, Odense University Hospital applied for and received the grant to write this document.

The aim of this project is to produce a stringent and critical review of the scientific literature concerning asbestos exposure and its causation of lung cancer. There will be particular emphasis on the exposure-response relationship between low-level asbestos exposure and lung cancer. The possibility of establishing a safe low-level no effect threshold will be investigated. The project will elucidate how asbestos should be compared to and weighed against other lung cancer causes. The resulting document will provide a solid evidence base for developing new guidelines how asbestos-related lung cancer can be identified and recognized as a compensable occupational disease.

2. BACKGROUND

2.1 LUNG CANCER

EPIDEMIOLOGY

There is strong evidence that exposure to asbestos causes asbestosis, pleural and peritoneal mesotheliomas as well as lung cancer [1-4]. The evidence is based on both human and animal evidence.

Lung cancer is the most commonly diagnosed cancer worldwide with an estimated 1,600,000 new cases and 1,380,000 deaths in 2008 [5, 6]. In Denmark lung cancer accounts for 13.3% of all new cancers in males and 12.3% of all new cancers in females. Since the 1950s lung cancer incidence has steadily been increasing among females. In males morbidity and mortality was declined after the 1980s [7]. Smoking is the main cause, but occupational, environmental and life style exposures may play a role.

HISTOLOGY, STAGING OF LUNG CANCER AND CHANGES IN CELL TYPE OVER TIME

Lung cancer is classified according to pathohistological types into two major groups: small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC). SCLC accounts for about 15% of all cases and is characterized by early hematogenous dissemination, rapid progression and poor prognosis [8]. NSCLC includes squamous cell carcinoma, adenocarcinoma, large-cell carcinoma and some rare subtypes. NSCLC (approximately 30% of all cases) has been shown to be more frequent in men, whereas adenocarcinoma (approximately 30%–40% of all lung cancer cases) is more frequent in women. Adenocarcinoma is more frequent in non-smokers than in smokers. Patients are staged according to the International System for Staging Lung Cancer. Over the last few decades, the

proportion of squamous-cell carcinomas, which used to be the predominant type, has decreased while adenocarcinomas have increased [9].

VALIDITY OF LUNG CANCER DIAGNOSIS

Most lung cancer cases in Denmark are diagnosed pathologically based on cytology or histology. Standardized methods are used for both preparing and reading specimens [10, 11]. Niels Christian Hansen (NCH), senior consultant at Department of Pulmonary Medicine, Odense University Hospital, Denmark has reviewed all cases of lung cancer diagnosed at the Department of Pulmonary Medicine, Odense University Hospital between 2007 and 2010. A total of 856 lung cancer cases were diagnosed. Of these 40 (4.7%) were based only on a clinical diagnosis. Thus, 95.3% had a pathological diagnosis. Data for all lung cancer cases in Denmark were not available.

2.2 ASBESTOS

DEFINITION OF FIBER TYPES AND EXPOSURE CATEGORIES

Asbestos is a generic term that represents six naturally occurring fibrous minerals that can be generally grouped based on chemical composition differences into two distinct classes: serpentine and amphibole. The serpentine class includes chrysotile (white), while the amphibole class includes amosite (brown), crocidolite (blue), tremolite, actinolite, and anthophyllite asbestos [1]. The two main classes differ significantly in terms of their physical and chemical properties, which result in a much greater degree of biopersistence of amphibole fibers. Chrysotile fibers form large parallel sheets, but are curly and pliable due to the misfit between the two layers [12]. In contrast to chrysotile, amphiboles are arranged in long, linearly-organized chains, forming straight, inflexible, rod-like and relatively acid-resistant fibers that have more tensile strength than chrysotile [13]. Chrysotile fibers are cleared more readily by mucociliary action and more easily broken down [14]. Amphibole fibers are far more resistant with a much longer residence time [15-17]. The biological half-life of inhaled amphibole fibers is in the range of years to decades, whereas the half-life of chrysotile fibers is only days to weeks [13, 18, 19].

Assessment of asbestos exposure can be grouped into two categories: occupational exposure (worker and by-stander) and non-occupational/environmental exposure. Occupational exposure occurs in the workplace where asbestos-containing products were manufactured or used. There is also potential for by-stander exposure in the occupation setting [20]. Non-occupational exposure may involve non-occupational asbestos containing product use and secondary exposure from occupationally exposed worked, "take-home" exposure [21]. Environmental exposure may result from either a naturally occurring point source or contamination of the water or air supplies from anthropologic means.

MEASURING METHODS IN A HISTORICAL PERSPECTIVE

A reliable means to collect and quantify airborne levels of asbestos is required to accurately evaluate lung cancer risk in relation to occupational asbestos exposure. Unfortunately, there are many uncertainties pertaining to historical airborne fiber concentration data. Methods to collect as well as analyze airborne fiber samples have changed dramatically over the past 80 years. Prior to the impinger, early methods of dust collection included the sugar tube, the Palmer apparatus, the konimeter, the filter paper thimble, and the dust determinator. However, the results from these methods were not regarded as absolute. The impinger and later the midget impinger were devised to reconcile the comparability issues starting in the 1930s [22]. The concentrations of particulates were first assigned units of million particles per cubic foot (mppcf; 0.1 mg/m^3 is estimated around 1 mppcf). The usefulness of the impinger method is limited by short sampling periods, difficulty in differentiating asbestos from non-asbestos fibers and poor efficiency [23, 24].

The membrane filter method from the late-1950s allowed for full-shift sampling and could be used with PCM and TEM [25, 26]. PCM does not discriminate between asbestos and other fibers. The concentrations of fibers were assigned units of fibers per milliliter (f/ml=f/cc) and defined being greater than 5 μm in length, smaller than 0.25 μm in diameter, and having greater than a 3 to 1 aspect ratio [27]. Unlike PCM, TEM can differentiate between asbestos mineral fiber types and distinguish asbestos fibers from non-asbestos fibers [28, 29]. The reference TEM method specifies asbestos structures (fibers, bundles, clusters, and matrices), all sizes, widths, and aspect ratios [29]. Although TEM has much greater sensitivity than PCM and scanning electron microscopy (SEM), TEM data cannot be compared to historical airborne fiber concentrations collected by PCM.

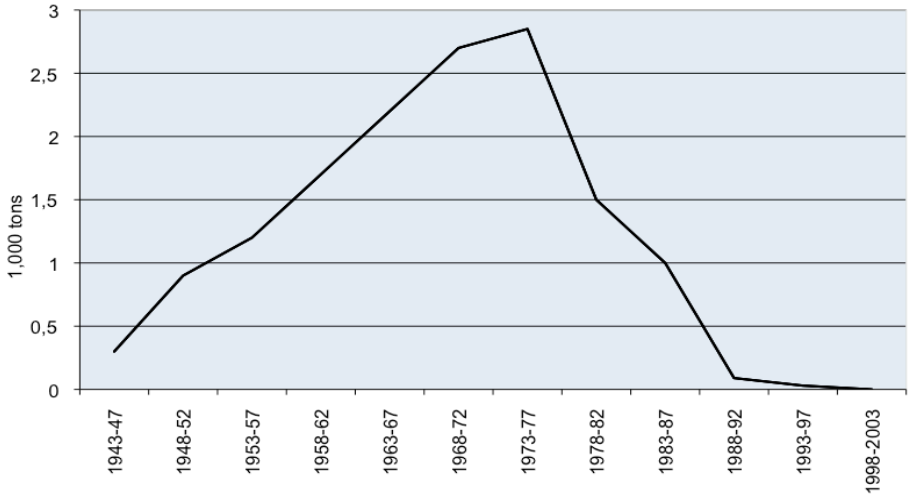
UNCERTAINTIES IN ASBESTOS AIR MEASUREMENTS

Many historical studies collected exposure data using the impinger (and midget impinger) method. Therefore, it is necessary to convert this data, which is reported as mppcf (or mg/m^3) to f/ml in order to be used in a contemporaneous exposure assessment. Unfortunately, there are no standard methods to convert mppcf to f/ml. One mppcf using the impinger method was roughly equivalent to 6 f/mL when counting fibers >5µm in length using the membrane filter method [23]. Historical measurements can only be converted using this conversion if the sample was collected using the impinger method. The use of other collection methods would add further uncertainty to this estimated conversion.

HISTORICAL TREND IN ASBESTOS USE IN DENMARK

Denmark has no asbestos mines. Thus all asbestos has been imported. The first partial ban was introduced in 1980. Asbestos cement products were however not included. Six years later a complete ban on amosite and crocidolite asbestos, including asbestos cement products was enacted. Only asbestos gaskets for special purposes were allowed. Finally, in 2004 chrysotile was included. Figure 1 shows the annual imported asbestos to Denmark from 1943 to 2003.

Figure 1 Annual imported asbestos to Denmark, 1943-2003 [30].



INDUSTRIES AND JOBS WITH POTENTIAL ASBESTOS EXPOSURE

The most important sources of asbestos exposure are described in the table below.

Table 1. Industries with potential asbestos exposure [31].

OCCUPATION	TASKS WITH POSSITBLE ASBESTOS EXPOSURE
Asbestos abatement	Specialized asbestos abatement jobs
Automotive component manufacture	Automotive component manufacturing jobs, automotive assemblers and related jobs
Cement factory workers	Cement and cement products manufacturing workers
Furnace industries	Jobs closely associated with furnaces and related fixed plant, including foundry, smelter, glassworks, brickworks, ceramic manufacture and power generation jobs with likely furnace related tasks
Insulators	Specialist insulation jobs, including insulators and buildings, ships, trains, boilers, etc.
Land transport	Drivers, mechanics & other vehicle repairers of land vehicles, military or civilian, passenger or freight
Textile worker	Textile and floor covering manufacturing jobs
Tip worker	Tip/landfill or waste transfer jobs, including waste truck drivers and tip site workers
Trades	All trades not elsewhere classified, including metal, building, electrical, plumbing & mechanical trades and related workers, such as trades assistants, general maintenance workers, etc.
Water transport	Shipbuilders, ship repairers, seamen and waterside workers - military or civilian
Others	Laundry workers/drycleaners, bakers, industrial/factory cleaners, miscellaneous labourers and manufacturing workers

239 cases of ARLC were recognized by the National Board of Industrial Injuries in Denmark between 2207 and 2010. The main occupations are describes in the table below. Classifications of occupations for the 239 cases according to the Danish version of the International Standard Classification of Occupations (DISCO) are shown in appendix 1.

Table 2. Main occupational groups with recognized ARLC in Denmark 2007-2010 [32].

OCCUPATION (DISCO-08)	RECOGNIZED NUMBER OF ARLC (%)
Clerks and service workers (1-5)	7 (3)
Crafts and related trades workers (7-)	162 (68)
Plant and machine operators (8-)	44 (18)
Elementary occupations (9-)	26 (11)
Total	**239 (100)**

DANISH OCCUPATIONAL ASBESTOS MEASUREMENTS

In appendix 2 occupational asbestos measurements are presented. There are measurements from 4 Danish sources. In addition, the data is supplemented with measurements from a Swedish asbestos cement industry as well as with data from a Danish review article that presents a summary of international asbestos measurements.

Unfortunately information about measurement methods and how they counted and analyzed the data is not available. For example is it unknown how an asbestos fiber is defined, if TEM or scanning has been used, and for most studies if it is person-borne or area measurements. This un-standardized method for asbestos measurements made comparison between data from different studies problematic.

REPORTED AND COMPENSATED ARLC IN DENMARK

The below table (men only) shows the number of reported and compensated ARLC cases in Denmark between 2004 and 2010. The criteria for these cases are defined in Guidance on Occupational Diseases [33]. The total number of lung cancer cases from the entire country obtained from the Danish Cancer Registry is also included in the table.

Table 3. Reported, compensated and total lung cancer incidence cases among Danish men 2004-10 (Data from The National Board of Industrial Injuries in Denmark [34]).

	Reported ARLC	Total male lung cancer in DK	% of all male lung cancer	Compensated ARLC (male)	% of all male lung cancer
2004	54	2,134	2.5%	30	1.4%
2005	58	2,153	2.7%	37	1.7%
2006	68	2,172	3.1%	30	1.4%
2007	101	2,269	4.5%	40	1.8%
2008	101	2,224	4.5%	40	1.8%
2009	63	2,252	2.8%	26	1.2%
2010	79	2,262	3.5%	29	1.3%
Total	524	1,5466	3.4%	232	1.5%

2.3 HISTORICAL REVIEW OF RISK ASSESSMENTS OF ARLC

The U.S. Environmental Protection Agency (EPA) and the Occupational Safety and Health Administration (OSHA) have developed and evaluated several risk models. The basic approach was developed in the early 1980s. Briefly, data on asbestos exposure and cancer outcomes was drawn from fifteen epidemiologic studies (11 lung cancer and 4 mesothelioma). It should be noted that each of these studies individually have issues, such as data gaps and classification problems. A exposure-response relationship, called the potency factor (K), was then developed for each individual study. Potency factors were generated for both lung cancer (K_L) and mesothelioma (K_M). Finally, a new exposure-response model was constructed based on the composite potency factors for lung cancer and mesothelioma. The 1983 Nicholson exposure-response model is based on the following assumptions:

- Chrysotile and amphiboles have equal potency.
- All fibers longer that 5 μm have equal potencies.
- There is no threshold exposure level for carcinogenicity.
- There is a multiplicative interaction between smoking and asbestos for lung cancer.
- Relative risks for lung cancer are linearly associated with cumulative exposure based on 10-year lag time.

Both OSHA and the EPA have used this model for more than 25 years. In 1993, the EPA further developed the Nicholson model and formed their current asbestos policy: Carcinogenicity over Life-time Exposure [35]. The EPA repeated their previous caution that quantitative estimates are limited by uncertain exposure estimates, lack of early exposure data and uncertain conversion between various analytic measurements. In the mid-1990s the EPA attempted to develop a more comprehensive and updated risk model [36]. The Berman & Crump model added 6 modifications to Nicholson's original model.

- Twenty lung cancer and 14 mesothelioma studies were included
- Chrysotile and amphibole potency factors were estimated separately
- New fiber dimension categories were used
- Correction factors were applied to historic fiber counts based on selected TEM
- A new parameter was added to the lung cancer model in an attempt to account for differences between background lung mortality rates and rates in studied populations
- Statistical models to calculate uncertainty ranges in exposure data were added

The 1987 IARC report [37] and Hodgson and Darnton´s article from 2000 [38] also had considerable influence on the risk assessment debate. The final EPA report [36] acknowledged key data flaws: unrepresentative sampling strategies, use of surrogate estimates in the absence of actual asbestos measurements, lack of data from earlier time periods and use of area samples instead of personal breathing zone measurements. However, this final report was never adopted by the EPA.

In 2003, the EPA initiated a renewed attempt to further develop the asbestos risk model. The new proposed OSWER risk assessment model (Office of Solid Waste and Emergency Response), based on 23 lung cancer and 8 mesothelioma studies, was completed in 2008 [39]. A new Bayesian Markov Chain Monte Carlo statistical method was adapted to better fit risk models with epidemiological data. The model estimated cancer potency for 20 "bins"; each bin is composed of different combinations of asbestos fiber types and dimensions. It was reviewed by the EPA's Scientific Advisory Board (SAB), which found that the scientific basis for the model was weak and inadequate primarily due to the lack of available TEM data to estimate exposure levels. The EPA agreed that exposure data was inadequate and the proposed model was not pursued further.

Many countries including Denmark base their compensation policies on the 1997 Helsinki criteria (see appendix 3).

3. METHODS

This review was performed by following a standard methodology introduced by Wright and colleagues [40]: formulating primary research questions, devising of a research protocol, literature search, data extraction, quality appraisal, data analysis with a simple descriptive evaluation of each study and finally interpretation of results. The formulation of research questions was obtained directly from the grant announcement and resulted in 19 search questions divided into 4 main groups: lung cancer (LC), asbestos exposure (AE), exposure-response (ER) and competing and predisposing conditions (CPC) with 4, 5, 5 and 5 questions, respectively (see table 4).

Table 4. Search questions obtained directly from the grant announcement.

LUNG CANCER

1) How valid is the diagnosis of lung cancer? (LC1)
2) How has the distribution of lung cancer cell types changed over time? (LC2)
3) Does the distribution of cell type of asbestos-related lung cancer differ from that of other lung cancers? (LC3)
4) Does the location of asbestos-related lung cancer differ from that of other lung cancers? (LC4)

ASBESTOS EXPOSURE

1) Which jobs and industries can be associated with asbestos exposure? (AE1)
2) Can the presence of bilateral pleural plaques be used to estimate previous asbestos exposure? (AE2)
    a. Can the presence of diffuse pleural thickening be used to estimate previous asbestos exposure? (AE2a)
3) Can the presence of asbestos bodies be used to estimate previous asbestos exposure? (AE3)
4) How can the degree of exposure (intensity) be evaluated? (AE4)
5) How can the length of exposure be evaluated? (AE5)

DOSE-RESPONSE

1) What is the dose-response and dose-effect response between asbestos and lung cancer? (DR1)
2) Has a no effect level for asbestos and lung cancer been described in humans or laboratory animals? (DR2)
3) What is the latency between asbestos exposure and the development of lung cancer? (DR3)
    a. How does lung cancer risk develop after the cessation of asbestos exposure? (DR3a)
4) What is the prognosis for asbestos-related lung cancer? (DR4)
5) How does the degree of asbestos exposure effect prognosis? (DR5)

COMPETING AND PREDISPOSING CONDITIONS

1) Which other diseases or conditions can influence the development of asbestos-related lung cancer? (CPC1)
    a. What is the risk of developing lung cancer among those with asbestosis? (CPC1a)
2) What are the non-occupationally related causes of lung cancer? (CPC2)
3) Is non-occupational asbestos exposure related to lung cancer? (CPC3)
4) How do other non-occupationally related factors influence the development of lung cancer (e.g. sex, age, genetics)? (CPC4)
5) How can the effect of occupation-related asbestos exposure compared to non-occupational factors be measured? (CPC5)

On the basis of these search questions, relevant key statements for each main area were composed (appendix 4). These statements were carefully thought out as to be particularly useful when evaluating compensation cases.

3.1 SEARCH STRATEGY

To obtain all relevant original epidemiological articles the search strategy consisted of a series of top-down (broad) and bottom-up (specific) librarian-assisted searches. The top-down literature search included all citations in the fields of asbestos and lung cancer. The resulting large numbers of references were subdivided into smaller segments correlating to the search questions. In the 19 bottom-up literature searches the 19 search questions served as the base to supplement the broader top-down search.

The top-down searches were performed on July 2-3, 2012 in the electronic bibliographic databases PubMed Medline and EMBASE with the search terms asbestos and lung cancer. The combination of the two databases was chosen to achieve the best coverage of both U.S. and European Journals. Afterwards, the hits from the two databases were merged and duplicates removed.

The bottom-up search to identify additional relevant studies consisted of 19 specific searches for each of the predefined search questions. This procedure was performed between July 23 and 27, 2012 and was restricted to PubMed Medline. An overview of search details is given in appendix 5. Before the pools of hits from the top-down and bottom-up searches were merged a comprehensive citation selection was performed.

3.2 SELECTION OF PUBLICATIONS USED IN THE ANALYSIS

The selection of publications to be included in the analysis was a multistep, iterative process. A flow diagram of the process is given in appendix 6. Studies were included when the main focus was on associations between lung cancer and asbestos exposure. The exclusion criteria were: 1: case reports, case series or expert opinions, 2: very old publications and/or small study populations, 3: high risk of bias and 4: older studies that were followed-up with a more recent updated publication.

Step 1 - 1st screening

The initial top-down literature search in PubMed Medline and EMBASE database searches yielded 4,088 discrete publications. The citations were rapidly screened for inclusion eligibility. If the title was out of the scope of the review one member of the writing group (DS) deemed the citation ineligible for further consideration (n=3,677). An example of an ineligible citation is: *A breath test for malignant mesothelioma using an electronic nose* [41]. In addition the remaining citations were grouped into four

groups: Lung cancer (LC) (n=88), asbestos exposure (AE) (n=119), exposure-response (ER) (n=155) and competing and predisposing conditions (CPC) (n=93) with the possibility for a citation to appear in more than one group. Even articles not primarily in English were considered eligible and grouped if they included an English language abstract (n=4). This was done to reduce the risk of English language bias because positive findings are more likely to be published in English [42].

Step 1 - 2nd screening

After the first screening and grouping the 455 citations in the four groups (LC, AE, ER and CPC) were further screened for inclusion eligibility based on their abstracts. This was done by the same member of the writing group (DS). Afterwards the remaining citations were sub-grouped according to which of the 19 search questions they were related to (see table 4, page 25). Citations from the LC group were subdivided into 4 LC subgroups (LC_1, LC_2, LC_3 and LC_4). Citations from the AE, ER and CPC group were sub-grouped in the same way resulting in the subgroups $AE_{1\text{-}5}$, $ER_{1\text{-}5}$ and $CPC_{1\text{-}5}$. Also, the subgroups were marked with a B, which refers to Broad search (top-down search) (see appendix 6). The screening resulted in 166 citations across the 19 groups. Again, it was possible for a citation to appear in more than one group.

Step 2 – 3rd screening

The next step consisted of the PubMed Medline specific bottom-up searches based on the 19 search questions. The citations were grouped according to their associated search question, which resulted in 19 groups: $LC_{1\text{-}4}$, $AE_{1\text{-}5}$, $ER_{1\text{-}5}$ and $CPC_{1\text{-}5}$. The subgroups were marked with an S, which refers to specific search (bottom-ups search). DS screened the hits in each group for inclusion eligibility based on title and abstract.

Step 3 – Merging of hits

The hits in the 19 groups from the top-down search were merged with the hits in the corresponding 19 groups from the bottom-up searches and doublets removed: LC_{1B} was merged with LC_{1S} and called $LC1_{B+S}$, LC_{2B} was merged with LC_{2S} and called LC_{2B+S} etc.

Step 4 – 4th screening

In order to exclude papers that lacked sufficient data or analytic structure to warrant in-depth review DS made a fourth screening of the articles in the 19 groups based on exclusion criteria. The numbers of articles in each group after this procedure are shown in appendix 6 under 4th screening.

The pool of citations from the electronic searches was supplemented with additional relevant citations achieved by manual review of the bibliographies. In addition, bibliographies of review articles and meta-analyses were searched as well as inputs from the writing group given (n=123). Finally, a few recent citations were identified through PubMed alerts that appeared after July 3, 2012, which was cut-off for the broad electronic key word electronic search. The added number of citations for each subgroup is shown in brackets in the rightmost column in appendix 6.

3.3 DATA EXTRACTION OF PUBLICATIONS DEEMED ELIGIBLE

For the original studies a data extraction sheet based on the Scottish Intercollegiate Guidelines Network (SIGN) and adjusted to the present review was developed (appendix 7) [43]. In addition to the generic items containing study design, study population, exposure measurement, outcome measurement, potential study limitations and description of key findings, more specific data collection items on exposure and outcome measurement were added.

Initially it was planned to double review all included articles with the data extraction sheets. However, due to time limitations, the main focus was placed on the key questions concerning exposure-response as well as lung cancer histology and location. The 6 meta-analyses and 3 reviews related to the exposure-response questions were double evaluated with the R-AMSTAR checklist quality assessment sheet (appendix 8) [44].

3.4 QUALITY APPRAISAL

In August 2012 the members of the writing group (DS, JB, JR, SD, MA and LSN) were divided into review teams to systematically read, evaluate and quality grade the full papers concerning the exposure-response association. Each of the 28 original articles of cohort and case control studies, 6 meta-analyses and 3 reviews were read and graded by two members of the writing group. Afterwards, the quality appraisals were compared and discrepancies reconciled by mutual agreement. A member of the group (MA) was co-author of one of the included publications and was therefore disqualified as a reviewer of that publication. Five publications related to the two lung cancer questions LC3 and LC4 were subsequently evaluated with the same method (DS and KEO). Cohort and case-control studies were restricted to 2++ (very low risk of confounding, bias, chance), 2+ (low risk of confounding, bias,

chance) or 2- (high risk of confounding, bias, chance), with 2+ as the most common grade. For meta-analyses and reviews the R-AMSTAR score was a mean of the two independent scores.

3.5 STRUCTURE OF DATA PRESENTED

The result section is structured around the 4 main question groups: Lung cancer, asbestos exposure, exposure-response and competing and predisposing conditions. Data presentation is structured differently depending on whether data extraction sheets had been completed. For two lung cancer questions (LC3 and LC4) and the key exposure-response question (ER1) the meta-analyses and reviews as well as original studies achieving 2+ or better quality appraisal were included and presented as both narratives and tabular format. In addition, original studies with a 2- grade are also presented in table form as they also added useful information. The narrative descriptions in appendix include basic study design information and key findings. The table presentation includes more details of the study including strengths and limitations as well as the final quality grading. All included references concerning the questions where data extraction sheets were not filled out were carefully read and relevant and essential results were summarized in text form. A brief summary of key findings concludes each result section. Information in the summaries is particularly relevant to the related statements.

3.6 ASSESSMENT OF CAUSAL ASSOCIATION OR TO SUBSTANTIATE THE STATEMENT

To accommodate the varied nature of the statements, where not all concerned a causal association, e.g. statement 2, we adapted the evidence model recommended by the Danish Working Environmental Authority (appendix 9) for the current review. The categories (explanations) used were stated in more general terms, referring to the extent to which the statement is substantiated by evidence, of which causal association is only one particular case. Hence:

+++	Strong evidence (to substantiate the statement)
++	Moderate evidence (to substantiate the statement)
+	Limited evidence (to substantiate the statement)
0	Insufficient evidence (to substantiate the statement)
-	Evidence suggesting lack of knowledge to substantiate the statement

3.7 REVIEW AND REVISION OF THE FINAL REPORT

In November 2012, the first draft of the document was sent to an expert group (internal reviewers) for comments and corrections. In addition, a two-day seminar with 15 participants from the writing and internal expert groups was held to discuss major issues and reach a consensus regarding statement grading (see appendix 10 for the seminar program and list of participants). After revising the first draft, a second draft was provided to two external reviewers for their comments (appendix 22). The third and final draft was edited based on the external reviewers' comments.

4. RESULTS

4.1 ARLC: HISTOLOGY, LOCATION, PROGNOSIS AND SCREENING

SUMMARY

Studies published before 1980 were poorly controlled and showed inconsistent results concerning lobe of origin and histology of ARLC. More recent well-controlled studies have failed to show any significant differences between ARLC and non-ARLC regarding cell type or location. Our literature search did not find any references that specifically dealt with the prognosis of ARLC. The only available data was obtained from reviewing lung cancer cases at the Pulmonary Department, Odense University Hospital. No survival differences were seen in Kaplan-Meier curves when ARLC and non-ARLC cases were compared (see appendix 11, figure A2). 1-year survival was about 35% and 5-year survival was about 10%. The U.S. National Lung Screening Trial (NLST) has recently demonstrated a relative mortality reduction of 20%. On this background the National Comprehensive Cancer Network (NCCN) published recommendations in 2012 concerning low-dose CT screening for heavy smokers including those with previous asbestos exposure. Screening is costly and complicated by numerous false positives. Results from the ongoing European prospective screening trials are not yet available [20, 45-75]. These subjects are reviewed in appendix 11.

Statement 1

When evaluating ARLC, location and cell types do not differentiate asbestos and non-asbestos related lung cancer. (+++)

4.2 ASBESTOS EXPOSURE

EXPOSURE ASSESSMENT

Reliable and valid assessment of asbestos exposure is critical in risk estimations, since exposure misclassification might bias risk estimates. In general, three steps are involved in an exposure assessment: hazard identification, exposure-response analysis, and exposure quantification. The results of these steps are combined to produce an estimate of risk. Reliable retrospective asbestos exposure assessment continues to be a challenge in most population-based studies [76].

An asbestos exposure assessment should comprise a multidimensional approach. A careful exposure history from a face-to-face interview is the first and most important step. Questionnaire, expert assessments, job exposure matrices (JEMs) and measurement data from the workplace and the published literature can provide useful supplementary information [72, 73, 77]. For the purpose of conducting an exposure assessment, it is acceptable to rely on a combination of qualitative, semi-quantitative and quantitative exposure metrics.

Case-by-case expert assessment is generally considered the best possible method for assessing exposure in population-based studies. Expert assessment enables one to take into account exposure differences between individuals with similar jobs, which can result in less exposure misclassification. However, the estimate of an expert can also be of such poor quality that true exposure-effect relationships can be obscured or even reversed in direction [78]. In comparison to measured exposures, expert assessments are usually slightly better than self-reports, but then again there is great variability in reliability and validity estimates by agent and study [79].

Questionnaires are frequently used in the exposure assessment of occupational and environmental epidemiological studies. Questionnaires may allow a larger study size and greater statistical power than would be possible with more accurate measurement techniques. However, very few standardized exposure questionnaires have been validated and therefore the extent of exposure misclassification and the effect on risk estimates leaves uncertainty whether the questionnaire actually measures what it needs to measure [79].

Retrospective occupational exposure assessments remain a challenge in most population-based studies, because accurate exposure measurements are not available. The main advantage of using a

JEM is that occupations are translated into specific exposures in a standardized way giving a more reproducible methodology [76]. The job titles, collected from a questionnaire, can then be applied to a JEM where coded job titles can be converted to estimates of exposure levels for known/suspected occupational lung carcinogens including asbestos [80]. JEMs allocate the same exposure estimate to all workers within a job code, thereby disregarding possible inter-individual variability within job codes. This is a major drawback since there may be large differences in exposure levels between individuals with the same job in the same company. JEMs can be quite different in their assessment approach e.g. DOMJEM (asbestos, PAHs), FINJEM (asbestos, PAHs and welding fumes) and Asbestos JEM [81]. Therefore, care should be taken when choosing the appropriate JEM.

Uncertainties in exposure assessment may have strong implications for both the health risks of exposed workers and for the industries to achieve safe exposure levels [82]. Although, case-by-case expert assessment and JEMs are commonly used, reliability of questionnaires and of a JEM depends on study design, exposure of interest, and the quality of work history/exposure information available. Case-by-case expert assessment is generally considered the best possible method for assessing occupational exposures in population-based studies; however, it requires considerable resources [83-85]. JEMs have proven to be rather similar in agreement when compared with the expert assessment and could therefore be appropriate to use in asbestos exposure assessment. However, the reliability of exposure duration in JEMs has often been adequately addressed and may result in misclassification.

In summary, a sufficient occupational history combined with an appropriate JEM and published measurements can be considered to give the most reliable estimate of asbestos exposure.

Statement 2

Job Exposure Matrices (JEMs) are useful in estimating previous asbestos exposure in addition to individual exposure evaluation. (+)

BIOLOGICAL MARKERS: PLEURAL PLAQUES (PP), ASBESTOS BODIES (AB) AND ASBESTOS FIBERS (AF)

SUMMARY

Numerous studies have verified that PPs are associated with previous asbestos exposure. They usually develop after about 20 years, but may occur as early as 10 years after exposure. PPs are particularly useful as a marker of asbestos exposure when they are bilateral and other causes have been eliminated. They are best identified with CT scans. PPs do not reflect the degree of exposure. AF and AB counts in BAL and lung tissue are associated with asbestos exposure. In Denmark there is neither tradition nor routine in identifying and counting ABs and AFs. Identifying ABs and AFs in BAL or lung tissue reflects some degree of asbestos exposure. However, the absence of PPs, ABs or AFs does not preclude considerable previous asbestos exposure [86-111]. This area is reviewed in appendix 12.

Statement 3

The existence of pleural plaques increases the likelihood of previously asbestos exposure. (++)

Statement 4

The presence of pleura plaques cannot be used to estimate degree of previous asbestos exposure (+++)

Statement 5

The presence of asbestosis reflects previously high asbestos exposure and is associated with an increased risk of lung cancer. (+++)

4.3 EXPOSURE-RESPONSE

INTRODUCTION

Estimation of exposure–response has been dealt with in numerous studies, which have been analyzed in reviews and meta-analyses. In the individual studies the validity of the measured exposure-response relation relies on the following parts:

Quality criteria for individual exposure:

Coverage with measurements, quality of measurements, conversion factors between different methods.

The exposure implies an at least semi-quantitative, but preferably quantitative estimation of the individual lifetime asbestos exposure expressed as the average air concentration in fibers per ml times the number of years exposed (f-y/ml). In most studies exposure has been collected in categories where all persons have been assigned the mean or median group exposure. At least two groups are needed, but preferably more. Categorical analysis may be sensitive to the choice of cut-off points and the underlying distribution of exposures within each category.

Quality criteria for response measures:

Length and completeness of follow-up of cases and survivors, diagnosis quality. Comparison with a relevant reference population without exposure.

The response in a group has been estimated as a relative risk (RR) in relation to the unexposed controls. Most cohort studies have used Standard Mortality Ratio (SMR), which calculates an expected number of deaths in the exposed group having the same age- and sex-specific mortality /morbidity as the reference population. SMR is then obtained from the number of observed cases divided by the number of expected cases. The age distribution of the cohorts has a considerable influence on SMR as well as the mortality of the background population.

Quality criteria for the analysis:

A sufficient span of varied levels in exposure and number of observations in each group. Information about competing factors for lung cancer among the studied population, mainly smoking habits and other occupational exposure to carcinogens.

Analysis of exposure-response relationship implies a hypothesis in the form of the curve. A linear relation has been the primary model where the RR increases steadily with the exposure (in f-y/ml) and RR. In a formula this can be shown as:

$$RR_{exp\ i} = 1 + k_L * exp_i$$

This model suggests that RR is 1 when exposure is 0, and k_L denotes the increase in RR per unit of exposure measure, i.e. the potency of carcinogenicity.

However, as the investigated population is not always compatible with the reference population a constant link is inserted

$$RR_{exp\ i} = a_i\ (1 + k_L * exp_i)$$

where a_i is the RR of population *i* with no exposure. In the case of lung cancer, $a_i > 1$ is often assumed to be due to more smoking in the exposed population than in the reference population. However, it may also be due to misclassification of exposure (e.g. subjects with high exposure being misclassified as having low exposure). a_i and k_L are not independent as less steep k_L due to misclassification may increase a_i.

Various ways of expressing k_L have been shown in different articles. In the present paper all these have been expressed as the number x 10^{-3} $(\text{f-y/ml})^{-1}$ (i.e. n excess cases in 1,000 persons for each increase in f-y /ml).

A deviation from linearity has also been tested. This can be lower than expected at low exposures suggesting a threshold for the carcinogenicity, or lower than expected at high exposures, suggesting competing causes of death (e.g. a high proportion of workers dying from asbestosis since this occurs earlier than lung cancer at high exposure intensities), or misclassification of exposure. More recently methods to analyze exposure-response, which do not assume linearity have been introduced (fractional

polynomial and spline regression), but they have only been used in a few studies included in this review, e.g. [112-114].

Since solid cancers, like lung cancer, usually develop over more than a decade from initiation until clinical diagnosis (latency time). Cancers occurring during the first 10-15 years after onset of exposure have often been excluded in cohort analyses. Conversely, the exposure accumulated during the last 10-15 years before end of follow-up is sometimes excluded from the total exposure metric (10-15 year lag).

The influence of life style factors, mainly smoking, has been included to a various degree. Few studies have individual information, while others make assumptions of trade- and job-related smoking frequencies in the different time periods. These factors and the fact that exposure has taken place over several decades adds to the large heterogeneity of the exposure-response estimate.

ORIGINAL STUDIES

There are 28 original studies of which 24 are cohort studies and 4 are case control studies [112-139]. A tabular presentation of the studies inclusive their distinctive features, strengths, limitations and a grading are given below. In addition, narratives of the studies are presented in appendix 13.

Table 5. Tabular presentation of cohort studies.

First author, year of publication, reference no	Characteristics of participants	Measurement methods and potential confounders			Results	Grading
	N, sex, country, type of industry/job	Exposure *Asbestos type, unit*	Outcome	Confounders taken into account and other factors		
Albin, 1990 [115] (Nested case-control study for mesothelioma)	1,465 males Cement workers Sweden	Cumulative exposure Chrysotile (>95%) + smaller amounts of crocidolite and amosite f/ml	Death of lung cancer Death certificates + Cancer Register	Age, sex, calendar year	No significant increased risk for lung cancer among asbestos exposed. Increased risk only for combined mesothelioma and lung cancer. Lung cancer RR incidence (F-y/ml): <15 = 1.8 (CI 0.8-3.9), 15-39 = 1.9 (CI 0.7-5.3), >40 = 1.9 (CI 0.5-7.1)	2+
Clin, 2011 [116]	2,004 France Production of textile and friction materials	Cumulative exposure Chrysotile (80%) + crocidolite (20%) f/ml	Lung cancer Cancer Register	Age, sex, 10 years lag-time	No significant dose-response association between the number of years during which subjects were exposed (cumulative exposure) and lung cancer. However, the adjusted relative risk for lung cancer corresponding to the last exposure tertile (≥9 to <107 fibers/ml, ref: <3 fibers/ml) was 3.99 (95% CI 1.15 to 13.86). Other Very good exposure documentation. Increased relative risk for mixed exposure vs. chrysotile exposure only.	2+
Dement, 1982 [118]	768 white males USA Textile production	Cumulative exposure Chrysotile f/ml Conversion: 3 fibers cm^{-3} for 1 mppcf (Preparation: 8 fibers cm^{-3})	Death of lung cancer Death certificates	Sex, age, race, calendar time. Minimum latency of 15 years since initial employment.	A linear dose-response relationship for lung cancer with no threshold. SMR of 223 for <10,000 fibers cm^{-3} days, 357 for 10,000-40,000 fibers cm^{-3} days, 978 for 40,000-100,000 fibers cm^{-3} days, 1553 for 100,000-200,000 fibers cm^{-3} days. Steep dose-response as estimated from regression line based on categorical analysis gave RR of approximately 5 for 100 f-y/ml. Estimation of smoking prevalence among the workers was compared to smoking patterns among USA males.	2+

First author, year of publication, reference no	Characteristics of participants	Measurement methods and potential confounders			Results	Grading
	N, sex, country, type of industry/job	Exposure *Asbestos type, unit*	Outcome	Confounders taken into account and other factors		
Dement, 1994 [117]	3,022 white males + females and black males USA Textile production	Cumulative exposure Chrysotile and a little crocidolite f/ml	Death of lung cancer Death certificates	Concurrent exposure to mineral oils was examined in a nested case-control study, and was not a confounder.	White males and females experienced statistically significant excess mortality due to lung cancer, SMR = 2.30 (1.88-2.79) and 2.75 (2.06-3.61), respectively. Increased risk for death due to lung cancer with increasing cumulative exposure. The trend was significant for white males ($Z=2.88;p<0.01$) but not for white females ($Z=1.71;p>0.05$). Data for the entire cohort demonstrated an increase in the lung cancer relative risk of 2-3% for each f/cc-year of cumulative chrysotile exposure. Estimated prevalence of smoking in the cohort was compared to prevalence among the USA population	2++
Deng, 2012 [119]	586 men China Textile, brakes, cement	Cumulative exposure Chrysotile (very high) Mppcf and f/ml (internal paired comparisons)	Death of lung cancer Death certificates	Smoking (two categories, no pack-y), age, calendar time	Strong significant association between exposure to chrysotile asbestos and lung cancer deaths ($p<0.001$) in which clear exposure-response relationships were observed. No threshold for asbestos causing lung cancer was identified. The power model fitted data best with 10 years lag time.	2+
Elliott, 2012 [112]	6,136 predominately white males USA Textile production North Caroline (NC) and South Carolina (SC)	Cumulative exposure Chrysotile and small amounts of crocidolite and amosite f/ml	Death of lung cancer Death certificates	Race, sex, age, calendar time, birth cohort. Individual smoking information was not available, and systematic differences seemed to be present related to ethnicity	Significantly higher lung cancer mortality than expected (SMR 1.90, 95% CI 1.70 to 2.11). However, a linear model did not give the best fit. The lung cancer slope was steeper for workers from SC than NC. Likely explanations were exclusion from work of workers with pneumoconiosis, workers with short exposure not being enumerated and less precise exposure information for NC workers. The slope for SC was judged to be less prone to such bias, and was 2% per f-y/ml as excess RR (linear model). <u>Other</u> Linear model did not give best fit. Other models and tailing off- reaching a plateau as opposed to linearity is discussed. A 10-year lag (0,5,20, 30 was also tried), gave a slightly better fit than other lags.	2++

First author, year of publication, reference no	Characteristics of participants	Measurement methods and potential confounders			Results	Grading
	N, sex, country, type of industry/job	Exposure *Asbestos type, unit*	Outcome	Confounders taken into account and other factors		
Enterline, 1987 [120]	1,074 white men USA Asbestos company manufacturing insulation, roof materials and engineered products	Cumulative exposure Chrysotile, amosite and crocidolite mppcf	Death of lung cancer Death certificates	Age, sex	Statistically significant dose-response relationship for lung cancer death that had become increasingly linear. SMR = 182, 203, 322, 405 and 699 for dust exposure <125, 125-249, 250-499, 500-749, and ≥750 mppcf-y respectively.	2-
Hein, 2007 [121]	3,072 mainly white men and women USA, South Carolina Textile industry (Same study population as in Dement et al., 1982, 1994)	Cumulative exposure Chrysotile f/ml	Lung cancer death Death certificate	Sex, race, age, calendar year. Smoking was not included. However, the main results are from internal analyses which is likely to reduce such a bias, although smoking may still be associated with intensity of exposure.	Dose-response associations were observed with steeper slope for 10-year lag time than for no lag time or 5-year lag time. The increase in relative risk of lung cancer after 10-year lag time was 0.0198 per f-y/ml (SE 0.000496). The lung cancer mortality was lower for females and non-whites. Other There was some evidence for a healthy worker effect. Lower mortality for females and non-whites in the model. These groups, also had much higher loss to follow-up (white males 1.2%, white females 16.7%, non-white males 6.9%, non-white females 19%), and non-retrieved death certificates (2.1, 4.0, 7.1, and 19.0%, respectively). Overall loss to follow-up and missing death certificates added up to 12.5%.	2+
Hughes, 1987 [122]	6,931 black and white males in two cement manufacturing plants USA	Cumulative and duration of exposure Chrysotile, amosite and crocidolite f/ml and mppcf 1.4 f/ml = 1 mppcf	Death of lung cancer Death certificates	Race, age at hire. Smoking habits were compared to smoking prevalence among the USA population.	Statistically significant excess of death due to lung cancer (115.5 expected, 155 observed, $p \leq 0.01$). The relation (RR = 1 + 0.0076 x, for x in f/ml-yrs) predicts a relative risk of 1.038 for workers exposed to 0-2f/ml for 25 work years, or about two lifetime lung cancers per 1000 workers based on United States male lung cancer rates. Those with exposure to a mixture of asbestos type showed a higher risk than those who had been exposed to chrysotile only.	2-

First author, year of publication, reference no	Characteristics of participants	Measurement methods and potential confounders			Results	Grading
	N, sex, country, type of industry/job	Exposure *Asbestos type, unit*	Outcome	Confounders taken into account and other factors		
Lacquet, 1980 [123]	29,366 man-years of observation Asbesos cement factory Belgium	Cumulative exposure Chrysotile (mainly) crocidolite and amosite f/ml	Lung cancer death Personnel records and interviews with family doctors and social workers	Sex, age	No significant (p=0.11) risk in respiratory cancers with increasing chrysotile, crocidolite and amosite asbestos exposure (no latency or lag employed; 1 mesothelioma included). Other External comparison of questionable validity due to difference in ascertainment of cause of death. Estimated exposure claimed to be "at best a good guess" by the authors (assumed to be roughly 10 times higher pre 1977 as compared to post 1977. Basic data (loss to follow-up, number in mortality analysis) not reported.	2-
Levin, 1998 [124]	1,121 males Texas, USA Pipe insulation	Amosite f/ml	Lung cancer death Death certificates	Sex, race	The study supported a significant excess of death from lung cancer due to amosite exposure, SMR=277 (CI 193-385). Other Fine exposure-response with exposure length. Very limited information about exposure and measuring methods.	2-
Liddell, 1997 [125]	10,918 males Quebec, Canada Mining and milling	Cumulative exposure Chrysotile mppcf	Lung cancer death Death certificates	Smoking information was available but not taken into account in the analysis of dose-response	A negligible excess lung cancer risk below 300 mppcf-years. However, SMRs are 1.3-1.5 for 30 mppcf-years and on (except for two categories which would have been merged to obtain similar distribution of cases, and would then have been consistent). Other Very old cohort. Relatively low RR of heavy smoking 2.55 vs. 0.55 (non-smokers). An internal non-categorical dose-response analysis taking smoking habits into account, is missing (although the data are available). No conversion factor for mppcf to f/ml.	2-

First author, year of publication, reference no	Characteristics of participants	Measurement methods and potential confounders			Results	Grading
	N, sex, country, type of industry/job	Exposure *Asbestos type, unit*	Outcome	Confounders taken into account and other factors		
Loomis, 2009 [126]	5,770 men and women USA Textile industry	Cumulative exposure Chrysotile mppcf and f/ml Own conversion factors from duplicate measurements.	Lung cancer death Death certificates	Age, sex, race, decade of follow up, birth cohort. Smoking data on < 15%.	Significantly higher mortality from lung cancer than expected with SMR of 1.96 (95% CI 1.73-2.20). Also, the risk of lung cancer increased with cumulative fiber exposure (RR 1.102 per 100 f-y/ml, 95% CI 1.044 to 1.164) which amounts to about 10% increase per 100 f-y/ml. A smoothed exposure-response curve with 10 year lag was the best fit. When referred to the Hodgson-Danton index, the risk increased with 1.38% per f-y/ml for all workers and 1.67% per f-y/ml for workers with > 20 year exposure.	2+
McDonald, 1983 [127]	4,137 males USA Textile industry, Pennsylvania	Cumulative exposure Chrysotile (mainly) and some amosite, less crocidolite mppcf	Death from respiratory neoplasms (lung cancer + mesothelioma) Death certificates	Sex, age	SMR for lung cancer reported as a percentage increased from 66.9 to 416 for exposures from 0 to >80 mppcf (SMR = 4.16). In a linear model the slope was: RR 1+0.051 mppcf-year. However, mesothelioma was included in the dose-response analysis (approximately 20% of total respiratory cancers). Other Since a minimal dose of crocidolite is sufficient given an adequate latency time, this may have arbitrarily flattened the dose-response association.. Discussion of smoking around 25 % non-smokers.	2-
McDonald, 1984 [128]	3,641 males USA Conneticut friction products and packing manufacturing facility	Cumulative exposure Chrysotile mppcf	Death from respiratory neoplasms (lung cancer + mesothelioma) Death certificates	Age, sex, race	Raised risk of lung cancer with SMR = 148.7. However, lack of any clear or systematic exposure-effect pattern. A reverse exposure-response was shown with duration of exposure and SMR was greatest for those working < 1 y. No dose-response association with cumulative exposures (mppcf-y).	2-

First author, year of publication, Reference no	Characteristics of participants	Measurement methods and potential confounders			Results	Grading
	N, sex, country, type of industry/job	Exposure *Asbestos type, unit*	Outcome	Confounders taken into account and other factors		
Peto, 1980 [129]	679 males United Kingdom Textile industry Exposed after 1993 and exposed at least 10 till 1972	Unknown asbestos type f/ml converted from mppcf and adjusted to modern counting rules	Lung cancer death Death certificates	Sex	RR from lung cancer death peaked at 25-35 years since first exposure (based on 28 cases). No formal dose-response analysis was undertaken but there was an overall excess of lung cancer death, and findings claimed to be compatible with a RR of 2-3 for 200-300 f-y/ml of exposure from area measurements. However, the limitation of these as compared to personal sampling is pointed out as a possible major source of exposure misclassification, and it is suggested that dose-response associations may mainly be driven by duration of exposure due to such misclassification. Other Dose response insufficiently described, mismatch between numbers in text and tables.	2-
Peto, 1985 [130]	3,211 males (non-asian) United Kingdom Rochdale textile factory	Cumulative exposure Chrysotile (95%) and crocidolite (5%) Particles/ml and f/ml	Lung cancer death Death certificates	Sex, age	The dose-response was SMR 1,53 *10^(-4) per particle-y/ml, approximated for SMR 0.005 per f-y/ml (entire cohort) and SMR 0.015 (those employed 1951 or later), respectively. Suggested prediction: SMR = 1+0.01xf-y/ml. RR for lung cancer was lower 35 years or more after first exposure as compared to 20-34 years. Risk was independent of age at first exposure. A five year lag (exposure last five years was ignored) was employed, and only cases occurring 20 years or more from first exposure were included. Other Particles/ml and f/ml, conversion factors estimated by internal standard. Conversion factor 35. Individual smoking habits were not available, but a survey in the study population indicated some more smokers than in the general population, expected to account for an overall excess mortality in lung cancer of 5%, but some more in short term (<12 months) workers.	2+
Pira, 2009 [131]	1,056 miners Italy	Chrysotile f/ml	Mortality from lung cancer Death certificates	Sex, age	No significant increased risk for lung cancer death in spite of high exposures over 400 f-y/ml, SMR 1.27 (CI 0.93-1.70). No dose-response association was shown for lung cancer. Other Low power.	2-

First author, year of publication, Reference no	Characteristics of participants	Measurement methods and potential confounders			Results	Grading
	N, sex, country, type of industry/job	Exposure *Asbestos type, unit*	Outcome	Confounders taken into account and other factors		
Seidman, 1986 [132]	820 white males New Jersey, USA Insulation of pipes, boilers and turbines of ships	Cumulative exposure Amosite and very little chrysotile f/cc	Lung cancer mortality. Death certificates + best evidence from additional information from autopsy, surgical specimens, x-ray films and clinical findings	Age, sex, race, calendar year	A linear zero threshold dose-response association seemed implausible. The SMR was 541 for lung cancer from 5 to 40 years after onset of work. The heavier the dose, the greater the response tended to be in terms of higher SMRs. Marked excesses were evident within 15 years for the longer-tern workers. For those worked shorter periods of time it took 25 years or more.	2-
Selikoff, 1991 [133]	17,800 males USA and Canada Insulation workers	Amphiboles	Death certificates and best evidence from pathology	Sex, race, age. Only deaths in cohort revised	Large RRs of lung cancer was found. The relative risk increased from 2.32 at <15 years from start of exposure up to the maximum at 4.90 after 30-40 years since onset. Other Latency time (death certificate and best evidence, respectively) is carefully analyzed. Smoking was not included, base-line estimate may be confounded but unlikely to bias trends with latency time.	2+
Sluis-Cremer, 1991 [134]	7,317 white men South Africa Amphibole miners	Cumulative exposure Crocidolite f/ml	Lung cancer death Death certificates	Sex, race, age, smoking, occupational data (incl. exposures in non-asbestos mines)	Good dose-response for both year of exposure and cumulative exposure. A tendency for SMR values to increase with increasing exposure time, starting 1-4 years of asbestos exposure. Increased SMR of 223.5 ($p<0.05$) for 10-19 years residence time with 1-4 f-y/ml exposure. SMR for bronchogenic carcinoma according to cumulative dust exposure was 143.9 for the 1-5 f-y/ml group. The relative risk of lung cancer was 1.01 (1-1.01) for each increment of 1 f-y/ml and 1.12 (1.04-1.20) for each year of exposure. Other Methods poorly described - better description in Sluis-Cremer et al., 1992.	2+
Sluis-Cremer, 1992 [135]	7,317 white males South Africa Mines and millers	Cumulative exposure Gross + net service Residence time Amosite, crocidolite f/ml	Lung cancer death Death certificates and best evidence from clinical, radiological, biopsy and necropsy reports.	Sex, race, smoking, silica, radon	There were 26.4 more deaths from lung cancer than expected, given a SMR of 1.72 (1.32-2.21). Crocidolite had higher toxicity than amosite for lung cancer. The SMRs were 1.38 (CI 0.97-1,91) and 2.03 (CI 1.43-2.80) for amosite and crocidolite respectively.	2+

First author, year of publication, reference no	Characteristics of participants	Measurement methods and potential confounders			Results	Grading
	N, sex, country, type of industry/job	Exposure *Asbestos type, unit*	Outcome	Confounders taken into account and other factors		
Stayner, 1997 [136]	3,041 women and men predominately whites USA Textile industry	Cumulative exposure Chrysotile f/ml	Death certificates	Age, race, sex, calendar year. No smoking information	Detailed dose-response analysis using different models of life time risks were tested. A multiplicative model fitted the data better than a linear (additive) model. Moreover, there was no evidence for a threshold. The slope was estimated to 0.021 per fiber/ml-year (95% CI 0.08-0.036). <u>Other</u> No evidence for interaction (sex, age, race, year). Smoking was not taken into account. Since it was an internal analysis this is only a confounder if smoking was associated with cumulative exposure. The effect of smoking is probably small to moderate.	2++
Sullivan, 2007 [137]	1,672 white men USA Vermiculite mine and mill, and process workers	Cumulative exposure Amphibole f/cm^3	Lung cancer death Death certificates	Age, sex, race, calendar time.	Clear dose-related increases in lung cancer mortality. Increased lung cancer SMR of 1.7 (CI 1.4-2.1) with 15 years lag time and a borderline significant SMR for low exposures (<4.5 f-y/ml) of 1.5 (CI 0.9-2.3). Short term employment (< 1 year) also increased SMR to 1.6 (CI 1.1-2.1). <u>Other</u> Vermiculite includes substantial and varied forms of amphibole. Thus hard to compare with Danish exposures.	2++

Table 6. Tabular presentation of case-control studies.

First author, year of publication, reference no.	Characteristics of cases	Characteristics of controls	Meaurement methods and potential confounders			Results	Grading
			Exposure *Asbestos type, unit*	Outcome	Confounders and other factors		
Berry, 1983 [138]	106 men, working with production of friction materials, dead of lung cancer United Kingdom	318 workers from the same factory matched for startec in the factory, date of birth, survival up to time of death from lung cancer	Cumulative + total duration of exposure Chrysotile and crocidolite f/ml	Death of lung cancer Death certificates	None	No indication of an increased risk of lung cancer with either duration of exposure or cumulative exposure in the categorical analysis. A fitted coefficient for a linear relationship was estimated to 0.00058 per f-y/ml.	2-
Gustavsson, 2000 [139]	1,038 cases: all lung cancer male cases 1985-1990, Stockholm, age 40-75 years. Type of industry defined from questionnaire and interviews	2,364 referents. Random selection from the general population fequency-matched with regard to age and year of inclusion	Cumulative exposure Mixed exposure f/ml	Lung cancer Cancer Register	Smoking, radon, NO_2	Dose-response for mean cumulative exposure. Poor correlation with length of exposure. RR increased about 14% per f-y/ml.	2+

First author, year of publication, reference no.	Characteristics of cases	Characteristics of controls	Meaurement methods and potential confounders			Results	Grading
			Exposure *Asbestos type, unit*	Outcome	Confounders and other factors		
Gustavsson, 2002 [113]	1,038 lung cancer cases 1985-1990, Stockholm, age 40-75 years. Type o industry defined from questionnaire and interviews	2,359 referents. Random selection from the general population fequency-matched with regard to age and year of inclusion	Cumulative exposur Chrysotile f/ml	Lung cancer Death certificates	Smoking, age	Clear excess risk of lung cancer at low-dose levels and a fine dose-response association of 4 f-y/ml associated with a RR of 1.9 (CI 1.32-2.74). The asbestos-smoking interaction was between additive and multiplicative but closest to additive. The RR was 1.55 for smokers with 4 f-y/ml asbestos exposures. <u>Other</u> Robust methods. Exposure assessments: expert judgment better than self-assessment. Linear extrapolation from high exposure levels underestimates the risk at low doses.	2+
Pohlabeln, 2002 [114]	839 West German male patients in Bremen with lung cancer and a small group in Frankfurt 1988-93.	839 male control individually matched on age and region from all hospitals in Bremer 1988-1993 and Frankfurt/Main 1989-March 1990	Cumulative exposure Mixed exposures f/ml	Incident cases of lung cancer. Hospital-based Register	Smoking, but not other occupational exposures	Log transformed (ln[f-y/ml+1]) gave the best fit. The estimate was ln(f-y/ml+1): OR = 1.18 (95% CI 1.05-1.32), corresponding to a doubled risk from exposure to 25 F-y/ml. <u>Other</u> Re-analysis of earlier publications. Refinement of exposure assessment by expert judgment slightly increases dose-response. A two-stage analysis based on expert evaluation of a subsample and applied on the whole group increased the dose-response slightly compared to duration. Regression ln(OR) ~ 0.164 * ln (f/ml year). Sample demands, recent diagnosis, and fit for long interview, may have selected cases.	2++

REVIEWS

Hendersson, 2004 [140]

This review includes studies between 1997 and 2004 containing information on: interactive effects of asbestos and smoking, lung cancer-/mesothelioma ratios and the cumulative exposure model for lung cancer. The search methodology is weak and does not include search terms and number of hits. However, this review is extremely informative based on the extensive number of references (346), which are insightful organized and discussed by an obviously very knowledgeable author. There were no significant differences in the phenotypic repertoire or the anatomical distribution of lung cancers related to asbestos versus those that are not. All 4 major lung cell types occur among asbestos-exposed subjects with no differences when compared to controls. For asbestos-exposed patients with PPs as the only tissue marker of past exposure, the increase in lung cancer RR may be too small (<1.5) after allowance for other factors such as tobacco smoke. Thus the use of PP as a marker of significant asbestos exposure is questionable. Evidence supports a cumulative exposure model. Different attribution criteria (e.g. greater cumulative exposures) are appropriate for chrysotile-only exposures. There is insufficient evidence to draw meaningful conclusions concerning variation in asbestos-mediated lung cancer risk relative to individual resistance and susceptibility factors. R-AMSTAR score 16 of 33.

Pierce, 2008 [141]

This review concentrates on the stratification of mortality or RR for predominantly chrysotile-exposed cohorts. A systematic literature search found over 300 studies. After careful review only 14 studies were included. The preponderance of cumulative “no-effect” exposures (i.e. no statistical significance) for lung cancer were about 25-1000 f-y/ml. However, many studies were too small and thus lacked statistical power to assess possible increased risk at the reported “no effect” level. This is an interesting review, but due to the above mentioned limitations a lack of statistical significant increased risk cannot be equated with true no effect level. R-AMSTAR score 20.5 of 44.

Steenland, 1997 [142]

This older review was quite broad covering silica, man-made mineral fibers as well as asbestos. Twenty four asbestos cohort studies were included. A systematic literature search was not performed. Among these studies 15 showed an exposure response. The lowest lung cancer risk among workers was found in cement and friction products industries. Highest risks were among mining and textile

workers. Smoking differences could not explain the variable industry risks. Smoking-asbestos interaction is between additive and multiplicative. R-AMSTAR score 15 of 44.

META-ANALYSES

A series of meta-analyses elucidating exposure-response relationships based on more than 50 epidemiological studies have been carried out (appendix 14). They cover different aspects of asbestos exposure, mainly related to type of asbestos (amphiboles vs. chrysotile) and type of industry (mining milling, asbestos cement workers, textile fiber processing, brake production and repair).

The oldest is the paper by *Michael Goodman* et al. [143]. They collected 69 cohorts of various asbestos exposed groups and various forms of cancers. Lung cancer was analyzed based on 37 /69 studies including 10 or more years latency and 55/69 studies without. They only looked on SMRs in the various groups and did not take into account any exposure level information. Analyses were made both without and with 10 years latency. A rough indication of exposure was suggested by grouping the studies in three groups according to the percentage of deaths of mesothelioma.

The main result was very large heterogeneity of the studies with SMRs ranging from unity (=100) to 1,700 in Finnish asbestos sprayers. Including latency increased the common SMR from 148 (144-152) to 163 (158-169), but it was not shown whether this increase was due to exclusion of 18 studies or inherited within the single study.

Some variation between different occupations was seen with asbestos product manufacturing and cement workers having the highest SMRs, 196 (95% CI: 176-209) and 170 (95% CI: 156-185), respectively. Railroad workers and friction material workers had the lowest, 90 (95% CI: 79-101) and 112 (95% CI: 101-124), respectively. All estimates included 10 years latency.

An attempt to show some exposure-response was done by stratifying studies by the proportional mesothelioma mortality. 13 studies with more than 2.4% mesothelioma deaths showed a common SMR of 285 (271-299) while the those below 0.6% and between 0.6% and 2.4% had values of 127 (121-134) and 138 (126-151), respectively. Without latency the latter two groups differ a bit more. However, the expert group noted that mesothelioma mortality is not an optimal marker for cumulative exposure, since mesothelioma risk is heavily dependent also of latency time and fiber type. Also,

variation in proportional mortality is determined not only by the index disease but also by the total mortality.

Given the very large heterogeneity and varying quality of the studies included, only limited information on exposure-response can be obtained from this meta-analysis. R-AMSTAR score 16 of 44.

Lash et al. [144] explored exposure-response associations, based on cumulative exposure, in cohort studies published 1966-1995 with a focus on sources of heterogeneity. Based on 15 cohorts (reported in 22 publications) they found that estimates of the study specific exposure-response coefficient (k_L) ranged from 0 to 42 x 10^{-3} f-y/ml. They identified mainly smoking habits and type of asbestos industry, but also standardization to different populations between the cohorts, and possibly conversion between different measures of asbestos exposure (i.e. between mppcf and f/ml), as sources of heterogeneity. The effect of fiber type (predominantly chrysotile, mixed, or other) was not significant when type of industry (mining and milling, asbestos cement and cement products, or manufacturing and textile products) was accounted for, nor was cohort age, calendar period of exposure, or duration versus concentration of exposure. Under the random effects model, implemented due to the heterogeneity between the studies: the maximum likelihood estimate of k_L was found to be 2.6 x 10^{-3} (95% CI: 0.65 to 7.4 x 10^{-3}) $(\text{f-y/ml})^{-1}$ and the estimate for the intercept (a_i) to be 1.36 (95% CI: 1.05 to 1.76). The expert group noted that study quality was not included in the assessment. R-AMSTAR score 19 of 44.

Hodgson (2000) [38] reviewed cohort mortality based on studies with quantified exposure data. Seventeen studies were selected, from the studies included in 3 earlier reviews: Doll and Peto, 1985 [145]; Health Effects Institute, 1991 [4]; INSERM, 1996 [146]. For each study a single risk rate per f-y/ml was calculated and common values were calculated for amphiboles, mixed fibers, and pure chrysotile. Excess lung cancer risk for amphibole exposure was about 5% per f-y/ml. For mixed fibers and chrysotile large heterogeneities were seen. Chrysotile risk was less consistent, around 0.1 to 0.5% per f-y/ml with very large variation, especially between the Quebec miners and the South Caroline textiles. Inter-study exposure-response for amphibole suggests a non-linear relationship, between linear and square. However, due to statistical uncertainties a linear relationship remains arguable for lung cancer. The study confirms the very large heterogeneity also shown by Lash et al. [144]. No specific evaluation of study quality was made. R-AMSTAR score 21 of 44.

A recent meta-analysis conducted by *Lenters et al.* (2011) [147] explored the slope of the exposure-response associations in 19 original epidemiological studies (including one population-based case-control study) from a literature search covering the period 1950-2009, based on classification of five aspects of the quality of the exposure assessment (documentation, contrast in exposure, conversion factor between measurement methods, coverage of exposure data, completeness of job histories). Three independent quality assessments were performed for each study. Stratified by quality in the exposure assessment, they found that studies with better exposure assessment generally had higher k_L values, and that this was most pronounced for studies with better exposure data, and better completeness of job histories. There was much less effect on the intercept. However, the studies with lower quality had on average higher intercepts, indicating that an observed intercept above RR=1 may partly be due to misclassification of exposure. Under the random effects model, the unrestricted meta-k_L was 1.3 x 10^{-3} (95% CI: 0.4 to 2.2 x 10^{-3}) $(\text{f-y/ml})^{-1}$, increasing by step-wise exclusion to k_L 5.5 x 10^{-3} $(\text{f-y/ml})^{-1}$, however only based on two studies. An effect of fiber-type was no longer evident when the analysis was restricted to high-quality studies, but the data for such comparisons were sparse in this category and thus inconclusive. Indications of publication bias were observed. The expert group observed that this paper met most quality requirements for a systematic review. R-AMSTAR score 34 of 44.

The paper by Lenters et al. was based on a Dutch governmental expert report on asbestos [148]. A slightly different approach was taken here including 18 studies, which were excluded stepwise according to lack of information down to 4 with sufficient information. Furthermore a regression forced to origin (not including a constant) gave k_L values increasing from 7.2 (95% CI: 4.8-9.6) $*10^{-3}$ $(\text{f-y/ml})^{-1}$ to 16.4 (95% CI: 3.4-29.5) $*10^{-3}$ $(\text{f-y/ml})^{-1}$.

A possible heterogeneity in the slope of the exposure-response associations at high-exposure and low-exposure was investigated in a companion paper [149] covering the same 19 studies as Lenters et al. [147]. They fitted both linear and non-linear models to risk estimates of 104 exposure categories extracted from these studies. The best fit was obtained with a natural spline model. This model suggested a nearly linear increase in the relative lung cancer risk at low levels of exposure, and a slight decrease in the slope at exposures > 150 $(\text{f*y/ml})^{-1}$. The highest estimates were obtained when the model was fitted without an intercept (thereby not assuming a difference in background rate between exposed and non-exposed subjects). For a cumulative exposure level of 4 f-y/ml the RR for lung cancer was estimated to be between 1.013 and 1.027, and for 40 f-y/ml to be between 1.13 and 1.30. The predicted risk was higher in studies that used a 10 year lag time (i.e. discarded exposure 10 years before end of follow-up) as compare to those which did not (4 f-y/ml: RR=1.030 vs. RR= 1.012; 40 f-

y/ml: RR= 1.329 vs. RR=1.126). Also, as observed by Lenters et al. (2011) [147], restriction of the analyses to studies with few or no limitations in the exposure assessment provided higher risk estimates than a non-restricted on (e.g. 40 f-y/ml: RR=1.301 vs. RR=2.019 for model fitted without intercept). A non-significant difference (3-4 folds) in the RR was observed between exposure to amphibole and mixed fibers versus chrysotile fibers for exposures below 40 f-y/ml. A sensitivity analysis showed that the estimates of the lung cancer risk from low chrysotile exposure were heavily influenced by the Quebec mining (downwards) and South Caroline textile (upwards) studies. The authors suggest that the discrepant slopes in mining and textile may be due lower quality in exposure assessment and significant presence of non-asbestos structures counted as asbestos by phase-contrast microscopy in mining. The expert group noted that this review overall had high quality. R-AMSTAR score 26 of 44.

Berman and Crump (2008) [150] had access to and re-analyzed the raw data from the four major cohorts, the South Carolina textile cohort [118], The Australian Wittenoom cohort exposed to mainly amphiboles [151-153], the Quebec chrysotile mining cohort [125], and the New Jersey insulation manufacturers cohort [132]. In addition they analyzed a number of studies from the published data in order to see the variation in k_L and analyzed the different studies for uncertainty factors assigned to problems in exposure estimation, conversion factors, job histories with the former being by far the largest giving combined uncertainty factors between 1.5 [121] and 5.9 [154].

In the analysis of raw data they found that k_L values were one third to one tenth in models assuming α being estimated than when α was set to 1. However, they stated that the variability of α was far larger than differences in background rates could explain, but also reflecting uncertainties in exposure estimation. In the study of published results including many of the same studies as Lash et al. they calculated "uncertainty intervals" based on the above-mentioned factors for each study. Using this method they showed a blurred picture. The association with industry seems to be at least as strong as for fiber type, mining being the least and textile production by far the highest. For mining, however, exposure to mixed or amphibole fibers showed higher k_L values than chrysotile. As in other reviews a sharp discrepancy between the Quebec mining and South Carolina textile factory handling the same chrysotile asbestos stands out (values with the uncertainty intervals 0.29 (0.085-1.1) vs. 1.8 (7.5-5.6) x 10^{-3} $(\text{f-y/ml})^{-1}$.

Using the same studies, but categorizing the exposure according to fiber type, length and width the authors tried to correlate lung cancer and mesothelioma risk with these factors across the studies [150]. Contrary to mesothelioma the difference between chrysotile and amphiboles was less pronounced.

Long fibers were more potent than short. However, these analyses still do not resolve the unexplained differences in potency seen in the different studies. In a later paper [155] the influence of length and width is further discussed stating it being the main risk factor for lung cancer overruling the influence of fiber types while amphiboles still are more potent according to mesothelioma. The expert group finds that the review is of high quality contributing with valuable information about uncertainties in the calculation of k_L. R-AMSTAR score 23 of 44.

SUMMARY OF EXPOSURE-RESPONSE

The later meta-analyses of lung cancer and asbestos have revealed a very large difference between studies, especially the industrial cohort studies with a common k_L of 1.6 to 6 * 10^{-3} (f-y/ml)$^{-1}$. A debate between Berman [156] and the group of Lenters [157] has been published. The discrepancy lies on the value and criteria for emphasizing on quality of the exposure assessment and the influence of the single cohort of South Carolina textile workers having the highest k_L. However, this discrepancy between the estimates of the two groups does not take into account the high k_L values found in the population based study by Gustavsson (k_L = 155 * 10^{-3} (f-y/ml)$^{-1}$) and to some extend Poehlaben (k_L = 40 * 10^{-3} (f-y/ml)$^{-1}$). These studies are based on generally lower exposures than the industrial cohort studies.

Thereby it cannot be ruled out, that the exposures seen in these mainly jobs handling asbestos products and waste are more potent than the industrial exposures, either because of an altered type of exposure or some curve linearity in the dose response relationship decreasing with higher levels. Extended analysis of population studies is needed to elucidate these relations.

Statement 6

The exposure-response relationship is approximately linear, but levels off at very high exposures (>150 f-y/ml). (+++)

Statement 7

An increase in RR of 0.01 to 0.04 per f-y/ml (corresponding to a doubling of risk at 25 to 100 f-y/ml) has been observed with the highest estimates obtained in the few high quality epidemiological studies. One high quality population-based case-control study in the low-exposure range found a higher risk estimate (a doubling of risk around 4 f-y/ml). (++)

NO OBSERVED EFFECT LEVEL (NOEL)

The possible existence of a level where no cancer risk due to asbestos exposure exists has been discussed. Browne [158] looked at data from a series of cohorts and looked at risk rates at various exposure levels. Based on visual inspection of these exposure-response patterns the author suggests that no increased lung cancer risk was seen below an exposure of about 25 f-y/ml or at a level of risk for clinical asbestosis. The paper does not provide any formal statistics to back up the statement.

On the other hand the various meta-analyses all have been based on linear models, which imply no threshold. In the population based study by Gustavsson et al. [139] an elevated risk was seen at an estimated exposure of 4 f-y/ml. The recent meta-analysis by van der Bij et al. [159] has analyzed the exposure-response at especially low exposures and they calculate from a series of studies relative risks of 1.012 to 1.03 at 4 f-y/ml and 1.12 to 1.32 at 40 f-y/ml not indicating any threshold, albeit in the lower exposures the uncertainties in risk estimates causes them to be not significant from unity.

Conclusion: the expert group did not find evidence for a threshold for lung cancer risk due to asbestos.

Statement 8

There is no evidence for a NOEL concerning ARCL. (++)

Statement 9

The lowest documented increased ARLC risk is seen at about 4 f-y/ml. (+)

LATENCY

Two types of latency have been defined assuming that it takes at least 10 years to develop a solid tumor as lung cancer. In studies two approaches have been taken, one is to only including subjects who were observed 10 years or more after first exposure (latency time). The other approach has been to exclude the last 10 years of exposure (lag time).

Berman and Crump [160] on the other hand looked at the possible decrease in lung cancer risk after cessation of exposure based on re-analysis of the data from the two of the main cohorts (Wittenoom miners and South Carolina textiles) and found a striking difference with only a marginal decline in the

Witttenoom cohort [151-153] exposed to crocidolite even after 40 years while a decline in RR was seen after 20- 30 years in the South Carolina cohort [118] exposed predominantly to chrysotile.

The expert group concluded that lung cancer probably first develops some years after start of exposure. Limited evidence suggests that lung cancer risk may be reduced or absent 7-15 years after the cessation of asbestos exposure [161]. Due to limited evidence the expert group concluded that it is likely that lung cancer risk decreases decades after exposure cessation.

Statement 10

Lung cancer risk decreases decades after the cessation of exposure. (+)

Statement 11

No minimal latency time for ARLC has been established. For practical purposes it can be assumed to be 10 years after exposure onset. (+)

Statement 12

The prognosis of ARLC does not differ from that of other lung cancers. (+)

CARCINOGENICITY OF FIBER TYPES

The different types of asbestos have been thoroughly studied. All fiber types have been shown to be carcinogenic in laboratory animals [162]. Epidemiological studies of amphibole as well as chrysotile exposed workers have shown varying degrees of increased lung cancer risk [38, 140]. In spite of some areas of controversy [13] the expert group concluded that all types of asbestos fibers should be considered carcinogenic.

Statement 13

All types of asbestos fibers are associated with lung cancer risk. (+++)

Statement 14

Different exposure-response estimates for lung cancer have been reported according to fiber type (amphibole vs. chrysotile), size, distribution and industry. However, these patterns are not clear, when study quality is taken into account. Thus, there is not sufficient evidence to derive different risk estimates for different fiber types. (++)

4.4 COMPETING AND PREDISPOSING CONDITIONS

DISEASES AND CONDITIONS INFLUENCING THE DEVELOPMENT OF ARLC

SUMMARY

Lung cancer develops in a minority of individuals exposed to carcinogens such as asbestos or tobacco smoke. This suggests that individual susceptibility is important. Family history of lung cancer predicts lung cancer risk. The risk of developing a second primary cancer is 5-11 times greater compared with patients without a malignancy. The genetics and molecular epidemiology of lung cancer are actively investigated. However, present knowledge is insufficient to calculate susceptibility when evaluating most cases of potential ARLC [163-182].

A full review of this topic is though beyond the scope of this report. The above areas are reviewed in appendix 15.

Statement 15

There is insufficient evidence to include predisposing factors (age, sex, and genetics) in the individual apportionment of ARLC. (++)

Statement 16

It is rarely relevant to account for other diseases or disorders in individual apportionment assessments in Denmark. However, this does not apply to lung fibrosis of any origin. (+++)

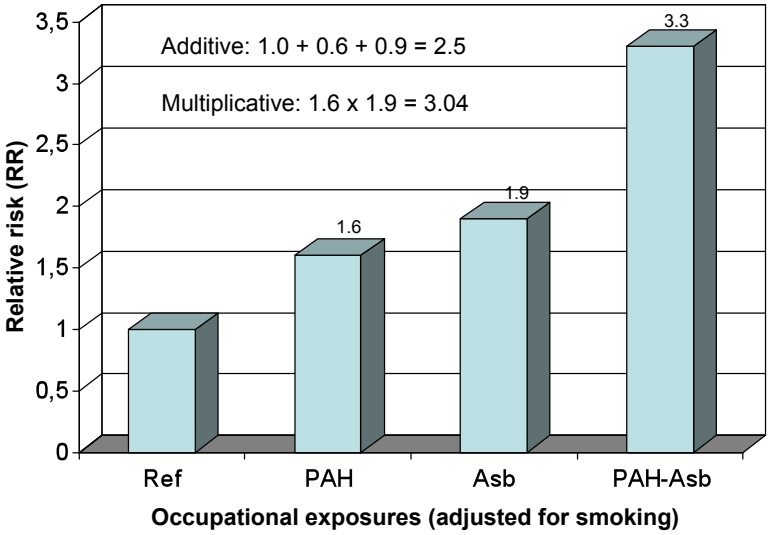
RISK FACTORS FOR LUNG CANCER OTHER THAN ASBESTOS

OCCUPATIONAL RISK FACTORS

SUMMARY

Asbestos workers have frequently been exposed to other occupational exposures, which should be considered when evaluating ARLC. Welding and PAH are among those often encountered. Two epidemiological studies describe a synergistic effect between PAH and asbestos exposure. Gustavsson et al. (2003) [183] analyzed 1,042 lung cancer cases. The RR for asbestos exposure was 1.61, for combustion products 1.67 and for both exposures 2.24, suggesting an additive effect. In a case control study of 204 lung cancer cases Pastorino et al. (1984) [184] found a RR for PAH exposure of 1.6, for asbestos exposure 1.9 and for both exposures 3.3, consistent with a multiplicative effect (figure 2) [1, 163, 183-185]. However, for compensation purposes it is preferable to use AF for the occupational carcinogens one has been exposed to and not only rely on RR. The area is reviewed in appendix 16.

Figure 2. Interaction between exposure to PAH and asbestos [184].



Statement 17

Assessment of work-related risk for lung cancer needs to consider all established occupational lung carcinogens in the individual case. (+++)

ENVIRONMENTAL RISK FACTORS

SUMMARY

Radon and air pollution have been associated to increased lung cancer risks. The excess risk of lung cancer from exposure to radon is dose-dependent and ranges between 2 and 25% per 100 Bq/m3. About 25% of houses in Denmark are estimated to have a radon concentration >100 Bq/m^3 and 5% above 200 Bq/m^3. The number of annual deaths in the Danish population attributable to radon is estimated to be about 240, the majority of this being the joint effect of radon and smoking. Overall it has been estimated that 1 to 2% of lung cancers in Denmark may be related to air pollution which corresponds to 35-70 cases annually in Denmark. As exposure ranges are generally low in Denmark they can usually be discounted when considering ARLC apportionment [140, 163, 165, 186-202]. Results concerning lung cancer and environmental factors are reviewed in appendix 17.

Statement 18

In Denmark, there is no need to include environmental radon and air pollution exposures in individual apportionment assessments. (++)

SMOKING AND OTHER LIFE STYLE RISK FACTORS

SUMMARY

There is some evidence in the literature that smoking filtered cigarettes is less hazardous than smoking unfiltered cigarettes, but evidence is inconsistent. There is also concern about potential new harmful effects due to cigarettes' additives. There is no proof that any cigarette is safe and there is no substitute for stopping smoking. Passive smoking is more weakly associated with lung cancer than active smoking. The excess risk of second-hand tobacco smoke at home is of the order of 20% for women and 30% for men. Second-hand tobacco smoke at the workplace increases risk for lung cancer by 12−19%.

Although several studies have reported that more physically active individuals have a lower risk for all-site cancers the results for lung cancer are less clear. The latest cohort studies suggest a slight

protective effect of physically activity on lung cancer incidence. Smoking and physical activity interactions have not been delineated. Cigarette smoking needs to be considered as an alternative explanation when evaluating life style factors, including diet, due to potential confounding [203-216]. This area is reviewed in detail in appendix 18.

ACQUIRED LUNG DISEASES AND LUNG CANCER RISK

SUMMARY

Pulmonary fibrosis is associated with an increased lung cancer risk. The presence of asbestosis is associated with considerable asbestosis exposure, sufficient to cause ARLC. Pulmonary tuberculosis has also been associated with increased lung cancer risk. Those with primary cancer have an increased risk of developing a second primary cancer, including lung cancer. Numerous studies have demonstrated associations between lung cancer risk and COPD. As smoking is the main cause of both, it is difficult to completely control for [163, 173, 217-231]. This subject is reviewed in appendix 19.

NON-OCCUPATIONAL/ENVIRONMENTAL ASBESTOS EXPOSURE AND LUNG CANCER

SUMMARY

Non-occupational asbestos exposure is not significantly related to lung cancer except in special e.g. household exposure inhabited by asbestos workers, areas with very high exposures (residence near mines or processing plants), and areas where asbestos occurs naturally in the soil. The level of environmental asbestos exposure in Denmark is not known, but based on Dutch and English studies the background level in outdoor city air is about 0.0001-0.0005 f/ml. This is orders of magnitude below the levels measured in occupational settings on which risk is assessed and extrapolated. WHO estimates that based on a lifetime exposure of 1,000 f/m^3 (0.001 f/ml) the excess lung cancer risk would be in the order of 10^{-6}–10^{-5}. In Denmark this would account for 10 out of 3,600 lung cancer deaths, based on an exposure level about 10 times higher than expected based on exposure

measurements from comparable countries [38, 145, 186, 191, 232-247]. This subject is fully reviewed in appendix 20.

Statement 19

In Denmark, there is no evidence that non-occupational asbestos exposure is associated with lung cancer. (+++)

INTERACTION BETWEEN ASBESTOS AND SMOKING

SUMMARY

There has been inconsistent data on the interaction between asbestos exposure and smoking and their joint impact on lung cancer risk. Some studies have suggested a multiplicative effect, others an additive model, where asbestos exposure and smoking are independent of each other. Studies from the 1970s or earlier based on populations with very high asbestos exposures tended to support the multiplicative model. Later studies with low or moderate exposures including mathematical and statistical analyses tend to conclude, that the effect is "more than additive and less than multiplicative relation". This rather imprecise statement seems to be representative for the present state of knowledge. With risk expressed as ***attributable proportion*** due to asbestos among never-smokers estimates are approximately 30%-40%. Recent data from Great Britain with exposure levels and regulations comparable to the Denmark are in accordance with that, and showed that risk attributable to the combined effect of asbestos and smoking was 96% among smoking asbestos workers. Thus about 96% of lung cancer deaths could have be avoided by avoiding both asbestos and smoking [236, 248-254]. This subject is reviewed in appendix 21.

Statement 20

Asbestos exposed smokers are at higher risk of lung cancer compared to asbestos exposed non-smokers. (+++)

Statement 21

20 years after smoking cessation relative risk of lung cancer due to smoking is reduced by about 90%. (+++)

5. DISCUSSION

Asbestos is one of the most carefully characterized and researched occupational hazards. Numerous risk assessment models have been developed in an attempt to provide reliable information about workplace lung cancer risks. In spite of these efforts important knowledge gaps exist generating both scientific interest and difficulties in establishing regulations. Some of the key issues concern the validity of exposure assessments, the validity of outcome measures as well as study bias, confounding and effect modification.

Asbestos exposure

As previously mentioned methods for both sampling and analyzing asbestos have changed dramatically through the years. Unfortunately these developments have introduced substantial uncertainties that still are difficult to overcome. Exposure misclassifications may make it difficult or impossible to demonstrate true associations between exposures and effects. Systematic misclassification may lead to risk estimates that are either too low or too high. True associations may be masked by random misclassifications. Some of the key reasons for uncertainty are discussed below.

Research has shown that thin fibers (defined as fibers with a width less than 0.25 μm) are more carcinogenic than thicker ones [255, 256]. Unfortunately, early airborne concentration measurements using PCM did not account for these thin fibers, thereby potentially underestimating asbestos exposures to the thinnest fibers. As PCM is limited and cannot identify thin fibers, incorrect risk attributions may be attributed to the countable thicker fibers. Including these less biologically relevant exposures in most cases leads to an overestimation of the exposure, and thereby to a less steep exposure-response-curve.

There are more than 30 “standard” methods of analyzing asbestos fibers. The same sample analyzed by different methods can vary 2 or 3 orders of magnitude [36]. A U.S. program for standardizing the testing and measurements of asbestos samples (The National Voluntary Laboratory Accreditation Program) was first introduced in 1976. Many of the measurements in epidemiologic studies were obtained before 1976.

In various studies the type of asbestos fiber measurements has been unclear. In earlier studies stationary or area samples have predominated, while samples using personal samplers have been the standard during the last decades. Area samples are less connected to individual exposures, and may either under- or overestimate this. Besides it has often been unclear if the measurement was taken to evaluate worst case of especially dusty processes or aimed at being representative for a typical full working day. Worst case measurements tend to overestimate exposure. Lack of data concerning local ventilation and respiratory protection add additional uncertainties when using area sampling to estimate personal exposures. Measurements from one job may be used to estimate exposures at other jobs, other shifts or time periods, which may add uncertainties that cannot be adequately accounted for. In addition work histories are often incomplete with possible job misclassifications. Relative air concentrations of amphibole and chrysotile are often unknown. The relative amounts of purchased amphibole and chrysotile have been used as a proxy.

There have been numerous attempts to convert historical air measurements to newer units. There have been two types of conversion attempts. Midget impinger dust counts have been converted to PCM fiber counts. Based on paired analyses conversion multipliers are generated. A number of studies have used 1 mppcf = 3 f/ml. However, generated conversion factors from parallel sampling have actually ranged between 0.1 and 52 [39].

The other conversion area has been from total fiber counts to specific fiber counts with fiber type, length and diameter. These specific fiber counts were made with TEM starting around 1980, but this technique is still not a routine method for monitoring occupational asbestos exposures. These measurements were applied to earlier epidemiological studies where exposures were judged to be similar. Thus, measurements from one time and place are applied to another time and place. Additional uncertainties arise when PCM fiber data are converted to TEM exposures. There is only a reasonable correlation for fibers > 5 μm in length. TEM measurements have shown substantial variation in the ratio of total fibers to fibers over 5 μm, which can vary from 2 to > 130 [257]. Thus there is generally poor correlation between PCM and TEM measurements.

Reliability and validity of outcome measurements

Besides the above-mentioned problems with exposure assessment, the reliability and validity of outcome measurements is associated with uncertainties. In cohort studies SMR has mainly been used to estimate RR. Using SMR induces variation, as the comparison is made with a hypothetical population with the same age distribution as the exposed cohort, and not that of the background population. In elderly cohorts [120, 125] this will automatically tend to give SMRs close to 100 due to

high background mortality [258]. Another factor is that very high exposure levels give rise to high absolute rates of cancer as well as competing risks (i.e. for asbestosis). As you can only die once, this may tend to underestimate the risk, when interpolating to lower levels.

Problems dealt with in the various studies include other influencing factors, of which smoking is predominant. Smoking is the main risk factor for lung cancer and the interaction with asbestos is still not totally clear. Very few studies have sufficient information on smoking habits. Others looking especially at this interaction have come to various results. However, the initial pure multiplicative effect claimed by Hammond et al. in 1979 [236] has never been reproduced. A model somewhere between additive and multiplicative is the most likely. This has some effect on the estimated relative etiological fractions due to smoking and asbestos as well as on the common estimated risk in the epidemiological studies.

Exposure-response analyses

Very large variation in the exposure-response calculated increase per f-y/ml has been shown ranging from almost zero in Quebec miners [125], over high values in the textile factories [121] to very high values in a Swedish case-control study [139, 259].

In case-control studies exposure has mainly been to end products or waste, either as the main task or only occasionally. Therefore the estimated exposures tend to be much lower, and more in agreement with the exposure of the more recent lung cancer cases. The very high k_L ($140^* 10^{-3}$ $(f^*y/ml)^{-1}$) of Gustavsson is mainly based on exposures below 5 f-y/ml, while most studies in the meta-analyses have much higher exposures: Lash et al. (1997) [260], Lenters et al. (2011) [147], van der Bij et al (2012) [149]. The other case-control study [114] showed an intermediary k_L ($40^* 10^{-3}$ $(f\text{-}y/ml)^{-1}$ and suggested a curve linear exposure-response in accordance with the Swedish study. A joint ongoing analysis of several case control studies (SYNERGY) will be anticipated to get a better estimate of k_L in these low exposures in various jobs.

Based on the reviews and meta-analyses it seems that k_L increases with increasing study quality. The best estimate may be taken from Lenters (2011) [147] and the Dutch position paper [148], k_L being 4-6 $*10^{-3}$ $(f\text{-}y/ml)^{-1}$ calculated to double lung cancer risk at 150-250 f-y/ml, a k_L considerably lower than estimated from the more recent case-control studies. Therefore weighing the evidence between a series of mainly older studies based on high asbestos concentrations in selected trades and a few newer studies with lower exposures with various tasks in different jobs is still an enigma.

Possible under reporting of ARLC and etiological fraction

Järvholm et al., found a 16% attributable lung cancer risk due to asbestos [261]. As shown in table 3 between 2004 and 2010 there were 524 reported and 232 compensated cases of ARLC among men in Denmark. This corresponds to about 3.4 and 1.5% of all male lung cancer cases in Denmark in the same period. Some evidence suggests that ARLC may be under reported. Our own data has shown that 25.3% of male lung cancer cases from Odense had reported asbestos exposure (table A10, appendix 11). In the EAGLE study 32% of lung cancer cases had been exposed to asbestos resulting in a population attributable fraction (PAF) of 18.1% (95% CI: 12.6-23.3) [80]. Gustavsson study (2000) [139] found that 12.2% of lung cancer cases in the largely non-industrial Stockholm area had reported asbestos exposure. Gustavsson reported a 4% attributable fraction for asbestos. If this attributable fraction is used as a conservative estimate for Denmark, then around 619 of the 15,466 male lung cancer cases diagnosed in Denmark between 2004 and 2010 could be attributed to asbestos while only 238 were compensated.

6. CONCLUSION

Lung cancer accounts for about 13% of all new cancers in males and 12% in females in Denmark. It has been estimated that about 4% till 8% of lung cancer cases may be related to asbestos exposure. Data suggests that there is an underreporting of asbestos-related lung cancer in Denmark. There is not enough evidence to include age, sex or family lung cancer history when evaluating cases of potential asbestos-related lung cancer. Neither should most other diseases be taken into consideration except for lung fibrosis. Exposure to radon and air pollution in Denmark is generally low and thus need not be considered when evaluating individual cases of possible asbestos-related lung cancer.

The exposure-response between asbestos exposure and lung cancer risk is basically linear, but may level off at very high exposures. Many studies demonstrate that the relative risk for lung cancer increases between 1 and 4% per f-y/ml, corresponding to a doubling of risk at 25-100 f-y/ml. However, one high quality study has shown a doubling of lung cancer risk at about 4 f-y/ml. Cell type and location of lung cancer are not helpful in differentiating asbestos-related lung cancer from other lung cancers. The presence of pleural plaques, asbestos bodies or asbestos fibers is useful as markers of asbestos exposure and as such helpful in supporting previous asbestos exposure. The interaction between asbestos and smoking regarding lung cancer risk is between additive and multiplicative.

7. APPENDICES

APPENDIX 1. OCCUPATIONAL GROUPS WITH COMPENSATED ASBESTOS RELATED LUNG CANCER, FUNEN (DK) 2007-2010.

Occupation (DISCO-08)	Compensated occupational asbestos related lung cancer (%)
132100	1
234120	1
311120	1
311300	1
315100	2
541900	1
711210	7
Carpenter (711510)	58 (24)
711520	1
Plumber (712600)	21 (9)
713110	1
713120	1
713200	1
713320	1
721100	3
721200	2
721300	3
721400	4
722100	6
722200	6
Metalworker (722300)	11 (5)
Mechanics (723110)	19 (8)
723120	5
723190	1
731300	2
731500	1
741100	3
741200	4
742100	1
Cement workers (811400)	34 (14)
812100	2
816040	1
818210	1
818290	1
821900	1
833220	1
834200	1
835000	2
911220	1
931290	1
Insulators (931310)	14 (6)
931390	2
932100	1
932900	3
933410	3
961100	1
Total	**239 (100)**

APPENDIX 2. DANISH ASBESTOS MEASUREMENTS (2.2)

DANSK ETERNIT FABRIK, LTD

Dansk Eternit Fabrik LTD, founded in 1927 in Aalborg, was a manufacturer of asbestos fiber-cement products e.g. roofing and interior and exterior cladding. The average annual consumption of asbestos, mainly chrysotile, increased dramatically from 500 metric tons in 1928 to the highest of 26,000 metric tons in the early 1970s [262]. Between 1945 and 79 some amosite was also used, and between 1950 and 1969 in addition, crocidolite was used.

In 1949 the first measurement of asbestos exposure was taken at two processes: *asbestos mill during unloading and fill up* and at "*Dutchman" during fill up* (Table A2). The result for asbestos milling showed 85 and 150 asbestos particles/cm^3 for 2-15 and 15-200 μm, respectively. The concentration for the "Dutchman" was 350 and 800 asbestos particles/cm^3 for 2-15 and 15-200 μm, respectively [262]. Follow up measurements at the same factory given in another report were 10-100 f/ml in 1957 and <5 f/ml in 1973 [240].

Table A2. Abestos measurements from Dansk Eternik Fabrik LDT, 1949 [262].

	Particles of dust/cm^3	Asbestos particles/cm^3	
	0.5-5 μm	2-15 μm	15-200 μm
Asbestos mill during unloading and fill up	990	85	150
"Dutchman" during fill up	5500	350	800

Interpretation problems:

- Fiber type and the proportion of chrysotile to crocidolite are unknown.
- Unknown how asbestos particles were measured (TEM?) or estimated?
- Was the size of the asbestos particles width or length measured?

THE NATIONAL RESEARCH CENTRE FOR THE WORKING ENVIRONMENT (NFA)

Between 1982 and 1987 the National Research Centre for the Working Environment performed personal airborne asbestos concentration measurements in different industries (table A3). Most measurements were below 1 f/ml. However, a few very high asbestos levels were seen in electricity production (46.51 f/ml) and for carpenters (30.00 and 47.00 f/ml).

Table A3. Asbetos measurements 1982-1987 (filter measurements, person-borne). Information from the Danish National Institute of Occupational Health.

INDUSTRY	NO OF MEASURE-MENTS	AVERAGE EXPOSURE LEVEL (F/ML)	RANGE
CAR REPAIR			
83-432-369	1	0.20	-
83-432-429	2	0.14	0.10-0.16
84-432-1196	2	0.45	0.20-0.70
85-432-1769	5	8.82	0.40-17.00
87-078	2	0.23	0.11-0.34
PARKING AND ROAD SIDE ASSISTANCE			
83-432-561	2	7.89	0.98-14.80
GENERAL PUBLIC SERVICES			
83-432-565	1	0.00	-
83-432-696	1	-0.10	-
84-432-1262	3	0.37	0.14-0.71
ELECTRICITY PRODUCTION			
83-432-741	1	0.70	-
86-432-2295	5	0.11	0.07-0.14
86-432-2526	2	23.29	0.07-46.51
87-6432-89	2	5.92	0.62-11.23
CARPENTRY			
84-432-1013	2	38.00	30.00-47.00
84-432-1259	7	0.24	0.07-0.39
OTHER TEACHING			
84-432-1061	3	-0.00	-
TRAIN TRANSPORTATION AND REPAIR			
84-432-1292	1	0.50	-
85-432-1824	2	9.1	0.20-18.00
85-432-1927	1	0.10	-
84-432-1950	4	0.63	0.55-0.70
85-432-1967	3	0.03	0.00-0.10
HOSPITAL			
86-432-2617	2	0.14	0.11-0.17
87-6432-108	1	0.14	-
OTHER PRODUCTION INDUSTRY			
87-6432-88	2	0.07	0.07-0.07

Problems:

- Unknown method of measurement and analysis
- The industries are not further described

ASBESTOS ABATEMENT MESUREMENTS

In a report by Baelum & Staun [263] data from three types of abatement of asbestos-containing building materials are given: Dismantling of ceiling tiles, removal of pipe insulation and prying up floorings. The highest fiber exposures among asbestos abatement workers were seen in those prying up floorings with an average fiber exposure of 48.9 f/ml (3.3-92.0 f/ml). The second most exposed process was dismantling of ceiling tiles with an average fiber exposure of 2.8 f/ml (1.41-4.93 f/ml) followed by removal of pipe insulation with 1.7 f/ml (0.24-4.11).

Table A4. Personal airborne asbestos concentration measurements from Nordgårdsskolen in Aarhus, Aarhus Kommunehospital and Randers Centralsygehus [263].

DISMANTLING OF CEILING TILES			
STUDY 1		STUDY 2	
	Fiber/ml (95% CI)		Fiber/ml (95% CI)
Day 1		**Day 1**	
Person C	3.62 (3.42-3.87)	Person F	4.93 (4.52-5.50)
Person E	2.63 (2.46-2.84)	Person G	1.41 (1.28-1.62)
Day 2		**Day 2**	
Person C	4.14 (3.89-4.45)	Person F	2.18 (1.96-2.49)
			2.79 (2.55-3.13)
Person D	3.03 (2.84-3.26)	Person G	2.39 (2.16-2.72)
			2.12 (1.92-2.42)
Day 3			
Person C	1.77 (1.65-1.93)		
Person D	2.67 (2.53-2.83)		
Day 3 (cleaning)		**Day 3 (cleaning)**	
Person C	0.02 (0.00-0.07)	Person F	4.64 (4.24-5.11)
			8.70 (7.98-9.71)
		Person F (under mask)	0.02 (0.02-0.03)
Person D	0.95 (0.87-1.06)	Person G	2.19 (1.99-2.48)
			1.87 (1.67-2.18)
			0.74 (0.64-0.93)
		Person G (under mask)	0.004 (0.00-0.02)

REMOVAL OF PIPE INSULATION			
STUDY 1		STUDY 2	
	Fiber/ml (95% CI)		Fiber/ml (95% CI)
Day 1		**Day 1 (2nd measurement)**	
Person A	0.24 (0.20-0.30)	Person A	1.17 (1.01-1.47)
			1.64 (1.44-1.96)
			1.57 (1.35-2.00)
Person B	0.31 (0.27-0.38)	Person B	0.40 (0.33-0.61)
			2.76 (2.49-3.15)
			4.11 (3.70-4.73)

(cont.)

REMOVAL OF PIPE INSULATION *(cont.)*			
Day 2		**Day 2**	
Person A	1.34 (1.20-1.57)	Person A	1.74 (1.52-2.13) 3.46 (3.07-4.08) 2.47 (2.18-2.95)
Person B	0.84 (0.73-1.02)	Person A (under mask)	0.058 (0.05-0.07) 0.018 (0.00-0.04) 0.007 (0.00-0.03)
Day 2 (2nd measurement)			
Person A	1.46 (1.35-1.63)		
Person B	1.59 (1.46-1.77)		

PRYING UP ASBESTOS FLOORINGS	
STUDY 1	
	Fiber/ml (95% CI)
Day 1 (removal of the upper layer)	
Person H	3.3 (3.01-3.64)
	92.0 (86.7-98.0)
Person I	17.2 (15.8-19.0)
	71.9 (67.3-77.3)
Day 2 (scrapping of concrete floor)	
Person H	61.2 (58.2-64.5)
	36.0 (34.1-38.0)
Person I	60.5 (57.2-64.6)

ROULUND FABRIKKER (ROULUNDS BRAKING)

Roulunds Braking was founded in 1736 in Odense, Denmark as a manufacturer of friction materials to the automotive industry. The portfolio includes flexible brake linings, brake pads, brake shoes, brake discs and brake shoe kits, for passenger car and light commercial. No information about amount of asbestos is available.

Table A5. Asbestos measurements (f/ml) 1980-1997 (4th quarter of the year) personal information from Roulunds Braking.

	1980	1981	1982	1987	1992	1997
Mixing	1.4-15.8	0.2-0.6	0.8-4.4	0.3-0.5[1]	<0.1	0.1[3]
Pre-forming	0.7-2.8	0.6-2.3	0.5	0.1	<0.1-0.2	0.2[3]
Pressing	0.5-3.0	0.5-1.5	1.2	0.1-1.4	<0.1-0.2	0.1
Sawing	0.6-1.7	0.9-6.7	-	0.3-0.5	0.2[2]	<0.1
Grinding	0.3-2.4	0.2-11.0	0.7-9.6	0.1-0.3	<0.1	0.1
Drilling	0.6-0.8	0.8-1-7	0.6	<0.1-0.6	<0.1	0.1[4]
Owen work	2.9	-	-	0.2	<0.1	<0.1

1: 3rd quarter of 1987
2: 3rd quarter of 1992
3: 2nd quarter of 1997
4: 1st quarter of 1997

SWEDISH ASBESTOS CEMENT INDUSTRY

The tables below give measurements from a Swedish asbestos cement industry.

Table A6. Measured values of fibers and total dust in air at different times and operations [264].

	1956			1965	1969			1975		1979[4]	
Job task	Particles (mppcf)[1]	Fibers (F/ml)[2]	Total dust (mg/m3)[1,3]	Particles (mppcf)[1]	Particles (mppcf)[1]	Fibers (F/ml)[2]	Total dust (mg/m3)[1,3]	Fibers (F/ml)[2]	Total dust (mg/m3)[1,3]	Particles (mppcf)[1]	Fibers (F/ml)[2]
Milling	15	6.0	6.7	21	11	5.0	3.25	1.7	4.5	0.5	0.2
Mixing	29	3.0	5.5	4	3	0.3		1.25	5.0		
Machine line	8	1.5		11	2	0.3	0.5	0.9	2.25	0.3	0.1
Sawing	24	4.0	2.8	16	9	1.7	2.5	1.15	4.5	0.8	0.6
Finishing, edges	47	6.3	0.7	45	9			1.5	4.0		
Face grinding	16	2.5	1.6	16			2.2	1.0	5.0	0.6	0.8

1: Measured value
2: Estimated value for mean exposure level according to Table 2
3: Stationary sample
4: Measurements from a corresponding factory. Analysis of the fibers utilized of more advanced method than previously determinations

Table A7. Estimated average exposures to asbestos in air[1] for various jobs and professions in an asbestos cement industry [264].

Job task/profession	-1941[2]	1942-1946	1947-1951	1952-1956	1957-1961	1962-1966	1967-1971	1972-1977
	Average exposure (fiber/ml)							
Milling	10.0	3.5	10.0	6.0	5.0	5.0	4.0	1.7
Mixing	5.0	2.5	5.0	3.0	2.7	2.0	1.8	1.25
Machine line	1.7	1.0	1.7	1.5	1.5	1.2	1.2	1.0
Separators, pressers	1.4	0.7	1.4	1.2	1.2	0.9	0.7	0.7
Hand moulding	0.7	0.4	0.7	0.7	0.7	0.7	0.6	0.4
Stone saw	3.8	2.5	4.8	4.0	3.5	2.8	1.6	1.3
Wet saw								0.7
Trimming saw				3.8	3.1	3.1	1.5	1.1
Automatic saw						2.2	1.0	1.0
Cylinder saw				5.6	5.0	4.8	2.2	1.6
Face grinding					2.5	2.2	1.2	1.0
Finishing, edges					6.3	5.5	2.0	1.5
Polishing machine					1.35	1.2	1.0	0.7
After-treatment						1.5	0.9	0.7
Dye works								0.25
Cleaners - factory	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.8
Electricians – repair men	1.0	1.0	1.0	0.9	0.8	0.8	0.6	0.5
Carpenters - assemblers								
Laboratory	0.8	0.8	0.8	0.8	0.6	0.6	0.5	0.3
Driver – truck drivers						0.6	0.5	0.5

1: Adjustment for today´s filter preparation - and counting procedures is not made
2: In the absence of information, we assume the same values for the period 1947-1951

INTERNATIONAL ASBESTOS MEASUREMENTS

Table A8. International asbestos measurements [240].

Tabel 1. Typisk udsættelse målt som fibre/ml i luften i en arbejdsperiode, men ikke tidsvægtet.

Arbejdsproces	Fibre/ml	Reference	Årstal	Analyse-metode	Bemærkninger
Jernbaneværksteder					
Boring, savning i isoleringsbræt	2-10	9	1985	Optisk mikr.	Målinger, refereret fra en undersøgelse af Advisory Committee fra 1979.
Anvendelse af asbesthandsker	0-3	9	1985	Optisk mikr.	
Fjernelse af rør- og maskinisolering	90	9	1985	Optisk mikr.	Målinger, refereret fra en undersøgelse af Selikoff og Lee fra 1978.
Syning af asbestmåtter	1-4	9	1985	Optisk mikr.	
Isolering af udstødningsrør i diesellokomotiver	1,5	9	1985	Optisk mikr.	Målinger, refereret fra Statens Järnväger i Sverige.
Fjernelse af asbestisolering ved ombygning af jernbanevogn	1,7	9	1985	Optisk mikr.	
Fjernelse af asbestisolering omkring kedler	2,5-7,5	8	1994	Optisk mikr.	Simulation af forhold fra før 1970
Eftersyn og vedligeholdelse af pendeltog (S-tog) i Stockholm og fjerntog (under vognen og inde i vognen, på værksted)	De fleste <0,01.	4	1985	Elektronmikr.	Ved omstilling af ventilationsanlæg og slag mod tag måltes lidt højere værdier, men alle under 0,1.
Arbejdsmænd på vedligeholdelsesværksteder	0,02-0,03	7	1993	Optisk mikr.	
Jernbanetog					
Svenske pendeltog (S-tog) i Stockholm og fjerntog					Målinger foretaget efter at asbesten var blevet forseglet/saneret. Målinger under kørsel og driftslignende forhold.
Passagerafdelinger	0,002-0,005	4	1985	Elektronmikr.	
Førerrum	Ingen asbestfibre i luftmålingerne.	4	1985	Elektronmikr.	
Franske jernbanevogne					
Lokofører i førerrum	maks. 0,05	7	2001	Optisk mikr.	
Elektriker i lokomotivet	omkring 0,1	7	2001-2003	Optisk mikr.	

(Fortsættes)

Tabel 1 (fortsat).

Arbejdsproces	Fibre/ml	Reference	Årstal	Analyse-metode	Bemærkninger
Britiske jernbanevogne	De fleste målinger var uden påviselige fibre. Alle målinger var under 0,05.	5	1979	Optisk mikr.	Målinger i passagervogne, der var isoleret med sprøjteasbest (blå asbest). Målinger under driftslignende forhold.
Finske jernbanevogne					Asbestholdigt
Førerrum i diesellokomotiv	<0,1	8	1994	Optisk mikr.	materiale omkring rør. Simulation af forhold fra før 1970.
Skibsværfter					
Aftagning af isoleringsmåtter	4	11	1974	Optisk mikr.	
Bæring af aftaget isoleringsmateriale	14	11	1974	Optisk mikr.	Målt på "håndlangeren"
Aftagning af isolering fra damprør	25	11	1974	Optisk mikr.	På et ældre fartøj
Fremstilling af asbestcement					
Målinger på Dansk Eternit Fabrik		12	1990	Optisk mikr.	
1948	50-800				
1957	10-100				
1973	næsten alle <5				
Bearbejdning af asbestcement					
Fjernelse af asbestcementplader	< 0,5	13	2006*	Optisk mikr.	
Manuel savning	< 1	13	2006*	Optisk mikr.	
Maskinel stiksav på asbestisoleringsplade	5-20	13	2006*	Optisk mikr.	Uden punktudsugning
Opsætning af asbestcementplader	2-3	11	1974	Optisk mikr.	
Isoleringsarbejde					
Sprøjteisolering	8	11	1974	Optisk mikr.	
Afrydning efter sprøjteisolering	6-7	11	1974	Optisk mikr.	
Isolering af rør	1	11	1974	Optisk mikr.	
Afisolering	15	11	1974	Optisk mikr.	

* Rapporten er fra 2006, men målingerne er udført i 1999 og 2003

APPENDIX 3. HELSINKI CRITERIA (2.3)

The Helsinki criteria were adopted in 1997 [110]. An international expert meeting was held January 20-22, 1997 in Helsinki. Nineteen asbestos experts from 8 countries participated and discussed asbestosis, pleural disorders, mesothelioma, and lung cancer [107]. For clinical purposes any of the following were recommended to identify individuals with a high probability of asbestos exposure at work:

- Over 0.1 million amphibole fibers (>5 μm) per gram dry lung tissue
- Over 1 million amphibole fibers (>1 μm) per gram dry lung tissue
- Over 1000 asbestos bodies per gram dry lung tissue or 100 per gram wet lung tissue
- Over 1 asbestos body per ml bronchoalveolar lavage fluid

The significance of pleural plaques and diffuse pleural thickening was evaluated. Pleural plaques mainly involve the parietal pleura and may be calcified. Diffuse pleural thickening mainly involves the visceral pleural. The specificity of pleural plaques as defined by the ILO 1980 International Classification of Radiographs of Pneumoconiosis is low unless the plaques are well defined. Low exposure levels from work-, households or natural environmental sources can induce pleural plaques, while diffuse pleural thickening may require higher exposure levels.

Lung cancer and asbestos was thoroughly discussed. All 4 major lung cancer cell types can be associated with asbestos-related lung cancer. Both the histology and location of lung cancer had no significant value in deciding whether or not an individual lung cancer could be attributable to asbestos. The following examples of asbestos exposure were judged adequate to increase the risk of lung cancer by two-fold or more:

- 1 year of heavy exposure (e.g. manufacturing of asbestos products, asbestos spraying, insulation work with asbestos, demolition of old buildings)
- 5-10 years of moderate exposure (e.g. construction, shipbuilding)

The relative risk of lung cancer was estimated to increase 0.5-4% for each f-y/ml. Based on the upper boundary of this range 25 f-y/ml was associated with a two-fold increased lung cancer risk. This limit has been and is still widely used in many countries including Denmark, Germany, and the Netherlands. Tissue sample measurements related to the same two-fold risk were recommended: 2 million amphibole fibers (>5 μm) per gram dry lung, 5 million amphibole fibers (>1 μm) per gram dry

lung, 5,000 to 15,000 asbestos bodies per gram dry lung or 5-15 asbestos bodies per ml of bronchoalveolar lavage fluid. Chrysotile fibers do not accumulate in lung tissue at the same rate as amphiboles due to faster clearance rates. Thus f-y/ml is probably a better indication of previous exposure than tissue measurements for chrysotile-exposed individuals.

Indicators of exposure were also evaluated. The presence of asbestosis indicates high exposure. Pleural plaques also indicate exposure. However, as low-level exposure can cause pleural plaques, the attribution of lung cancer to asbestos exposure should be supported by an occupational history of substantial asbestos exposure. Diffuse pleural thickening is often associated with moderate or heavy asbestos exposures. A minimum lag-time of 10 years from first asbestos exposure is required to attribute a lung cancer to asbestos. Tobacco smoking affects the total lung cancer risk. However, this effect does not detract from the risk of lung cancer attributable to asbestos exposure. The Helsinki report did not attempt to apportion the relative contributions of asbestos exposure and tobacco smoking.

APPENDIX 4. STATEMENTS (3.)

LUNG CANCER

Statement 1
When evaluating ARLC, location and cell types do not differentiate asbestos and non-asbestos related lung cancer.

ASBESTOS EXPOSURE

Statement 2
Job Exposure Matrices (JEMs) are useful in estimating previous asbestos exposure in addition to individual exposure evaluations.

Statement 3
The existence of pleural plaques increases the likelihood of previously asbestos exposure.

Statement 4
The presence of pleura plaques cannot be used to estimate degree of previous asbestos exposure.

Statement 5
The presence of asbestosis is a marker of previously high asbestos exposure and is associated with an increased risk of lung cancer.

EXPOSURE-RESPONSE

Statement 6
The exposure-response relationship is approximately linear, but levels off at very high exposure levels (>150 f-y/ml).

Statement 7
An increase in RR of 1-4% per f-y/ml (corresponding to a doubling of risk at 25 to 100 f-y/ml) has been observed with the higher estimates obtained in the few high quality epidemiological studies. One high quality population-based case-control study in the low-exposure range found a higher risk estimate (a doubling of risk around 4 f-y/ml).

Statement 8
There is no evidence for a NOEL concerning ARCL.

Statement 9
The lowest documented increased ARLC risk is seen at about 4 f-y/ml.

Statement 10
Lung cancer risk decreases decades after the cessation of exposure.

Statement 11
No minimal latency time for ARLC has been established. For practical purposes it can be assumed to be 10 years after exposure onset.

Statement 12
The prognosis of ARLC does not differ from that of other lung cancers.

Statement 13
All types of asbestos fibers are associated with lung cancer.

Statement 14
Different exposure-response estimates for lung cancer have been reported according to fiber type (amphibole vs. chrysotile), size, distribution and industry. However, these patterns are not clear, when study quality is taken into account. Thus, there is not sufficient evidence to derive different risk estimates for different fiber types.

COMPETING AND PREDISPOSING FACTORS

Statement 15:
There is insufficient evidence to include predisposing factors (age, sex, and genetics) in the individual apportionment of ARLC.

Statement 16
It is rarely relevant to account for other diseases or disorders in individual apportionment assessments in Denmark. However, this does not apply to lung fibrosis of any origin.

Statement 17
Assessment of work-related risk for lung cancer needs to consider all established occupational lung carcinogens in the individual case.

Statement 18
In Denmark, there is no need to include environmental radon and air pollution exposures in individual apportionment assessments.

Statement 19
In Denmark, there is no evidence that non-occupational asbestos exposure is associated with lung cancer.

Statement 20

Asbestos exposed smokers are at higher risk of lung cancer compared to asbestos exposed non-smokers.

Statement 21
20 years after smoking cessation relative risk of lung cancer due to smoking is reduced by about 90%.

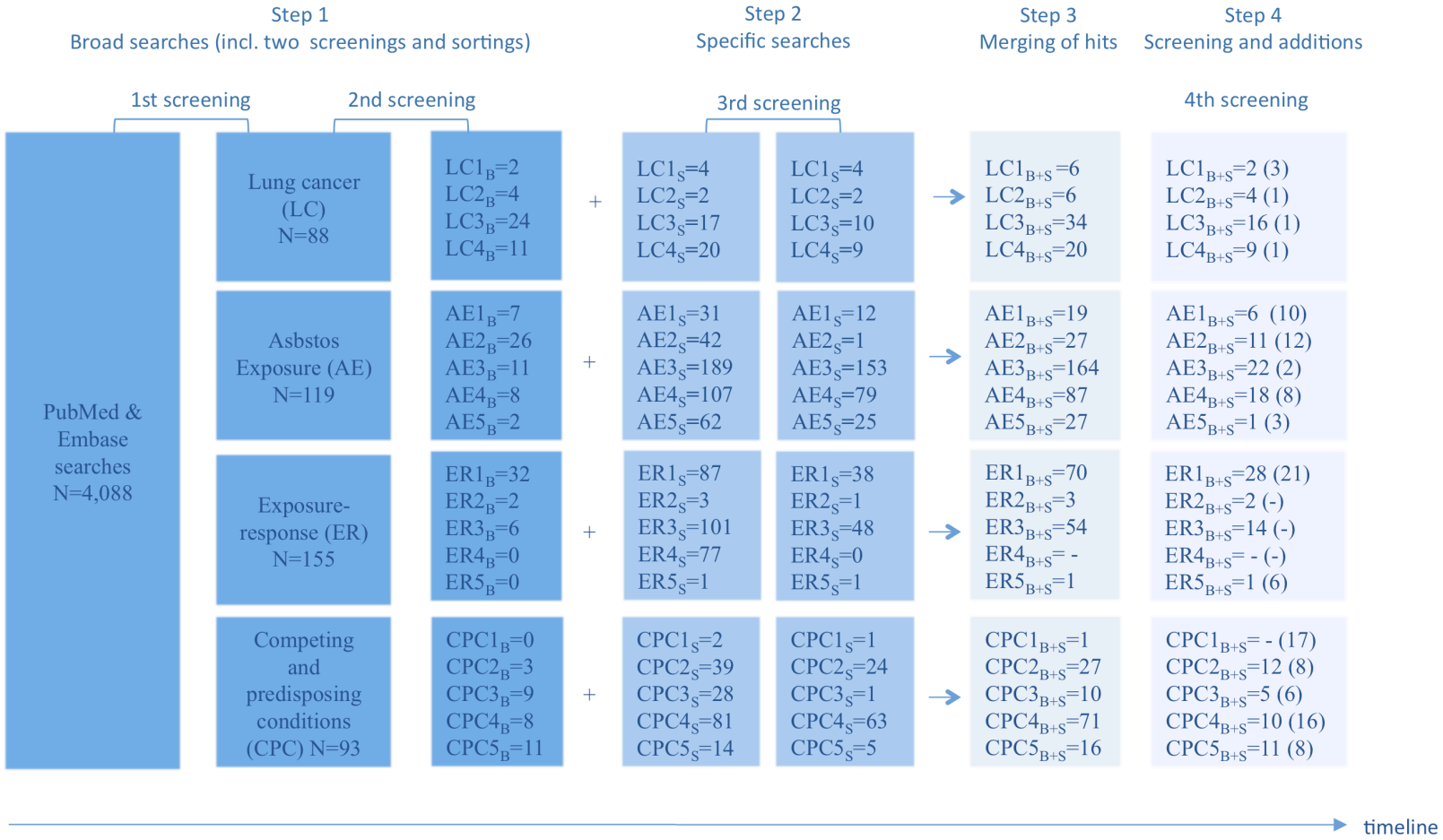
APPENDIX 5. SEARCH DETAILS (3.1)

Table A9. Search details (publication year: PubMed Medline 1940-2012, Embase 1947-2012).

Step 1. Broad searches in PubMed and Embase (top-down approach)		
DATABASE AND DATE	SEARCH TERM	HITS
PubMed 3.7.2012	("asbestos"[MeSH Terms] OR "asbestos"[All Fields]) AND ("lung neoplasms"[MeSH Terms] OR ("lung"[All Fields] AND "neoplasms"[All Fields]) OR "lung neoplasms"[All Fields] OR ("lung"[All Fields] AND "cancer"[All Fields]) OR "lung cancer"[All Fields])	3,132
Embase 4.7.2012	(asbestos and lung cancer).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2,732
	Total number of discrete publications	4,088
Step 2. Specific searches in PubMed (bottom-up approach)		
SEARCH QUESTION AND DATE	SEARCH TERM	HITS
LC1A 23.7.12	"diagnostic validity"[All Fields] AND "lung Cancer"[All Fields]	4
LC2A 23.7.12	"lung Cancer"[All Fields] OR "lung neoplasm"[All Fields] AND "cell type"[All Fields] AND (("Change"[Journal] OR "change"[All Fields]) AND over[All Fields] AND ("time"[MeSH Terms] OR "time"[All Fields]))	2
LC3A 23.7.12	"lung Cancer"[All Fields] OR "lung neoplasm"[All Fields] AND "cell type"[All Fields] AND ("asbestos"[MeSH Terms] OR "asbestos"[All Fields])	17
LC4A 23.7.12	"lung cancer"[All Fields] OR "lung neoplasm"[All Fields] AND (("asbestos"[MeSH Terms] OR "asbestos"[All Fields]) AND location[All Fields])	20
AE1A 23.7.12	"asbestos exposure"[All Fields] AND job[All Fields] AND "lung cancer"[All Fields]	31
AE2A 24.7.12	"asbestos exposure"[All Fields] AND "pleural plaques"[All Fields] AND ("review"[Publication Type] OR "review	42
AE3A 24.7.12	"asbestos bodies"[All Fields] AND ("sputum"[MeSH Terms] OR "sputum"[All Fields]) "asbestos bodies"[All Fields] AND "bronchoalveolar lavage"[All Fields] "asbestos bodies"[All Fields] AND "lung tissue"[All Fields]	43 69 120
AE4A	"asbestos exposure"[All Fields] AND measurements[All Fields]	82

23.7.12	"asbestos exposure"[All Fields] AND "job exposure matrix"[All Fields]	25
AE5A 23.7.12	"asbestos exposure"[All Fields] AND duration[All Fields] AND "lung cancer"[All Fields]	62
ER1A 25.07.12	(("asbestos"[MeSH Terms] OR "asbestos"[All Fields]) OR "asbestos exposure"[All Fields]) AND ("lung cancer"[All Fields] OR "lung neoplasm"[All Fields]) AND ("dose response"[All Fields] OR "dose effect"[All Fields])	87
ER2A 23.7.12	("asbestos"[MeSH Terms] OR "asbestos"[All Fields]) AND "lung cancer"[All Fields] AND "No observed adverse effect level"[All Fields]	3
ER3A 23.7.12	("asbestos"[MeSH Terms] OR "asbestos"[All Fields]) AND "lung cancer"[All Fields] AND ("lag time"[All Fields] OR latency[All Fields] OR (("time"[MeSH Terms] OR "time"[All Fields]) AND onset[All Fields] AND exposure[All Fields]))	101
ER4A 23.7.12	(("asbestos"[MeSH Terms] OR "asbestos"[All Fields]) OR "asbestos exposure"[All Fields]) AND ("lung cancer"[All Fields] OR "lung neoplasm"[All Fields]) AND ("prognosis"[MeSH Terms] OR "prognosis"[All Fields])	77
ER5A	(Se ovenfor – del af samme spørgsmål)	
CPC1A 23.7.12	(("asbestos"[MeSH Terms] OR "asbestos"[All Fields]) OR "asbestos exposure"[All Fields]) AND ("lung cancer"[All Fields] OR "lung neoplasm"[All Fields]) AND ("predisposing conditions"[All Fields] OR "predisposing diseases"[All Fields] OR "predisposing factors"[All Fields])	2
CPC2A 27.7.12	("lung cancer"[All Fields] OR "lung neoplasm"[All Fields]) AND (non-occupational[All Fields] OR (residential[All Fields] AND ("etiology"[Subheading] OR "etiology"[All Fields] OR "causes"[All Fields] OR "causality"[MeSH Terms] OR "causality"[All Fields]))) AND ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields])	39
CPC3A 26.7.12	("lung cancer"[All Fields] OR "lung neoplasm"[All Fields]) AND ("asbestos"[MeSH Terms] OR "asbestos"[All Fields]) AND (non-occupational[All Fields] OR residential[All Fields])	28
CPC4A 26.7.12	("lung cancer"[All Fields] OR "lung neoplasm"[All Fields]) AND exposures[All Fields] AND ("effect modification"[All Fields] OR ("Interaction"[Journal] OR "interaction"[All Fields]))	81
CPC5A 26.7.12	("lung cancer"[All Fields] OR "lung neoplasm"[All Fields]) AND (("asbestos"[MeSH Terms] OR "asbestos"[All Fields]) AND exposure[All Fields]) AND ((non-occupational[All Fields] AND exposures[All Fields]) OR ("environmental exposure"[MeSH Terms] OR ("environmental"[All Fields] AND "exposure"[All Fields]) OR "environmental exposure"[All Fields] OR ("environmental"[All Fields] AND "exposures"[All Fields]) OR "environmental exposures"[All Fields])) AND ("Measurement (Mahwah N J)"[Journal] OR "measurement"[All Fields])	14

APPENDIX 6. FLOW DIAGRAM (3.2)



APPENDIX 7. DATA EXTRACTION SHEET FOR ORIGINAL STUDIES (3.3)

Key question:
First author:
Title:
Journal year, number, pages:

Study design:

☐ Meta-analysis ☐ Systematic review ☐ Cross sectional study

☐ Cohort study ☐ Case control study ☐ Economic analysis

☐ Survey ☐ Longitudinal follow-up of cases ☐ Other, specify:

☐ Case series ☐ Case report _____

☐ Descriptive study of disease register (reporting/surveillance)/occupational statistics

Selection of study population/patients:

☐ Convenience sample ☐ Consecutive sample ☐ Random selection

☐ Not reported ☐ Other, specify: _____

Population/patient characteristics (age, sex, country, …): _____

Type of industry/job: _____

Comparison group: ☐ Yes

Characteristics (age, sex, country,…): _____

☐ No

☐ Not applicable ☐ Do not know

Response rate: _____ %

Sample size: n = _____ of which number with lung cancer: n = _____ (%)

Measurement of exposure:

☐ Industry ☐ Self-reported agents

☐ Occupation ☐ Group measurement in the workplace

☐ Task ☐ Individual measurement in the workplace

☐ Other, specify: _____

Type of **exposure**:

☐ Chrysotile ☐ Amphiboles

☐ Mixed ☐ Unknown

Level of **exposure**:

Unit (e.g. fiber/ml, mppcf): _____

Mean/median: _____ Minimum: _____ Maximum: _____

☐ Not specified ☐ Low ☐ Moderate ☐ High ☐ Various

Duration of exposure: _____

Is the exposure adequately described?

☐ Yes ☐ Breathing zone ☐ No mention

☐ Yes, partly ☐ No ☐ Do not know

☐ Stationary ☐ Not applicable

Measurement of outcome

☐ Questionnaire ☐ Cancer Register ☐ Hospital-based register

☐ Death certificates ☐ Other, specify: _____

Is the **outcome** adequately described?

☐ Yes ☐ No ☐ Not applicable

☐ Yes, partly ☐ No mention ☐ Do not know

Was the measurement of the outcome sound?

☐ Yes ☐ No ☐ Not applicable

☐ Yes, partly ☐ No mention ☐ Do not know

Limitations:

Data probably **confounded**?

☐ Yes ☐ Yes, partly ☐ Not applicable

☐ Yes, by smoking ☐ No ☐ Do not know

☐ Other, specify: _____

Potential confounders taken into account? _____

Data probably **biased?**

☐ Yes Yes, partly misclassification of… ☐ Other, specify:

☐ No ☐ Exposure _____

☐ Not applicable ☐ Disease _____

☐ Do not know ☐ Selection of study population _____

☐ Healthy worker effect adequately addressed _____

Are the results probably due to **chance**?

☐ Yes ☐ Yes, partly (confidence interval contains 1 or p-value ≥ 0.05)

☐ No ☐ No mention ☐ Not applicable

☐ Do not know

Key findings that are relevant to the key question: _____

Source of **funding**: _____

First author, journal year:

Grading of the study:

Meta-analysis or **systematic reviews of RCT**s / **RCT** with risk of bias

☐ 1++	☐ 1+	☐ 1 -
(High quality/very low risk)	(Well conducted / low risk)	(High risk)

Case control or **cohort studies** with risk of confounding, bias, or chance

☐ 2++	☐ 2+	☐ 2 -
(Very low risk of confounding, bias or chance)	(Low risk)	(High risk)

☐ 3 Non-analytic studies

☐ 4 Expert opinion

APPENDIX 8. R-AMSTAR DATA EXTRACTION SHEET FOR META-ANALYSES AND REVIEWS (3.3)

How to use the R-AMSTAR tool?

The tool contains 11 questions with regard to the quality of the review. These questions are in the left column. Based on the criteria mentioned in the right column, every question should be assigned a score from 1 to 4. The sum of all scores is the overall quality score of the systematic review.

AMSTAR items	*Criteria*
1. Was an "a priori" design provided? The research question and inclusion criteria should be established before the conduct of the review.	A A clearly focused (PICO-based) question B Description of inclusion criteria C Study protocol is published and/or registered in advance 3 criteria→4, 2→3, 1→2, 0→1
Explanation: A. It should be explicitly mentioned that a protocol was published or registered, for example in PROSPERO an online international prospective register of systematic reviews. C. The question contains Population, Intervention/exposure, Comparator/controll and Outcome.	
2. Was there duplicate study selection and data extraction? There should be at least two persons who independently extracted data and a consensus procedure for disagreements should be in place.	A At least two persons independently extracted the data, explicitly stated B Statement of consensus procedure for disagreements C Disagreements among extractors resolved properly as stated or implied 3 criteria→4, 2→3, 1→2, 0→1
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated, and where feasible, the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	A At least two electronic sources are searched B Years and databases used are mentioned C Key words and/or MESH terms are stated and where feasible the search strategy outline is provided D Searches should are supplemented by consulting current contents, reviews, textbooks, registers and by reviewing the references in the studies found E Journals are hand-searched or manual searched 4 or 5 criteria→4, 3→3, 2→2, 1 or 0→1
Explanation: E. hand-searched means identifying highly relevant journals and conducting a manual, page-by-page search of their contents looking for potentially eligible studies.	
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	A The authors state that they searched for reports regardless of their publication type. B The authors state whether or not they excluded any reports based on their publication status, language etc. C "Non-English papers were translated"or readers sufficiently trained in foreign language D No language restriction or recognition of non-English articles 3 or 4 criteria→4, 2→3, 1→2, 0→1
5. Was a list of studies (included and excluded)	A Table/list/figure of **included** studies, a

AMSTAR items	*Criteria*
provided? A list of included and excluded studies should be provided.	reference list does not suffice B Table/list/figure of **excluded** studies either in the article or in a supplemental source C Satisfactory/sufficient statement of the reason for exclusion of the seriously considered studies D Reader is able to retrace the included and the excluded studies anywhere in the article bibliography, reference or supplemental source 4 criteria→4, 3→3, 2→2, 1→1
Explanation: "Excluded studies" refers to those studies seriously considered on the basis of title and/or abstract, but rejected after reading the body of the text.	
6. Were the characteristics of the included studies provided? In an aggregated form, such as a table, data from the original studies should be provided on the participants, interventions/exposure, and outcomes. The ranges of characteristics in all the studies analyzed, e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	A In an aggregated form such as a table, data from the original studies are provided on the participants, interventions/exposure and outcomes B Ranges are provided of the **relevant** characteristics in the studies analyzed C The information provided appears to be complete and accurate 3 criteria→4, 2→3, 1→2, 0→1
7. Was the scientific quality of the included studies assessed and documented? ''A priori'' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo-controlled studies, or allocation concealment as inclusion criteria); for other types of studies, alternative items will be relevant.	A 'A priori'methods are provided B The scientific quality of the included studies appears to be meaningful C Discussion/recognition/awareness of level of evidence is present D Quality of evidence is rated/ranked base on characterized instruments 4 criteria→4, 3→3, 2→2, 1 or 0→1
Explanation: D. A characterized instrument is a created instrument that ranks the level of evidence, e.g. GRADE [Grading of Recommendations Assessment, Development and Evaluation].	
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	A The scientific quality is considered in the analysis and the conclusions of the review B The scientific quality is explicitly stated in formulating recommendations C Conclusions integrated/drives towards practice guidelines D Clinical consensus statement drives toward revision or confirmation of practice guidelines 4 criteria→4, 3→3, 2→2, 1 or 0→1
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I^2). If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).	A Statement of criteria that were used to decide that the studies analyzed were similar enough to be pooled B For the pooled results, a test is done to ensure the studies were combinable, to assess their homogeneity C a recoginition of heterogeneity or lack of thereof is present D If heterogeneity exists a 'random effects model' is used and/or the rationale of combining is taken into consideration

AMSTAR items	*Criteria*
	E If homogeneity exists, author state a rationale or a statistical test 4 or 5 criteria→4, 3→3, 2→2, 1 or 0→1
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	A Recognition of publication bias or file-drawer effect B Graphical aids (e.g. funnel plot) C Statistical tests (e.g. Egger regression test) 3 criteria→4, 2→3, 1→2, 0→1
11. Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	A Statement of sources of support B No conflict of interest. This is subjective and may require some deduction or searching. C An awareness/statement of support or conflict of interest in the **primary** inclusion studies 3 criteria→4, 2→3, 1→2, 0→1

APPENDIX 9. EVIDENCE MODEL (3.6)

Degree of evidence of a causal association between an exposure to a specific risk factor and a specific outcome (Danish Working Environment Authority, 2010)

THE FOLLOWING CATEGORIES ARE USED
+++ strong evidence of a causal association
++ moderate evidence of a causal association
+ limited evidence of a causal association
0 insufficient evidence of a causal association
- evidence suggesting lack of a causal association

DESCRIPTION OF CATEGORIES
Strong evidence of a causal association (+++):
A causal relationship is very likely. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It can be ruled out with reasonable confidence that this relationship is explained by chance, bias or confounding.

Moderate evidence of a causal association (++):
A causal relationship is likely. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It cannot be ruled out with reasonable confidence that this relationship can be explained by chance, bias or confounding, although this is not a very likely explanation.

Limited evidence of a causal association (+):
A causal relationship is possible. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It is not unlikely that this relationship can be explained by chance, bias or confounding.

Insufficient evidence of a causal association (0):
The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of a causal association (-):
Several studies of sufficient quality, consistency and statistical power indicate that the specific risk factor is not causally related to the specific outcome.

COMMENTS
The classification does not include a category for which a causal relation is considered as established beyond any doubt.

The key criterion is the epidemiological evidence.
The likelihood that chance, bias and confounding may explain observed associations are criteria that encompass criteria such as consistency, number of 'high quality' studies, types of design etc.
Biological plausibility and contributory information may add to the evidence of a causal association.

APPENDIX 10. SEMINAR PROGRAM AND LIST OF PARTICIPANTS (3.7)

PROGRAM FOR ASBESTOS SEMINAR
ODENSE, 22.-23. NOVEMBER 2012

Thursday

10-12	Plenum
12-13	Lunch
13-15	Working groups
15-15.30	Coffee
15.30-16.30	Working groups
16.30-18	Plenum
18-19.30	Break/walk (rapporteurs revise text and mail it to working group)
19.30	Dinner

Friday

8.30-9.00	Read revisions
9-10.30	Working groups (possible to shift group)
10.30-11	Coffee
11-13	Plenum (statements)
13-14	Lunch

Working groups:

Lung cancer: (LC)	David Sherson (CM), Niels Christian Hansen (R), Karen Ege Olsen
Asbestos exposure: (AE)	Jesper Rasmussen (CM), Lene Snabe Nielsen (R), Christy Barlow
Exposure-response (ER)	Maria Albin (CM), Jesper Bælum (R), Dick Heederik, Panu Oksa, Marcello Lotti
Competing and pre-disposing factors: (CPC)	Thomas Kraus (CM), Søren Dahl (R), Sverre Langård, Johnni Hansen

CM: Chairman
R: Rapporteur

Nov. 30: Deadline for major disagreements/revisions

Participants

Christy Barlow, USA	cbarlow@chemrisk.com
David Sherson, Denmark	david.sherson@ouh.regionsyddanmark.dk
Dick Heederik, The Netherlands	d.heederik@uu.nl
Jesper Bælum, Denmark	jesper.baelum@ouh.regionsyddanmark.dk
Jesper Rasmussen, Denmark	jesper.rasmussen@slb.regionsyddanmark.dk
Johnni Hansen, Denmark	johnni@cancer.dk
Karen Ege Olsen, Denmark	karen.ege.olsen@ouh.regionsyddanmark.dk
Lene Snabe Nielsen, Denmark	lenesnabe@gmail.com
Marcello Lotti, Italy	marcello.lotti@unipd.it
Maria Albin, Sweden	maria.albin@med.lu.se
Niels Christian Hansen, Denmark	niels.christian.hansen@ouh.regionsyddanmark.dk
Panu Oksa, Finland	panu.oksa@ttl.fi
Sverre Langård, Norway	svlangaa1@online.no
Søren Dahl, Denmark	soren.dahl@svs.regionsyddanmark.dk
Thomas Kraus, Germany	thomas.kraus@post.rwth-aachen.de

APPENDIX 11. ARLC: HISTOLOGY, LOCATION, PROGNOSIS AND SCREENING (4.1)

LOCATION AND HISTOLOGY

Tumor location and histology may be two discriminating features pointing to the cause of lung cancer. Many studies have examined possible relationships between asbestos-related lung cancer and both tumor location and cell type. Tobacco-related lung cancers often occur in the upper lobes with a typical upper: lower lobe ratio of about 2.5:1.0 [45-47]. In contrast, there is considerable conflicting data concerning the lobe of origin associated with asbestos-related lung cancer. A number of earlier studies demonstrated a reverse location for asbestos-related lung cancer. A lower lobe association with asbestos exposure was described by Antilla & Karjalainen, Hillerdal (1983), Sluis-Cremer (1980) and Weiss (1981) [48-51]. This was thought to be biologically plausible as asbestos-related fibrosis is typically found in the dependent lung portions [50, 52]. However, other studies have shown upper lobe location similar to tobacco-related lung cancers [46, 54, 55, 265]. Concerning histology of ARLC some studies have shown excess adenocarcinomas [54, 56-58]. However, many other studies have failed to show increased risk of adenocarcinoma [46, 55, 59-61, 266]. Thus, as in the case of tumor location results concerning histology of asbestos-related lung cancer are conflicting. As many of the above studies have not adequately controlled for smoking and sex the associations between asbestos and lung cancer, histology and location become even less distinct.

THE FOLLOWING 5 STUDIES WERE REVIEWED WITH SIGN (SEE TABLE A11)

Brodkin and colleagues (1997) [63] performed a nested case-control study, which investigated the consecutive hospitalized lung cancer cases. Histology and lobe origin in 78 asbestos-exposed and 214 non-exposed heavy smokers was evaluated. All subjects were from the prospective U.S. CARET Study, where randomized preventive treatment with carotene and retinol was tested. The asbestos-exposed subjects had at least 5 years in high-risk trade or radiographic evidence of asbestos- related effects. No significant differences in cell types in exposed and non-exposed: adenocarcinoma 32%/30%, squamous 32%/20%, large cell 16%/24% and small cell 15%/21%. There was a tendency for asbestos-exposed to have more lower lobe tumors, OR 1.92 (95% CI: 1.03-3.55). However, both exposed (67%) and non-exposed (80%) had mainly upper/middle lobe tumors. SIGN 2+

A recent cohort study from 2012 investigated tumor location in 1,701 consecutive lung cancer cases diagnosed 1997 and 2009 at two French University Hospitals. [64]. Asbestos-exposed had a minimum exposure of 6 months obtained by a standard questionnaire. Cumulative exposure scores were calculated for lung cancer cases. Tumors were subdivided into central or peripheral locations. Central tumors were defined as those accessible and visible by white light bronchoscopy. Smoking data was obtained from face to face interviews. Histology was strongly related to tumor location. More adenocarcinoma tumors (53.9%) were located peripherally (OR=4, CI 2.88-5.54). Asbestos-exposure was associated with a more central location: 65%vs 58.9% in non-exposed (p=0.016). A positive exposure-response relationship with cumulative exposure index to asbestos and central location was demonstrated (p=0.001). SIGN 2+

Karjalainen et al. (1999) [65] carried out a large study in 1999, which included all notified cases of asbestosis (n=1376) and benign pleural disease (n=4887) in Finland between 1967 and 1995. 13 job titles were identified. Subsets were compared to compensation decisions with a high degree of agreement (92% and 94%). Cancer cases were identified by the Finnish Cancer Registry. SIR was calculated from date of notification. No data on smoking or non-occupational exposures were available. Men with asbestosis had a lung cancer SIR of 6.7 (95% CI: 5.6-7.9). Lung cancer risk was raised for all cell types and did not change markedly over time. Men with benign pleural disease had an increased mesothelioma risk (SIR 5.5, 95% CI: 1.5-14) and a slightly elevated risk of lung cancer (SIR 1.3, 95% CI: 1.0-1.8). SIGN 2-

A U.S. case-control study from 1998 investigated 456 lung cancer cases [45]. An asbestos exposure index was calculated and different jobs and different time periods were weighed differently. Tumors were divided into upper and lower lobe locations. Adenocarcinoma tumors were compared to the other cell types. Sex, age, family history and smoking were controlled for. Heavy smokers tended to have more upper lobe tumors: 54.7 vs. 46.2% (p=0.07). Asbestos exposure was associated with upper lobe location. Of upper lobe tumors 14.6% were associated with significant asbestos exposure, compared with 5.4% associated with lower lobe tumors (p<0.01). Asbestos exposure did not predict tumor histology in multiple regression analyses. SIGN 2+

In 2003 Paris and colleagues studied 1,493 consecutive lung cancer cases from two French hospitals diagnosed between 1997 and 2006 [267, 268]. Face-to-face interviews including an occupational questionnaire were performed. Minimum occupational exposures were defined by at least 5% of work time for at least 1 year. Sex, age and smoking were controlled. Significant associations were observed between adenocarcinoma and exposure to welding fumes and silica, but not to asbestos. No

associations were demonstrated between adenocarcinoma and age, sex or smoking except for a negative association with smoking duration ($p<0.0001$). SIGN 2+

A recent Danish study evaluated 857 consecutive hospitalized lung cancer cases. All subjects were asked if they had been exposed to asbestos: Table A10 shows results from the 423 male. There were no significant differences in cell type between asbestos exposed and non-exposed.

Table A10. Lung cancer subtypes for 423 consecutive male patients with or without self-reported occupational asbestos exposure. All diagnosed at Department of Respiratory Medicine, Odense University Hospital 2007 to 2010. (Hansen NC. Personal communication).

	Occupational asbestos exposure		
	Yes	No	Total
Small cell lung cancer	15 14.0%	51 16.1%	66 15.6%
Squamous cell carcinoma	31 29.0%	85 26.9%	116 27.4%
Adenocarcinoma	30 28.0%	89 28.2%	119 28.1%
Other non small cell lung cancer	27 25.2%	74 23.4%	101 23.9%
Clinical diagnosis	4 3.7%	17 5.4%	21 5.0%
Total	107 100.0%	316 100.0%	423 100.0%

Table A11. Tabular presentation of LC3+LC4 studies.

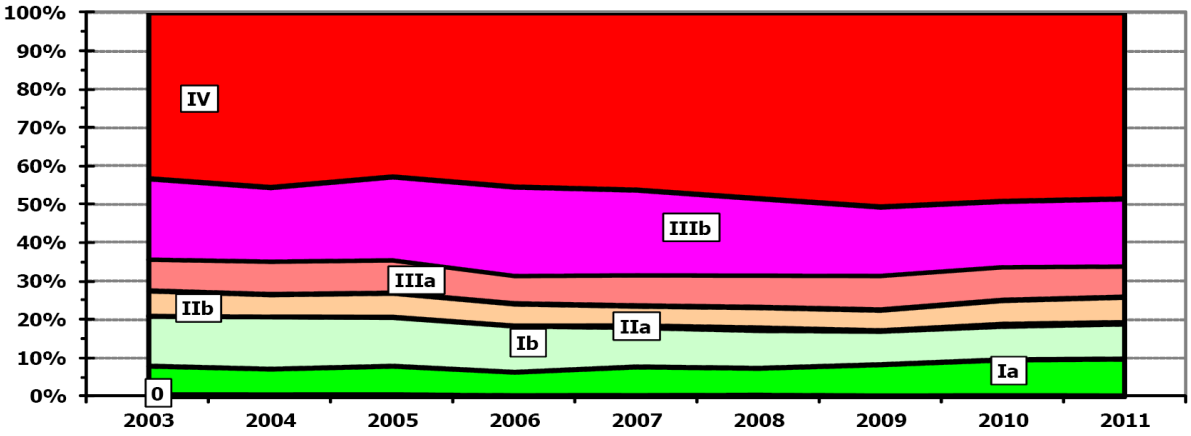
First author, year of publication, reference no.	Characteristics of participants	Measurement methods and potential confounders			Results	Grading
	N, sex, country, type of industry/job	Exposure *Asbestos type, unit*	Outcome	Confounders and other factors		
Brodkin, 1997 [63]	78 asbestos-exposed and 214 non-exposed heavy smokers. All from CARET Study, USA	>5 years in high risk trade or radiographic evidence of asbestos-related effects	Histology and lobe of origin	Randomized preventive treatment with catotene and retinol	No significant differences in cell types in exposed and non-exposed: adeno 32%/30%, Squamous 32%/20%, large cell 16%/24% and small cell 15%/21%. There was a tendency for asbestos-exposed to have more lower lobe tumors, OR 1.92 (95% CI 1.03-3.55). However, both exposed (67%) and nonexposed (80%) had mainly upper/middle lobe tumors.	2+
Gonzales, 2012 [64]	A case-case study with1701 lung cancer cases from 2 French University Hospitals. Diagnosed 1997-2009	Minimum exposure of 6 mos. obtained by questionnaire. Cumulative exposure scores calculated	Central or peripheral location. Central tumors were accessible and visible by white light bronchoscopy	Smoking data from face to face interview	Histology was strongly related to tumor location. More adeno tumors (53.9%) were located peripherally (OR 4, CI 2.88-5.54). Asbestos exposure was associated with a slightly more central location: 65% 8.9% in nonexposed (p=0.016). A positive dose-response relationship with cumulative expose index to asbestos was demonstrated (p=0.01)	2+
Karjalainen, 1999 [65]	Notified cases in Finland: 1967-95. Asbestosis=1376 Benign pleural disease=4887	13 job titles were identified. Subsets were compared to compensation decisions with a high degree of agreement (92% and 94%)	Cancer identified by the Finnish Cancer Registry. SIR calculated from date of notification	No data on smoking or non-occupational exposures	Men with asbestosis had a lung cancer SIR of 6.7 (95% CI 5.6-7.9). Lung cancer risk was raised for all cell types and did not change markedly over time. Men with benign pleural disease had increased mesothelioma risk (SIR 5.5, 95% CI 1.5-14) and a slightly elevated risk of lung cancer (SIR 1.3, 95% 1.0-1.8).	2+
Lee, 1998 [45]	Case-control study based on 456 lung cancer cases (U.S.)	An asbestos exposure index was calculated. Different jobs and different time periods were weighed differently	Tumor location: upper vs. lower Cell type: adeno vs others	Controlled for sex, age, family history and smoking	Heavy smokers tended to have more upper lobe tumors: 54.7 vs 46.2% (p=007). Asbestos exposure was associated with upper lobe location. Of upper lobe tumors 14.6% were associated with significant asbestos exposure, compared with 5.4% associated with lower lobe tumors p<0.01). Asbestos exposure did not predict tumor histology in multiple regression analyses.	2+
Paris, 2010 [268]	Consecutive lung cancer cases from 2 French hospitals. 1997-2006	Face-to-face occupa-tional questionnaire. Minimum exposure : >5% of work time for at least 1 year	Histological cell type	Controlled for sex, age and smoking	Significant associates were observed between adenocarcinoma and Exposure to welding fumes and silica, but not to asbestos. No associations were demonstrated between adenocarcinoma and age, sex or smoking except for a negative association with smoking duration (p<0.0001).	2+

LUNG CANCER PROGNOSIS

The 5-year survival rate has changed very little in the past 50 years. The 5-year survival for Danish males was 7% in 1964-68 and 9% in 1999-2003. Lung cancer prognosis is directly dependent on the stage of diagnosis. Thus data concerning stage at diagnosis will predict survival.

Figure A1 shows diagnoses stages of all lung cancer cases in Denmark from 2003-2011 [75]. No improvement in earlier diagnosis is evident.

Figure A1. Stage at diagnosis of 4918 primary lung cancer cases in Denmark [62].



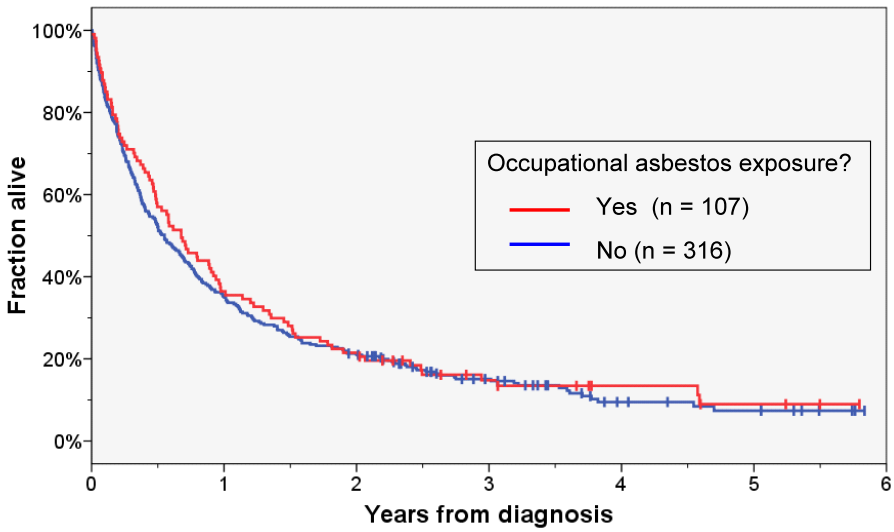
The only available data concerning the diagnosis stage of ARLC shows no differences when compared to other lung cancers [62]. Table A12 below shows data from 857 male and female lung cancer cases from the island of Funen compared with all lung cancer cases in Denmark. Of the 857 cases 118 had previous asbestos exposure.

Table A12. Stage at diagnosis for lung cancer cases in men and women from Funen compared with all Danish cases 2007-2010 [62].

Denmark			Funen 2007-2010			
			Asbestos exposure		Total	
	2007-2010		Yes	No		
IA	8.4%		8.5%	9.6%	9.5%	
IB	9.3%		11.0%	7.3%	7.8%	
IIA	0.7%	32.3%	0.8%	2.0%	1.9%	31.9%
IIB	5.3%		1.7%	2.6%	2.5%	
IIIA	8.5%		8.5%	10.6%	10.3%	
IIIB	19.2%	67.7%	17.8%	11.8%	12.6%	68.1%
IV	48.6%		51.7%	56.2%	55.5%	
Total	10.0%	100%	100%	100%	100%	100%

There is very little data concerning survival of ARLC cases. No survival differences are seen in figure A2 where ARLC and non-ARLC cases are compared. There is no reason to suspect that survival for these cases would differ significantly from other cases of lung cancer.

Figure A2. Survival curves (Kaplan-Meier) for 423 consecutive male lung cancer patients with or without self-reported occupational asbestos exposure. All diagnosed at Department of Respiratory Medicine, Odense University Hospital 2007 to 2010. Estimated survival curves (Hansen NC. Personal communication).



Numbers at risk:

Exposed	39	23	11	6	3
Not exposed	111	66	31	11	7

LUNG CANCER SCREENING CONSIDERATIONS FOR ASBESTOS EXPOSED WORKERS

It has now been shown that annual low-dose CT screening can reduce mortality. This was clearly demonstrated in 2011 with the large randomized control trial, the National Lung Screening Trial (NLST) [68]. A relative mortality reduction of 20% was demonstrated. In March 2012 the National Comprehensive Cancer Network published their recommendations concerning low-dose CT screening [69]. The NCCN panel recommended annual low-dose CT screening for 2 high risk groups:

1. 30 pack-years or more, age 55-74 and smoking cessation < 15 years. This is a category 1 recommendation, meaning that all members were in agreement and the evidence is strong.
2. 20 pack-years or more, age > 50 plus an occupational exposure not including second-hand smoke. The following occupational carcinogens were included: asbestos, silica, cadmium, arsenic, beryllium, chromium, diesel fumes and nickel. This is a category 2B recommendation. The evidence is somewhat less without unanimous agreement among panel members.

This is the first time an international organization has recommended annual screening for well-defined high risk groups. However, this remains controversial and has been recently reviewed [70]. The two key problems are many false positives and high costs. In the NLST study 94% of the positive screening tests were false positives. To further complicate the question a recent randomized controlled trial in Denmark did not show mortality reduction so far, but the observation period continues [71]. This study was much smaller than the NLST with less power. 4104 individuals were randomized and the risk group wasn't as high based on 20 pack-years or more. The borderline significant increase in all mortality causes in the screened group suggests that this group may have been sicker than the control group. There are ongoing screening trials in several European countries. Should we wait for these results? It will probably be a number of years before these trials are completed and data can be integrated in a meta-analysis.

Another key question is how can previously exposed asbestos workers be identified? Factory personnel files are ideal, but may have been destroyed after workplaces close. Once workers with previous asbestos exposure have been identified, how can their level of risk be estimated? Existing air measurements are only available in a minority of workplaces. There are published reviews of previously published asbestos measurements as well as a few attempts at job-exposure matrices [20, 72-74]. These may be useful. The next key question is how the asbestos-exposure level should be found. Which of the previous asbestos-exposed workers should be screened? Should the level of 25 fiber/cm^3-years be chosen? Or is this too high?

Workers with previous asbestos exposure are getting older and older. Low-dose screening programs of this population may reduce their mortality from lung cancer. However, screening is costly and complicated with many false positives. Coming screening results from European studies may help clarify this dilemma.

APPENDIX 12. BIOLOGICAL MARKERS: PLEURAL PLAQUES (PP), ASBESTOS BODIES (AB) AND ASBESTOS FIBERS (AF) (4.2)

Pleural abnormalities are divided into PP (localized pleural thickening) and diffuse pleural thickening, DPT [86]. PPs represent localized pleural thickening, generally of the parietal pleura, and may be seen on the diaphragm, on the chest wall and at other sites. According to the ILO 2000 Classification a minimum width of about 3 mm is required for an in-profile plaque to be recorded as present [86]. DPT is thickening of the visceral pleura. For the purpose of the ILO 2000 Classification DPT extending up the lateral chest wall is recorded *only* in the presence of, and in continuity with, an obliterated costophrenic angle. Its extent is recorded in the same manner as for pleural plaques. A minimum width of about 3 mm is required for in-profile DPT to be recorded as present [86]. PP and DPT can also be classified with the International Classification of HRCT for Occupational and Environmental Respiratory Diseases [87].

PLEURAL PLAQUES [269]

The occurrence of bilateral PP on a chest X-ray is a strong indicator of previous exposure to asbestos fibers with a specificity of 80-90% [89]. This specificity has been observed after applying strict criteria for occurrence of PPs on the chest X-ray: Bilateral lesions, at least 5 mm thick and/or calcified, well demarcated, and no remnants of pleurisy, i.e. costophrenic angles not obliterated [88]. These criteria are more specific than the ILO criteria from 1980 [90].

Most authors state that PPs are rarely seen until 20 years after the initial exposure to asbestos. However, by re-evaluating previous chest X-rays in exposed workers who all later had developed PP, it was possible retrospectively to identify PP as early as 10 years after initial exposure [91]. A recently published study has found that smokers for the same degree of asbestos exposure more easily develop PP as found on chest X-ray [92]. A positive association between the degree and duration of asbestos exposure and the likelihood of finding PP on a chest X-ray has recently been confirmed [93].

In a review from 2011 [94] it is emphasized that most of the current knowledge about the relation between PP and thoracic malignancies is based on the detection on PP from chest X-ray. However, studies using CT for detection of CT have become more common in recent years. An early study showed that CT of the chest could detect PP in subjects without any signs of PP on chest X-ray according to ILO-criteria. In a group of 231 asbestos exposed workers seeking compensation and

having no PP according to ILO-criteria on a chest X-ray, CT showed bilateral PP in 46 and unilateral PP in 26 [95]. Contrary to this, a recent review stated, *"when compared with computed tomography (CT) scan, most pleural plaques are in fact identified via CXR*" [270]. However, this seems to be a misinterpretation of the quoted reference [96]. Elshazeley et al. only studied individuals with PPs found on chest x-rays. No individuals without PPs on chest x-rays were studied.

As for chest X-ray CT has shown that longer time since first exposure and higher estimated dose increase the incidence of PP [97]. Despite the sensitivity of CT, lack of PP on a CT does not rule out asbestos exposure. In the study by Paris et al. all participants were considered to have some degree of asbestos exposure, but no more than about 20% had PP in the most exposed group. Data from the same French cohort study have been used to study the agreement between the initial evaluation of the CT and a final consensus evaluation by a specialist panel. Only a moderate agreement with a kappa = 0.58 was found. A recent study has shown that CT may systematically overestimate the true prevalence of PP, if the patient is only studied in the supine position. It was observed the some of the suspected PP disappeared when the CT was repeated in the prone position [98]. A CT did not find at relation between the PP area and the estimated asbestos exposure [99].

Many studies have investigated possible increased lung cancer risk among persons with PP. Weiss published a review of 13 studies in 1993 [100]. Ten of the reviewed studies showed no association between PP and lung cancer in subjects without asbestosis. A panel of French experts reanalyzed lung cancer mortality from the 6 cohort studies included in the Weiss review [94]. They found an SMR of 1.5 (95% CI: 1.2-1.9) based on 83 observed lung cancer cases in individuals with PPs. Hillerdal showed that asbestos-exposed individual have an increased lung cancer risk compared to the general population [88]. In the CARET study 2089 asbestos-exposed individuals were followed. A nearly doubling of lung cancer risk was observed among those with pleural thickening or plaques (RR = 1.91, 95% CI: 1.25-2.92). Age, smoking and asbestos exposure duration were controlled for. However, there was no data on cumulative exposure [104]. The American Thoracic Society concluded in 2004 that PPs are associated with an increased lung cancer risk compared with those with similar exposure but without PPs [111].

Bilateral PPs on a chest X-ray are strong indicator of previous asbestos exposure beginning 20 or more years ago. Individuals with PPs have an increased lung cancer risk compared to the general population. However, there is insufficient and contradictory evidence concerning an increased lung cancer risk in persons with PPs compared to others with similar asbestos exposure but without PPs.

There is a lack of evidence concerning the importance of PP only visible on CT. There is a need for prospective CT studies of asbestos-exposed individual with PPs.

ASBESTOS BODIES (AB) AND ASBESTOS FIBERS (AF)

Asbestos bodies are asbestos fibers covered with an iron-protein coat [101]. There are also a number of characteristics that asbestos fibers typically have in order to induce the formation of asbestos bodies: insoluble, length greater than 10 µm, diameter less than 1 µm, and a straight and rigid shape [102, 108]. Subsequently, asbestos bodies rarely form on chrysotile asbestos fibers. It should be noted that ferruginous bodies are not the same as asbestos bodies as ferruginous bodies are any mineral fiber, non-mineral fiber, or non-fibrous particles that acquire an iron-containing coat.

In Denmark there is no tradition for identifying and counting AF in biological specimens. Thus it is only relevant to look into possibility of using ABs as a marker of previous asbestos exposure. ABs are a hallmark of asbestos exposure. Studies have demonstrated good correlations between ABs recovered in bronchoalveolar lavage (BAL) and ABs in lung tissue [105, 106]. ABs in BAL correlate well with the number of amphibole (amosite and crocidolite) fibers, but not chrysotile fibers in lung tissue [107]. The European Respiratory Society has published recommended methods for identifying and counting ABs in BAL [271]. One AB/ml reflects between 100 to 10,000 ABs/cm^3 wet lung tissue [103]. One AB/ml is considered to reflect asbestos exposure [106, 109]. However, it is not possible to estimate when the exposure has taken place.

With this background, the Helsinki Criteria from 1997 recommended that the presence of >1 AB/ml should be used to indicate probable work-related asbestos exposure [110]. The American Thoracic Society [111] has adopted the position that the presence of ABs in BAL is a reliable and clinically useful marker of previous asbestos exposure.

APPENDIX 13. NARRATIVES OF COHORT AND CASE-CONTROL STUDIES (4.3)

A number of articles arise from a limited number of cohorts, which are also basis for many of the meta-analyses shown in section 4.3.

COHORT STUDIES

Mining and milling

The Quebec mining cohort. One of the oldest cohorts is the Canadian miners comprised of 10,918 males and working with mining and milling in Quebec summarized by [125]. The persons were born between 1893 and 1920 and followed until 1992. The authors stated that there was a negligible excess lung cancer risk below 1,000 f-y/ml (300 mppcf-years). However, RRs were 1.3-1.5 in the highest group above 100 f-y/ml (30 mppcf-years).

The Wittenoon crocidolite miners [152, 153, 272]. This Australian study comprised 6,910 men and 4,415 women employed between 1943 and 1966 and followed until 2007. Exposure was estimated from a survey in 1966 and was high with a median of 17.8 f/ml, while the period of employment was short, in median 128 days. Of the 2,421 deceased 222 died of mesothelioma and 302 from lung cancer. A relatively high loss to follow up was seen, 27%. This study has been the main source of exposure-response relation to crocidolite.

In a South African study with 7,317 amphibole miners [273] there was a exposure-response association for both years of exposure and cumulative exposure. SMR values increased with increasing exposure time, starting 1-4 years of asbestos exposure. Increased SMR of 223.5 ($p<0.05$) for 10-19 years residence time with 1-4 f-y/ml exposure. SMR for bronchogenic carcinoma according to cumulative dust exposure was 143.9 for the 1-5 f-y/ml group. The relative risk of lung cancer was 1.01 (1-1.01) for each increment of 1 f-y/ml ($k_L \sim 10 * 10^{-3}$ per f-y/ml) and 1.12 (1.04-1.20) for each year of exposure.

Sluis-Cremer and colleagues performed new analysis of the same study population of South African amphibole miners as Sluis-Cremer did in 1991 [135]. Data suggested that there were 26.4 more deaths from lung cancer than expected, given a SMR of 172 (CI 132-221). Crocidolite had higher toxicity than amosite for lung cancer; SMRs were 138 (CI 97-191) and 203 (CI 143-280) for amosite and crocidolite respectively.

The study of 1,672 American vermiculite mine, mill and process workers [137] exposed to amphibole asbestos showed clear exposure-related increases in lung cancer mortality. There was an increased lung cancer SMR of 170 (CI 140-210) with 15 years lag time and a borderline significant SMR for low exposures (<4.5 f-y/ml) of 150 (CI90-230). Short-term employment (< 1 year) also increased SMR to 160 (CI 110-210).

Data from a study on mortality from cancer in the Balangero cohort of 1,056 chrysotile asbestos miners [131] showed no significant increased risk for lung cancer death in spite of high exposures over 400 f-y/ml, SMR 1.27 (CI 0.93-1.70). No exposure-response association was shown for lung cancer.

Asbestos textile manufacturing

The South Carolina Textile study. A series of articles have dealt with this cohort of persons working at this plant producing asbestos textiles from mainly chrysotile but also small fraction crocidolite [118] reported about a cohort of 768 white males working with textile production and who were exposed to chrysotile asbestos suggested a linear exposure-response relationship for lung cancer with no threshold. SMR = 223 for <275 f-y/ml, 357 for 275 -1,100f-y/ml, 978 for 1,100 – 2,750 f-y/ml, 1,553 for 2,750-5,500f-y/ml. This steep exposure-response as estimated from regression line based on categorical analysis gives RR of approximately 5 for 100 f-y/ml or a $k_L = 50 * 10^{-3}$ per f-y/ml.

In the subsequent follow up slightly different inclusion criteria were used [117]. The subjects were 3,022 white males and females and black males exposed to chrysotile and a little crocidolite. White males and females experienced statistically significant excess mortality due to lung cancer, SMR= 2.30 (1.88-2.79) and 2.75 (2.06-3.61) respectively. There was increased risk for death due to lung cancer with increasing cumulative exposure. The trend was significant for white males ($Z=2.88$; $p<0.01$) but not for white females ($Z=1.71$; $p>0.05$). Data for the entire cohort demonstrate an increase in the lung cancer relative risk corresponding to a k_L of 20-30 $(\text{f-y/ml})^{-1}$ of cumulative chrysotile exposure

Stayner and colleagues [136] made a detailed exposure-response analysis of this material using different models of life time risks. They concluded that a multiplicative model fitted the data better than a linear (additive) model. Moreover, there was no evidence for a threshold. The slope k_L was estimated to 21 (95% CI: 8-36)$*10^{-3}$ per f-y/ml.

Hein and colleagues [121] analyzed the same population with follow up till 2001. Exposure-response associations were observed with steeper slope for 10-year lag time than for no lag time

or 5-year lag time. The increase in relative risk of lung cancer after 10-year lag time was 19.8 * 10^{-3} per f-y/ml. The lung cancer mortality was lower for females and non-whites.

North Carolina and Pensylvania textile workers. A study from the American textile industry was conducted by McDonald and colleagues [127] and consisted of 4,137 males from a Pennsylvania textile factory. The subjects were mainly exposed to chrysotile asbestos and less to crocidolite. SMR for lung cancer increased from 66.9 to 416 for exposures from 0 to >80 mppcf (corresponding to 250 f-y/ml)

A relatively new study by Loomis and colleagues [126] analyzed the association between chrysotile asbestos and lung cancer death among 5,770 American men and women employed in North Carolina textile plants. The authors found significantly higher mortality from lung cancer than expected with SMR of 1.96 (95% CI: 1.73-2.20). Also, the risk of lung cancer increased with cumulative fiber exposure (RR 1.102 per 100 f-y/ml, 95% CI: 1.044 to 1.164) which amounts to about to a k_L of 10.2 (95% CI: 44- 164)*10^{-3} per f-y/ml.

In a recently published study the population comprised of 6,136 predominantly white American males exposed to chrysotile asbestos and small amounts of crocidolite and amosite in the North Carolina (NC) and South Carolina (SC) textile production industry [112]. The researchers found significantly higher lung cancer mortality than expected (SMR 1.90, 95% CI: 1.70 to 2.11). However, a linear model did not give the best fit. The lung cancer slope was steeper for workers from SC than NC. Likely explanations were exclusion from work of workers with pneumoconiosis, workers with short exposure not being enumerated and less precise exposure information for NC workers. The slope for SC was judged to be less prone to such bias, and was 20 * 10^{-3} per f-y/ml as excess RR (linear model).

In Peto´s published article [129] with information on 679 males from United Kingdom working in the textile industry, RR from lung cancer death peaked 25-35 years since first exposure. No formal exposure-response analysis was undertaken but there was an overall excess of lung cancer death, and findings claimed to be compatible with a RR of 2-3 for 200-300 f-y/ml.

Among 3,211 male workers from United Kingdom Peto and colleagues [130] analyzed the relationship of mortality to measures of environmental chrysotile and crocidolite asbestos pollution in the Rochdale asbestos textile factory. The exposure-response was SMR 1.53*10^{-4} per particle-year/ml, approximated for SMR 0.005 per f-y/ml (entire cohort) and SMR 0.015 (those employed 1951 or later), respectively. Suggested prediction: SMR = 1+0.01xf-y/ml. RR

for lung cancer was lower 35 years or more after first exposure as compared to 20-34 years. Risk was independent of age at first exposure.

Insulation manufacturing and work

The New Jersey insulation workers. In a study of 820 white American males exposed to amosite asbestos and very little chrysotile when working with insulation of pipes, boilers and turbines of ships [132] a linear zero threshold exposure-response association seemed implausible. The SMR was 541 for lung cancer from 5 to 40 years after onset of work. The heavier the exposure, the greater the response tended to be in terms of higher SMRs. Marked excesses were evident within 15 years for the longer-tern workers. For those worked shorter periods of time it took 25 years or more.

Another study with insulation workers analyzed amphibole asbestos-associated deaths in a cohort of 17,800 American and Canadian males [133]. Large RRs of lung cancer was found. The RR increased from 2.32 at <15 years from start of exposure up to the maximum at 4.90 after 30-40 years since onset.

Asbestos cement workers

Belgium data from an asbestos cement plant with 29,366 man-years of follow up [123] showed no significant (p=0.11) risk in respiratory cancers with increasing chrysotile, crocidolite and amosite asbestos exposure.

A Swedish study of 1,465 chrysotile asbestos exposed cement workers (with nested case-control analysis for mesothelioma) found no significant increased risk of lung cancer death among the asbestos exposed [115]. Lung cancer RR incidence (f-y/ml): <15 f-y/ml= 1.8 (CI 0.8-3.9), 15-39 f-y/ml= 1.9 (CI 0.7-5.3), >40 f-y/ml= 1.9 (CI 0.5-7.1).

Mixed industries

A study of Clin and colleagues [116] comprised of 2,004 French men and women working with textile, brakes and clutches. The subjects were mostly exposed to chrysotile (80%) but crocidolite was also present. There was no significant exposure-response association between the number of years during which subjects were exposed (cumulative exposure) and lung cancer. However, the adjusted relative risk for lung cancer corresponding to the highest exposure tertile (140 - 853 f-y/ml) was 3.99 (95% CI: 1.15-13.86).

586 Chinese men working with textile, brakes and cement were assessed for an association between chrysotile asbestos and lung cancer death [119]. Data suggested a strong significant

association between exposure to chrysotile asbestos and lung cancer death ($p<0.001$) in which clear exposure-response relationships were observed. No threshold for asbestos causing lung cancer was identified. The power model fitted best with 10-year lag time.

Among 1,074 white men exposed to chrysotile, amosite and crocidolite in an American asbestos company manufacturing insulation, roof materials and engineered products, Enterline and colleagues [120] demonstrated a statistically significant exposure-response relationship for lung cancer death that had become increasingly linear. SMR = 182, 203, 322, 405 and 699 for dust exposure <125, 125-249, 250-499, 500-749, and ≥750 mppcf-y, respectively.

Data from an American study showed significant ($p\leq 0.01$) excess of death due to lung cancer among 6,931 black and white males working in two cement manufacturing plants and exposed to chrysotile (primarily), amosite and crocidolite asbestos [122]. The relation (RR = 1 + 0.0076 x, for x in f/ml-years) predicts a relative risk of 1.038 for workers exposed to 0-2f/ml for 25 work years, or about 2 lifetime lung cancers per 1000 workers based on United States male lung cancer rates.

An American research group conducted a study of 1,121 males working with pipe insulation and exposed to amosite asbestos in 1998 [124]. The study supported a significant excess of death from lung cancer due to amosite exposure, SMR = 277 (CI 193-385).

Another study by McDonald and colleagues was based on data from an American chrysotile asbestos friction products plant [128]. Data from 3,641 males were analyzed. There was a raised risk of death from lung cancer with SMR of 148.7. However, any clear or systematic exposure-effect pattern was lacking. A reverse exposure-response was shown with duration of exposure and SMR was greatest for those working <1 year. No exposure-response association with cumulative exposures was shown (mppcf-year).

CASE-CONTROL STUDIES

In United Kingdom 106 men dead from lung cancer who had worked with production of friction materials (chrysotile and crocidolite exposure) were matched with 318 workers from the same factory [138]. There was no indication of an increased risk of lung cancer with either duration of exposure or cumulative exposure in the categorical analysis. A fitted coefficient for a linear relationship was estimated to be $0.58 * 10^{-3}$ per f-y/ml.

Gustavsson and colleagues carried out a population-based case-referent study where the 1,038 cases were all lung cancer cases from 1985 to 1990 in Stockholm aged 40-75 years [139]. Two

referent groups were used; the main group was population-based. However as most of the cases (93%) were deceased, a separate group with the same mortality was included to analyze the possible bias due to different mortalities. An elaborate estimation of life time exposure to asbestos, engine exhaust, metal dust, oil mists and welding was obtained by a combination of interview, and expert judgments, for asbestos supported by results from a nationwide measurement program from 1969-73. Exposure was categorized both according to probability and intensity distributed in classes unexposed, 0-0.99, 1-2.49, 2.5-4.99, and >4.5 f-y/ml. The highest exposure was 20.4 f-y/ml. Data indicated an excellent exposure-response for mean cumulative exposure with an increased RR 149 (CI95% 119-187) $*10^{-3}$ per f-y/ml [113]. There was poor correlation with length of exposure. Comparing the risk of lung cancer due to asbestos with the other exposures, asbestos clearly provided most lung cancers both estimated from the risk rates and from the attributable cases.

Gustavsson and colleagues further analyzed the Stockholm lung cancer population in 2002 with focus on exposure-response relations and the interactive effect of asbestos and smoking [113]. The authors found that lung cancer risk increased with cumulative exposure according to an almost linear relationship. The calculated risk at cumulative exposure of 4.0 f/ml-years was 1.90 (95% CI: 1.32-2.74), and was 5.38 among never-smokers and 1.55 for current smokers. This corresponded to k_L values much higher than from the industrial cohorts, about 480 $*10^{-3}$ per f-y/ml. The asbestos-smoking interaction was between additive and multiplicative but closest to additive.

In 2002 results from a German two-phase case-control study was published [114]. The study population consisted of 1,678 West German lung cancer male patients from Bremen and a small group from Frankfurt between 1988 and 1993. 164 cases were matched with 164 controls according to asbestos exposure estimated by interview supported by expert judgment. Log transformation of exposure (ln[f-/ml+1]) gave the best fit. The estimate was ln(f-y/ml+1): OR = 1.18 (95% CI: 1.052-1.318), corresponding to a doubled risk from exposure to 25 f-y/ml.

A project merging a set of different population based studies of asbestos and lung cancer with updated exposure assessments, project SYNERGY [274, 275] is underway. The status of the project is not known, but this study will give a more solid basis for estimating exposure-response in the lower range of exposure.

APPENDIX 14. LIST OF INCLUDED STUDIES IN THE META-ANALYSES (4.3)

Table A13. List of included studies in the meta-analyses.

First author, year of publication, (ref no.)	Lash et al.,1997	Goodman et al., 1999	Berman et al., 2008	Lenters et al., 2011	van der Bij et al., 2012	Hodgson et al., 2000
Acheson, 1982		X				
Acheson, 1984		X				
Albin, 1990		X	X	X	X	X
Alies-Patin, 1985		X				
Amandus, 1987	X	X				
Armstrong, 1988	X	X				
Berry, 1983			X	X	X	
Berry, 2004			X	X	X	
Blasetti, 1990		X				
Clemmesen, 1981		X				
Danielsen, 1993		X				
De Klerk, 1994						X
Dement, 1983	X					
Dement, 1994	X	X				X
Enterline, 1967 cohort I,II,III		X				
Enterline, 1986			X			
Enterline, 1987		X		X	X	X
Finkelstein, 1983	X					
Finkelstein, 1984	X	X	X	X	X	X
Finkelstein, 1989		X				
Fletcher, 1993		X				
Gardner, 1986		X				
Giaroli, 1994		X				
Gurvich, 1993		X				
Gustavsson, 2002				X	X	
Hein, 2007			X	X	X	
Henderson, 1979	X					
Hilt, 1991		X				
Hobbs, 1980		X				
Hodgson, 1986		X				
Hughes, 1987	X	X	X	X	X	X
Jones, 1980		X				
Kolonel, 1985		X				
Lacquet, 1980		X	X	X	X	
Levin, 1998			X	X	X	

First author, year of publication, (ref no.)	Lash et al.,1997	Goodman et al., 1999	Berman et al., 2008	Lenters et al., 2011	van der Bij et al., 2012	Hodgson et al., 2000
Liddell, 1977	X					
Liddell, 1997		X	X	X	X	X
Loomis, 2009				X	X	
Magnani, 1986		X				
Magnani, 1996		X				
Mancuso, 1963		X				
McDonald, 1980	X					
McDonald, 1982	X	X				
McDonald, 1983a	X					X
McDonald 1983b		X	X	X	X	X
McDonald, 1984	X	X	X	X	X	X
McDonald, 1986	X					
McDonald, 1993	X	X				
McDonald, 2004			X			
Menegozzo, 1993		X				
Meurman, 1994		X				
Morinaga, 1990		X				
Moulin, 1993		X				
Neuberger, 1990	X	X				X
Newhouse, 1985		X				
Newhouse, 1985		X				
Newhouse, 1989		X				X
Nokso-Koivisto, 1994		X				
Ohlson, 1984		X				
Ohlson, 1985	X	X				
Oksa, 1997		X				
Pang, 1997		X				
Peto cohort I,II,III 1985	X	X	X	X	X	X
Piolatto, 1990	X	X	X			X
Pira, 2009				X	X	
Puntoni, 1979		X				
Raffn, 1989, 1993, 1996		X				
Robinson, 1979		X				
Rosler, 1994		X				
Rossiter, 1980		X				
Sanden, 1992		X				
Seidman, 1979	X					
Seidman, 1990						X
Seidman, 1986	X	X	X	X	X	X
Selikoff, 1991		X	X	X	X	
Sluis-Cremer, 1992		X				X

First author, year of publication, (ref no.)	Lash et al.,1997	Goodman et al., 1999	Berman et al., 2008	Lenters et al., 2011	van der Bij et al., 2012	Hodgson et al., 2000
Sullivan, 2007			X	X	X	
Szeszenia-Dabrowska, 1986		X				
Szeszenia-Dabrowska, 1991		X				
Talcott, 1989						X
Tarchi, 1994		X				
Teta, 1988		X				
Thomas, 1982		X				
Tola, 1988		X				
Ward, 1994		X				
Weill, 1979	X					
Weiss, 1977		X				
Woitowitz, 1986		X				

a) Dust exposure and mortality in an American chrysotile textile plant. Br J Ind Med 1983; 39: 361-367

b) Dust exposure and mortality in an American factory using chrysotile, amosite, and crocidolite in mainly textile manufacture. Br J Ind Med 1983; 40: 368-374

APPENDIX 15. DISEASES AND/OR CONDITIONS THAT INFLUENCE THE DEVELOPMENT OF ARLC (4.4)

RACE AND ETHNICITY

There are significant racial and sex differences in lung cancer incidence and mortality rates. The lowest incidence in the USA is 19.2 per 100,000, among white women in Utah, and the highest is 149 per 100,000 among black men in Wisconsin. This difference likely reflects differences in smoking prevalence [173]. Lung cancer occurrence is approximately 45% higher among African-American men than among white men. This racial disparity may be partially due to greater susceptibility of African-American smokers to smoking-induced lung carcinogenesis [163]. Worldwide comparisons are hampered by differences in smoking habits and by the fact, that lung cancer is predominantly a disease of the elderly. It rarely occurs before age of 40 and in Denmark half of the cases occur in persons over 70 years old. In countries with much lower life expectancy lung cancer incidence therefore might differ markedly.

SEX

Although sex differences largely reflects smoking differences, "true" sex differences might exist. Bilello et al. [173] reviewed both case-control and cohort studies on sex differences in lung cancer and found that in 4 case-control studies odds of developing lung cancer were from 1.2 – 2.8 folds higher in women than in men when adjusted for smoking habits. In contrast, five of six major cohort studies showed lower relative risks for lung cancer death among women than among men [173]. If women do have an enhanced biologic susceptibility to lung cancer, it could be related to endocrine factors or to sex differences in genetics and activation and detoxification of carcinogens. In support of a possible role of estrogens in the development of lung cancer, it has been shown that estrogen replacement therapy was associated significantly with lung adenocarcinoma (OR 1.7), with even higher risk among women who used estrogen and smoked (OR 32.4). Conversely, early age at menopause (40 years old or younger) was protective (OR 0.3) [173].

Also major differences between men and women in the relative distribution of histologic types of lung cancer has been found. Adenocarcinoma used to be the most common type of lung cancer in women and squamous cell carcinoma in men [173]. Over the last few decades, the proportion of squamous cell carcinomas has decreased and an increase of adenocarcinomas has taken place in both sexes. The risk for all major histologic types is strongly associated with smoking in both sexes [179]. The changes in

the prevalence of smoking among women in the past decades have been reflected in the increased incidence of lung cancer among women so that the former sex differences have almost disappeared in Denmark [7]. No evidence for sex differences in the susceptibility for tobacco smoking in relation to lung cancer was found in a Danish cohort study [180].

FAMILY HISTORY OF LUNG CANCER

It has been estimated that between 3% and 6% of all lung cancer cases have a positive family history of the disease [165]. Familial aggregation of lung cancer has been studied in both case-control and cohort studies with conflicting results. Matakidou et al. [167] performed a systematic review of 28 case-control, 17 cohort and 7 twin studies of the relationship between family history and risk of lung cancer. Meta-analysis of data from the case-control and cohort studies combined showed an increased lung cancer risk with a RR = 1.84 (CI: 1.64–2.05). Risk appeared to be greater in relatives of cases diagnosed at a young age and in those with multiple affected family members. Familial risks reflect both common exposures and genetic predisposition. Smoking is the most important environmental risk factor of lung cancer, and the association between a person's smoking habits and that of his parents or siblings has been well documented. Only four of the studies included in the analysis attempted to address this issue by taking into account the smoking habits of both the study subjects and their family members. To minimize the impact of shared smoking habits in families, a few studies have estimated familial risks associated with nonsmoker status. Pooling of the data in never-smokers resulted in an elevated risk of lung cancer associated with a family history of the disease that was statistically significant; supporting the view that genetic or other environmental factor than smoking may play a role in familial aggregations. It is however noteworthy, that follow-up of 15,924 male twin pairs in the United States did not show greater concordance in monozygotic compared with dizygotic twins, and death rates from lung cancer were similar by zygosity group in surviving twins whose sibling died of lung cancer [174]. A larger study including 44,788 pairs of twins listed in the Swedish, Danish, and Finnish twin Registries found non-statistically significant hereditable factor of 0.27 (95% CI: 0 – 0.49). The concordance for lung cancer in male monozygotic twins was 0.11. It was estimated that shared environmental factors accounted for 12%, and non-environmental factors for 62% of the variance in the cohort [177]. The familial relative risk of lung cancer decreased with increasing smoking prevalence [164] indicating the dominant role of this exposure in developing lung cancer.

THE GENETIC BASIS OF LUNG CANCER

Direct evidence for a genetic predisposition is provided by the increased risk of lung cancer associated with carriers of constitutional TP53, retinoblastoma, individuals with xeroderma pigmentosum,

Bloom's and Werner's syndromes [167]. These conditions are however so rare that they play an insignificant role in the development of lung cancer in the population at large.

This rapidly expanding area includes research on several levels: dosimetry and metabolism of carcinogens at the cellular and molecular level, genetic determinants of susceptibility, and in vivo genetic tissue changes. An example of the latter is seen in epigenetic methylation of DNA cystine leads to hypermethylation of promoter regions that are frequently found in lung cancer [163, 276].

Much of this research is based on studying tobacco and lung cancer. Carcinogens are often metabolized in two phases. In phase 1 highly reactive intermediates are produced due to oxidation. For example cytochrome p450 forms (e.g. CYP1A1) reactive intermediaries that bind to DNA and cause genetic damage, which has been linked to lung cancer risk [163]. In phase 2 conjugant reactions phase 1 intermediaries form complexes with conjugated molecules. Phase 2 enzyme glutathione S-transferase (GST) detoxify reactive metabolites, e.g. polycyclic aromatic hydrocarbons (PAH). Gene-gene interaction may be important. For example the combination of two variant genotypes, GSTM1 null and CYP1A Ils462Val polymorphisms, are associated with a greater than four-fold lung cancer risk in non-smokers [163].

Other factors determining lung cancer susceptibility in smokers are oncogenes, suppressor genes and DNA repair capacity. The tumor suppressor gene, p53, has particularly been in focus. This gene is muted in > 90% of small cell cancers. However, studies have found strong associations between the common p53 polymorphisms and lung cancer [163, 171]. Much research has focused on DNA repair and susceptibility. Historically, the classic example is the increased cancer risk among individuals with the rare recessive disorder, xeroderma pigmentosa. A number of DNA repair genes have been studied in relation to lung cancer susceptibility, but it has been difficult to demonstrate consistent and significant associations [166].

Genome-wide association studies (GWAS) have identified some novel loci for lung cancer risk. A recent study has looked specifically at the gene-environment interaction of asbestos exposure and lung cancer [172]. The most significant gene was C7orf54 located on 7q32.1. This pilot study attempts to evaluate how SNPs, genes and pathways are related to gene-asbestos interaction in lung cancer risk. Although interesting, this study does not present any clinically applicable information. Recently Wright et al. [182] have tried to differentiate ARLC from non-ARLC using whole genome array comparative hybridization profiling. Some regions with significant copy number gain and loss unique to ARCL were identified.

In a series of studies Nymark et al. have identified genetic abnormalities related to lung cancer associated with asbestos exposure, and the findings may be helpful for identifying lung cancer caused by asbestos in the future. In a broad spectrum of 18 chromosomal regions with copy number alterations [277] there was 6 regions which also had miRNA changes [169].

These results were further studied on material from 13 asbestos exposed and 13 non-exposed lung cancer patients, matched for age, sex, nationality, smoking history, and histological cancer type. All were interviewed for smoking and work history. Quantification of fiber count of lung tissue was performed by electron microscopy with energy dispersive spectrometry. Analysis were performed with investigation of miRNA, mRNA and CGH (comparative genomic hybridization) from cancer and non-cancer tissue from patients and 8 control samples of non-lung cancer patient: thirty-four miRNAs differed between paired samples of tumor and normal tissue. In integration with mRNA and CGH there was association with copy number alterations [277] and inverse correlation with target genes [168].

The results were taken to a larger study of 225 patients with 126 asbestos exposed and 99 non-exposed based on pulmonary fiber count by electron microscopy with energy dispersive spectrometry (not all materials were included in all tests). Based on the former study genomic alterations in 19p13, 2p16 and 9q33.1 were investigated for CNA and allelic imbalance (AI). A combination of 2 out of 3 genomic alterations (CNA and/or AI) was associated with asbestos exposure with a sensitivity of 38% and specificity of 96%. The study is confounded with smoking in the exposed group, and therefore the sensitivity and specificity might be higher. The combined test might be helpful in identifying asbestos exposed patients [170].

MOLECULAR PATHOLOGY OF ARLC

Molecular changes in asbestos-related lung cancer are relevant for tumor pathogenesis, for use in screening/identification and specific diagnosis, and for targeted therapy. Although a large amount of information is available on the responses of cells to asbestos, understanding the pathogenesis of ARLC has been hampered by the complexity of and differences between fiber types and multiple interactions between tobacco smoke and asbestos. More recent studies of the mechanisms of asbestos-induced injury and disease have focused on the importance of the creation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which can lead to cellular damage and toxicity. *In vitro*, asbestos fibers have been shown to stimulate the production of ROS and RNS though iron-mediated and cell-mediated mechanisms. These mechanisms involve indirect effects that are thought to lead to DNA

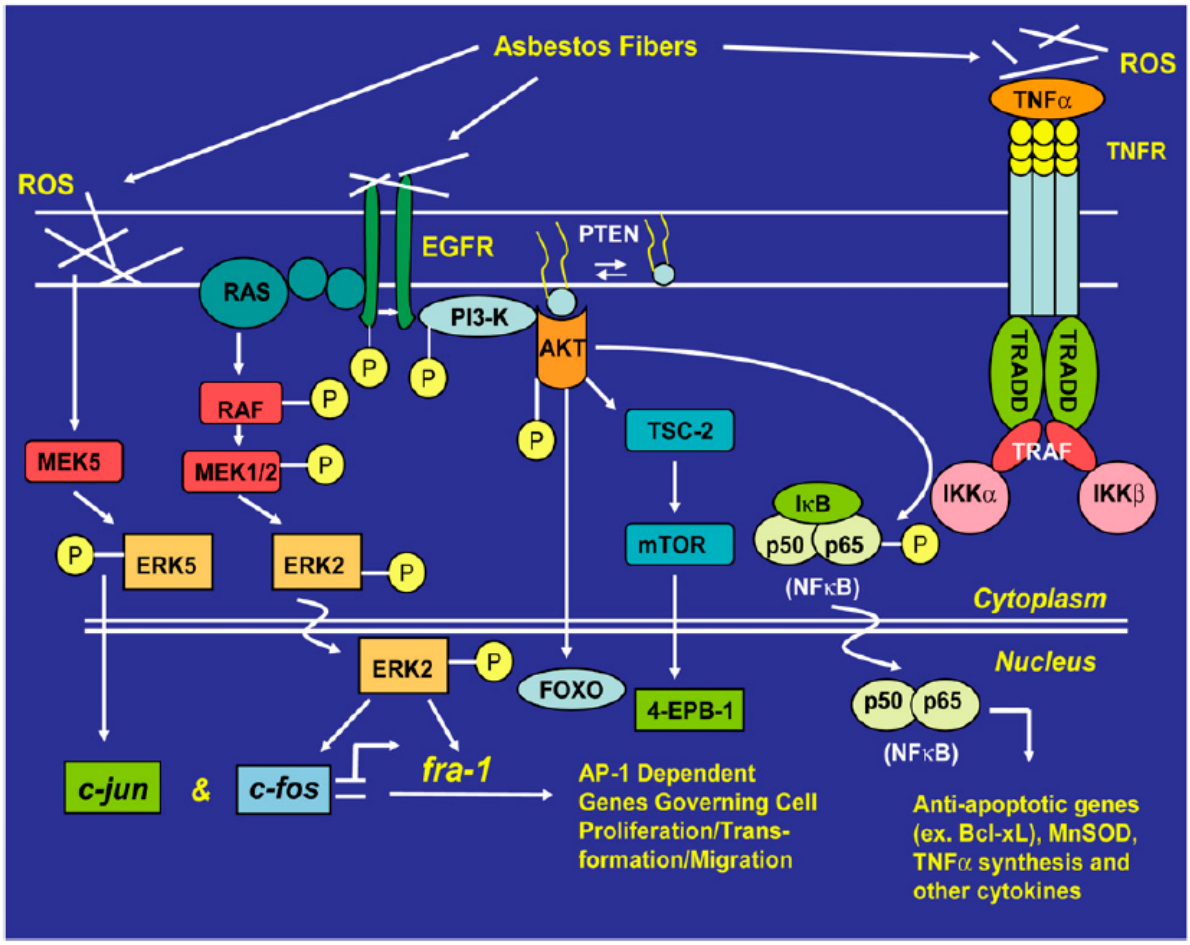
damage, and in some cases, may lead to carcinogenesis. Several different explanations have been put forth for how asbestos might cause or be contributing to lung cancer. These include:

- Redox processes in combination with disturbance of iron homeostasis
- Generation of oxidants by inflammation elicited by asbestos fibers and interaction with other cell types, i.e. macrophages (frustrated phagocytosis)
- Direct action of asbestos fibers on receptors on the alveolar epithelial cell surface

Asbestos fibers have been shown to stimulate the production of reactive oxidative species (ROS) and reactive nitrogen species (RNS) through iron-mediated and cell-mediated mechanisms. Cell signaling by asbestos is thought to occur when asbestos fibers or products of asbestos fibers, such as ROS/RNS interaction with the cell membrane or are phagocytosed [181]. After interaction with cells, asbestos fibers trigger numerous signaling cascades, including mitogen-activated protein kinases (MAPK) and nuclear factor κB (NFκB) [178, 278]. These events promote cellular responses, such as cell transformation, proliferation and apoptosis (programmed cell death). It has been shown that asbestos-mediated apoptosis may trigger compensatory cell proliferation [175, 176].

Relation to lung cancer:
In lung cancer genetic alterations accumulate during tumor progression, resulting in severe genomic complexity in most lung cancers. For the time being, two mutations are tested for targeted therapy: EGFR and EML4/ALK translocation. It is not known, if some of the EGFR mutated lung cancers responsive to targeted therapy are related to asbestos.

Figure A3. Central pathways and interactions involved in asbestos related disease [279].



APPENDIX 16. OCCUPATIONAL RISK FACTORS FOR LUNG CANCER (4.4)

Lung cancer has been observed to be associated with many workplace exposures. Among cancers that are associated with occupational exposures, cancer of the lung is the most common. Estimates derived from case-control studies of the proportion of lung cancer that is contributed to by occupational exposures, via independent or shared causal pathways, have ranged widely, but most point estimates or ranges have included values from 9 to 15%. Although disagreement persists concerning specific estimates, the lung cancer burden is small compared with that of cigarette smoking, but large compared with contributions of most other exposure classes [163] and high in occupational groups heavily exposed over a long time to workplace agents, such as asbestos.

Table A14. Present state of knowledge on occupational carcinogen agents evaluated by International Agency for Research on Cancer [1].

Carcinogenic agents with *sufficient evidence* in humans (Group 1)	Agents with *limited evidence* in humans (Group 2A)
Aluminium production	Acid mists, strong inorganic
Arsenic and inorganic arsenic compounds	Art glass, glass containers and pressed ware (manufacture of)
Asbestos (all forms)	Acid mists, strong inorganic
Beryllium and beryllium compounds	Biomass fuel (primarily wood), indoor emissions from household combustion of
Bis(chloromethyl)ether; chloromethylmethyl ether (technical grade)	Bitumens, occupational exposure to oxidized bitumens and their emissions during roofing
Cadmium and cadmium compounds	Bitumens, occupational exposure to hard bitumens and their emissions during mastic asphalt work
Chromium(VI) compounds	Carbon electrode manufacture *alpha*-Chlorinated toluenes and benzoyl chloride (combined exp.)
Coal, indoor emissions from household combustion	Cobalt metal with tungsten carbide
Coal gasification	Creosotes
Coal-tar pitch	Engine exhaust, diesel
Coke production	Frying, emissions from high temperature
Engine exhaust, diesel	Insecticides, non-arsenical (occupational exposures in spraying and application)
Hematite mining (underground)	Printing processes
Iron and steel founding	2,3,7,8-Tetrachlorodibenzo*para*-dioxin
MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture)	Welding fumes
Nickel compounds	
Painting	
Plutonium	
Radon-222 and its decay products	
Rubber production industry	
Silica dust, crystalline	
Soot	
Sulphur mustard	
Tobacco smoke, second-hand	
Tobacco smoking	
X-radiation, gamma-radiation	

Compared to cigarette smoking and partly to asbestos, other exposures are far less thoroughly evaluated. Often precise data are lacking on exposure-response correlations and the extent to which cigarette smoking or concomitant occupational exposures potentiate (or attenuate) the effect of other occupational lung carcinogens. Effects of smoking were not well controlled in many studies and thus might represent a significant bias. In case-control studies very high odds ratios have been reported for the risk of lung cancer - for instance a 16 fold increase for lung cancer was reported in industrial manufacture of mustard gas – but RR of that order of magnitude are only rarely observed apart from for asbestos and tobacco.

Because tobacco use is a frequent confounding factor in studies of occupational risk for lung cancer, a European multicenter case-control study (650 patients and 1542 controls) was designed to address occupational risk factors for lung cancer in non-smokers [185]. An increased risk for lung cancer was shown in men and women who had worked in occupations known to be associated with an increased risk for lung cancer (shipyard or dockyard and railroad manufacture workers, painters, workers in nonferrous metal basic industries). However, the CIs were broad and the only statistically significant increase in RR for lung cancer was detected in women who were employed in occupations suspected to be associated with an increased risk for lung cancer - e.g., laundry and dry cleaning; work in rubber manufacturing; and ceramic, pottery, or glass workers (Table A15). The relative low RRs may reflect the fact, that in most European countries, the well-known hazards on IARC's lists have been adequately controlled.

Table A15. Risk of occupational lung cancer [185].

Odds Ratios of Lung Cancer for Ever Working in a List A[1)]- or List-B Occupation								
	Men				Women			
	Cases	Controls	Odds Ratio	95% CI[2)]	Cases	Controls	Odds Ratio	95% CI[2)]
Never A, never B	101	366	1,00		463	942	1,00	
Ever A or ever B	40	165	1,20	0,76-1,92	46	69	1,67	1,10-2,52
Ever A	17	58	1,52	0,78-2,97	5	10	1,50	0,49-4,53
Ever B, never A	23	107	1,05	0,60-1,83	41	59	1,69	1,09-2,63
Total	141	531			509	1011		

[1)] List A: A subset of the most common used industrial chemical classified in Group 1 by IARC. List B: A subset of the most common used industrial chemical classified in Group 2A by IARC
[2)] Confidence interval

APPENDIX 17. ENVIRONMENTAL RISK FACTORS FOR LUNG CANCER (4.4)

AIR POLLUTION

During a typical day, the average adult inhales approximately 10,000 liters of air. Consequently, even the carcinogens that are present in low concentrations may be associated to lung cancer risk.

Air pollution is a complex mixture of particulate matter (PM) and gas contaminants. PM is made up of solid and liquid particles suspended in the air: acids (e.g. nitrates and sulphates); organic chemicals (e.g. polyaromatic hydrocarbons, PAHs); metals; soil; and dust particles. According to the particles' size, they are categorized into coarse particles (<10 μm and >2.5 μm, PM10), fine particles (2.5 μm and >0.1, PM2.5), and ultrafine particles (<0.1 μm) [165]. Combustion of fossil fuels, road traffic, industrial sites, and waste dumps are the major sources of air pollution. In industrial areas, high levels of PAH air levels correlate with DNA adducts in peripheral lymphocytes, and with an increased incidence of lung cancer [280]. PAHs are mutagenic and carcinogenic compounds [194].

Extrapolation of the risks associated with occupational exposures to the lower concentration of carcinogens in polluted ambient air suggests that only a small proportion of lung cancer cases could be due to air pollution. A recent World Health Organization report on environment and health concluded that 19% of all cancers are globally attributable to environmental factors including occupational exposures [196]. Other reviews, not including occupational exposures, resulted in much lower estimates [191]. Most estimates are uncertain depending on estimated cancer risk and exposure (i.e. dose).

Air pollution has been assessed as a risk factor for lung cancer in both case-control and cohort studies. Early studies, many with inadequate adjustment for smoking and other potential confounders, typically showed about 50% higher lung cancer incidence rates in urban areas and in communities polluted by industrial sources compared to rural, less polluted areas. Several case-control and cohort studies with adequate adjustment for smoking and other potential confounding factors similarly indicated higher risks for lung cancer in association with different measures of air pollution [198]. Whitrow et al. [201] systematically searched the literature regarding evidence for a causal relationship between air pollution and lung cancer. Ten case-control and four cohort studies fulfilled their search criteria. Of these eight studies demonstrated significant positive associations between environmental exposure and

lung cancer with a RR range of 1.14-5.2. One study found a negative association with RR 0.28. Smoking and occupational exposure were addressed in all studies, though often crudely with possible misclassification. Exposure-response relationships were evident in three studies. The authors concluded that evidence for causality is modest, with intermediate consistency of findings, limited exposure-response evidence and crude adjustment for important potential confounders.

In a European case-control study controlled for potential confounders Vineis et al. [200] estimated lung cancer risk among non-smokers attributable to air pollution. They found that 5–7% of lung cancers in European never smokers and ex-smokers were attributable to high levels of air pollution, as expressed by NO_2 or proximity to heavy traffic roads. The latter indicator has limitations, mainly related to the fact that it is associated to social class. The authors argue that NO_2 is a better indicator for air pollution, at least in Europe, compared to fine or ultrafine particles. This has been extensively discussed in the recent revision of the WHO World Air Quality Guidelines [202]. The thresholds for indicators of air pollution exposure they used correspond to the high levels of exposure that characterize mainly Southern European countries (30 $\mu g/m^3$ or higher) while levels of NO_2 in Denmark and Sweden are closer to 10–20 $\mu g/m^3$.

Two prospective Danish cohort studies [197] that partially addressed weaknesses of earlier studies add evidence suggesting that Danish air pollution from traffic is also associated with lung cancer risk. The IRRs (incidence rate ratio) for lung cancer were 1.30 (95% CI: 1.07-1.57) and 1.45 (95% CI: 1.12-1.88) for NOx concentrations of 30 to 72 and >72 $\mu g/m^3$, respectively, when compared with <30 $\mu g/m^3$. This corresponds to a 37% (95% CI: 6-76%) increase in IRR per 100 $\mu g/m^3$ NOx. This corresponds to results from other similar studies from other parts of the world. Overall it has been estimated that 1 to 2% of lung cancer cases are related to air pollution [165]. The Danish studies showed tendencies of stronger associations between air pollution and lung cancer among non-smokers. Raaschou-Nielsen et al.'s study is remarkable for better exposure data and better control for potential confounding factors than most previous studies. The authors state that the proportion of lung cancer cases attributable to air pollution in the whole Danish population is probably substantially less than 14%. A precise estimate was however not given [198]. Doll and Peto [193] estimated that 1 to 2% of lung cancer was related to air pollution. Even in light of more recent findings Alberg concludes that this still seems to remain a reasonable estimate [163]. Overall it has been estimated that 1 to 2% of lung cancer are related to air pollution which is 35-70 cases in Denmark per year.

RADON

The source of radon is uranium. It is estimated, that an average Danish one family house plot contains 1 kg of uranium. From soil and rocks radon can diffuse through the ground and become concentrated in homes. In outdoor air the concentration is diluted by wind and extremely low. In Denmark radon is abundant in soil in the eastern part of Jutland and all the islands in the eastern part of the country, especially in the eastern and southern part of Zealand and Bornholm.

Although radon is chemically inert and electrically uncharged, it is radioactive, which means that radon atoms can spontaneously decay. As radon decays, it produces short-lived decay products (radon progeny). They are electrically charged and can attach themselves to tiny dust particles in indoor air. These dust particles can easily be inhaled into the lung and can adhere to the lining of the lung. As the deposited atoms decay, they emit alpha radiation. The unit radiation intensity from radon is Bequerel per cubic meter (Bq/m^3). One Bq is one decay in one second. Alpha radiation may damage cells in the lung by disrupting DNA of lung or bronchial cells. This DNA damage has the potential to be first step in a chain of events that can lead to cancer. Alpha radiations travel only extremely short distances in the body. Thus, alpha radiations from decay of radon progeny in the lungs cannot reach cells in any other organs. This may explain why lung cancer is the only important cancer hazard posed by radon in indoor air.

There is good evidence that a single alpha particle can cause major genomic changes in a cell, including mutation and transformation. Even allowing for a substantial degree of repair, the passage of a single alpha particle has the potential to cause irreparable damage in cells. In addition, many cancers are of monoclonal origin, that is, they originate from damage to a single cell. These observations provide a mechanistic basis for a linear relationship between alpha-particle dose and cancer risk at low exposure levels. On the basis of these mechanistic considerations and in the absence of credible evidence to the contrary, a linear-non-threshold model for the relationship between radon exposure and lung cancer risk is generally accepted. Although it is recognized that a threshold relationship between exposure and lung cancer risk at very low levels of radon exposure cannot totally be excluded.

About 25% of houses in Denmark are estimated to have a radon concentration >100 Bq/m^3. Radon concentrations above this level are found in about 5% of Danish houses.

The epidemiological evidence of the carcinogenicity of radon decay products is derived mainly from cohort studies of underground miners that had been exposed to high levels of radon. Occupational

exposure in mining can cause lung cancer in humans, while the evidence for an effect on other neoplasms is not conclusive [195].

The excess risk estimated from occupational cohorts, which included over 2500 cases of lung cancer occurring among over 60,000 miners, has been estimated in the order of 0.0049 per working level month of exposure [190]. Further refinements of this estimate took into account age at exposure and time since first exposure as well as smoking status, and showed a stronger effect among never-smokers than among smokers.

As the higher end of residential exposure range is comparable to exposures that caused lung cancer in underground miners with the lowest exposures, and as a linear relationship also applies to the lowest levels of exposures, residential exposures might be relevant for lung cancer risk (National Research Council, 1999).

Since valid risk estimates could not be derived from a single study, a combined analysis of 7 North American case-control studies were carried out by Krewski et al. [188]. A total of 3662 cases and 4966 controls were included. ORs for lung cancer increased with residential radon concentration. The estimated OR after exposure to radon at a concentration of 100 Bq/m^3 in the exposure time window 5 to 30 years before the index date was 1.11 (95% confidence interval = 1.00-1.28). The authors stated, that this estimate was compatible with the estimate of 1.12 (1.02-1.25) predicted by downward extrapolation of data from uranium miner workers previous published. Analyses restricted to subsets with presumed more accurate radon dosimetry resulted in increased risk estimates. The same researchers in 2006 published a follow up with an extended data set including 4081 cases and 5281 controls but with the same exposure time window, 5 to 30 years [172]. The estimated lung cancer OR generally increased with radon concentration. The OR trend was consistent with linearity ($p = .10$) and the excess OR was 0.10 per Bq/m^3 with 95% confidence limits (−0.01, 0.26). For the subset of the data considered previously [188], the excess OR was 0.11 (CI: 0.00-0.28). Further limiting subjects based on more strict criteria for exposure (residential stability and completeness of radon monitoring) led to increased estimates of the excess OR. For example, for subjects who had resided in only one or two houses in the 5–30 exposure time window and who had alfa-track radon measurements for at least 20 year of the 25-year period, the excess OR was 0.18 (CI: 0.02-0.43) per 100 Bq/m^3. Both estimates were compatible with the excess OR of 0.12 (0.02, 0.25) per 100 Bq/m3 predicted by downward extrapolation of miner data [189].

A pooled analysis of European studies of residential radon exposure and lung cancer resulted in a RR of 1.08 (95% CI: 1.03–1.16) for an increase in radon exposure of 100 Bq/m^3 [187]. The population-weighted average indoor radon exposure in 29 European countries has been estimated to be 59 Bq/m3 [199] resulting in an attributable fraction of 4.5%. The average radon exposure level was higher than the level found in a recent Danish prospective cohort study on long-term association between residential radon and lung cancer with 57,053 persons that were recruited during 1993–1997. In that study the median estimated radon concentration was 24 and 39.5 Bq/m^3 for cases and the control, respectively, whilst NOx levels were higher among cases [192]. Cohort members were followed for cancer occurrence until 2006 and 589 lung cancer cases were identified. Cohort members' 173,419 residential addresses from 1971 to 2006 were traced and radon exposure at each of these addresses was calculated using information from central databases regarding geology and house construction. Persons living in single detached homes had higher radon levels compared to persons living in apartments. IRR and 95% CI for lung cancer risk associated with residential radon exposure with and without adjustment for sex, smoking variables, education, socio-economic status, occupation, body mass index, air pollution and consumption of fruit and alcohol. Potential effect modification by sex, traffic-related air pollution and environmental tobacco smoke was assessed. The adjusted IRR for lung cancer was 1.04 (95% CI: 0.69–1.56) in association with a 100 Bq/m^3 or higher radon concentration. Among non-smokers, the IRR was 1.67 (95% CI: 0.69; 4.04) and the IRR was dose-dependently higher over four radon exposure quartiles (<17.6, 17.6–39.5, 39.5–66.1, and >66.1 Bq/m^3). No evidence of effect modification was found, but as cases on average had lower radon concentration than controls, other factors than radon and the factors accounted for must play a role – for instance chance due lack of statistical strength. The positive association between radon and lung cancer risk in the Danish study was consistent with results from previous American and European studies. Also a fairly consistence in increased risk or excess OR was found in these studies.

Several estimates have been proposed of the number of lung cancers attributable to residential radon exposure. In one of the most detailed studies, Darby and colleagues estimated that radon is responsible for 6.5% of all deaths from lung cancer in the UK, including 5.5% attributable to the joint effect of radon and smoking and 1% to residential radon alone. The figure of 1% corresponds to 349 deaths in the UK, or 9.4% of lung cancer deaths not due to tobacco smoking [281]. Using this estimate on the Danish population corresponds to 36 deaths due to residential radon alone and 200 deaths attributable to the joint effect of radon and smoking.

Summary estimates of the number of lung cancers attributable to environmental factors in Europe 2002 was given by Boffetta in 2006 [186] (see table A16). The author states that the number of lung

cancers attributable to outdoor air pollution is the most uncertain of the figures. No estimate was provided for lung cancer due to environmental asbestos exposure because of the lack of statistically significant increase in risk found in the meta-analysis. By comparison the number of mesothelioma cases was 381.

Table A16. Estimates of lung cancers attributable to environmental factors (modified from Boffetta 2006 [186]).

Summary estimates of lung cancers attributable to environmental factors, Europe 2002				
	Percentage			Number of cases
	Men	Women	All	
Outdoor air pollution	8,28	2,42	10,70	27.054
Second-hand smoke, spouse	0,28	3,35	3,63	2.250
Second-hand smoke, workplace	0,72	1,24	1,96	1.771
Residential radon decay products	3,48	1,02	4,50	11.377
Lung cancers (sum)	15,06	5,81	20,87	42.833

Other authors have estimated that about 4–12% or more of lung cancers are related to occupational asbestos exposure [282]. In a review of the epidemiology of lung cancer, Alberg and Samet [163] claim that about 90% of lung cancers are related to smoking, 9–15% to occupational exposures, 10% to radon, and perhaps 1–2% to air pollution. Henderson et al. [282] refer to Scandinavian studies where it has been estimated that more than a quarter of all lung cancer cases are related to occupational exposures. Therefore it is not possible to give an exact estimate of the significance of the different environmental factors. Risks are often expressed in different terms (for instance relative risk, odd ratio, or hazard ratio) and are not directly comparable. Furthermore, because two or more causal factors are implicated in many cases and the combined effects of those factors may be more than additive, the sum of the reported risk factors may exceed 1.0 (100%). A meaningful way of expressing risk is as attributable fractions (AF) or attributable fractions of the exposed (AFE). AFE can be defined as the proportion of exposed cases attributable to the risk factor, and can be interpreted as the proportion of disease cases over a specified time that would be prevented following elimination of the exposures, assuming the exposures are causal [282]. However, only very few studies provide risk estimates in form of attributable fractions. The estimates given by Alberg et al. [163] claiming that about 90% of lung cancers are related to smoking (primary or second-hand), 9–15% to occupational exposures, 10% to radon, and 1–2% to air pollution seems be the best estimate for the times being; at least it probably reflects – with some uncertainty – the mutual relationship between the individual risk factors.

APPENDIX 18. SMOKING AND OTHER LIFE STYLE RISK FACTORS (4.4)

For the population as a whole the epidemiology of lung cancer is first and foremost the epidemiology of smoking. An increase in tobacco consumption is paralleled some 20 years later by an increase in the incidence of lung cancer; similarly, a decrease in consumption is followed by a decrease in incidence. Occupational and other factors may be important in exposed or predisposed individuals. Asbestos, radon and other industrial chemicals, as well as environmental air pollution in general may be important risk factors in exposed individuals, and individual susceptibility may also be an important factor in disposed individuals.

By far, the most important environmental carcinogen is tobacco smoke. Many men began smoking cigarettes during World War I. The incidence of lung cancer among men began a rapid rise 20 years later. An identical delayed pattern has been observed in women. The unequivocal role of cigarette smoking in causing lung cancer is one of the most thoroughly documented causal relationships in biomedical research.

CARCINOGENS IN CIGARETTES

More than 3,000 chemicals have been identified in cigarette smoke. Some of these chemicals detected in cigarette smoke have been extensively studied and more than 60 carcinogens are identified in particulate or gaseous phase including: aromatic hydrocarbons, nitrosamines, nitrosonormicotine, polonium, and arsenic.

Risk in Smokers: duration of smoking and cigarettes per day

In general, the risk of developing lung cancer is 10-20 times greater in male smokers than that of non-smokers. The risk increases with the length of time an individual has smoked, the number of cigarettes smoked daily and the depth of inhalation. This observation has been made repeatedly in cohort and case-control studies.

Risk models have been derived to estimate quantitatively how lung cancer risk varies with number of cigarettes smoked, duration of smoking, and age. In one widely cited analysis, Doll and Peto [205] proposed a quantitative model for lung cancer risk on the basis of data from the cohort study of British physicians. This model predicted a stronger effect of duration of smoking than of amount smoked per day. Thus, a tripling of the number of cigarettes smoked per day was estimated to triple the risk,

whereas a tripling of duration of smoking was estimated to increase the risk 100-fold [283]. The exponential effect of duration of smoking on lung cancer risk markedly increases the lifetime risk for those who become regular smokers in childhood and they also have an increased risk at younger ages.

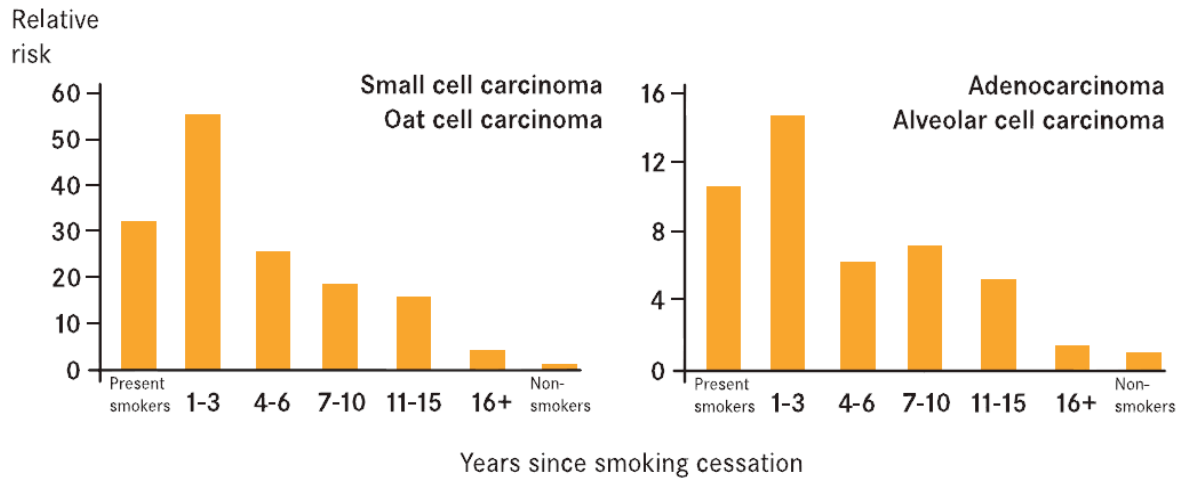
In a later study the same researchers [206] reported the findings at 50 years of follow-up of their original cohort. Compared with lifelong non-smokers, the risk for lung cancer was increased fourfold among former smokers and 14-fold among current smokers. Among current smokers, the RRs increased from 7.7 to 13.7 to 24.5 among smokers of 1 to 14, 15 to 24, and >25 cigarettes per day, respectively. The risk of developing lung cancer was three to five times greater in female smokers than in non-smokers.

RISK AFTER STOPPING SMOKING

The likelihood of developing lung cancer decreases among those who quit smoking as compared with those who continue to smoke. As the period of abstinence from smoking cigarettes increases, the risk for lung cancer decreases, approximately approaching the level of the non-smoker at 10-15 years. However, some studies show, that even for periods of abstinence of 40 years, the risk for lung cancer among former smokers remains elevated compared with never-smokers [284, 285].

The time necessary for decreasing the incidence of lung carcinoma depends on the duration and quantity of cigarette smoking. A person who has smoked fewer years will have a risk for lung carcinoma equal to the non-smoking population in less than 15 years after smoking cessation. Thus, for a given period of abstinence, the decrease in risk enhances as the duration of smoking decreases [285]. In figure A4 the relative risk of lung cancer is markedly lower five years after quitting, and decreases further with time (by comparison with those who continue to smoke).

Figure A4. Relative risk of lung cancer after smoking cessation [179].



FILTERS AND DIFFERENT TYPES OF CIGARETTES AND TOBACCO

The composition of cigarettes has evolved since the 1950s and consumption has shifted from mainly unfiltered cigarettes to predominantly filtered cigarettes. The filters in use in the U.S. and Denmark are predominantly cellulose acetate. In the mid-1960s, ventilation holes were added to the filter, which dilute the smoke with air drawn through them. There have also been substantial changes in the design of the cigarette and in the tobacco used. Reconstituted tobacco has been used increasingly since the 1960s and there have been changes to the cigarette paper and additives used. Most cigarettes are more ammoniated, and a concomitant shift toward lowered levels of "tar" and nicotine was seen.

A very extensive and comprehensive review of the influence and significance of filters and different types of cigarettes and tobacco on lung cancer was published in Chest in 2003 by Alberg and Samet [163], and the following summary is based on that review:

Tar and nicotine yields are measured with a smoking machine according to a standardized protocol established by the US Federal Trade Commission (FTC) that specifies such details as puff volume, the frequency of puffing, and the length to which the cigarette is to be smoked. In the course of time cigarette producers reduced the yields of tar and nicotine as measured by these machines. The gradual reduction in machine-measured tar yield would be expected to have reduced smokers' exposures to carcinogens. But when collecting saliva for analysis for cotinine level and end-tidal breath samples for measurement of carbon monoxide level, and taking account of numbers of cigarettes smoked, biomarker levels were not associated with the yields of tar and nicotine as measured by smoking machines. Other studies using biomarkers of exposure showed little relationship with tar or nicotine

yield as measured by the FTC protocol. Comparing actual smokers smoking habits with that of the machines showed that smokers had greater puff volumes and frequencies than are specified in the FTC protocol and consequently smokers had substantially greater intakes of tar and nicotine than implied by the brand listings.

Epidemiologic studies have been conducted to assess whether the seemingly substantial changes in tar and nicotine yield, have resulted in parallel changes in the risk of smoking. *Case-control studies* that compared risks in people who had used filter-tipped cigarettes with people who had smoked non-filtered cigarettes exclusively suggests that filtered cigarettes and cigarettes with lower tar yields slightly reduce the risk for lung cancer associated with cigarette smoking compared with non-filtered cigarettes or cigarettes with higher tar yields. *Cohort studies* where smokers were placed into three categories of products smoked: low yield (<17.6 mg per cigarette), high yield (25.8 to 35.7 mg per cigarette), and medium yield (intermediate) confirmed that risk for lung cancer death increased with tar yield. But on the other hand comparing smokers with disease developing from 1960 to 1972 (when tar yield per cigarette was high) with a similar group of smokers with disease developing from 1980 to 1986 (when tar yield was low) did not show the expected reduction in risk for developing lung cancer. In fact, the opposite was observed, with increasing lung cancer mortality in male and female smokers in during the last period compared to the first. In an analysis with a similar pattern of findings, Doll et al. [207] compared the risks for death from lung cancer and other causes during the first and second 20 years of the 40-year follow-up of the British physician cohort. Lung cancer mortality increased from 264 to 314 per 100,000 among smokers in the second 20 years (from 1971 to 1991), even though products smoked during this period would have had a substantially lower tar and nicotine yield than those smoked during the first 20 years (from 1951 to 1971).

Successive birth cohorts have had differing patterns of exposure to cigarettes of different characteristics and yields. Age-specific trends of lung cancer mortality therefore should be expected to decrease when the cohort of individuals who were born between 1930 and 1940 and started to smoke non-filtered cigarettes were compared to subsequent birth cohorts who would have had access to the increasingly lower yield and filtered products. Data on lung cancer mortality in younger men in the United Kingdom have been interpreted as indicating a possible reduction in lung cancer risk associated with changes in cigarettes composition when changes in prevalence, duration, and amount of smoking, were accounted for. The anticipated pattern of temporal change in age-specific rates of lung cancer mortality in younger men however has not taken place in the United States. Uncertainty remains with regard to the interpretation of these conflicting data, and alternative explanations have been proposed, including less intense smoking at younger ages in more recent birth cohorts. The

results highlight the complexity of isolating the precise effect on lung cancer risk of the continually changing cigarette. The data available to evaluate these effects have limitations, particularly in capturing the experience of successive birth cohorts in either case-control or cohort studies that were appropriately designed. The UK mortality data suggest a greater effect of changes in cigarettes than is found in the case-control and cohort studies. Several expert panels have reviewed these findings. The Institute of Medicine conducted a comprehensive review on various harm reduction strategies for reducing the disease burden caused by smoking, including lower yield cigarettes and concluded that smoking lower-yield products had not been shown to benefit the health of smokers. This topic was also addressed in the 2004 report of the US Surgeon General with the conclusion that "although characteristics of cigarettes have changed during the last 50 years and yields of tar and nicotine have declined substantially, as assessed by the Federal Trade Commission's test protocol, the risk of lung cancer in smokers has not declined". Differences in smoking habits for instance higher puff volume, the frequency of puffing, and the length to which the cigarette is to be smoked might account for that.

The same authors [163] also reviewed the literature on menthol cigarettes, which may cause a greater increase in lung cancer risk than non-menthol cigarettes, either by increasing systemic exposure to toxicants from tobacco smoke or by affecting the metabolism of nicotine and/or tobacco smoke carcinogens. Menthol potentially increases nicotine uptake in the respiratory tract and increases the smoothness of tobacco smoke, which promotes deeper inhalation; stimulation of cold receptors, which results in airway cooling effects that mask the irritation caused by cigarette smoke, promoting deeper inhalation and altered inhalation frequency; further masking of irritation through anesthetic effects; and increased permeability and diffusibility of smoke constituents has been proposed.

Black, male, heavy smokers of mentholated cigarettes (37.5 pack-years, or 21 cigarettes per day) had a higher risk than white men with similar smoking histories. In the cohort study the RR for lung cancer among men but not women was slightly elevated in menthol smokers compared with non-menthol smokers, with a graded increase in lung cancer risk with increasing duration of menthol cigarette use. The evidence does not indicate that menthol cigarettes are an important contributor to the high rates of lung cancer in African-American individuals.

PASSIVE SMOKING

Passive smokers inhale a complex mixture of smoke now widely referred to as second-hand smoke or as environmental tobacco smoke (ETS). Passive smoking was first considered as a possible risk factor for lung cancer in 1981, when two studies that described increased lung cancer risk among never-smoking women who were married to smokers were published [163]. In 1986 The National Research

Council reviewed the epidemiologic evidence and concluded that non-smoking spouses who were married to cigarette smokers were approximately 30% more likely to develop lung cancer than non-smoking spouses married to non-smokers and that this relationship was biologically plausible. Almost one fourth of lung cancer cases among never-smokers were estimated to be attributed to exposure to ETS [286]. Since the 1980s more than 50 studies of ETS and lung cancer risk in never-smokers, especially spouses of smokers, have been published. These studies were evaluated by IARC in 2004. The excess risk is of the order of 20% for women and 30% for men and remains after controlling for some potential sources of bias and confounding. The excess risk increases with increasing exposure. Meta-analyses of lung cancer in never-smokers exposed to second-hand tobacco smoke at the workplace have found a statistically significant increase in risk of 12−19%. This evidence is sufficient to conclude that ETS is a cause of lung cancer in never-smokers. The IARC expert-group concluded: Involuntary smoking (exposure to second-hand or 'environmental' tobacco smoke) is carcinogenic to humans (Group 1).

PHYSICAL ACTIVITY

Several studies have reported that more physically active men and women have a lower risk from all-site cancer than those who are more sedentary, even after adjustment for cigarette smoking. Physical activity was also in some studies associated with decreased risk of lung cancer in men and women, after adjusting for smoking. However, the proportions of smokers in former studies were low and the results may not be generalizable to all smokers. Alfano et al. [287] studied all-site cancer and lung cancer incidence and mortality in a sample of current and former smokers (n = 7,045). An association with physical activity was found for incidence of all-site cancers but not for lung cancer. Mortality was only reduced for physical active women both for all-site cancers and lung cancers. HR associated with a 1 SD increase in physical activity were 0.69 (95% CI: 0.53-0.90) for lung cancer among women.

The relation between physical activity, inflammation, and lung cancer risk was evaluated by Sprague and colleges [288] in a prospective cohort of 4,831 subjects, 43–86 years of age. White blood cell count was includes as a marker of chronic inflammation, which was supposed to provide a potential mechanistic explanation for the expected reduced incidence of lung cancer. During an average of 12.8 years of follow-up, 134 incident cases of lung cancer were diagnosed. After multivariable adjustment, participants in the highest tertile of total physical activity index had a 45% reduction in lung cancer risk compared to those in the lowest tertile (OR 0.55, 95% CI: 0.35–0.86). Participants with white blood cell counts in the upper tertile were 2.81 (95% CI: 1.58–5.01) times as likely to develop lung

cancer as those with counts in the lowest tertile. These data suggest that physical activity and white blood cell count are independent risk factors for lung cancer.

Cardiorespiratory fitness was associated with lung cancer mortality but only among smokers in a prospective cohort included 38,000 men followed between 1974 and 200 [289]. A total of 232 lung cancer deaths occurred during follow-up (mean=17 years). After adjustment for age, examination year, BMI, smoking, drinking, physical activity, and family history of cancer, hazard ratios (95% confidence intervals) for lung cancer deaths across low, moderate and high cardiorespiratory fitness categories were: 1.0, 0.48 (0.35–0.67), and 0.43 (0.28–0.65) respectively. There was an inverse association between cardiorespiratory fitness and lung cancer mortality in former (P for trend = 0.005) and current smokers (P for trend <0.001), but not in never smokers (trend P = 0.14). Joint analysis of smoking and fitness status revealed a significant 12-fold higher risk of death in current smokers (HR 11.9, 95% CI: 6.0–23.6) with low cardiorespiratory fitness as compared with never smokers who had high cardiorespiratory fitness.

DIET

Research on diet and lung cancer has now been conducted for 3 decades. The possible role of diet in modifying the risk for lung cancer has focused on the assumption that specific micronutrients might have anti-carcinogenic activity. The most thoroughly investigated dietary factors are also those that seem to have the greatest implications for prevention: fruits, vegetables, and specific antioxidant micronutrients that are commonly found in fruits and vegetables. Much of the research on diet and lung cancer has been motivated by the hypothesis that diets that are high in antioxidant nutrients may reduce oxidative DNA damage and thereby protect against cancer. The results of case-control and prospective cohort studies have tended to show that individuals with high dietary intake of fruit or vegetables have a lower risk for lung cancer than those with low fruit or vegetable intake [163]. Evidence from cohort studies published since 2000 has tended to reinforce this notion. The latest published update from the European Prospective Investigation into Cancer and Nutrition showed a strong protective association was observed in the whole study population for fruit consumption while no association was found for vegetable consumption. The cohort data was collected between 1992 and 2000; detailed information on diet and life-style of 478,590 individuals was primary based on questionnaire data. During a median follow-up of 6.4 years, 1,126 lung cancer cases were observed. Multivariate Cox proportional hazard models were applied for statistical evaluation. In current smokers, lung cancer risk significantly decreased with higher vegetable consumption; this association became more pronounced after calibration, the hazard ratio (HR) being 0.78 (95% CI: 0.62–0.98) per 100 g increase in daily vegetable consumption. In comparison, the HR per 100 g fruit was 0.92 (0.85–

0.99) in the entire cohort and 0.90 (0.81–0.99) in smokers. Exclusion of cases diagnosed during the first 2 years of follow-up strengthened these associations. Cancer incidence decreased with higher consumption of apples and pears (entire cohort) as well as root vegetables (smokers). In addition to an overall inverse association with fruit intake, the results of this evaluation add evidence for a significant inverse association of vegetable consumption and lung cancer incidence in smokers [213]. Also a stronger protective association was observed for fruit than vegetable consumption in a pooled analysis of seven cohort studies. But in this analysis associations were similar between never, past, and current smokers [215].

The above results suggest that elevated fruit and vegetable consumption is associated with a modest reduction in lung cancer risk, which is mostly attributable to fruit. However, the possibility cannot be ruled out that the results are due to residual confounding by smoking.

ALCOHOL

In a review of eight case-control studies and nine cohort studies published between 1966 and 2000 Bandera [290] found that the studies reviewed provided some indication that alcohol and particularly beer intake may increase lung cancer although the evidence was not conclusive. A meta-analysis showed, that alcoholics had a fairly substantial increase in lung cancer risk in relation to general population rates, with a pooled RR of 1.99 (95% CI: 1.66-2.39). Studies of brewery workers had a questionable excess risk of lung cancer, with a pooled RR of 1.17 (95% CI: 0.99-1.39). For cohort studies, the pooled smoking unadjusted RR in relation to nondrinkers was 1.19 (95% CI: 1.11-1.29) and the pooled smoking-adjusted odds ratio was 1.39 (95% CI: 1.06-1.83) [212]. Similarly Freudenheim et al. [208] found a slight elevated risk of lung cancer associated with the consumption of more than 30 g alcohol/day compared with no alcohol consumption. In this study alcohol consumption was strongly associated with greater risk in males who did not smoke, which is in contrast to later studies that found no excess risk in never smokers [291]. A recent meta-analysis exclusively in never smokers showed that alcohol consumption was not associated with lung cancer risk in never smokers and that alcohol does not play an independent role in lung cancer etiology [291].

The results of studies on association between alcohol consumption and lung cancer are conflicting. Since drinking and smoking are strongly associated, residual confounding by smoking may bias the estimation of alcohol consumption and lung cancer risk relation. Recent studies on alcohol and lung cancer risk in never smokers suggests that alcohol does not play an independent role in lung cancer etiology.

ANTHROPOMETRIC MEASURES

Since the 1980s a number of studies have examined the relation between leanness and lung cancer risk. Most of these studies showed an increasing risk with decreasing body mass index for current smokers, ex-smokers and never smokers. Many of these studies had sufficiently controlled for smoking or pre-existing diseases [210].

Subsequently better controlled studies have shown associations between leanness and lung cancer: Gorlova et al. [209] analyzed never smokers, 280 cases compared with 242 hospital-based controls. Cases at the time of diagnosis were leaner than controls (BMI 28.5; $p < 0.001$). Cases also tended to have been leaner 5 years prior to enrolment to controls.

Reeves et al. [214] followed 1.2 million UK women recruited during 1996-2001. Both lung cancer incidence and mortality were inversely associated with BMI when adjusted for age, geographical region, socioeconomic status, reproductive history, smoking status, alcohol intake, physical activity, and, where appropriate, time since menopause and use of hormone replacement therapy. Trend for mortality per 10 BMI-units was 0.72 (95% CI: 0.66-0.79) and for incidence 0.74 (95% CI: 0.67- 0.82). An inverse relationship between BMI and lung cancer risk was also found in women [211].

Smith et al. [216] prospectively examined the association between BMI and lung cancer risk among 271,238 men and 177,494 women. 6,093 men and 3,344 women were diagnosed with lung cancer. Of these, 166 men and 249 women were non-smokers. In a multivariate model that adjusted for smoking status, BMI was significantly and inversely associated with lung cancer risk in both men and women. For men, the HR for men with a BMI of 35 or higher vs. men with a BMI between 22.5 and 24.99 was 0.81 (95% CI: 0.70-0.94). For women, the decreased risk was even more pronounced, with a HR of 0.73 (95% CI: 0.61-0.87.).

Some studies have shown decreased risk of lung cancer with the use of menopausal hormones but results are not consistent [204]. The stronger inverse association among women suggests that increased estrogen levels may play an etiologic role [216].

Cigarette smoking is closely associated with less healthy lifestyles. Thus it is difficult to disentangle dietary and other lifestyle factors from smoking effects [163]. Smokers tend to have lower circulating concentrations of antioxidant micronutrients even after accounting for differences in dietary intake. Associations between dietary factors and lung cancer risk are much weaker than smoking associations.

Diet estimations are prone to greater error than smoking [163]. Therefore residual confounding from smoking cannot be set aside when evaluating lifestyle factors.

APPENDIX 19. ACQUIRED LUNG DISEASES AND LUNG CANCER RISK (4.4)

PULMONARY FIBROSIS AND ASBESTOSIS

For many years it has been observed that lung cancers frequently arise in lung areas with hyperplastic epithelium or fibrosis. Idiopathic lung fibrosis (IPF) and systemic sclerosis (SSc) have been consistently linked to increased lung cancer risk, also when adjusting for smoking [163]. Archontogeorgis et al. [217] reviewed 7 IPF studies. Only 3 reported incidences of lung cancer (2.7%, 22.4%, and 31.3%). The one study that included a background population showed a RR of 4.96 (95% CI: 3.00-8.18). The use of immunosuppressive drugs and radiographs add to lung cancer risk [163].

Previously the presence of asbestosis was required before concluding that lung cancer was work-related. However, it has been commonly accepted for the past few decades that ARLC can occur in the absence of asbestosis. Hessel [218] critically reviewed 7 studies, 5 of which found asbestosis unnecessary. As asbestosis reflects considerable asbestos exposure, its presence is useful in risk evaluations of possible ARLC. However, some degree of disagreement remains as to whether or not asbestosis is required before ARLC can be diagnosed [219].

TUBERCULOSIS

In the late 1960s Steinitz evaluated a population in Israel with relatively few heavy smokers, and found that patients with previous tuberculosis (TB) had an increased risk of developing lung carcinoma, approximately five times greater than the general population males and ten times greater in females. Since then several studies of various quality have been published. The latest major systematic review was conducted in 2009 by Liang et al. [221]. Using very strict inclusion and exclusion criteria they included 37 case-control, 4 cohort studies and one meta-analysis of risk estimates. To avoid the potential confounding by tobacco use among subjects with TB they combined data from 31 results of 24 studies in which proper adjustment was made for smoking. Combined adjusted data showed a statistically significant increase in risk of lung cancer, RR = 1.97 (95% CI: 1.60–2.41). There was, however, evidence of significant heterogeneity between the studies ($Q = 73.56$, $p < 0.001$, $I^2 = 59.2\%$). The total pooled RR was 1.78 (95% CI: 1.42–2.23) without evidence of significant heterogeneity ($Q = 19.28$, $p = 0.115$, $I^2 = 32.6\%$). The increased lung cancer risk remained 2-fold elevated for more than 20 years after TB diagnosis and the association was significant with adenocarcinoma (RR = 1.6, 95%

CI: 1.2–2.1), but no significant associations were found for squamous and small cell type of lung cancer. The authors concluded, that although no causal mechanism has been demonstrated the study supports a direct relation between TB and lung cancer, especially adenocarcinomas.

Since 2009 two large studies have been published from Taiwan [223] and [224] where TB, lung cancer, and smoking are prevalent in men (50-60%), but not in women (3-4%). The risk estimates from these studies were very much higher than in the result from Liang's review, but smoking was not controlled for on an individual level. TB per se seems to be a risk factor for lung cancer. The association was not due to confounding by the smoking or ETS.

RISK OF SECOND PRIMARY LUNG CANCER

Many studies have established that individuals with cancer have an increased risk of developing a second cancer. The increased risk for lung cancer as a secondary tumor may be associated with the both treatment and smoking. Non-smoking women who received post-mastectomy radiotherapy had no higher risk of second primary lung cancer compared to ever-smokers. The joint effects of smoking and post-mastectomy radiotherapy showed adjusted OR 10.5 (95% CI: 2.9 to 37.8) for the contralateral lung and 37.6 (95% CI: 10.2-139.0) for the ipsilateral lung indicating a more than additive effect of smoking and post-mastectomy radiotherapy [222].

The risk of second primary lung cancer in lung cancer patients is substantial, and enhanced by smoking. In patients with small cell carcinoma who stopped smoking at the time of diagnosis, the RR of a second lung cancer was 11 (95% CI: 4.4-23). In those who continued to smoke, the RR was 32 (95% CI: 12-69) [225]. Second lung cancer risk was increased 13-fold among those who received chest irradiation in comparison to a sevenfold increase among non-irradiated patients. It was higher in those who continued smoking, with evidence of an interaction between chest irradiation and continued smoking (RR = 21). Patients treated with various forms of combination chemotherapy had comparable increases in risk (9.4 to 13-fold), except for a 19-fold risk increase among those treated with alkylating agents who continued smoking [226].

The risk seems higher for small cell carcinoma. Johnson [231] found, that the risk of developing a second lung cancer in patients who survived resection of NSCLC was approximately 1%–2% per patient per year. The average risk of developing a second lung cancer in patients who survived SCLC was approximately 6% per patient per year.

Cancers other than breast and lung have been associated with second primary lung cancer. In a retrospective cohort study the RR of second primary cancer was studied in Queensland, Australia [229]. Significant elevated SIR of second primary lung cancer was found for all cancers combined, head and neck cancers and esophageal cancers.

Chen et al. [227] found an increased risk of second primary lung cancer. For esophageal cancer a multicenter study was carried out based on 13 population-based cancer registries in Europe, Australia, Canada, and Singapore. SIR for all second primary cancers was 1.15 (95% CI: 1.08-1.22), and second primary lung cancers were 1.55 (95% CI: 1.28-1.87) [228].

An elevated risk (8-50%) for second primary lung cancer is associated with head and neck cancers and esophageal cancers, radiotherapy affecting the lungs, and various forms of combination chemotherapy. Smoking remains the predominant risk factor also for second primary lung cancer especially for SCLC.

CHRONIC OBSTRUCTIVE PULMONARY DISEASES, BRONCHITIS, EMPHYSEMA, AND ASTHMA

The associations between lung cancer and COPD have been demonstrated in many years. In a meta-analysis comprising 35 studies (22,010 cases and 44,438 controls) Wang et al. [292] found that COPD was significantly associated with increased lung cancer risk (pooled OR = 2.76; 95% CI: 1.85–4.11). In the 10 studies where smoking habits were accounted for, the pooled OR for lung cancer among persons with COPD was 3.13 (95% CI: 2.02-4.96). A positive association was found for chronic bronchitis, OR = 1.88 (95% CI: 1.49–2.36), increased in both smokers (OR 2.38, 95% CI: 1.45-3.92) and non-smokers (OR=1.54, 95% CI: 1.24-1.93). The same pattern was seen for emphysema, OR = 3.02 (95% CI: 2.41–3.79) but not for asthma, OR = 0.93 (95% CI: 0.32-2.71).

Smoking is the principal cause of both COPD and lung cancer, being so strongly causally associated with both of these illnesses presuming that statistical adjustment procedures “remove” the effect of cigarette smoking may not be well founded. Therefore, clarifying the relevance of COPD to the development of lung cancer awaits further proof that this association is not accounted for by cigarette smoking [163]. Hypotheses for the association between COPD and increased risk for lung cancer include impaired clearance of carcinogenic substances in tobacco smoke and chronic inflammation with injury to the bronchial epithelium. Alternatively, COPD and lung cancer may develop simultaneously by some process incited by tobacco smoke common to both diseases [173]. Another potential mechanism that is hypothesized to link COPD with lung cancer is α-1-antitrypsin deficiency,

and evidence to support this notion includes the observation that the prevalence of α-1-antitrypsin deficiency carriers was higher in patients with lung cancer than in the general population and higher in patients who had lung cancer and had never smoked [163]. The modest association found among non-smoker might be attributed to environmental or occupational exposures and/or other of the before mentioned factors. COPD is, however, a useful clinical indicator of lung cancer risk.

APPENDIX 20. NON-OCCUPATIONAL/ENVIRONMENTAL ASBESTOS EXPOSURE AND LUNG CANCER (4.4)

THE CONCEPT OF ENVIRONMENT

The term 'environment' is often used broadly in the medical literature, including all non-genetic factors such as diet, lifestyle and infectious agents. In this broad sense, the environment is implicated in the causation of the majority of human cancers. In a more specific sense, however, environmental factors include only the (natural or manmade) agents encountered by humans in their daily life, upon which they have no or limited personal control. The most important 'environmental' exposures, defined in this strict sense, include outdoor and indoor air pollution as well as soil and drinking water contamination [191]. It is in this narrower sense environmental or non-occupational exposures are used in this section of the report while host factors are dealt with separately.

EXPOSURE IN INDOOR AND OUTDOOR AIR

The previous widespread use of asbestos-containing building materials and brake linings may have led to a general increase in the quantity of asbestos fibers in both surface soil and in the air. The "natural" background level may therefore be raised as a result of a general environmental exposure, particularly in peri-urban areas and around roads. There is no available information about the Danish background asbestos levels in the air. A British study from the 1980s on outdoor concentrations of asbestos fibers in the air at two traffic junctions in London showed that the total asbestos fiber levels were from 0.00055 f/ml to 0.0062 f/ml. The same study found that the content of regulated fibers was > 0.0004 f/ml. (Regulated fibers include the proportion of asbestos fibers determined analytically with the recommended test methods, and includes asbestos fibers with lengths greater than 5 μm, an average width of less than 3 μm and a length/width ratio greater than 3:1). Miljøstyrelsen (The Danish environmental protection agency) sets the background level in outdoor air in cities to about 0.0001-0.0005 fibers/ml based on Dutch and English studies.

Neither is the asbestos concentrations known in indoor air buildings in Denmark. But Miljøstyrelsen quoted foreign studies on asbestos concentrations in indoor air from a level less than the detection limit and up to 0.0007 f/ml in buildings without building materials containing asbestos, while measured concentrations of airborne asbestos particles in the air in buildings with asbestos-containing building materials was up to 0.075 f/ml. Of 235 samples analyzed 13% showed a concentration greater

than 0.01 fibers asbestos/ml. The investigation included determination of airborne asbestos fibers and other fibers in 39 buildings with asbestos containing materials in both building constructions air-heat supplies.

WHO states, that the actual indoor and outdoor concentrations of asbestos fibers in air range from below one hundred to several thousand fibers per m^3 [239].

EXPOSURE LIMITS FOR ASBESTOS

The threshold limiting value for asbestos dust in the working environment laid down by Arbejdstilsynet (the Danisk Labour Inspectorate) is 0.1 f/cm^3 (f/ml).

Miljøstyrelsen has established a B-value for the content of asbestos fibers in air. A B-value (contributory value) is a threshold value for a company's contribution to air pollution in the surroundings. B-value for asbestos fibers is 400 f/m^3 equivalent to 0.0004 f/ml.

WHO's guideline values based on conclusions from multiple experts is a lifetime exposure of 1,000 f/m^3 (0.001 f/ml). This value should be adjusted to 500 f/m^3 (0.0005 f/ml), optically measured. In a population of whom 30% are smokers, the excess risk due to lung cancer would be in the order of 10^{-6}–10^{-5}. For the same lifetime exposure, the mesothelioma risk for the general population would be in the range 10^{-5}–10^{-4} [239].

EXTRAPOLATIONS FROM EPIDEMIOLOGICAL STUDIES OF OCCUPATIONAL ASBESTOS EXPOSURE

Many epidemiological studies are available on asbestos exposed workers. In many epidemiological studies, the crucial effect of smoking has not been properly taken into account. Differentiation of the observed risks according to smoking habits has been carried out, however, in the cohort of North American insulation workers studied by Hammond et al. [236].

In an extensive review of quantitative risks from asbestos exposure, Hodgson and Darnton [38] summarize information on the risks of lung cancer (and mesothelioma) for various occupational exposure levels. Included were mortality studies on asbestos exposed cohorts that gave information on exposure levels; 17 such studies were identified.

On that basis Hodgson and Darnton generated estimates of risks for various cumulative exposures including exposures outside the range for which direct observations were available. Under such circumstances there are two primary sources of uncertainty in the estimated risks:

- Firstly there is the usual statistical uncertainty of inferring underlying risk from observations in particular groups. This uncertainty can to some extent be quantified and expressed as a confidence interval
- The second type of uncertainty relates to whether the relationship between exposure and outcome seen in the observed range is also valid outside that range. This uncertainty cannot be quantified statistically.

Uncertainty about the slopes of exposure-response lines has an increasing impact with increasing distance from the observed range. For these reasons Hodgson and Darnton considered that simply presenting a table of risk estimates for different cumulative exposures was not appropriate, as this would not capture the changing balance of the different types of uncertainty. They therefore produced a table (reproduced below in table A17) giving a numerical and qualitative assessment of lifetime risk at a range of cumulative exposures. No estimates were given for lifetime risks lower than 1 in 100.000 and this level is referred to as 'insignificant'.

For mesothelioma the results clearly show that exposure to amphibole fibers is more hazardous than exposure to chrysotile - broadly in the ratio 1:100:500 for chrysotile, amosite and crocidolite respectively. For lung cancer the conclusions are less clear with a risk differential between chrysotile and the two amphibole fibers of between 1:10 and 1:50 [38].

Table A17. Numerical and qualitative assessment of lifetime risk at a range of cumulative exposures. No estimates were given for lifetime risks lower than 1 in 100.000 and this level is referred to as 'insignificant' [38].

FIBERS	MESOTHELIOMA	LUNG CANCER
RISK SUMMARIES FOR CUMULATIVE EXPOSURES BETWEEN 10 AND 100 F/ML.YEARS		
Crocidolite	Best estimate about 400 deaths per 100 000 exposed for each f/ml.yr of cumulative exposure. Up to 2-fold uncertainty.	Rising from about 150 (range 100 to 250) excess lung cancer deaths per 100 000 exposed for each f/ml yr of cumulative exposure at 10 f/ml.years to 350 (range 250 to 550) at 100 f/ml.years.
Amosite	Best estimate about 65 deaths per 100 000 exposed for each f/ml.yr of cumulative exposure. 2-fold to 4-fold uncertainty	

Chrysotile	Best estimate about 2 deaths per 100 000 exposed for each f/ml.yr of cumulative exposure. Up to 3-fold uncertainty.	Best estimate about 5 excess lung cancer deaths per 100 000 exposed for each f/ml yr of cumulative exposure. Cautious estimate 30. In exceptional circumstances (see note c) it is arguable that an estimate of 100 might be justified
RISK SUMMARIES FOR CUMULATIVE EXPOSURES OF 1 F/ML.YEARS		
Crocidolite	Best estimate about 650 deaths per 100 000 exposed. Highest arguable estimate 1500, lowest 250	Best estimate about 85 (range 20 to 250) excess lung cancer deaths per 100 000 exposed.
Amosite	Best estimate about 90 deaths per 100 000 exposed. Highest arguable estimate 300, lowest 15.	Best estimate about 2 excess lung cancer deaths per 100 000 exposed. Cautious estimate 30 per 100 000. In exceptional circumstances (see note c) it is arguable that an estimate of 100 per 100 000 might be justified. The case for a threshold—ie. zero, or at least very low risk—is arguable.
Chrysotile	Best estimate about 5 deaths per 100 000 exposed. Highest arguable estimate 20 lowest 1.	
RISK SUMMARIES FOR CUMULATIVE EXPOSURES OF 0.1 F/ML.YEARS		
Crocidolite	Best estimate about 100 deaths per 100 000 exposed. Highest arguable estimate 350, lowest 25.	Best estimate about 4 (range 1 to 25) excess lung cancer deaths per 100 000 exposed.
Amosite	Best estimate about 15 deaths per 100 000 exposed. Highest arguable estimate 80, lowest 2.	Best estimate about 4 (range 1 to 25) excess lung cancer deaths per 100 000 exposeed
Chrysotile	Risk probably insignificant, highest arguable estimate 4 deaths per 100 000 exposed	Excess lung cancer deaths probably insignificant. Cautious estimate 3 per 100 000. In exceptional circumstances (see note c) it is arguable that an estimate of 10 per 100 000 might be justified. The case for a threshold—ie zero, or at least very low risk—is strongly arguable.
RISK SUMMARIES FOR CUMULATIVE EXPOSURES OF 0.01 F/ML.YEARS		
Crocidolite	Best estimate about 20 deaths per 100 000 exposed. Highest arguable estimate 100, lowest 2.	Risk is probably insignificant (range 1 to 3 excess lung cancer deaths per 100 000 exposed). Mesothelioma is now the dominant risk, so precise estimation of the lung cancer risk is not critical.
Amosite	Best estimate about 3 death per 100 000 exposed. Highest arguable estimate 20, lowest insignificant.	
Chrysotile	Risk probably insignificant, highest arguable estimate 1 deaths per 100 000 exposed	Risk of excess lung cancer very probably insignificant except in exceptional circumstances (see note c) when it is arguable that an estimate of 1 death per 100 000 might be justified. The case for a threshold—i.e. zero, or at least very low

		risk—is strongly arguable
RISK SUMMARIES FOR CUMULATIVE EXPOSURES OF 0.005 F/ML.YEAR AND LOWER AT THESE LEVELS ONLY MESOTHELIOMA NEED BE CONSIDERED. THE ABSOLUTE RISK IS LOW, BUT QUANTITATIVE UNCERTAINTIES ARE VERY CONSIDERABLE.		
Crocidolite	Best estimate about 10 deaths per 100 000 exposed. Highest arguable estimate 55, lowest. Best estimate falls to insignificant level at 0.0002 f/ml.year, and highest arguable risk becomes insignificant at 6´1026 f/ml.year	Insignificant, possibly zero
Amosite	Best estimate about 2 deaths per 100 000 exposed highest arguable lifetime risk 15, falling to ,1 (ie. insignificant) at 7´1025 f/ml.year	
Chrysotile	Insignificant	Insignificant, very possibly zero

EPIDEMIOLOGICAL STUDIES OF NON-OCCUPATIONAL ASBESTOS EXPOSURE

The assessment of non-occupational exposure to asbestos presents difficulties, since levels are low, and the duration and frequency of exposure and the type of fiber are seldom known. Most studies on the evaluation of lung cancer and environmental or non-occupational exposure to asbestos have been investigations carried out in:

- Household exposure in cohabitants of asbestos workers and arising from dust brought home on clothes
- Areas with very high exposures - e.g. residence near a mine or a processing plant
- Areas where asbestos occurs naturally.

From a research point of view this may be reasonable, as large exposure contrast in study groups maximize the study's ability to detect an elevated risk. However, problems arise when data from these studies were extrapolated to the much lower concentrations found in the general environment. If for instance the true relationship is not linear, the impact on low dose extrapolations could be significant. The same applies from the extrapolation of estimated risks from industrial exposures at relatively high levels (> 10 f/ml-years) for long periods of time to the much shorter or lower exposures many asbestos exposed workers may be let in for.

By using residence in mining areas or near processing plants the possibility of confounding by employment in the asbestos industry is a source of bias that was not excluded in all studies [191].

RISK IN HIGHLY EXPOSED POPULATION

Bofetta et al. [293] reviewed 8 studies on lung cancer risk from outdoor air pollution published before 2000.

Five of these studies showed an increased risk, three did not. Relative risk varied from 0.8 to 5.7. The available data does not permit a joint estimation for the relative risk but the rough confidence intervals varied from 0.4 to 9.3. Results are shown in Table A18.

Three of the studies considered areas with high concentrations of naturally occurring asbestos in the local environment. These included a case control study in New Caledonia [294], where naturally occurring asbestos were used in building materials, notably whitewash, and two ecological studies, one in China [233] and one in Austria [247].

Table A18. Studies of risk of lung cancer and mesothelioma: Modified from: Boffetta et al., (2003) [293] (Studies without information on lung cancer are omitted).

STUDIES OF RISK OF LUNG CANCER AND MESOTHELIOMA FROM ENVIRONMENTAL EXPOSURE TO ASBESTOS

Country	SD	TF	Source of exposure	Mesothelioma			Lung cancer		
				Ca	RR	95% CI	Ca	RR	95% CI
South Africa	Ec	A	Res. in mining area [a)]	61	8,7	6,7–11,4	86	1,7	1,2–2,5
South Africa	CC	A	Res. in mining areas [a)]				16	3,6	1,4–9,3
Canada	Ec	C	Res. in mining area [b)]	7	7,6	3,4–14,9	71	1,1	0,9–1,4
USA	CC	A	Res. near to asbestos plant				41	0,9	0,6–1,3
Austria	Ec	A	Res. in polluted town [a)]				36	0,8	0,4–1,6
China	CC	C	Res. >20 years <0,2 km from asbestos plant [a)]				47	1,9	0,5–6,4
China	Co	A	Res. in polluted area	NA	182	NA	NA	5,7	NA
New Caledonia	CC	A	Use of contaminated building materials [a)]	14	40,9	5,1–325	56	0,9	0,6–1,3

SD, study design: CC, case–control study; Co, cohort study; Ec, ecological study.
TF, predominant type of fibers: A, amphiboles; C, chrysotile.
Ca, Number of cases; RR, Relative Risk; 95% CI, 95% confidence interval.
[a)] Results derived from raw data reported in the publication.
[b)] Women only.

Two studies related to environmental exposures resulting from residence in asbestos mining or shipping regions. One of these was an ecological study considering the impact of environmental exposures on female residents in two chrysotile mining areas in Quebec [295]. The other was a case control study considering exposures in mining areas and areas where asbestos was shipped in South Africa [235]. The remaining studies, all ecological, investigated the impact of environmental exposures from particular industrial plants processing or manufacturing asbestos containing materials in Austria [247], Italy [234] and the USA [236].

For four of the studies considered it was stated that no excess risk of lung cancer was detected in the exposed population (Italy, Austria, USA, and Canada). Three of the studies indicated an increased risk of lung cancer in the exposed population. The highest RR of 6.7 was a result of exposure from naturally occurring asbestos present in a region of China. The New Caledonia study identified an increased risk from the use of asbestos containing building materials for women (OR 2.51. 95% CI: 1.01-6.22) but not for men (OR 0.89. 95% CI: 0.51-1.54). The South African study [235] derived ORs ranging from 1.1 (95% CI: 0.3-3.9) to 5.4 (95% CI: 1.3-22.5) for individuals in asbestos mining or shipping areas, with risks higher in the more heavily polluted mining areas. Only one of the studies, Camus et al. [295], included asbestos exposure estimates for the exposed populations. For the study an average cumulative lifetime chrysotile exposure of 25 f/ml-years was estimated with a range of 5 — 125 f/ml-years. This study of women living in two chrysotile mining areas in Quebec [295] generated an age standardised mortality ratio for the exposed population, in comparison to the unexposed, of 0.99 with a range of 0.78 to 1.25 and they estimated the excess deaths in the population between 0 and 6.5.

Hodgson and Darnton [38] concluded that the best estimate lung cancer risk for cumulative chrysotile exposure levels between 10 and 100 f/ml-year was about 5 excess deaths per 100,000 exposed for each f/ml-year of cumulative exposure. An exposure of 25 f/ml-years would therefore imply a risk of 125 deaths per 100,000 exposed. Using this risk estimate on the Quebec cohorte would imply in the region of 15 deaths[1] compared to the number 0-6.5 estimated by Camus et al. 1998. So the number of cases reported by Camus et al. 1998 was significantly lower than that predicted using the standard estimates from Hodgson and Darnton [38]. However, Hodgson and Darnton indicate that their best estimate excess lung cancer risks represent an average for a population with a past pattern of smoking similar to that of older British men and that for non-smokers the risk would be between a third and a sixth of those quoted. Camus et al. indicate that smoking levels within the exposed population were slightly

[1] Assuming that the number of exposed persons was about 221.375 person-years/19 years (= 11651 persons) and an average exposure of 25 f/ml-years leading to 125 deaths per 100,000 exposed.

lower than those in the non-exposed populations. This factor however does not explain the whole difference and illustrates the broad uncertainty in these estimates.

Since 2000 a couple of studies were published from Anatolia, Turkey where tremolite and, to a lesser extent, chrysotile asbestos is found in high concentration in the environment. In one of these studies that dealt with lung cancer risk, the risk was 1.3-fourfold higher in regions with high asbestos concentration compared to the general population of Turkey [237]. Another approach to evaluate the significance of asbestos exposure in a general population was done by Liu 2001 [238]. Pulmonary asbestos fibers counts increased in an age-dependent manner ($P<0.01$) in autopsy cases in Hong Kong Chinese. Lung cancer cases (N=65) however had significant more coated fibers (asbestos body) and males cases a higher total fibers count in their lungs tissue compared to the non-lung cancer cases (N=107). The results suggest that there is an environmental exposure to asbestos in Hong Kong Chinese and that asbestos exposure in Hong Kong males may be one of the carcinogenic factors leading to lung cancer.

RISK IN THE GENERAL POPULATION

Neither studies from Turkey nor the studies listed in Table 1 or 2 in fact fills the knowledge gap between occupational exposures and exposures in the general population for instance in Denmark. Few estimates are available of the significance or the proportion of the population experiencing non-occupational asbestos exposure.

EXPOSURE-RESPONSE MODELS

A number of exposure-response models for asbestos have been developed. Peto et al. [246] showed that the incidence of mesothelioma was dependent on time since first exposure, but not dependent on age at first exposure nor smoking habit nor gender. An increased risk of mesothelioma has consistently been detected among individuals experiencing residential exposure to asbestos. One might therefore expect that recent predictions were based on these models and measurements or other reliable estimates of asbestos exposure in the population, and that these estimates could be used as the basis for corresponding predictions of frequency of lung cancer caused by environmental asbestos exposure. But three of the often-cited studies [38, 244, 245] contain no precise assumptions about the actual level of exposure to asbestos, but solely used mathematical extrapolation models based on previous disease patterns. Hodgson et al. [38] refer to a British Health and Safety Executive Regulatory Impact Assessment from 2002 that suggested that population exposure in 2000 was around 4% of the peak value reached in the 1960s. For their own projections, Hodgson et al. assumed a continuing decline in asbestos exposure, from 4% of the peak level in 2000 to 2% by 2010 and 0.75%

by 2050. However these figures probably comprise both occupational and non-occupational exposures.

Because mesothelioma is almost exclusively linked to asbestos exposure and not to smoking or other known exposures, extrapolations of the incidence of mesothelioma is less complicated than for lung cancer and may apply to exposure levels for the general population [242]. Lung cancer on the other hand is one of the most common forms of cancer. As several exogenous noxious agents can be etiologically responsible for bronchial carcinoma, the extrapolation of risk and comparison between different studies is considerably complicated. Exposure-response models for asbestos has also been developed for asbestos and lung cancer, but the models proposed by Doll and Peto [145] and other researchers, are based primarily on projections of occupational exposures' significance for lung cancer and not based on environmental exposures in the general population.

A review of the predicted risks for lung cancer from a number of asbestos studies has been carried out by WHO with the objective of estimating risks from background environmental asbestos exposure levels. The risks were based on evidence from epidemiological studies concerning occupational exposure. Data from these studies were conservatively extrapolated to the much lower concentrations found in the general environment using a formula that stated, that the relative risk at a given time is approximately proportional to the cumulative amount of fine asbestos dust received up to this point, for both smokers and non-smokers. The risks for non-asbestos-exposed non-smokers and smokers must therefore be multiplied by a factor that increases in proportion to the cumulative exposure. The exposure–response relationship was described by the following equation:

$$I_L \text{ (age, smoking, fibers exposure)} = I_L^0 \text{ (age, smoking)}[1 + K_L \times C_f \times d]$$

where:
K_L = a proportionality constant, which is a measure of the carcinogenic potency of asbestos
C_f = fibers concentration
d = duration of exposure in years
I_L = lung cancer incidence, observed or projected, in a population exposed to asbestos concentration C_f during time d
I_L^0 = lung cancer incidence expected in a group without asbestos exposure but with the same age and smoking habits (this factor includes age dependence).

The proportionality constant K_L is a measure of the carcinogenic potency of asbestos and can be derived from different sources. The WHO report used data from Liddell et al. 1985 [241]. In Liddell's study alone this constant varied considerably (by a factor 150). By using KL = 1.0 per 100 F*years/ml[2] and based on the figures for smokers and non-smoker reported by [236]. WHO estimated, that for a given asbestos exposure, the risk for smokers is about 10 times that for nonsmokers. In extrapolating from workers to the general public, a factor of 4 for correction of exposure time was applied to K_L. Thus the incidence of lung cancer in the general population exposed to 100 F*/m^3 was calculated as follows:

$$IL = I_L^0 (1 + 4 \times 0.01 \times 10^{-4} \text{ F*/ml} \times 50 \text{ years})$$

or

$$IL = I_L^0 (1 + 2 \times 10^{-4} \text{ F*/ml})$$

The extra risk is IL - I_L^0. Values for I_L^0 are about 0.1 for male workers and 0.01 for male nonsmokers Lifetime exposure to 100 f*/m3 (lifetime assumed to be 50 years since, in a lifetime of 70 years, the first 20 years without smoking probably do not make a large contribution) is therefore estimated as follows.

Table A19. Risk of lung cancer per 100,000 [239].

Status	Risk of lung cancer per 100 000 (using a value of 1 for K_L)	Range (using the highest and lowest value of K_L)
Smokers	2	0.08–3.2
Nonsmokers	0.2	0.008–0.32

The estimated risks from the WHO review are for lifetime exposures and do not differentiate between asbestos types although WHO acknowledge that chrysotile is less potent than amphiboles; chrysotile was as a precaution attributed the same risk in these estimates.

WHO compared this risk estimate, when adjusted to 100 f*/m^3, with estimates for male smokers made by other authors or groups:

Breslow (Great Britain): 7.3×10^{-5}

[2] F* indicates that measurement were based on light (optical) microscope counting, which meant that only fibers longer than 5 μm and thicker than 0.5 μm were counted. If concentrations measured by optical microscopy are to be compared with environmental fiber concentrations measured by scanning electron microscopy, a conversion factor has to be used: 2 F/m^3 = 1 F*/m^3

Schneiderman et al. (Germany): $(14–1.4) \times 10^{-5}$

US Environmental Protection Agency (USA): 2.3×10^{-5}

In order to calculate an attributable fraction, one needs an estimate of the proportion of the population experiencing circumstances of exposure comparable with those experienced by the populations included in the studies on which the calculations in table 3 are based. A meta-analysis estimated the relative risk (RR) of mesothelioma from residential exposure to asbestos at 3.5 (95% CI: 1.8–7.0); the corresponding RR of lung cancer was 1.1 (95% CI: 0.9–1.5). According to the model used by WHO, 5% of the European population experience residential exposure to asbestos. However, the studies included in the meta-analysis were conducted in populations with high level of exposure and a more plausible estimate of prevalence of exposure to such circumstances is in the order of 2% [186]. Combining these results leads to estimated annual numbers of 338 cases of mesothelioma in men and 43 in women. No estimate is provided for lung cancer because of the lack of statistically significant increase in risk found in the meta-analysis [186].

CONCLUSION

Non-occupational asbestos exposure is probably not significantly related to lung cancer except in special occasions as for instance in household exposure in cohabitants of asbestos workers, areas with very high exposures (e.g. residence in a mining area or near processing plants), and areas where asbestos are naturally occurring in the soil.

The level of environmental asbestos exposure to the general population in Denmark is not known, but based on Dutch and English studies the background level in outdoor air in cities is about 0.0001-0.0005 f/ml, which is orders of magnitude from the levels measured in occupational settings on which risk is assessed and extrapolated. WHO estimates that by a lifetime exposure of 1,000 f/m^3 (0.001 f/ml) the excess risk due to lung cancer would be in the order of 10^{-6}–10^{-5}, and for mesothelioma in the range 10^{-5}–10^{-4}. In the Danish population this accounts for 10 deaths by lung cancer and 100 by mesothelioma. At least for mesothelioma this seems grossly to overestimate the number of deaths as the total number of deaths from mesothelioma in Denmark for the time being is just fewer than 100 per year. However, the figures for mesothelioma probably comprise both occupational and non-occupational exposures.

APPENDIX 21. INTERACTION BETWEEN ASBESTOS AND SMOKING (4.4)

The risk for lung cancer associated with asbestos exposure varies with the level of exposure and possibly fiber type, but the most important concomitant factor being cigarette smoking. In an often-cited study by Hammond et al. [236] asbestos exposure alone conferred a five-fold relative risk for lung cancer; cigarette smoking without asbestos exposure was associated with an 10-fold increase in risk, but asbestos exposure with cigarette smoking yielded a relative risk for lung cancer of 59. By adding the effect of asbestos exposure and cigarette smokers in the Hammond study a 15-fold risk increase might be expected. The observed risk however was nearly 4 times greater suggesting some sort of synergistic or perhaps multiplicative effect. A “true” multiplicative effect implies that the effect of asbestos exposure is a proportional to the effect of smoking, whereas in an additive model asbestos exposure and smoking are independent of each other.

There is inconsistent information in the literature on the interaction between asbestos exposure and smoking and their joint impact on lung cancer risk. Since Hammond’s study a number of other studies have dealt with the question of estimating the magnitude of an eventual multiplication factor, and different studies have given different result varying from no synergistic/multiplicative factor at all [254] to figures comparable to Hammond’s [249].

Erren 1999 [248] examined data from 12 epidemiologic studies for quantitative evidence of biologic synergy between asbestos and smoking on lung cancer risks. Estimates of the effect associated with joint exposure to the two agents exceeded the sum of their separate effects in each study. They also used a 'synergy index' S, proposed by Rothman [296] calculated from the relative risks of lung cancer due to smoking and asbestos, separately and combined, to examine departures from the additive model, for which S = 1. The values of S ranged from 1.22 to 5.30, and the heterogeneity was quite slight (P~0.32). The authors found no explanation for it, whether in methodological differences or in type of fibers, and despite wide variations of the smoking relative risks and of the relative risks due to asbestos alone (1.1-25.0). It was concluded that the excess lung cancer arising from exposure to both asbestos and smoking is higher, by a factor of about 1.64, than the sum of the two risks—in other words the additive model did not fit but a multiplicative model did. The attributable proportion associated with this average S was estimated as 33%, that suggests that one-third of cancer cases among smokers who were exposed to asbestos can be attributed to the synergistic behavior of the two

carcinogens, as distinct from their separate effects and those attributable to other ("background") factors.

Liddell [250] used a different approach by calculating what he called “Relative Asbestos Effect” (RAE) based on the ratio of lung cancer SMRs for non-smokers and smokers. On the multiplicative hypothesis, RAE=1, while RAE>1 indicates less synergism. The RAEs for the results from 13 different papers combined, was 1.8 times that of smokers' and so he argued that this showed, that “the multiplicative hypothesis is untenable”. Liddell only reviewed cohort studies, and also found that the relative risk of lung cancer from asbestos exposure was about twice as high in non-smokers as in smokers, which was in itself interpreted in favor of his rejection of the multiplicative hypothesis.

Lee reviewed the same cohort studies as Liddell but also included case referent studies [249]. Lee analyzed lung cancer risk in subjects unexposed to asbestos or smoking, exposed to asbestos only, to smoking only, or to both in order to evaluate if asbestos increased risk in non-smokers. Asbestos exposure was associated with a significantly increased risk in non-smokers in six studies and with a moderately increased, but not significant, increase in a further six. In 30 of 31 data sets analyzed, risk in the combined exposure group was greater than predicted by the additive model. There was no overall departure from the multiplicative model except for two of the reviewed studies.

Reid et al. (2006) [251] using of modified form of the Relative Asbestos Effect concluded, that the modified RAE of 1.59, which they found, indicated that the interaction between smoking and asbestos exposure was not additive but “less than multiplicative”. Using a mathematical/statistical approach to the question, Wraith and Mengersen [253] reviewed the literature on the combined association between lung cancer and asbestos exposure and smoking to assess evidence of interaction between the exposures. The meta-analysis combined separate indices of additive and multiplicative relationships and multivariate relative risk estimates. By making inferences on posterior probabilities they explored both the form and strength of interaction and found that this analysis was more informative than providing evidence to support one relation over another on the basis of statistical significance. Overall, they found evidence for a “more than additive and less than multiplicative relation”.

The most recent major contribution to the effect of smoking and the risk of lung cancer in asbestos workers was published in 2011 in Great Britain [252]. The aim of the study was to examine the effect of smoking and smoking cessation among asbestos workers in Great Britain and investigate the interaction between asbestos exposure and smoking. The study population consisted of 98,912 asbestos workers with 1,780,233 person-years of follow-up from 1971 to December 2005. There were

1878 deaths from lung cancer (12% of all deaths). Risk of lung cancer mortality increased with packs smoked per day, smoking duration, and total smoke exposure (pack-years). Asbestos workers who stopped smoking remained at increased risk of lung cancer mortality up to 40 years after smoking cessation compared to asbestos workers who never smoked. The effects of smoking and stopping smoking did not differ by duration of asbestos exposure, main occupation, age at first asbestos exposure, year of first exposure, or latency period. For those asbestos workers who smoked, an estimated 26% (95% CI: 14–38%) of lung cancer deaths were attributable to the interaction of asbestos and smoking. Among this group, there were more deaths attributable to smoking only than asbestos exposure only (68% versus 2%). Consequently, the estimated fraction of lung cancer deaths prevented if workers had not smoked (risk attributable to smoking in the presence of asbestos) was 94% (=26%+68%); the estimated fraction of lung cancer deaths prevented if workers had not been exposed to asbestos (risk attributable to asbestos in the presence of smoking) was 28% (=26%+2%); and the fraction of lung cancer deaths prevented if neither exposure had occurred (risk attributable to the combined effect of asbestos and smoking) was 96% (=26%+68%+2%) among asbestos workers who smoked. The attributable proportion due to the interaction between smoking and asbestos was slightly lower than the estimates found in the literature (33%-41%). The differences between the attributable proportion could be due to the use of low versus high asbestos exposure rather than unexposed versus exposed. This could lead to the estimated attributable proportion of lung cancer due to 'background' risk being greater than perhaps it should be, and therefore reducing the attributable proportion due to asbestos only, smoking only, and the interaction of the two. The authors calculated, that if a comparison group was used that was truly unexposed, then the attributable proportion due to asbestos among never-smokers would probably have been >37%.

The authors also specifically addressed the question of whether or not the interaction between asbestos exposure and smoking was additive or multiplicative. This was examined by using the Synergy (*S*) and Multiplicativity (*V*) indices, which tested the hypotheses of additive and multiplicative interaction, respectively. Index S was statistically significantly >1, providing evidence against the additive hypothesis of no interaction between smoking and asbestos exposure (S=1.4; 95% CI: 1.2–1.6). Index V was <1, but this was not a statistically significant difference and so the multiplicative hypothesis could not be rejected (V=0.9; 95% CI: 0.3–2.4). The use of different low and high asbestos exposure categories did not greatly affect these results.

From a Danish point of view this study is interesting. Regulatory efforts in Great Britain have been similar to the Denmark. This study includes not only asbestos miners and workers in asbestos mills as many of the earlier studies, but also asbestos exposed persons in jobs that also are common among

asbestos exposed workers in Denmark: carpenters, construction workers, demolition workers, electricians, merchant navy workers, metal plate workers, plumbers & gas fitters, production fitters, railway industry workers (e.g. carriage building), roofers, sheet metal workers, shipbuilding/dock yard workers, steel workers, thermal insulation engineers/laggers (e.g. pipe and boiler insulation), transport/haulage workers, vehicle body workers (e.g. brake and clutch linings and spray paint), welders.

APPENDIX 22. COMMENTS FROM REVIEWERS

January 13, 2013

To whom it may concern,

External review of the "Low-dose occupational asbestos exposure and lung cancer" prepared by the Department of Occupational and Environmental Medicine, Odense University Hospital, Denmark.

Assessment:

The reviewer was requested to conduct an external review with an objective to "point out important mistakes or misleading information in a short report" and/or to make "any suggestions for improvement." Because an initial review of the document did not reveal any important mistakes or misleading information, the current assessment focused on suggestions for improvement, which was grouped into major and minor comments as follows.

Major comments:

(1) The "Research Questions" are placed as Appendix 4 which served to produce the Statements, i.e., the most significant findings, or messages, produced by this document. The list of research questions thus provides the starting point, or theoretical *base* of the project. As such, it deserves a place in the body of the text, most adequately in the Methods section, rather than in the appendix.

(2) p.17, DEFINITION OF, para 2: "three categories: occupational exposure (worker and by-stander), *non-occupational* exposure and *environmental* exposure." Whereas the first category is obviously distinct from the other two, "non-occupational" and "environmental" overlap with each other and are thus confusing. If the intent is to emphasize 3 categories and not 2, a better terminology to distinguish the latter two should be sought. I reinforced this opinion after reading Appendix 21. In this appendix, the notion of non-occupational/environmental asbestos exposure is *not* distinguished as indicated by the use of slash (/) between the two words and the statement: "environmental or non-occupational exposures are used in this section of the report…" To avoid inconsistency between the body of the text and appendix, the three categories referred to in the text, can be merged into two categories.

(3) The search strategy of the literature constitutes another important part of this document as it relates to how the main findings were produced. However, the manner in which the relevant publications were identified could not be readily understood.

a) p.25, METHODS, Step 1 – 1st screening: Although some kind of contrastive method is suggested by the terms "top-down" search and "bottom-up" search, the terminology is not self-evident and warrant a concise explanation on first appearance.

b) p.25, METHODS, Step 1 – 2nd screening: "Afterwards the remaining citations were sub-grouped according to the 19 search questions, *i.e.* citations from the LC group were grouped into $LC_{1\text{-}4B}$, and citations from …" LC group is understandable but what does 1-4B mean? Similarly, for "citations from AE, DR and CPC were grouped into

$AE_{1\text{-}5b}$, $DR_{1\text{-}5B}$ and $CPC_{1\text{-}5B}$ respectively. B refers to the broad search, resulting in…" AE, DR and CPC are understandable, but what does 1-5B mean?

c) p.26, middle: "Scottish Intercollegiate Guidelines Network" and p.5, para 2: "SIGN-based data extraction sheet" seem to be the same. Yet, SIGN has no explanation despite its first appearance.

d) "Publication year" is particularly important in conducting any literature search and thus when describing a search algorithm, its range (from year xxxx to yyyy) should be clearly stated.

(4) p.28, ASSESSMENMT OF CAUSAL ASSOCIATION
+++ Strong evidence *for a causal association*
++ Moderate evidence *for a causal association*
….

I understood that the criterion is adapted from the Danish Working Environment Authority explained in detail by Appendix 10. The notes attached to, or the explanations given for, the "categories" expressed in terms of codes (+/0/-) confer the level of evidence *for causal association*. But statements 1 through 21 have varied nature, and so the type of notes (explanations) does not exactly match for every statement. A typical example is Statement 2: JEMs are useful in estimating previous asbestos exposure in addition to individual exposure evaluation, in which there is no connotation of "causal association."

I suggest that the notes (explanations) be stated in more general terms, conferring the extent to which the statement is substantiated by evidence, of which, causal association is only one particular case. Hence,
+++ Strong evidence (to substantiate the statement)
++ Moderate evidence (to substantiate the statement)
…
It can be stated that the Criterion advanced by the Danish Working Environment Authority has been *adapted* for the current exercise. Words in the brackets are not absolutely necessary.

(5) p.33, DOSE RESPONSE, INTRODUCTION, last sentence: "The age distribution of cohorts has a considerable influence on SMR." As SMRs are calculated exactly to address the problem of age distribution and adjust for its confounding bias, this statement certainly requires some qualification. See also Minor Comment (33).

Minor comments:

(1) p.4, INTRO, para 1: "4% *till* 8%" > "4% *to* 8%"

(2) p.4, INTRO, para 2: "sufficient to cause *of* lung cancer" > "sufficient to cause lung cancer"

(3) p.4, INTRO, para 2: "The *fiber for* fiber potency" >"The fiber potency"

(4) p.6, RESULTS, para 2: "There is *not good* evidence that…" > "There is insufficient evidence that…" or "The evidence is insufficient that…"

(5) p.15, INTRO, para 1: "sufficient to cause *of* lung cancer" > sufficient to cause lung cancer"

(6) p.15, INTRO, para 1: "interaction between smoking asbestos" > "interaction between smoking *and* asbestos"

(7) p.17, VALIDITY OF…, para 1: "NCH has reviewed…"
It is not obvious what NCH is, and it seems to be the first appearance. I could not find it in the list of abbreviations. Please spell out NCH.

(8) p.17, VALIDITY OF…, para 1: "..were based only on a clinical *diagnose*." > "were based only on a clinical *diagnosis*."

(9) p.18, MEASURING METHODS…, para 2: "…defined being greater than 5 micron in length, 0.25 micron in diameter, and having…" > The second clause of "0.25 micron in diameter" is unclear whether it is "*smaller* than 0.25 micron in diameter" or "*greater* than 0.25 micron in diameter." Probably the former.

(10) p.20, INDUSTRIES AND JOBS…., below Table 1: "All DISCO codes…" It is not self-evident what DISCO is, and it seems to be the first appearance. I could not find it in the list of abbreviations. Spell out DISCO. Something related to standard classification of occupations?

(11) p.22, Table 3: To avoid ambiguity whether the statistics pertain to mortality or incidence, and because I imagine the case to be the latter, I suggest inserting the word "incident" as an adjective to "cases."

(12) p.22, bottom line: "Relative risks for lung cancer *are linearly* with cumulative exposure…" Suggest rephrasing, e.g., "Relative risks for lung cancer are linearly associated with cumulative exposure…"

(13) p.23, middle section: "The 2003 final report acknowledged…" > "The 2003 final report [insert REFERENCE] acknowledged…"

(14) p.23, second para from bottom: "The new proposed OSWER risk assessment model, …" I found OSWER in the list of abbreviations, but I believe abbreviations should be spelled out on first appearance.

(15) p.24, first para: "following standard methodology *inspired of* Wright and colleagues" It is unclear what "inspired of" means. Should it be "introduced by"?

(16) p.29, RESULTS, SUMMMARY, first para: "*Earlier* studies were poorly controlled…" What is meant by "earlier"? At least a rough time-frame, *e.g.*, studies published before 1980, should be stated.

(17) p.29, bottom line, "Statement 1 When evaluating ARLC location and cell types…" Without a comma after ARLC, this statement is unclear and misleading. Suggest rephrasing to, "Statement 1 When evaluating ARLC, location and cell types…"

(18) p.30, EXPOSURE ASSESSMENT, para 1: "since exposure misclassification might bias and *attenuate* risk estimates." > Suggest rephrasing to "since exposure misclassification might bias risk estimates." Risk estimates may be biased to either direction and authors should adhere to the neutral stance adhered to in other sections of the report:

Page 30, middle: "…can be obscured or even reversed in direction."
Page 58, middle: "True association may be masked by random misclassifications."

(19) p.33, DOSE RESPONSE, INTRODUCTION, middle: "At least two groups are needed, but *preferable* more." > "At least two groups are needed, but *preferably* more."

(20) p.34, INTRODUCTION, top: "A sufficient *span* in exposure levels…" > Suggest rephrasing to "A sufficient span of varied levels in exposure…"

(21) p.34, INTRODUCTION, bottom: "but they have only been used in (a) few studies…" > I suggest referencing the few studies > "but they have only been used in a few studies [*e.g.*, REFERENCE and REFERENCE]

(22) p.35, para 1: "Cancers occurring during the first 10-15 years after onset of exposure have often been excluded in cohort analyses. *In analogy*, the exposure accumulated during the last 10-15 years before end of follow-up is sometimes…" > For what reason is the term "in analogy" being used? Can this be simply replaced by "*Conversely*, the exposure accumulated during the last 10-14 years…" ?

(23) p.48, META-ANALYSIS, second para from bottom: "per f-y/ml with very large *span*, …" > Suggest replacing with "per f-y/ml with very large *variation*, …"

(24) p.49, middle: "different approach was taken *her* including 18 studies, …" > I cannot comprehend the use of the word "her."

(25) p.49, middle: "16.4 (*CI95%*: 3.4-29.5)" > "16.4(*95%CI*: 3.4-29.5)"

(26) p.50, para 1: "this review had (*a*) high quality?" > "this review had high quality."

(27) p.50, para 3: "k_L values were 3 to 10 *times lower* in models…" > Suggest rephrasing to "k_L values were one third to one tenth in models…"

(28) p.51, bottom: "Conclusion: the expert does not evidence for a threshold…" > Verb is missing; suggest rephrasing to ""Conclusion: the expert does not *find* evidence for a threshold…"

(29) p.52, para 2: "…South Carolina textiles) and *find* a striking difference…" > "…South Carolina textiles) and *found* a striking difference…"

(30) p.52, bottom: "Statement 13 All types of asbestos fibers are associated with lung cancer. (+++)" > This is a very important statement and merits a place in the list of statements. Nevertheless, it was unclear which references provided the evidence, or how it can be justified. My impression may have been formed because the preceding sections do not necessarily discuss fiber types in detail as the central theme. Some parts of Appendix 14 are contextually relevant but are not mentioned here. Can some writing be added or some connection made to Appendix 14?

(31) p.56, middle: "Pulmonary tuberculosis has also been associated with increased lung cancer risk." > It seems preferable to cite references here: "Pulmonary tuberculosis has also been associated with increased lung cancer risk [Insert REFERENCE]."

(32) p.59, second para from bottom: "…around 1980, but this technique still not a routine method…" > Missing verb; suggest inserting > "…around 1980, but this technique *is* still not a routine method…"

(33) p.60, para 1: "In the very *old* cohorts [115, 120], this will automatically tend to give SMRs close to 100 due to high background mortality [251]." > Does "old" mean chronologically old (if so, I suggest replacing with "early") or elderly in terms of age? If the latter, this is unconventional knowledge, so the statement would require good justification. See also Major Comment (5).

(34) p.61, para 1: "of mainly *older* studies based on …." > Again, does "old" mean chronologically old or elder age?

(35) p.61, middle: "…reported asbestos exposure. *The* may be explained…" > "…reported asbestos exposure. *This* may be explained…"

(36) p.62, para 1: "… and thus *should* not be considered when…" > "… and thus *need* not be considered when…"

(37) p.78, line 3 from bottom: "How can the effect of *occupational*-related asbestos exposure (be) compared to…" > "How can the effect of *occupation*-related asbestos exposure be compared to…"

(38) p.79, top, "Statement 1 When evaluating ARLC location and cell types…" Without a comma after ARLC, this statement is unclear and misleading. Suggest rephrasing to, "Statement 1 When evaluating ARLC, location and cell types…"

(39) p.97, middle, "SIR calculated from date of notification." > "SIR *was* calculated from date of notification."

(40) p.102, 3 lines from top: "…clearly demonstrated *last year* …" > "… clearly demonstrated in 2011…"

(41) p.102, bottom: "…asbestos-exposure level should be *fined*." > "…asbestos-exposure level should be *found*."

(42) p.105, top: "ILO-criteria on a chest X-ray CT showed bilateral PP" > insert comma (,) between chest X-ray and CT > "ILO-criteria on a chest X-ray, CT showed bilateral PP …"

(43) p.105, para 2: "…misinterpretation of the quoted reference Elshazeley et al could by CT confirm most PP…" > Due to some linguistic problems, I cannot understand the meaning.

(44) p.106, para 1 and 2: I can spot 4 missing periods '.' in this page:
a) coat [98]
b) iron-containing coat,
c) in lung tissue [102, 103]
d) in lung tissue [104]

(45) p.107, Mining and milling, "(30 mppcf-years) and *on*." Unfinished sentence. And on what?

(46) p.111, second para from bottom: "…was estimated to 00.58 * …" > "was estimated to be" or "was estimated at". Also, there are two zeros before a decimal point.

(47) p.112, second line from top: "…due to different mortalities). Remove the unclosed bracket ')'.

(48) p.118, para 3: "…are associated with a *four-double* lung cancer risk" > The meaning of four-double is unclear. Should this be "…are associated with a two to four-fold lung cancer risk"?

(49) p.119, para 2: "*Quantization* of fiber count…" > The meaning of quantization is unclear. Suggest "Quantification of fiber count…"

(50) p.120, middle: "Asbestos fibers have been shown to *stimulation* the production of…" > "Asbestos fibers have been shown to *stimulate* the production of…"

(51) p.120, middle: "…, such as ROS/RNS *interact* with…" > "…, such as ROS/RNS *interaction* with…"

(52) p.127, middle: "…earlier studies add evidence *that* suggesting that…" > the first that is uncessary > "…earlier studies add evidence suggesting that…"

(53) p.130, middle: "IRR and 95% (CI) for lung cancer risk…" > Unnecessary brackets found > "IRR and 95%CI for lung cancer risk…"

(54) p.134, bottom, "the decrease in risk *increases* as the duration of smoking decreases…" > This is a confusing sentence because of decrease, increase and decrease. Suggest rephrasing > "the decrease in risk *enhances* as the duration of smoking decreases…"

(55) p.143, second line from bottom: The total pooled RR based was 1.78…" I do not understand the meaning of this phrase, but I am unable to suggest an alternative.

(56) p.145, bottom paragraph, second line: "…both of these illnesses *that* presuming that…" The first "that" should be deleted.

(57) p.147, top sentence: "The term 'environment' is often used broadly the medical literature, …" > Missing preposition. "The term 'environment' is often used broadly *in* the medical literature, …"

(58) p.149, 3 lines from bottom: "…for chrysotile. amosite and crocidolite…" > Replace period with comma > "…for chrysotile, amosite and crocidolite…"

(59) p.151, middle: "in *a* study group*s*…" > "in study groups"

(60) p.154, second para: "…autopsy cases in *Hon* Kong Chinese." > "…autopsy cases in *Hong* Kong Chinese."

(61) p.155, second para: "…and almost *exclusive* liked to asbestos exposure…" > There are 2 errors here (exclusively) and (linked to). "…and almost exclusive*ly* li*n*ked to asbestos

exposure…"

(62) p.156, 4 lines from top: " ….reported by [229] WHO estimated…" > Period is missing between [229] and WHO.

(63) p.159, middle to bottom: "on posterior probabilities…" > I am uncertain as to the meaning. Was *a posteriori* intended here? > "on *a posteriori* probabilities…"

(64) p.161, line 2: "workers in Denmark: *C*arpenters, construction workers…" > "workers in Denmark: *c*arpenters, construction workers…"

Conclusion:

I found that the aim of the report "to produce a stringent and critical review of the scientific literature concerning asbestos exposure and its causation of lung cancer" was well met. The report is an excellent condensation and competent evaluation of the available and relevant information on the subject. The report did not contain any important mistakes or misleading information.

Professor Ken Takahashi, MD, PhD, MPH
Chair of the Department of Environmental Epidemiology, IIES
Director of the WHO Collaborating Center for Occupational Health
Director of the International Center
University of Occupational and Environmental Health
President of the Asian Association for Occupational Health

Remarks on report Low-dose occupational asbestos exposure and lung cancer

Title
I am not sure about the terminology used. From an exposure point of view, it is better to use the term exposure-response relationship rather than dose-response (throughout the document), since dose usually implies internal exposure. Second, the review is not limited to studies with low levels of asbestos exposure (that would be primarily environmental studies). Occupational cohorts included have high exposure levels. The extrapolation is towards low levels of asbestos exposure, that are typically not within the range of the exposure pattern in the occupational cohorts. I understood that the interest of on low level exposure, it would probably be a better reflection if one states: Occupational asbestos exposure and lung cancer: exposure-response relationship and consequences for low exposure levels.

Abstract
The statement about lack of evidence to include age in evaluation of individual cases may be right, but the underlying assumption may be stressed that although the occurrence of lung cancer is highly age-dependent, the attributable fraction to asbestos is most likely not age-dependent.

Chapter 2
P17: environmental exposure: most studies are actually on asbestos waste around factories (see Italy and Japan), the naturally occurring sources (eg USA) seem to be less important.

P18: it is not logical to present as a fact that mppcf equals a particular weighted exposure level!

P19: jobs with exposure; the first column in the table is a mixture of industries and jobs. In asbestos industries many different jobs were relevant, see the studies on occupational histories of mesothelioma cases. In this list I miss e.g. shipyards, construction industry

P21-22: What are the criteria for these cases of compensated ARLC ?

P23: Although I do not know right now what I will read later on, but the Hogdson and Darnton publication from 2000 is the most influential risk assessment published. Before that, WHO published a risk assessment in 1987, that influenced EU debates and most likely also debates and guidelines in Denmark. WHO drew upon the EPA model.

Chapter 3
P28: I think that the correct terminology in 3.6 would be to assess the likelihood/probability of causality, which in presented in levels of evidence.

Chapter 4:
P29: Statements like earlier studies and more recent studies are rather vague. Can this be linked to periods or, even better, the ICD code number?
With respect to survival, it is of interest to make a statement on actual survival after 1 resp 5 years, and how the Danish study compares to other countries.

P30: I think it would be good to discuss briefly the crucial distinction between individual and group-based assessments. There are quite a few sources that refer to the Berkson's error theory, which implies that grouping strategies in occupational cohort studies with assessment of average exposure of a distinctive group may be much better than assessment of individuals. It all depends on the pattern of variability between and within occupational groups and of between and within worker. I think it is not possible to make a statement about the better strategy (as is suggested in statement 2).
Thus, in occupational cohorts there a two crucial issues: reliable assessment of average exposure of (groups of) individuals and reliable assessment of duration of exposure in years. A JEM focusses on group-based average exposures. Reliability of duration of exposure is seldom addressed, but will easily result in misclassification.

P32: It reads rather odd that asbestosis is a marker. It the biomonitoring literature is would not be considered as marker of exposure or marker of disease, but simply a disease caused by asbestos exposure (it is in the definition!).

P33: the statement that exposure has been collected in categories and persons have been assigned the mean or median is unclear. I gather that exposure patterns are presented in categories and that individual workers within each category are assigned the mean/median of that category.
Sensitivity is indeed the cut-offs, but in theory also the actual distribution within the category, i.e. the midpoint is not necessarily equal to the mean/median exposure.
A point I made earlier, the duration is crucial in cumulative exposure and this requires very good job histories with information on job, time of job, activities, and place in the production process. In my experience that is a big problem in most historical records, since you may find a job title and maybe a department / plant location, but job titles are seldom updated adequately.

P33: the age distribution does indeed influence comparisons of SMR since SMRs are measures of indirect standardization whereby the age distribution of the cohort is applied to the age-specific mortality rate of the reference population. Thus, apart from age distribution also the mortality in the reference population is a crucial source of influence, see e.g. some studies in Bernman and Crump that have a reference population with high luca mortality. The classical fallacy is the healthy worker effect.

P34: it is of interest to note that estimation of the intercept ai is not independent from the estimation of Kl. It can be expected that is attenuation is present, Kl will decrease and as a consequence the intercept will be affected as well.

P36: The grading may require an explanation in the heading or footnote, since it refers to quality appraisal of a single study (and not to grading of evidence across studies)

P36: table 4. I have not read all original studies, but note some unclear statements:
- Clin 2011: results mention both RR and HR, were both measures indeed used?
- Dement 1982: it should read 10,000-40,000 etc
- overall, be careful with statements on statistical significance, since in risk assessment it if first about the magnitude.
- Dement 1994 was an update? Hence, can SMR be linked to exposure values? Is risk comparable to 1982?
- Loomis 2009: SMR and RR are mentioned, is this correct?
- Peto 1985: SMR and RR are mentioned
- Sluis-Cremer: why two different descriptions of the study population?
- Stayner 1997: no expression of exposure value, linked to the slope ?
- Gustavsson: excellent ? dose-response

P50: the debate between Lenters et al 2012 and Bernman in the Annals of Occupational Hygiene illustrate some of the complexities of interpretation and subsequent risk assessment. It could make sense to summarize this debate in a few lines and point at the issues of disagreement.

P51: Given both statements it should be noted that these statements focus on interpretation of the role of asbestos in individual luca cases, it is in fact about attribution and apportionment. With respect to occupational and environmental guidelines, the statements would be formulated different.
Also, the RR / SMR in the text are presented as fractions, whereas statemen7 has percentages. I suggest to explain this.

P51: Bij-study, see previous remark, why % instead of RR as fractions..

P52: Bengt Jarvholm published on decrease in risk after cessation of asbestos exposure (Eur j Respir 1992)

There is quite some evidence that the risk on luca decreased 10-15 years after quitting smoking. That seems an important statement, since why should we expect that asbestos is different ?

P54: I am always wondering what we really mean with additive and multiplicative effects. If 1.6*1.9 = 3.04, then this is close to the observed value of 3.3. Thus, this seems simply a combination of independent effects. I know that Mirjam Knol and colleagues have published several papers on this issue, for example explaining the RERI measure. It would make sense to use such a common concept and quickly explain whether there is some evidence for synergy, either at additive or multiplicative level.
Also, the area is reviewed in appendix 17..is this the correct referral?

Statement 17
This is not necessarily an inference from the data presented. For compensation purposes I would argue that one has to use the attributable fraction, that is the proportion of lung cancer cases among the exposed that is attributable to the exposure. Thus, the problem arises that the AF for smoking may be 0.90 and for asbestos 0.60. The RR presented are population measures. Thus, one should first establish whether a person is exposed to asbestos AND PAH. Second, when both exposures are present apportionment of AF could be considered. Clinical decisions models could be useful here. In short, statement 17 should be rephrased.Step 1, is the subject exposed to several carcinogens, Step 2, what are the exposure levels of these carcinogens. Step 3, what are the risks associated with these exposure levels. Step 4, how do we translate these risks into relative contribution to the likelihood of the disease.

P56. Summary. I would not write that there are areas with very high exposure ! What is the comparison here? Certainly not the occupational cohorts in the previous pages.

Chapter 5
P59: I have made a few remarks with respect to other exposure issues, for example job history in relation to estimation of exposure duration. It is not only about exposure level.

P60: I do not follow the remark on SMR and very old cohorts. It seems that you want to state that direct standardization is to be preferred (which is true), but age distribution per se does not tell us anything about underestimation of SMR, unless mortality rates are very high in old age groups and, hence, you will lack statistical power to demonstrate an excess mortality. However, it will not be easy to predict where power is optimal.

P61. With respect to the PAF, a recent debate between SYNERGY partners in Int J Epidem 2012, dec 24, epub (De Matteis et al) illustrates the problems nicely, and also, presents different estimates.
The recent estimates of Lesley Rushton may also be interesting to mention.

Lex Burdorf
Rotterdam. Jan 16, 2013

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