Occupational COPD

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Correlations between Chronic Obstructive Pulmonary Disease and various types of physical and chemical exposures at work

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

Aasen T.B. **Blanc P.D.** **Brisman J.**

Miller M.R. **Omland Ø.** **Pedersen O.F.**

Schlünssen V. **Sigsgaard T.** **Ulrik C.S.**

Viskum S. **Würtz E.T.**

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Summary

Introduction

In accordance with the specifications of the fund the objective of this scientific document is based on a definition of COPD that subsumes airway obstruction and emphysema but does not extend to chronic bronchitis in the absence of airflow compromise. According to the World Health Statistics 2008 COPD was ranked as the fourth leading cause of deaths in the world in 2004, and is predicted to rise to the third commonest cause of death by 2030. A consensus statement promulgated by the American Thoracic Society in 2003 concluded that 15% of COPD could be attributable to workplace exposures. Taken together, the prevalence of COPD and its occupational contribution indicate that COPD in general and occupational COPD specifically present a real health challenge worldwide.

Methods

A ten-member working group was formed by inviting occupational physicians, pulmonologist, and lung physicians with knowledge and interest in the study field. A multiple-step, iterative process was used to select the publications comprising the database used in this analysis. A series of searches with selected key words were performed (PubMed and EMBASE). This initial step yielded 4,348 citations. The key word algorithm was intentionally very broad and citations were screened for inclusion eligibility. Citations clearly unrelated by the content area based on publication title were relegated ineligible for further consideration. There were 300 articles remaining from the key word search for further detailed review. These citations were supplemented through manual assessment of reference lists of published systematic reviews of the literature on occupation and COPD. In addition, other eligible publications were identified by members of the working group. This supplemental retrieval process yielded 78 additional publications for inclusion. In total, 378 peer reviewed publications were identified for the next abstract-based review step. This step excluded papers based on the following criteria: lack of measurement of lung function, insufficient classification of an occupational exposure, no inclusion of external referents or internal referents, deficient analysis testing the association between exposure and a lung function-based outcome, or absence of an analysis taking into account age or smoking effects. The criterion for lung function measurement was subsequently modified so that population-based studies employing a clinical diagnosis of COPD (or a pathological diagnosis of emphysema) without corresponding spirometry data, nonetheless, could be considered further. Following this abstract-based review and exclusions, the full texts of remaining articles were available to the working group (147 papers).

This step included completion of a structured extraction sheet originally developed by the European Respiratory Society for quality assessment of scientific papers related to occupational asthma. This data extraction form included information regarding study design and population size, exposure assessment and quality, including the degree of exposure observed and the duration of exposure; the

COPD-related outcome assessed, potential study limitations (e.g. confounding or biases); quality of results, key findings, and grading of the study. This final component of grading utilized the established "SIGN System" (Scottish Intercollegiate Guidelines Network). The next selection step was that of study inclusion from among the eligible pool after exclusions as noted above.

In August 2009 the working group met and discussed the extracted articles. Inclusions were based on SIGN grade 2+ (low risk of confounding/bias/chance) or better, as well as the absence of other major methodological limitations. After this final inclusion step 84 papers remained in the final data set used for the core of this analysis. Of these, 68 publications were put to the Evidence Tables: population-based studies (n=25 + 1 article described additional findings from a previously selected population), industry or occupation specific studies of inorganic dust exposure (n=15 + 1 article described additional findings from a previously selected cohort), or industry or occupation specific studies of organic dust (n=19 + 7 articles described additional findings from a previously selected cohort). Of the remaining 16 papers not in the Tables but, nonetheless, to be discussed were: 7 studies of COPD in professional divers and 9 included findings relevant to COPD and occupation, but used analytic approaches and were not homogeneous with the format and criteria of the Evidence Tables.

An initial draft text of the document was circulated to the working group. The document was also provided to two external reviewers (Professors Giovanni Viegi and William MacNee) for their comments. The working group met for a second time in November 2009 for final discussions to address the comments from within the group and from the external reviewers. A consensus approach was used to adjudicate differing views on all key points.

Results

Among the 25 population-based studies with spirometric data included in the Evidence Tables, 22 studies found a significant smoking-adjusted association between airway obstruction and various occupational exposures. Two of the remaining analyses (both based on the European Community Respiratory Health Survey) were limited to individuals 20 to 45 years of age (that is younger than onset of typical COPD), and the third showed borderline association to manual work and low educational level. Among the 15 occupational cohort studies with exposure to inorganic material included in the Evidence Tables, 12 studies found a significant association between exposure and airway obstruction. The remaining three papers studied exposures potentially causing mixed restrictive-obstructive lung function impairment. Of the 19 occupational cohort studies with exposure to organic materials included in the Evidence Tables, 17 found a significant association between occupational exposure and airway obstruction. In one of the remaining studies past exposure to cotton dust was not associated with reduced FEV_1 but increasing working time in high exposure areas was associated with lower FEV_1. In the second study, wood dust exposure was not associated with airway obstruction.

There was insufficient data for an in depth evaluation of exposure and for a detailed estimate of any increased risk in relation to the nature, severity/scope and duration of the exposures. Supplemental evidence from studies not included in the Evidence Tables but still considered relevant also supported the association between work-related exposures and COPD including evidence of a link between such exposures and greater disease severity.

Conclusion

The reviewed studies were of varying design, from different populations, and used different measures of exposure and outcome. Across these studies there was a consistent association between occupational exposures and COPD. Also, there was a monotonic dose–response relation in several longitudinal studies but insufficient data for a detailed quantitative exposure evaluation.

Applying the criteria of the Danish Working Environmental Research Fund for an exposure – disease association and as a result of the literature review, the working group concluded that there is strong evidence (+++) for a causal association between various types of occupational exposures and chronic obstructive pulmonary disease (COPD). COPD should be considered as a potentially work-related condition.

Dansk resumé / Danish summary

Introduktion

Dette videnskabelige dokument er udarbejdet i henhold til de retningslinjer som Arbejdsmiljøforskningsfonden har beskrevet for projektet "Sammenhæng mellem kronisk bronkitis og forskellige former for fysiske og kemiske påvirkninger på arbejdet". I forståelse med Arbejdsmiljøforskningsfonden er dette videnskabelige dokument baseret på studier hvor der er målinger for lungefunktion. De evidensbaserede tabeller indeholder studier af kronisk obstruktiv lungesygdom (KOL), der primært omfatter målelig obstruktiv nedsat lungefunktion, men hvor emfysem kan være medinddraget, men ikke kronisk bronkitis uden samtidig lungefunktionspåvirkning. KOL rangerede ifølge WHO i 2008 som verdens fjerde hyppigste dødsårsag, og forventes i 2030 at være den tredje hyppigste dødsårsag. American Thoracic Society fandt i deres litteraturgennemgang i 2003, at 15 % af KOL tilfældene kunne tilskrives en erhvervsmæssig eksponering. KOL og arbejdsbetinget KOL må derfor opfattes som en betydelig udfordring for den globale sundhed.

Metode

Der blev nedsat en arbejdsgruppe på ti medlemmer bestående af arbejdsmedicinere, lungemedicinere og en lungefysiolog for at udarbejde det videnskabelige dokument. Medlemmerne af arbejdsgruppen blev inviteret på baggrund af deres kliniske eller videnskabelige interesse for området. Artikler der skulle med i dokumentet blev udvalgt ved en flertrins metode. Flere litteratursøgninger blev foretaget i databaserne PubMed og EMBASE med brug af flere brede søgeord. Dette resulterede i første trin i 4.348 artikler. Søgningen var bevidst meget bred. Artikler der ud fra titlen klart omhandlede emner uden for dokumentets formål udgik.

300 artikler gik videre til andet trin. De elektroniske litteratursøgninger blev suppleret med en manuel gennemgang af litteraturlisterne fra kendte systematiske reviews omhandlende arbejdsbetinget KOL. Desuden blev yderligere artikler foreslået fra medlemmer af arbejdsgruppen. Denne supplerende litteratursøgning resulterede i 78 ekstra artikler til nærmere gennemsyn. I alt blev 378 peer reviewed artikler gennemgået på abstrakt niveau. Ved gennemgang af abstrakts udgik artikler ud fra følgende kriterier: Manglende måling af lungefunktion, utilstrækkelig klassificering af en erhvervsmæssig eksponering, ingen eksterne eller interne referencepersoner, mangelfuld analyse af sammenhængen mellem eksponering og lungefunktion, eller manglende justering for effekten af alder eller rygning. Kriteriet om lungefunktionsmåling blev diskuteret i arbejdsgruppen og blev justeret, så populations-baserede studier med en klinisk diagnose af KOL (eller patologisk diagnose af emfysem) uden spirometriske data kunne indgå. Efter denne revision og ekskludering blev den fulde tekst af de resterende artikler sendt rundt til arbejdsgruppen (147 artikler).

På det tredje trin blev de enkelte artikler gennemgået. Der blev brugt en struktureret metode oprindeligt udviklet af Det Europæiske Lungemedicinske Selskab til kvalitetsvurdering af

videnskabelige artikler om arbejdsbetinget astma. Denne strukturerede analyse indbefattede beskrivelse af studie design, antal deltagere, en vurdering af eksponerings datas kvalitet, herunder graden og varigheden af eksponeringen, anvendt diagnostisk sygdomskriterium, potentielle begrænsninger i studiet (f.eks. confounding eller bias), kvaliteten af resultaterne samt de vigtigste resultater.

Det fjerde trin startede med at arbejdsgruppen mødtes i august 2009 for at diskutere de udvalgte artikler. Endelig inklusion var baseret på SIGN gradueringen (Scottish Intercollegiate Guidelines Network), mindst grad 2 + (lav risiko for confounding/bias/chance) og uden andre store metodologiske begrænsninger. Inklusionen foregik i plenum efter fremlæggelse og eventuel diskussion. Efter dette trin var 84 artikler inkluderet. 68 artikler indgik i evidenstabellerne: Populations-baserede studier (n = 25 + 1 artikel med supplerende resultater fra tidligere valgt population), industri eller erhvervsspecifikke studier af uorganisk støveksponering (n = 15 + 1 artikel med supplerende resultater fra tidligere valgt kohorte), eller industri eller erhvervsspecifikke studier af organisk støv (n = 19 + 7 artikler med supplerende resultater fra tidligere valgt kohorte). 16 artikler indgik ikke i evidenstabellerne, men er beskrevet i teksten: 7 artikler beskriver KOL blandt professionelle dykkere, og de resterende 9 artikler indeholder data om KOL og erhvervsmæssig eksponering. Helbredsudfaldene er anderledes end dem der er i evidenstabellerne og supplerer vor viden om arbejdsbetinget KOL. KOL blandt professionelle dykkere er ikke helt i tråd med opgavens ramme, men er en eksponering der bør beskrives.

Første udkast til dokumentet blev omdelt til arbejdsgruppen. Dokumentet blev ligeledes tilsendt to eksterne eksperter (professorerne Giovanni Viegi og William MacNee) til kommentarer. Arbejdsgruppen mødtes for anden gang i november 2009. Her blev udkastet gennemgået. Yderligere kommentar fra arbejdsgruppens medlemmer blev tilføjet efter diskussion i plenum sammen med de eksterne eksperters vurderinger og kommentarer. Der er enighed i arbejdsgruppen om det endelige manuskripts indhold og udformning.

Resultat

Blandt de 25 populations-baserede studier med lungefunktions målinger der indgik i evidenstabellen, fandt 22 studier en sikker statistisk sammenhæng mellem luftvejsobstruktion og forskellige erhvervsmæssige eksponeringer. I to studier (begge baseret på European Community Respiratory Health Survey) hvor personerne var fra 20 til 45 år (som er yngre end ved typisk indsættende KOL) fandtes ingen sammenhæng. Et studie viste en næsten sikker statistisk sammenhæng mellem luftvejsobstruktion og manuelt arbejde eller et lavt uddannelsesniveau. Blandt de 15 industri- eller erhvervsspecifikke studier af uorganisk støveksponering der indgik i evidenstabellen, fandt 12 studier en sikker statistisk sammenhæng mellem den erhvervsmæssige eksponering og luftvejsobstruktion. De resterende tre studier fandt en blandet restriktiv-obstruktiv lungefunktions nedsættelse. Af de 19 industri eller erhvervsspecifikke studier af organisk støv der indgik i evidenstabellen, fandt de 17 en sikker statistisk sammenhæng mellem den erhvervsmæssige

eksponering og luftvejsobstruktion. I et studie var tidligere udsættelse for bomuldsstøv ikke forbundet med nedsat FEV_1, hvorimod øget arbejdstid i områder med høj udsættelse for bomuldsstøv var forbundet med nedsat FEV_1. I et studie var eksponering for træstøv ikke forbundet med luftvejsobstruktion.

Der var ikke tilstrækkelige data til at foretage en detaljeret vurdering af mulig øget risiko i forhold til arten, intensiteten og varigheden af eksponeringerne. Supplerende dokumentation fra studier der ikke er medtaget i evidenstabellerne, støttede sammenhængen mellem en arbejdsrelateret eksponering og KOL, herunder en dokumentation for en sammenhæng mellem eksponering og alvorlig sygdom.

Konklusion

De studier der indgår i dokumentet er af varierende udformning, fra forskellige populationer, og der er anvendt forskellige mål for eksponering og udfald. Til trods herfor er der fundet en konsistent sammenhæng mellem erhvervsmæssig eksponering af forskellig type (uspecifik, organisk og mineralsk) og KOL. Ligeledes er der fundet dosis-respons sammenhænge i flere longitudinelle studier, men der er utilstrækkelige data til at foretage en indgående kvantitativ vurdering af eksponeringen på tværs af studierne i forhold til sygdomsrisiko.

Ved brug af Arbejdsmiljøforskningsfonden kriterier for årsagssammenhæng mellem eksponering og sygdom konkluderer arbejdsgruppen, at der er et stærkt bevis (+++) for en kausal sammenhæng mellem forskellige typer af erhvervsmæssig eksponering og kronisk obstruktiv lungesygdom (KOL). KOL bør betragtes som en potentiel arbejdsrelateret tilstand.

Members of the working group

Denmark:

Øyvind Omland	MD, PhD, Consultant, Ass. Professor Aalborg Hospital, Aarhus University Hospital and School of Public Health, Aarhus University
Ole F. Pedersen	MD, DMSc, Ass. Professor, School of Public Health, Aarhus University
Vivi Schlünssen	MD, PhD, Ass. Professor, School of Public Health, Aarhus University
Torben Sigsgaard	MD, PhD, Professor, School of Public Health, Aarhus University
Charlotte S. Ulrik	MD, DMSc, Consultant, Ass. Professor, Hvidovre Hospital and University of Copenhagen
Sven Viskum	MD, Consultant, Aalborg Hospital, Aarhus University Hospital

Norway

Tor B. Aasen	MD, Chief physician, Haukeland University Hospital, Bergen

Sweden

Jonas Brisman	MD, PhD, Consultant, Sahlgenska Academy and University Hospital Gothenburg

UK

Martin R. Miller	MD, Consultant, Selly Oak Hospital, University Hospital of Birmingham NHS Trust

USA

Paul D. Blanc	MD, MSPH, Professor, School of Medicine, University of California, San Francisco

Introduction

In June 2008 the Danish Working Environment Research Fund called for applications for reviews, in the form of reference documents, within the theme "Correlations between chronic bronchitis and various types of physical and chemical exposures at work". The project was described as "Against the background of the ongoing discussions of occupational disease, the National Board of Industrial Injuries and the Occupational Diseases Committee have found that there is a great need for a detailed review, in the form of a scientific reference document, of possible causalities between exposure to various types of dust (inorganic or organic), or exposures to various types of gases, smoke, irritants or chemicals etc. at work, and the development of chronic bronchitis".

The framework of the project was referred as: "Against the background of a primarily epidemiologically based examination of the most significant Danish and international research results in the field, the scientific reference document will elucidate in detail, summarise and assess knowledge of any causalities between the development of chronic bronchitis and exposure to various types of gases, smoke, irritants or chemical etc (including quartz and asbestos dust) at work. In this context there is a great need for description and assessment of the evidence of various exposures and the likely causality mechanisms, as well as a detailed estimate of any increased risk in relation to the nature, severity/scope and duration of the exposures" (1). In accordance with the granting fund the objective of this scientific document is based on studies with lung function measurements. Studies with other outcomes have been included into the document if their objective and findings have added to the understanding of causality between occupational exposure and outcome at focus.

The working group presenting this scientific reference document applied and accepted the conditions for the compilation of a review. Based on the findings, the working group will carry-out their review in accordance with the evidence model provided by the Scientific Committee of the Danish Society of Occupational and Environmental Medicine.

Background

Chronic bronchitis

As noted above, this systematic review of the biomedical literature relevant to occupational risk for COPD precludes (in accordance with the granting fund) chronic bronchitis with normal lung function. Nonetheless, it is important to provide a brief summary of this question. First, published data relevant to this topic have been included in two previously published systematic reviews. Second, from an epidemiological and public health perspective, COPD (defined by airflow limitation and quantified by lung function tests) and chronic bronchitis (defined clinically by chronic productive cough ascertained through the administration of a structured questionnaire) are often combined under the same disease heading. The rationale for this approach is that there is

considerable overlap in co-morbidity between these two conditions. And finally, data specific for Denmark, although neglible for COPD based on obstruction, are available for disease defined as chronic bronchitis. In one analysis, utilizing data from the Copenhagen Male Study, occupational dust exposure was associated with an elevated risk of chronic bronchitis (OR 1.5; 95% CI 1.0-1.6) (2). In a second study, utilizing data from the Copenhagen City Heart Study, exposure to dust and fumes at work was also associated with prospective risk of chronic bronchitis (OR 2.2; 95% CI 1.7-2.7) (3). Another Danish study relevant to chronic bronchitis is that of respiratory disease hospitalizations. That study reported an elevated risk among unskilled workers relative to senior salaried staff for both men (OR 2.3; 95% CI 2.1–2.5) and women (OR 1.6; 95% CI 1.4–1.9); it included chronic bronchitis along with COPD (as well as asthma) (4).

COPD prevalence and burden of disease

In 2004 COPD was the fourth leading cause of death worldwide and predicted to rise to the third leading cause in 2030, representing 5.1% and 8.6% of deaths, respectively, as a result of expected increases in tobacco use (5). Mathers and Loncar predicted that COPD would be the fourth ranked cause of death in the world in 2030 representing 7.8% of deaths depending of the income of the countries from 4.1 - 12% (6).

The burden of disease, disability-adjusted life years (DALYs) are used as an expression of the years lost and years lived with disability (7). In 1990 COPD was ranked as the twelfth leading cause of DALYs, representing 2.1% of the total DALYs in the world, and predicted to rise into fifth leading cause of DALYs 4.1% of the total in 2020 (8). Lopez et al. estimated COPD to be tenth leading cause of DALYs in 2002, representing 1.9% of the total DALYs in the world, and this is considered to be lower than the true burden of COPD (9). Furthermore, COPD is predicted to be the seventh leading cause of DALYs in 2030 (6).

COPD and spirometry

In the interpretation of spirometry there are two major problems. The first is how to define COPD. Contrary to asthma where the diagnosis depends on both symptoms and intermittent reversible airflow limitation (10) COPD is characterized only by poorly reversible airflow limitation defined by spirometry (11). This approach has been simplified to state that COPD is present when the ratio FEV_1/FVC (Forced Expiratory Volume in one second/ Forced vital capacity) is less than 0.7. Unfortunately this rule is not satisfactory because the normal ranges for this ratio vary with age, height and sex. Using this fixed ratio criterion will lead to false positive as well as false negative cases. The preferred criterion for diagnosing airflow obstruction is by using the lower limit of normal (LLN) (12,13), which is the confidence limit below which lies only 5 % of a healthy population. This requires defining reference equations for lung function from a representative healthy population and to find applicable and valid equations can sometimes be difficult. The second problem is how to define the severity of obstruction. This has usually been done by expressing the measured value as a percent of the predicted value but this methodology is not

without its difficulties (14). These problems are discussed in more detail in the Appendix B, page 52, and the interpretations for the results are emphasised in the discussion.

COPD and risk factors

Table 1 presents the main environmental risk factors for COPD as well as the host factors. Smoking is the major environmental risk factor for developing COPD, followed by various occupational exposures. The genetically determined deficiency of α_1-antitrypsin is the most well established host factor associated with the pathogenesis of COPD.

Table 1 Risk factors for developing chronic obstructive lung disease (15).

Degree of certainty	Environmental factors	Host factors
Supposed	Adenovirus infection Dietary deficiency of vitamin C Indoor air pollution	Genetic predisposition Blood group A
Good evidence	Outdoor air pollution Low socioeconomic status Alcohol intake ETS in childhood Other occupational exposures	Low birth weight Childhood respiratory infection Atopy (high IgE) Bronchial hyperresponsiveness Family case-history
Certain	Tobacco smoke Some occupational exposures	α_1-Antitrypsin deficiency

COPD and occupational exposure

During the last two decades multiple systematic reviews have been published addressing COPD and occupational exposure. In 1989, Becklake concluded that occupational exposure to dust and/or to dust and fumes may have a causal link to the pathogenesis of COPD (16). Oxman et al, reviewing of studies with quantitative inorganic dust exposure, reported a dose-dependent significant relationship between dust exposure and relevant health outcomes: a significant association was found between loss in lung function and cumulative respirable dust exposure controlling for age and smoking (17). A less firm conclusion was drawn in the review by Hendrick in 1996 that some occupational environments influence the development of COPD, but not with the same impact as smoking with interaction suggested to occur between smoking and environmental exposures (18). In 2002, similar conclusions were published independently by Burge (19) and Viegi and Di Pede (20). They stated that there was growing evidence that occupational exposure is indeed a risk factor for COPD. In 2003 ATS published a review of the evidence of the implication of occupational factors in the pathogenesis of obstructive airway diseases and quantified the contribution of work-related risk to the burden of these diseases in the general population. Based on the results it was concluded that about 15% of COPD could be attributable to workplace exposure (21). Two recent reviews by Blanc and Torén (22) and the Norwegian Medical Association (23) in 2007 have confirmed the findings of the ATS review. A recently published review focusing on COPD and

non-smokers estimates that 25-45% of patients with COPD are non-smokers and among these the major risk factors are biomass smoke, occupational dust and fume exposure, indoor air pollution, history of pulmonary tuberculosis, chronic asthma, and poor socioeconomic status (24). COPD and occupational exposure have been the topic of two editorials from 2005 Occupational and Environmental Medicine (25) and 2007 American Journal of Respiratory and Critical Care Medicine (26). In both, the importance of the occupational exposure is emphasized suggesting a population attributable risk (PAR) of 19% (smokers) to 31% (non-smokers) stating that the loss in lung function is of clinical importance and finally underlining the financial burden of the consequences of the occupational COPD.

Methods

Search strategy

A series of computerized librarian-assisted searches were performed in the period from 02.03.2009 to 05.05.2009 utilizing the databases PubMed and EMBASE. Two updates were performed in August 2009 (04.08. and 18.08.) and the last one 01.09.2009.

Table 2 The basic search strategy for this review

In the search the commands Explode and Keywords/text-words were used to ensure the broadest possible search profile.		Result
PubMed	COPD AND (occupation* OR work* OR workplace* OR employment OR industry OR dust* OR fume* OR airborne*) NOT ("respiratory function tests" [MeSH Terms]). Loss of lung function AND (occupation* OR work* OR workplace* OR employment OR industry OR dust* OR fume* OR airborne*) NOT ("respiratory function tests" [MeSH Terms]). ((Social class AND COPD)) OR ((Social Class AND loss of lung function)) NOT ("respiratory function tests" [MeSH Terms]).	2,622 hits 45 hits
Embase	COPD AND (occupation* OR work* OR workplace* OR employment OR industry OR dust* OR fume* OR airborne*). Loss of lung function AND (occupation* OR work* OR workplace* OR employment OR industry OR dust* OR fume* OR airborne*). ((Social class AND COPD)) OR ((Social Class AND loss of lung function)).	2,872 hits 40 hits
RefMan	Sorting for doublets reduced the hits to	4,450 hits

The strategy was the broadest possible search to find all possible original epidemiological peer-reviewed articles of relevance. A direct search in the search-field of the computer was used to utilize both the MeSH Terms and All Field described in Table 2. The search profile was tested for a number of articles by searching with the word as such or truncated and the search profile to be used was the one with the highest number of articles.

Selection of publications used in the analysis

We used a multiple-step, iterative process to arrive at the final group of publications used in this analysis. The initial step of the key word-driven electronic literature search, as described previously, yielded 4,348 discrete citations. Because this key word algorithm was intentionally very broad, these citations were rapidly screened for inclusion eligibility. Citations that were picked up by this search but clearly unrelated by the content area based on title were quickly deemed ineligible for further consideration after screening by a single member (ØO) of the working group (for example "Acoustic Trauma in Singers" or "Action Plans for Chronic Obstructive Pulmonary Disease"). Even if not primarily in English, articles were considered eligible for further consideration if, at a minimum, they included an English language abstract.

There were 300 articles (6.9% of the broad initial screen) that were deemed eligible for more detailed review. We supplemented this pool with citations yielded through manual assessment of the reference lists accompanying other systematic reviews of the literature on the question of COPD and occupation. In addition, other publications eligible for review were identified through input from the expert members of the working group who were asked to comment on potential omissions including recent publications that appeared after the August, 2009 cut-off for the initial key word electronic search. This supplemental retrieval process yielded 78 additional publications for further review. Finally another electronic key word search was repeated as of 01.09.2009, which also included "social class" as a surrogate for occupational exposure, but this search did not yield any additional eligible citations (in total 4,450 citations as referred in Table 2). In total, 378 peer reviewed publications were identified as meeting eligibility criteria for the next abstract-based review step.

The ten members of the working group were divided in to five pairs and assigned abstracts of the eligible papers for review. Four pairs consisted of a pulmonary physician and a specialist in occupational medicine, while one remaining pair consisted of a pulmonary physician and a lung physiologist. The purpose of this review step was to exclude papers that lacked sufficient data or analytic structure to warrant an in-depth review by the entire working group.

The initial criteria for exclusion were:

1. Lack of measurement of lung function.
2. Insufficient classification of an occupational exposure.
3. No inclusion of external referents (non-exposed) or internal referents (based on an exposure gradient).
4. Deficient analysis testing the association between exposure and a lung function-based outcome.
5. Absence of an analysis taking into account age or cigarette smoking effects.

The criterion for lung function measurement was subsequently modified so that population-based studies employing a clinical diagnosis of COPD (or a pathological diagnosis of emphysema) without corresponding spirometry data nonetheless could be considered further.

Following this abstract-based review and exclusions, the full texts of all the remaining articles were made available to the working group. In total, 147 papers remained at this step. Of these, five publications were translated fully into English for the purposes of this review (three from Italian, and one each from German and Polish). Each of the full papers was evaluated by the same reviewer pairs. The step included completion of a structural extraction sheet developed by the European Respiratory Society in accordance with Cochrane guidelines for systematic reviews (27). This data extraction form included information regarding study design and population size, exposure assessment and quality, including the degree of exposure observed and the duration of exposure; approach to and quality of the COPD-related outcome assessed, potential study limitations (e.g., confounding or biases); quality of results, key findings, and grading of the study. This final component of grading utilized the SIGN System (Scottish Intercollegiate Guidelines Network), a widely accepted approach (28). The most used gradings were 2++ (very low risk of confounding/bias/chance), 2+ (low risk of confounding/bias/chance), and 2– (high risk of confounding/bias/chance). The data extraction sheet is enclosed as Appendix C, page 55.

The next selection step was that of study inclusion. In August 2009 the member of the working group met face to face to discuss each of the extracted articles. At this meeting, the primary review teams were charged with the task of recommending publications for inclusion based on papers that allowed for sufficiently reliable interpretation. Overall, these inclusions were based on 2+ or better scores (see above) as well as the absence of other major methodological limitations revealed by the in depth review of the full paper. For studies of exposures that could lead to either obstructive or restrictive decrements in lung function (e.g., inorganic dusts such as coal mining), we further required for inclusion data on FEV_1/FVC ratios (that is, FEV_1 alone was not sufficient for inclusion). We also did not include studies of exposures predominantly associated with asthma (e.g., isocyanates or plicatic acid [Western red cedar]). If any member of the entire group suggested revisiting a proposed inclusion, further discussion by the whole group ensued until consensus was reached.

After this final inclusion step, 84 papers remained in the final data set used for the core of this analysis. We assigned 68 of these publications to one of three summary data Evidence Tables: population-based studies (n=26); industry or occupation specific studies of inorganic dust exposure (n=16), or industry or occupation specific studies of organic dust (n=26). Of the 16 papers not assigned to the Evidence Tables, 7 concerned studies of COPD in professional divers and the remaining 9 included findings relevant to COPD and occupation but were not homogeneous with the format and criteria of the Evidence Tables. The findings of these studies, even though not in these Evidence Tables, nonetheless, are summarized in the Results text.

Structure of the data presented

All of the included articles are described in the Evidence Tables, Appendix E-G page 58, arranged according to study design (first cross-sectional studies and secondly longitudinal studies) and according to the year of publication within study design.

The rationale for grouping the articles in population-based cross-occupational studies and occupational or industry specific cohort studies is an attempt to optimize the possibility for comparison between the studies. Most often, the exposure data in population-based studies (as opposed to studies in occupational or industry specific cohorts) is sparse and defined by one or a few survey items or by a semi-qualitative job exposure matrix (JEM). In occupational or industry cohort studies, in contrast, the exposure assessment is often better characterized. Aside from this distinction, studies equal in design share the same kinds of biases and confounding errors. The occupational or industry specific cohort studies have been subdivided into two groups depending on the description of exposure as predominantly inorganic/mineral or organic/biological exposures.

Assessment of causal association

The quality score of the studies was assessed using the ERS proposed extraction sheet with information of study design and population, measurement of exposure, level of exposure, duration of exposure, quality of the exposure description, quality of the outcome, limitation (confounding/bias), quality of results, key findings, grading of the study (2++ very low risk of confounding/bias/chance, 2+ low risk of confounding/bias/chance, 2 – high risk of confounding/bias/chance). Final evaluation of an association (exposure-disease) was assessed using the criteria described by the Danish Working Environmental Research Fund (29):

+++ strong evidence for a causal association
++ moderate evidence for a causal association
+ limited evidence for a causal association
0 insufficient evidence for a causal association
- evidence suggesting lack of a causal association

Additional description of the evidence model is provided in Appendix D page 57.

Review and Revision of the final Report

An initial draft text of the document, including its core Evidence Tables, was circulated to the members of the working group for review. At the same time the document was provided to two external reviewers (Professors Giovanni Viegi and William MacNee) for their comments. The working group met for a second time in November 2009 for final discussions to address the comments from within the group and from outside reviewers. A consensus approach was used to adjudicate differing views on all key points of discussion.

Results

Population-based cross-occupation

25 articles were original cohorts or populations. One article described additional findings from a previously selected cohort or population. The Evidence Table 1 on page 58 provides in a structured and focused form the major findings of these studies.

Cross-sectional studies

A recently published study from the USA assessed the association between COPD and occupational exposure for vapour, gases, dust and fumes (VGDF) exposures among subjects with known COPD aged 55 to 75 years. The study included 1,719 subjects of whom 67 fulfilled the criteria of Chronic Obstructive Lung Disease (GOLD) II+. For smoking subjects exposed to VGDF, the adjusted OR was 8.5 (95% CI 3.8-18.8), for subjects with minimal smoking history and VGDF exposure adjusted OR was 2.1 (95% CI 0.8-5.5). Population attributable fraction (PAF) was calculated to be 17%. Using physician reported COPD as outcome, the adjusted OR increased as did PAF the latter to 25% (30).

A similar study was performed among subjects aged 40 to 65 years using GOLD II+ as outcome and VGDF as the exposure variable. 742 subjects fulfilled these criteria and 302 referents were included. Using the questionnaire as the exposure variable, the adjusted OR was 2.13 (95% CI 1.55-2.93) with a PAF of 31% and the adjusted OR was the similar using a Job Exposure Matrix (JEM) in defining exposure 2.33 (95% CI 1.45-3.72) for highest JEM category) but the PAF was reduced to 14% (31).

A pooled ecological analysis based on group-level data from BOLD, PLATINO, and ECRHS II studies including 19,094 subjects aged ≥40 years found an association between occupational exposure expressed as dirty/dusty jobs and COPD GOLD II+ stage expressed as 0.8% increase in COPD prevalence for 10% increase in exposure prevalence, higher in females (1.0%) than males (0.8%) (32).

A slightly different outcome than $FEV_1/FVC < 0.70$ was used in another study from USA. The dependent variable was $FEV_1/FVC <$ LLN or COPD based on an algorithm developed for the study.

The study comprised 388 subjects with COPD and 356 referents. Exposure relied on industrial hygienists' assessment of job title, years of employment, and subjects' report of exposure to categories of respiratory exposure (gases, vapour, solvents, dust, diesel exhaust, and sensitizers). COPD was most strongly associated with diesel exhaust exposure OR 1.9 (95% CI 1.3-3.0), mineral dust OR 1.7 (95% CI 1.1-2.7), and irritant gases and vapours OR 1.6 (95% CI 1.2-2.2). PAR for any exposure was calculated to 24% (33).

Data from Spain based on a study of 576 subjects aged 20 to 70 years did not find an increased risk of COPD defined as GOLD II+ among those exposed to VGDF (ATS questionnaire). However, the FEV_1/FVC ratio among VGDF exposed ≥15 years was significantly lower than those non-exposed (-1.7 95% CI -3.3 - -0.2) (34).

A study from Australia used a JEM approach (ALOHA – modified JEM) to define exposure as biological-, mineral dust, and gases/fume exposure. The study included several outcomes among them were: GOLD II+ (moderate airflow obstruction), chronic obstructive bronchitis (GOLD I) with respiratory symptoms, and COPD defined as either chronic obstructive bronchitis or symptomatic emphysema. The study comprised 1,213 subjects aged 45 to 70 years. The prevalence of COPD defined as GOLD II+ was the same among exposed and non-exposed subjects. However, exposure to organic dust increased the risk of chronic obstructive bronchitis with respiratory symptoms (adjusted OR 3.19; 95% CI 1.27-7.97), and COPD (adjusted OR 2.70; 95% CI 1.39-5.23). The adjusted OR was highest in females. No increased risk was found associated with mineral dust exposure, while the adjusted OR for GOLD I with respiratory symptoms was 2.81 (95% CI 1.01-7.79) for subjects exposed to gases/fumes (35).

Data from the NHANES III survey was analysed for 9,495 subjects aged 30 to 75 years who underwent lung function tests. 14 occupational and 16 industry categories were identified by questionnaire. 693 subjects were diagnosed to have COPD defined as GOLD II+. Several occupations were identified with increased risk of COPD: among smokers, freight, stock, material handlers, adjusted OR 2.2 (95% CI 1.3-3.7) and armed forces, adjusted OR 2.0 (95% CI 1.1-3.6) and among never smokers records processing, distribution clerks, adjusted OR 2.9 (95% CI 1.1-7.6) and construction trades and labourers, adjusted OR 3.4 (95% CI 1.1-10.5). Attributable fraction of COPD from work was estimated to be 15.1% overall and among never smokers was estimated to be 25.6% (36).

A slightly different outcome variable than COPD GOLD II+ stage (FEV_1/FVC <0.75, FEV <0.8) was used in an analysis of the NHANES III survey which assessed the association between exposure and COPD in different ethnic populations. 9,120 subjects were included and 17 occupational and industry categories were identified by questionnaire (37). Like the previous study (36) several occupations were identified with an increased risk of COPD but different for ethnic populations. Attributable fraction of COPD derived from work by occupation exposure was

estimated to be 21.0% among Caucasians, 23.0% among African-Americans, and 54.4% among Mexican-Americans.

Data from the ECRHS study were used to analyse for association between occupational exposure and COPD (GOLD stage I) in 14,855 subjects aged 20 to 44 years. Exposure to VGDF was defined by questionnaire. No association was found between COPD (GOLD stage I) and occupational exposure (38).

Among 131 males with COPD (clinical history of ≥2 years) and FEV_1 <0.80 predicted with minimal bronchodilator reversibility and 298 male referents aged ≥45 years with no respiratory symptoms, the association with occupational exposure was determined. Subjects were classified in relation to occupation and exposures defined on the basis of a JEM and years spent in an occupation. Sixteen occupational categories were defined. Adjusted ORs were 3.80 (95% CI 1.21-12.0), 5.83 (1.82-18.6), and 8.86 (2.29-34.3) for workers exposed to a high level of mineral dust, gas/vapour/fume and biological dust, respectively (39).

Among 517 life-time never smokers with a mean age of 57 years, 67 fulfilled the criteria of GOLD II+. Occupational exposure was questionnaire defined (gas, dust, or fumes). The OR for the exposed to have COPD was 1.79 (95% CI 1.12-2.85) with a PAR of 29.6% (40).

Data from the New Zealand component of the ECRHS study comprised 1,132 subjects aged 20 to 44 years. Information on exposure was supplied by an additional questionnaire. FEV_1/FVC <0.70 without any symptoms was not associated with exposure to vapour, gas, dust, or fumes. However, FEV_1/FVC <0.75 and symptoms of chronic bronchitis as outcome were associated: OR 3.13 (95% CI 1.07-9.12) (41).

In a Finnish study of 1,191 subjects aged 64 to 97 years. COPD was defined as an FEV_1/FVC ≤0.65. Occupational exposure was obtained from a self-reported history of employment. The prevalence of COPD was 11.5% in males and 3.0% in females. There was a significant increase in the prevalence among male subjects in the lowest social class (III) (21.4%) compared with social class I (0%) (42). Additional analysis of the data combining exposure to dust and social class showed a significantly increase in the prevalence among subjects categorized as members of the lowest social class and exposed to dust OR 2.3 (95% CI 1.1-4.8) (43).

1,094 Chinese subjects aged 40 to 69 years who did not report the use of coal stove for heating were assessed for an association between occupational exposure to dusts, gases and fumes and pulmonary function. A trained reviewer was used to obtain data regarding duration and intensity of exposure. FEV_1/FVC was used as an outcome. Occupational exposure was not associated with FEV_1/FVC adjusting for age, sex, height, education, smoking, and area of residence. Dust exposure showed a significant deficit in FEV_1, $p<0.05$ (44).

Norwegian data obtained from Bergen and surrounding municipalities analysed for association between COPD (defined as GOLD II+) and occupational exposure among subjects aged 18-73 years. Exposure data contained information on asbestos, quartz, wood dust, metal gases, aluminium production and processing, welding, and soldering, together with information of actual and longest held job. Occupational exposure was not associated with COPD. However, when restricting the analysis to subjects aged >50 years, exposure to asbestos adjusted OR 2.8 (95% CI 1.1-7.3) and quartz adjusted OR 3.7 (95% CI 1.2-11.0) was significantly associated with COPD (45).

An Italian study involving 1,635 subjects aged 18 to 64 years assessed the respiratory effects of occupational exposure. Exposure was defined by questionnaire with information of occupational exposure to dusts, chemicals, and/or fumes and working experience over six months. Exposure was associated with impairment in lung function. Among exposed males the adjusted OR for FEV_1/FVC <0.7 or FEV_1 <0.70 was 1.45 (95% CI 1.03-2.05) (46).

From 6 cities in the USA, a total of 8,515 white adults aged 25 to 74 years were recruited to assess for an association between occupational exposures and chronic respiratory symptoms. COPD was defined as FEV_1/FVC <0.6. Lifetime occupational history was obtained by questionnaire with information of jobs, industry, and exposures to dusts and gases/fumes. Subjects exposed to dusts at work had an increased risk of COPD (Adjusted OR 1.68, 95% CI 1.18-2.40) but not those exposed to gases/fumes. The finding was only significant in males when the analysis was restricted to each gender (47).

In the Tucson Epidemiologic Study of Obstructive Lung Disease 1,195 white males age ≥18 years who had been employed for ≥6 months were included in an analysis of the association between occupational exposure and airway obstructive disease (AOD). AOD grade 2 was defined as FEV_1 <75% of predicted or FEV_1/FVC <0.80 or chronic productive cough or exertional dyspnea Gr. 3+. Occupational exposure data were questionnaire derived. The prevalence of AOD grade 2 adjusted for smoking and age was significantly higher in subjects reporting any exposure compared with no exposure (38.6% compared with 32.8, p<0.01) (48).

Longitudinal studies

Among 2,734 male workers from different working environments aged 18 to 58 years enrolled in an Italian health surveillance program 2,017 were followed with spirometry for ten years. Exposure was described as the presence of dust, fumes, and vapours in the current occupation supplemented by information from the Risk Assessment Document submitted by the relevant company. Overall incidence of COPD (defined as GOLD II+) was 7.3%. Along with cigarette smoking OR 1.75 (95% CI 1.27-2.41) occupational exposure OR 2.62 (95% CI 2.02-3.41) was a risk factor for COPD. A significant interaction was found between cigarette smoking and occupational exposure OR 2.51 (95% CI 1.97-3.20) (49).

5,335 subjects with COPD (post bronchodilator FEV_1/FVC <0.70 and FEV_1 >0.55 and <0.90) aged 34-67 years, all enrolled in the Lung Health Study in the USA, participated in a study that assessed the association with occupational exposure. Exposure data (dust exposure, fume exposure, and use of mask) were collected and questions repeated during interview at five consecutive follow-up visits over five years. In men, exposure to fumes was significantly associated with a reduction in post bronchodilator FEV_1 % predicted of 0.25% predicted per year of fume exposure. Loss of post bronchodilator FEV_1 % predicted was associated with continued smoking calculated as 1.2-1.9% predicted. No association was found with dust exposure. In females, no association was observed with any kind of occupational exposure (50).

ECRSH-I and ECRSH-II data were used to analyse for relationships between occupational exposure and lung pathology. The study comprised 6,481 subjects aged 20 to 45 years at baseline and the follow-up time was 8.9 years (range: 5.8-11.7 years; maximum age at follow-up =56). FEV_1/FVC <0.70 was used as one outcome and exposures to biological dust, mineral dust, and gases and fumes were assigned using a general population JEM. Occupational exposure was not associated with the incidence or prevalence of obstruction (FEV_1/FVC <0.70) (51).

In a population of 1,506 Swedish subjects with respiratory symptoms aged 36 to 67 years, n=1,109 (74%) were retested ten years later. The study aimed to measure the incidence and identifying risk factors for COPD. Exposure data were obtained by questionnaire. As outcomes, FEV_1/FVC <0.70 (GOLD) and FEV_1/VC <0.70 and FEV_1 <0.80 (BTS) were used. The incidence of COPD was 13.5% GOLD and 8.2% BST. OR for manual workers in the industry was 1.78 (95% CI 0.80-3.97) and for low social class 1.73 (95% CI 0.98-3.04) in a multiple logistic analysis model (52).

A Norwegian study analysed the association between airflow limitation and decline in FEV_1 and occupational exposure. The study included 911 subjects aged 22-54 years at baseline. Mean follow-up time was 23 years (range 20-25 years). Airflow limitation was defined as FEV_1/FVC <0.65. A questionnaire of past and present exposure to: asbestos, quartz, ammonia, chlorine, nitrous gas, ozone, sulphur dioxide, aldehydes, anhydrides, diisocyanates, chromium, nickel, and platinum were performed. The prevalence of airflow limitation at follow-up was 9.5% and was three times more prevalent in subjects with the highest exposure to asbestos ($p<0.05$), adjusted for age, body height, and smoking. Accelerated loss in FEV_1 was associated with exposure to sulphur dioxide, metals, and to increasing numbers of occupational exposures (53).

In a 13 year follow-up study from Poland consisting of 1,769 subjects aged at baseline 19 to 70 years, the outcome was decline rate in FEV_1 and COPD was defined as FEV_1 <0.65 predicted. Occupational exposure was defined by questionnaire and subjects exposed to particular hazards in the workplace for at least five years were regarded as “exposed” in the analysis. Occupational exposure to dusts was not associated with the incidence of COPD defined as FEV_1 <0.65 predicted.

In males, however, occupational exposure to dusts increased the annual decline in FEV_1 by 6.1 ml ($p<0.05$). In females increased FEV_1 decline was associated with exposure to variable temperature (54).

A study from the Paris area assessed the association between occupational exposure to dust, gas, and heat and the annual decline in FEV_1 expressed as slope (ml/year) in 556 male workers aged 30 to 54 years at baseline over a follow-up period of 12 years. Exposure assessment was based on self reported occupational history followed by a technical study by engineers and industrial physicians to define risks and level of exposure. Annual decline in FEV_1 adjusted for age, smoking, and FEV_1 at baseline was 44 ml if non-exposed or slightly exposed, 51 ml if exposed to heat, 53 ml if exposed mainly to dust, 55 ml if mainly exposed to dust and heat, and 60 ml if exposed mainly to dust, heat, and high concentration of gases (55). Multiple regression analyses from the same population found that occupational exposure, social class, and smoking were independent risk factors for annual decline in FEV_1 (56).

Inorganic exposures and occupational cohort studies

15 articles were original cohorts or populations. One article described additional findings from a previously selected cohort or population. The Evidence Table 2 on page 64 provides in a structured and focused form the major findings of these studies.

Welding workers

Three cross-sectional studies were identified from China, Italy and Croatia. The Chinese Study from 2006 included 117 welders and analysed an outcome of $FEV_1/FVC <0.75$. As referents were used 130 assemblers or office workers without welding exposure. There was no significant association with the outcome in both spot and arc welders (57).

657 shipyard workers participated in an Italian study. 483 workers were more exposed than metalworkers working on the scaffolding of the ship and who had the lowest exposure and were used as internal referents. They assessed for airways obstruction (low FEV_1/FVC) and mixed pulmonary function impairment (low FVC and low FEV_1/FVC). There were no significant associations with regard to job titles in any of the outcomes. However, estimates were significant for the impairment of mixed pulmonary function if the duration of exposure >20 years with OR 2.52 (95% CI 1.14-5.53) (58).

Croatian stainless steel workers were investigated in a cross-sectional study of welders. 106 welders exposed for 4-34 years and 80 matched referents with no occupational exposure were included. There was a significantly lower FEV_1/FVC ratio in exposed compared with referents in both smokers and non-smokers, 79.2 compared with 84.4%, $p<0.05$ and 80.4 compared with 92.8%, $p<0.01$, respectively (59).

A longitudinal study from USA, 1996, comprised 475 participants, with a follow-up at four to nine years had a defined outcome as FEV_1/FVC ratio. A multiple linear regression model estimated a significant change in FEV_1/FVC of -0.03%/yr, p=0.02 (60).

Coal miners

Studies in coal miners in which lung function was measured are described by Seixas, in two different publications from 1993 and 1992. Analysing the same cohort (National Study of Coal Workers' Pneumoconiosis, round four) the studies included "new miners" covering 977-1,185 miners who worked ≤18 years in the mines and measured FEV_1/FVC ratio as an outcome. Internal referents were those in the lowest quartile of cumulative exposure. The mean age of this cohort after 15-18 years of follow up was 40 years. The percentage change in the ratio was significantly associated with mean exposure (p=0.02). An estimated increase in exposure of 1 mg/m^3/yr was associated with an OR 1.05 (95% CI; 1.01-1.09) and an increase in exposure at 20 mg/m^3/yr was associated with OR 2.5 for FEV_1/FVC<0.8 in coal miners (61,62).

Coke workers

A cross-sectional study from China, 2006, involved 712 coke workers and 211 workers from an institute of equipment calibration as referents. Benzene soluble fraction was used as a surrogate of coke oven emissions. COPD, defined as GOLD II, was significantly associated with moderate exposure OR 4.00 (95% CI 1.80-8.89) and high exposure OR 8.22 (95% CI 3.76-17.97) the dose-response relationship was significant (63).

Asphalt workers

A cross-sectional study from Norway involved 64 asphalt workers and 195 outdoor construction workers as referents with a mean age of 37 and 40 years, respectively. COPD was defined as an FEV_1/FVC <0.7 combined with clinical symptoms. COPD was significantly associated with asphalt workers compared with referents OR 2.8 (95% CI 1.2-6.5) (64).

Silica exposure

The effect of low silica exposure was analysed in a cross-sectional study in a younger and smaller population of 144 exposed and 110 referents from an office equipment-producing factory with a mean age of 35.9 and 35.5 years, respectively. There was a significant lower FEV_1/FVC ratio in exposed compared with referents, p=0.02. However, there was no significant association between exposure and COPD defined as FEV_1/FVC ≤LLN (65).

A 13 year follow up study from USA included 815 foundry workers (included internal referents) with a mean age of 58.7 years. An abnormal FEV_1/FVC was defined as <0.70 if age <60 years and <0.65 if age ≥60 years. There was a significant association between outcome and cumulative silica exposure (p=0.03) and, when stratifying for smoking there was a significant trend in smokers (p=0.01) (66).

Cement dust

In 2003, Fell et al. studied occupational exposure to cement dust in Norway. In this cross-sectional study, COPD was defined according to the GOLD criteria standard as GOLD II+. The population consisted of 119 exposed workers and 50 referents from a plant with ammonia production. Workers had a mean age of 69.3 and 66.8 years, respectively. No significant association between COPD and exposure was observed (67).

Tunnel workers

A cross-sectional study from Norway consisted of 212 tunnel face workers, shotcreters or concrete workers and a reference group comprising 205 heavy construction workers with a mean age of 41 and 40 years, respectively. The outcome measure was FEV_1/FVC <0.7, which was significantly associated with exposure in tunnel working OR 2.50 (95% CI; 1.31-4.96) (68).

Cadmium workers

A cross-sectional study from 1988 by Davison involved 97 exposed workers and 92 matched referents from other divisions of the factory. A significantly lower FEV_1/FVC ratio was seen in exposed compared with referents, $p<0.001$. There was a dose-response relationship between the outcome according to 'year started exposure' (pre-1951, 1951-1970, post-1970) of $-0.29\%/(\mu g/m^3)/yr$, $p<0.001$, and a non significant relation to cumulative exposure was calculated. This study also showed an exposure response for impaired diffusing capacity (transfer factor) a marker of emphysema (69).

Glass bangle workers

The salts of heavy metals used as colouring agents in manufacturing of glass bangles were the subject of an Indian cross-sectional study from 1991. 220 exposed workers and 127 referents with mainly manual jobs participated (mean aged 30.9 and 30.6 years, respectively). A significantly lower FEV_1/FVC ratio was measured in the exposed subjects, 78% compared with 81% in referents, $p<0.001$ (70).

Bleach workers

Metha et al. investigated exposure to irritant gases in the bleaching process in pulp mills. This longitudinal study (mean follow-up 3.4 years) included 178 workers and 54 paper mill workers as referents aged 43.7 years (mean). Measurement and outcome were prevalence ratio of FEV_1/FVC <LLN. Significant association was estimated in "pre-baseline ozone gassings" (exposed to ozone gassings before the baseline of the study) PR 4.3 (95% CI 1.2-15.7) and in "pre-baseline and interval ozone gassings" (exposed to ozone gassings before baseline and during the study) PR 5.5 (95% CI 1.1-28.0) compared with the referents (71).

Organic exposures and occupational cohort studies

19 articles were original cohorts or populations. Seven articles described additional findings from a previously selected cohort or population. One cohort is described in six articles and two other studies are represented by two articles each. The Evidence Table 3 on page 68 provides in a structured and focused form the major findings of these studies.

Cotton workers

In two cross-sectional studies from UK in 1996 and 1986 (72,73), only the women in Elwood's study of ex-cotton workers showed a significantly increased deficit in FEV_1 compared with referents with no or other dust exposures (73).

In 2008 Wang et al. analysed data from a 15 and 20 years follow-up study of Chinese cotton workers, using silk workers as referents. The participants were 56-57 years at the end of the study and the exposed group showed over 15 years follow-up a significant difference in FEV_1 decline of 9.7ml/yr compared with referents. However, the differences in FEV_1 decline were not significant between the groups after 20 years follow-up (74).

Another study from USA conducted 1,817 mill workers, of who 773 worked in the cotton yarn manufacturing, 580 in the cotton slashing and weaving, and 464 worked in synthetic mills and served as referents, all with at least three pulmonary function tests over three years. Workers involved in cotton yarn manufacturing showed a significant annual decline in FEV_1 16.20 (± 3.27) ml/yr per 100 $\mu g/m^3$ average cotton dust exposure ($p<0.001$) (75).

An earlier longitudinal study of cotton workers in USA from 1982 with six years of follow-up showed a significantly increased decline in FEV_1 among men and women of 17 ml/yr and 16 ml/yr, respectively, compared with referents who had not worked in a cotton mill (76).

Flax workers

In a UK cross-sectional study of flax workers from 1986, in which 629 ex-flax workers aged 40-74 years participated, the deficit in FEV_1 was significantly higher in both men ($p<0.05$) and women ($p<0.01$) compared with referents never exposed to flax (77).

Jute workers

50 jute processing workers and 25 referents working in a paper-packing factory were studied longitudinally in China over five years. Data published in 1992 showed a significantly increased decline in FEV_1 of 57.1 ml/yr in the jute workers compared with referents (78).

Farming

The most recent and largest cross-sectional study from 2009 in Norway was comprised of an exposed group of more than 3,700 dairy farmers and nearly 1,000 crop farmers as referents. The OR

for FEV_1/FVC <LLN comparable with GOLD I+ was significantly higher among livestock farmers than crop farmers OR 1.4 (95% CI 1.1-1.7) and farmers exposed to organic dust had an increased risk of FEV_1/FVC <LLN for a 10-fold increase of exposure level OR 1.2 (95% CI 1.0-1.4) (79).

In two cross-sectional studies the outcome was GOLD II+. An Austrian study from 2007 consisted of 288 exposed farmers (ever worked ≥3 months in farming) and 970 referents with no report of farming all with a median age of 57 years. There was a significantly increased OR of 1.8 (95% CI 1.2-2.8) for GOLD II+ in farmers compared with referents (80). From the European Farmers' Study, Monsó et al. studied 76 non-smoking farmers stratified in four quartiles of exposure. In farmers with high exposure to dust the OR for COPD defined as GOLD II+ compared with first and second quartiles of exposure the OR was 6.60 (95% CI 1.10-39.54) (81).

A longitudinal study from France published in 1998 analysed data during a six year follow-up. The study comprised 190 dairy farmers and 138 non exposed rural administrative workers as referents, matched by age, sex, height and smoking habits. A significantly increased decline in FEV_1 was found in farmers compared with the referents, p=0.03 (82).

Grain workers

A Dutch five year follow-up study from 1998 comprised of 140 participants with a mean age of 37.7 years. The outcome was FEV_1 and estimated in a regression analysis standardised to that of a 40-year old non-smoker. The highest exposed workers had a significant decline in FEV_1 of 22.4 ml/yr compared with no and lowest exposed workers (83).

A six year follow-up study from South Africa published in 1991 involved 159 participants of whom <25% were referents (low exposed) with a mean age of 42.7 years. The outcome was FEV_1/FVC <0.7 and the highest exposed workers had a significant OR of 3.09 (95% CI 1.35-7.07) for obstruction compared with lowest exposed (84).

Wood workers

In a cross-sectional study from South Africa published in 1992, 145 exposed and 152 matched referents from a bottling firm, all non-smoking and aged 32 to 35 years, were included. Wood workers had a significantly lower FEV_1/FVC ratio than referents, p<0.01, and in those exposed who were employed ≥10 years compared with exposed employed <10 years the FEV_1/FVC ratio was also significantly lower, p<0.01 (85).

In a six year follow-up study Jacobsen et al. found dose-response relationship between baseline as well as cumulative wood dust exposure and decline in FEV_1 and FVC. This association was only seen among the 185 female workers, not among the 927 male wood workers. More female wood workers (fourth quartile of cumulative dust exposure) developed COPD in the follow-up period compared with 131 referents (first quartile), 11% compared with 4% (p =0.08) (86).

Glindmeyer et al. found no association between inhalable wood dust exposure and decline in FEV_1 or FEV_1/FVC in a five year follow-up study among 1,164 wood workers. In a subgroup of workers, however, they found "residual particulate matter" (non solid parts of dust) associated with annual decline in FEV_1 (milling and plywood sawmill) and FEV_1/FVC (milling) for the respirable dust fraction (87).

Paper workers

A Dutch cross-sectional study from 1987 included 46 exposed and 48 white collar workers as referents and assessed for the cross week deficit in FEV_1. The difference in FEV_1 deficit in exposed compared with referents was -195 ml (mean), $p<0.05$ (88).

Rubber workers

A Dutch cross-sectional study from 1998 estimated a significantly lower FEV_1/FVC ratio in 70 exposed rubber workers compared with 69 referents from an office-equipment producing factory, 80 compared with 82%, respectively, $p<0.05$ (89).

In a one year longitudinal study in 1976 in Rubber industry workers from the USA, 92 exposed and 141 referent subjects were assessed for the FEV_1/FVC ratio (cross-sectional) and FEV_1 (longitudinal). There were no differences in FEV_1/FVC ratio between the groups. In a multiple regression analysis years of exposure were significantly predictive of one year loss in FEV_1, $p<0.001$ (90).

Endotoxin exposure

The two studies on farmers were cross-sectional studies one as a Norwegian study and the other as a part of the European Farmers' Study. A significant OR 1.2 (95% CI 1.0-1.5) was found in the Norwegian study of 4,735 farmers (livestock compared with crop) for COPD as FEV_1/FVC <LLN among subjects exposed to endotoxin and a 10-fold increase of exposure level (79). There was no significant association between COPD defined as GOLD II+ and endotoxin exposure in a study of 76 non-smoking European farmers (81).

There was a non-significant association between endotoxin exposure and decline in FEV_1 in the Chinese cotton workers (20 years longitudinal study) (74), a finding similar to data from the Dutch study of grain workers (five years longitudinal study) (83).

Quantification of exposure

In order to address study charge to provide a: "Detailed estimate of any increased risk in relation to the nature, severity/scope and duration of the exposures" (1) studies with measurements of exposure, especially those with cumulative estimates are needed. Few studies fulfil these qualities for the description of the exposures involved. Studies using means, median, GM, or range to

describe exposure level are prevalent, but only a few use cumulative estimates. Studies that utilize time of exposure or duration of employment (or even age presuming a uniform age of first exposure) as surrogates of cumulative exposure might also be helpful.

Exposure level

In 18 of the selected studies, exposure has been measured. In five studies cumulative exposure measurements are reported, one study describes both mean and cumulative exposure. Twelve studies define exposure by mean, median, GM, and range. Of these, five studies are of inorganic exposures and thirteen of organic dust exposures.

Inorganic exposure

Measurements of cumulative exposure are available in two articles with no, low, moderate and high inorganic exposure: cadmium (69) and coke oven emissions (63). In cadmium workers, there was a significant lower FEV_1/FVC ratio in exposed compared with referents, $p<0.001$. Low, moderate and high cumulative exposure were defined by <400, 401-1,600 and >1,600 µg/m^3-years, respectively, but no significant trend related to the degree of cumulative exposure was reached. However the body burden of cadmium did demonstrate an effect gradient in that study (69). In coke oven workers, the exposure of emissions was significant associated with COPD defined as GOLD I+ and GOLD II. The prevalence was significantly increased in subjects with moderate and high cumulative exposures, with mean cumulative exposures at 1,147.8 and 7,141.6 µg/m^3-years, respectively. The mean low cumulative exposure was 449.5 µg/m^3-years. The dose-response relationship was significant in GOLD I+ and GOLD II (63).

One study by Meijer, 2001, defined dust and silica exposure in mg/m^3 by mean, range and median. Mean exposure of respirable dust and respirable silica were 0.77 and 0.059 mg/m^3, respectively. There was no significant association between FEV_1/FVC ≤LLN in exposed compared with referents. However, FEV_1/FVC was significantly lower in exposed compared with referents, $p=0.02$ (65). In a Norwegian cross-sectional study of COPD (GOLD II+) among subjects exposed to cement dust, no significant association between COPD and exposure was observed. Mean (range) concentration of total dust was 7.4 mg/m^3 (0.4 – 53.7 mg/m^3) and, for respirable dust, the mean (range) concentration was 0.91 mg/m^3 (0.0 – 2.3 mg/m^3) (67).

Norwegian tunnel workers were exposed to total and respirable dust of 3.6 and 1.2 mg/m^3 and referents to 1.05 and 0.21 mg/m^3 measured in GM, respectively. There was a significant association between FEV_1/FVC <0.7 and workers employed 10-20 years (n=95) compared with workers employed <10 years (n= 84) OR 2.56 (95% CI 1.13-6.32) (68).

Organic exposure

Measurements of cumulative exposure were present in a 20 year follow-up study in cotton workers from China. Mean cumulative organic dust and endotoxin exposures were 19.3 mg/m^3/yr and 48,479.5 EU/m^3/yr, respectively. No significant dose-response relationship was observed between

exposure and FEV_1 decline (74). In a six year follow-up study, a dose-response relationship between baseline as well as cumulative wood dust exposure and decline in FEV_1 and FVC was observed. An association was only seen for female wood workers, not for male wood workers. An additional loss in FEV_1 was seen of 14.50 ml/yr, and 27.97 ml/yr for females exposed to 3.75-4.71 mg/m^3-yr and >4.71 mg/m^3-yr compared with non-/low-exposed. More female wood workers developed COPD in the follow-up period compared with 131 unexposed referents, 11% compared with 4%, p =0.08 (86). In a study of yarn manufacturing from cotton textile, a significant ($p<0.001$) annual fall in FEV_1, FVC, and $FEF_{25-75\%}$ of 16.20 ± 3.27, 18.00 ± 3.94, and 23.30 ± 6.58, respectively was observed. The cumulative exposure in yarn manufacturing was calculated to 2,445 ± 3,253 $\mu g/m^3$-yr. (75).

When Meijer et al. studied rubber workers, they reported a mean concentration of dust of 2.0 mg/m^3 and the mean cumulative dust exposure as 32.5 mg/m^3-yr. The FEV_1/FVC ratio was significantly lower in exposed compared with referents and the cumulative dust exposure was significantly associated with lower FEV_1/FVC ratio (89).

Five studies had measurements of range of exposure. Fishwick's data from cotton workers had a range of static and personal dust exposures at 0.04-3.23 mg/m^3 and 0.14-24.95 mg/m^3, respectively. There was no significant FEV_1 deficit in exposed compared with referents (72). A study of workers in the grain processing and animal feed industry estimated a significant decline of FEV_1 in high dust exposed workers compared with referents. The dust exposure was defined as no/low ≤4 mg/m^3, intermediate 4-≤10 mg/m^3 and high >10 mg/m^3. The endotoxin exposure was defined as no/low ≤20 ng/m^3, intermediate 20-≤40 ng/m^3 and high >40 ng/m^3 and reached no significant difference in FEV_1 level between intermediate or high endotoxin exposed workers compared with no/low exposed workers (83). The study of non-smoking European farmers estimated a significant dose-response relationship between COPD defined as GOLD II+ and dust. The referents had a dust exposure ≤5.61 mg/m^3 (first and second quartile) while the third and fourth quartile ranged from >5.61-9.36 and >9.36-76.7 mg/m^3, respectively. In the same study, the dose-response relationship between COPD and endotoxin exposure was not significant. The referents had an endotoxin exposure of <687.1 units/m^3 (first and second quartile) while the third and fourth quartile ranged from ≤687.1-2,203.0 and >2,203.0-16,720.8 units/m^3, respectively (81). The large study of 4,735 Norwegian farmers had measurements of the interquartile range for dust 0.24-1.6 mg/m^3 and endotoxin 19,000-63,000 EU/m^3. The OR for GOLD I+ for a 10-fold increase in exposure was significant in dust and endotoxin exposures as continuous variables (79). In the six year follow-up study from South Africa 159 participants was involved. The outcome was FEV_1/FVC <0.7 and the highest exposed workers had a significant OR of 3.09 (95% CI 1.35-7.07) for airway obstruction. The mean (range) of grain dust was 6.10 mg/m^3 (0.0 – 95.59 mg/m^3) (84).

Mean concentration of exposure was present in additional four studies. The exposures in jute processing workers were measured by area sampling and had a mean range of 1.4-64.6 mg/m^3 in

different workplaces. The FEV_1 deficit was significant in men compared with referents, $p<0.01$ (78). In a study of non-smoking wood workers, the mean total dust concentration was 3.82 mg/cm^3 and significant more exposed workers had $FEV_1/FVC <0.7$ than referents (85). The study of paper dust had GM measurements of respirable and total dust concentrations of 4.9 and 5.8 mg/m^3, respectively. The FEV_1 deficit was significant in wood workers compared with referents (88). Glindmeyer et al. found no association between inhalable wood dust exposure and decline in FEV_1 or FEV_1/FVC in a five year follow-up study among 1,164 wood workers. In a subgroup of workers, however, they found residual particulate matter (non solid parts of dust) associated with annual decline in FEV_1 (milling and plywood sawmill) and FEV_1/FVC (milling) for the respirable dust fraction. Mean exposure in the milling facility was 0.147 mg/m^3 and in the plywood sawmill 0.255 mg/m^3 (87).

Exposure duration

In 21 of the selected studies cumulative exposure has been assessed by exposure duration or age of the exposed subject. Of these six are population-based studies; seven are studies with inorganic exposure, and eight with organic exposure.

Population-based studies

Two studies have used logistic regression modelling to estimate the relation between exposure duration and COPD. Among farmers, welders, painters, and textile workers there was a significant increase in COPD for each year of exposure. Lowest exposure time included in the model was ≤ nine years (39). There was a significant increase in the incidence of COPD with increasing age of birth strata (1919-20, 1934-35, and 1949-50) among subjects (52).

From the third US National Health and Nutrition Examination Survey it was found, that, high risk and low risk occupations were associated with duration of exposure. Additional risk for COPD in high risk occupations was OR 1.4 (95% CI 0.8-2.6) with 1-14 years of exposure and OR 1.7 (95% CI 1.1-2.5) with ≥15 years of exposure. In low risk occupations the additional risk for COPD was OR 1.4 (95% CI 1.0-1.9) with 1-14 years of exposure, and OR 1.5 (95% CI 1.2-2.0) with ≥15 years of exposure (36). In women, biological dust exposure was significantly associated with COPD risk. In women exposed 1-12 years the OR was 8.24 (95% CI 2.01-33.8), and OR was 6.90 (95% CI 1.75-27.2) for those exposed >12 years compared with women with no exposure (35). In an ECRHS study of subjects aged 20 to 44 years no change with cumulative exposure was observed in relation to lung function decline (51). In a study from Spain there was no significant difference in the prevalence of COPD among subjects exposed ≥15 years compared with subjects exposed less (34).

Inorganic exposure

Four studies have used logistic regression modelling. In two longitudinal studies (minimum 13 years follow-up) of coal miners FEV_1/FVC was associated with the cumulative exposure (61,62). There was a decrement of 0.078% in FEV_1/FVC pr year ($\beta= -0.0775$, $p=0.03$) (61) and there was an increase of 0.046 pr year in $FEV_1/FVC <80\%$ among exposed ($\beta= 0.0463$, $p=0.022$) (62). Among

steelworkers there was a significant effect of dust exposure on the change of FEV_1/FVC of 0.03% pr year of job at dusty areas (60). In cadmium exposed workers an association was observed between cumulative exposure and FEV_1/FVC% (slope -0.29, $p<0.001$). Exposure was defined as start of exposure before 1951, start of exposure between 1951 and 1970, and start of exposure after 1970. The study was conducted in 1983. Minimum exposure time was one year (69).

Studies in the glass bangle industry of exposed did not show any difference in FEV_1 or FEV_1/FVC but in $FEF_{25-75\%}$, $FEF_{75-85\%}$ between subjects exposed more or less than ten years (70). Among Italian shipyard workers there was a significant increase in OR of 2.52 (95% CI 1.15-5.53) for mixed impairment in lung function and a non significant increased OR 1.2 (95% CI 0.73-1.97) was observed for obstruction alone in subjects exposed >20 years compared with those with less exposure years (58). Norwegian tunnel workers exposed more than ten years had significantly more subjects with FEV_1/FVC <0.7 than those exposed less years (68).

Organic exposure

Seven studies have used logistic regression modelling to estimate an exposure response effect. In rubber workers, FEV_1/FVC was reduced by 0.04% pr. mg/m^3-years, $p<0.01$. Lowest exposure time for subjects included in the model was not indicated only mean (SD) exposure 25 (6.9) years (89). Among grain processing and animal feed industry, loss in FEV_1 was calculated in a model for a 40 years old non-smoker. Annual loss in FEV_1 was estimated to 74.7 ml for 0 to <5 years of work, 51.5 ml for 5 to <10 years of work, 35.3 ml for 10 to <20 years of work, and 17.8 ml for ≥20 years of work. The most pronounced effect was observed the first years with effect of just one year of exposure (83). In male jute workers, the annual loss in FEV_1 was 90 ml and in referents 32.9 ml with a calculated significant regression equation of FEV_1 ($y= 103.010 – 0.700x$, $p<0.05$). The lowest exposure time for subjects included in the model was ten years (78). In cotton and man made fibre operatives FEV_1 was associated with years working in the waste room (most dusty area) (β -1.012, $p<0.01$). There is no description of the range of the exposure time for subjects included (72). Among Norwegian farmers, FEV_1 in ml was significantly associated with duration of farming in years (β -3.1 (95% CI -4.8, -1.3). COPD was significantly increased in farmers with livestock compared with farmers with crop production: OR 1.4 (95% CI 1.1-1.7). The lowest exposure time for subjects included in the model was not indicated, only mean (SD) exposure 25 (14) years (79). Subjects involved in yarn manufacturing from cotton textile have a significant ($p<0.001$) annual fall in FEV_1, FVC, and $FEF_{25-75\%}$ of 16.20 ± 3.27, 18.00 ± 3.94, and 23.30 ± 6.58, respectively, per 100 μg/m^3 average cotton dust exposure. The lowest exposure time for subjects included in the model was not indicated only mean (SD) exposure 9.6 (5.5) years (75). Among curing workers in the rubber industry the one year loss in FEV_1 was significantly associated with years of curing fume exposure (β -10.9, $p=0.001$) (90).

In workers exposed to wood dust the prevalence of FEV_1/FVC <0.70 was significantly higher among subjects exposed and employed ≥10 years compared with workers exposed and employed less years (85).

Studies of airway obstruction not included in the Evidence Tables

Studies without spirometric data and emphysema

Some studies with or without spirometric data do not fit into the construction of the Evidence Tables due to their outcome, design, or exposure. Since these studies in their own way add to the understanding of causality between exposure and outcome they are included in the text and described in this subsection.

In one study, COPD defined as a physician diagnosis of emphysema or COPD was used as the outcome. The OR for COPD or emphysema was 2.6 (95% CI 1.6-3.5) for subjects exposed to VGDF (self-reported) and the corresponding PAR was 31%. By JEM, exposure assessment the OR for exposed increased from 1.0 in the lowest exposure to 1.9 (95% CI 1.2-3.2) in the highest exposure; the PAR for the highest exposure was 6% (91).

In a series of 185 male COPD patients mean age 66.2 years, the effect of occupational exposure on the clinical and functional characteristics was investigated. Exposure to mineral dust, biological dust, and dust or gas and fumes was independently associated with COPD severity (FEV_1 <30%), RR 11 (95% CI 1.4-95), clinical symptoms (dyspnoea and sputum production), and employment status (work inactivity) OR 2.4 (96% CI 1.4-4.2) (92).

Data from a Dutch longitudinal study with a follow-up time of 20 years used the concept chronic non-specific lung disease (CNSLD) as an outcome. The definition covers symptoms associated with asthma and COPD, as well as cases of asthma, chronic bronchitis or emphysema diagnosed by a clinical specialist. The data were analysed using occupational codes for “blue collar workers” compared with “white collar workers”. Hazard ratios for incidence of CNSLD was 1.68 (95% CI 1.18-2.39) among “blue collar workers” (93).

Standardized hospitalization ratio (SHR) for COPD were studied in three Danish cohorts of subjects aged 20 to 59 years in 1981, 1986, and 1991 including analysed 2,273,709, 2,330,037, and 2,458,792 males and females, respectively. Data were analysed both cross-sectionally and longitudinally. Risk ratio was 2.31 (95% CI 2.13-2.51) for unskilled workers compared with senior salaried staff for men and 1.62 (95% CI 1.38-1.92) for women. SHR increased during the observational period for all classic high risk occupations apart from farming (4).

A Swedish Study of mortality in COPD among construction workers comprised 317,629 subjects aged 15 to 67 years. Exposure was expert defined with information on exposure to inorganic dust, gases and irritants, fumes and wood dust. There was a significant increase in mortality among

subjects exposed to any of the above components with RR 1.12 (95% CI 1.03-1.22). Among never smokers the exposure to inorganic dust was associated with an increased risk, HR 2.30 (95% CI 1.07-4.96) (94).

Emphysema was analysed in autopsies from 616 coal miners and 106 non-miners. The severity of emphysema was elevated among coal miners compared with non-miners, and the cumulative exposure to respirable coal mine or coal dust retained in the lungs were significant predictors for emphysema severity. The contribution of coal mine dust and cigarette smoking were similar in predicting emphysema severity (95). An editorial in the same issue of the American Journal of Respiratory and Critical Care Medicine highlighted the actual implication of the findings by arguing that the standard USA dust levels in coal mines of 2 mg/m^3 does not protect against emphysema point up the substantial environmental burden of the coal production of five billion tons a year.

A cross-sectional study from USA analysed the effect of exposure to substances contaminated with 2,3,7,8-Tetrachlorodibenzo-p-dioxin on respiratory health but also ascertained occupational dust and fume exposure in the exposure group and in referents. 233 exposed workers and 226 referents aged 55.4 and 56.0 years, respectively (mean) were included. COPD defined as FEV_1 and FEV_1/FVC ratio < the lower 95% CI of the predicted. Although dioxin was not related to COPD, exposure to occupational dust and fume (cutting across the cases and referent groups) was associated with an approximate doubling of COPD odds (OR 1.55; 95% CI 0.59-4.05) (96).

From three general population surveys conducted in France, The Netherlands, and Norway associations between lung function (FEV_1) and occupational exposure defined either as self-reported or as specific JEMs were analysed. Significant associations between JEM and lung function were found in the French (FEV_1 scores -0.08 exposed compared with 0.03 unexposed) and the rural Dutch survey (FEV_1 scores -0.12 exposed compared with 0.04 unexposed). No significant association were found to self-reported exposure (97) Note that the French, Dutch and Norwegian cohorts are derived from analyses already included either in Evidence Table 1 or in this section.

A recent study from the USA of 150 subjects with moderate to very severe COPD (defined according to the GOLD guidelines) observed a trend towards lower FEV_1 with increasing duration of self-reported agricultural exposure (98).

Studies of divers

Diving as an occupational exposure is not characterized by exposure to organic nor mineral material, and published data describe findings more suggestive of small airway disease than COPD (99,100). In several studies an increase in FVC has been observed (101-104), but at the same time measurements of expiratory flow have revealed an obstructive component with reduced FEV_1 or FEV_{25-75} in divers compared with referents (101-105). Increased partial oxygen pressure and venous

gas embolus have been suggested as exposures associated with the observed pulmonary function changes in divers (105).

Discussion

The major task here is to discuss the evidence of causation between occupational exposure to various types of physical and chemical exposures at work and chronic obstructive pulmonary disease. This discussion needs to transcend the term correlation as stated in the call for application by the Danish Working Environmental Research Fund. Thus, the aim of this discussion is to delineate associations of causal association, even though we recognize that, given the complexities of the epidemiology of occupational COPD, it is impossible to meet this goal unequivocally. Nonetheless, a reasonable assessment of the potentially causal relationship between exposure and disease can be achieved by relying upon accepted criteria for such associations. The most known and most wildly used are the criteria for assessing evidence of causation published by Austin Bradford Hill in 1965 (106). Central criteria for evidence of causation in this schema are the strength, consistency and temporality of associations, together with a description of a plausible mechanism between cause and effect.

Consistency, strengths, and temporality of association

We have included 68 articles all graded 2+ (low risk of confounding/bias/chance). Of these, 59 present data from original cohorts or populations while nine others describe additional findings from these cohorts or populations. The studies originate from Europe, America, Asia, Latin-America and Africa. The exposure variables are multi-dimensional, heterogeneous, and have been described, evaluated, or measured differently. Multiple study designs have been used and the size of the population analysed has varied substantially. The outcomes in the analyses have not been uniform and similar outcomes have been defined differently among the studies. Yet, despite all of the differences in the structures of the studies, there is a pattern of consistency in the association between exposure and outcome.

Among the 25 population-based cross-occupational studies with spirometric data, 22 studies found a significant association between airway obstruction and occupational exposure. In two studies (38,51), the associations did not reach statistical significance and both were ECRHS based. The outcome was mild COPD equivalent to GOLD stage I and the age of the population was 20-45 years at recruitment (maximum follow-up approximately 10 years in one longitudinal analysis), an age span that is not optimal if the purpose of the study is to determine associations between occupational exposure and airway obstruction. In the other negative study, Lindberg et al. found a borderline association to manual work OR 1.78 (95% CI 0.80 – 3.97) and low educational level OR 1.73 (95% CI 0.98 – 3.04) and COPD in the logistic regression analyses findings close to a statistically significant association at the traditional 0.05 cut-off (52).

Among the 15 occupational cohort studies with exposure to inorganic material, 12 studies found a significant association between occupational exposure by at least one measure and airway obstruction. In one study there was an association with mixed pulmonary function impairment among shipyard workers, suggesting exposure to mineral dust quartz and asbestos with the potential to produce restrictive lung function impairment (58). Out of the other two negative studies (57,67), one have analysed for an association between COPD and measurable quartz from silica dust and cement dust (67). Luo et al. found a significant linear trend between restrictive pulmonary function defects and spot welding and a borderline linear trend (p=0.08) between a combination of obstructive and restrictive impairment and welding exposure (57).

Among the 19 occupational cohort studies with exposure to organic material, 17 studies found a significant association between at least one measure of occupational exposure and airway obstruction. For some of the studies the associations were only found for subgroups, e.g. females (86). In one study no association was observed between past exposure to cotton dust and a low FEV_1, however, an increased exposure time in the workplace and working in the waste room was associated with a low FEV_1 in that study (72). The study by Glindmeyer et al. is mostly a negative study. The results though are hard to interpret due to the vigorous stratification on type of factory, particle fraction, components of dust etc. making it difficult to judge the effect of wood dust per se. Even in that study, one of the measures (residual particulate) was indeed associated with COPD (87).

In all the studies described in the Evidence Tables the occupational exposure has occurred before clinical or spirometric signs of respiratory disease have been identified. Studies with odds ratios (OR) are shown in Figures 1-3. For the eight studies analysing for an association between VGDF and COPD, the OR was between 1.08 and 2.13. Five studies with OR have described the association between inorganic exposure and COPD. In one study the OR was <1, while in four the range of OR was 1.70 to 3.80. Likewise, five studies that have focused on organic exposure and COPD have OR data. In one study the OR was <1, while in four the OR range was 1.20 to 8.86. The Figures of the odds ratios suggest a robust association more than a very strong (high point estimate of risk) association.

Figure 1 Forest plot of the association between exposure expressed as VGDF or similar expressions and COPD (I+ and II+) in eight studies with calculated OR and 95% CI.

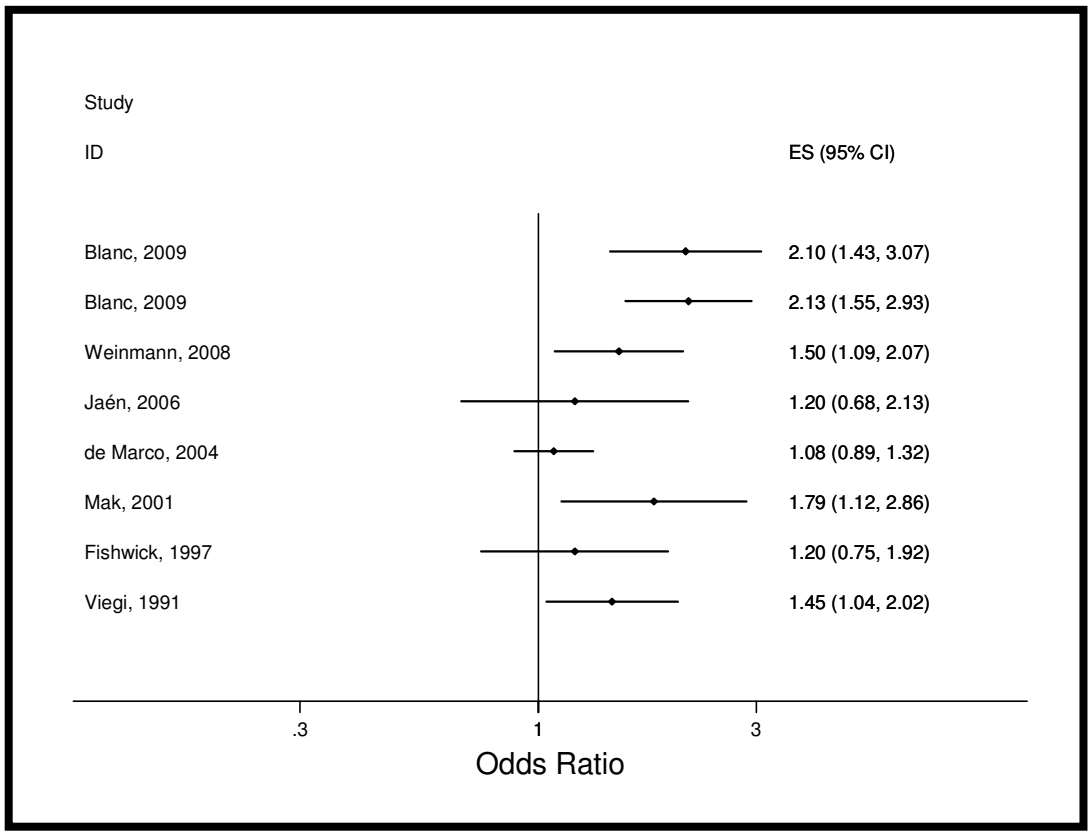


Figure 2 Forest plot of the association between exposures expressed as inorganic dust exposure and COPD (I+ and II+) in studies with calculated OR and 95% CI.

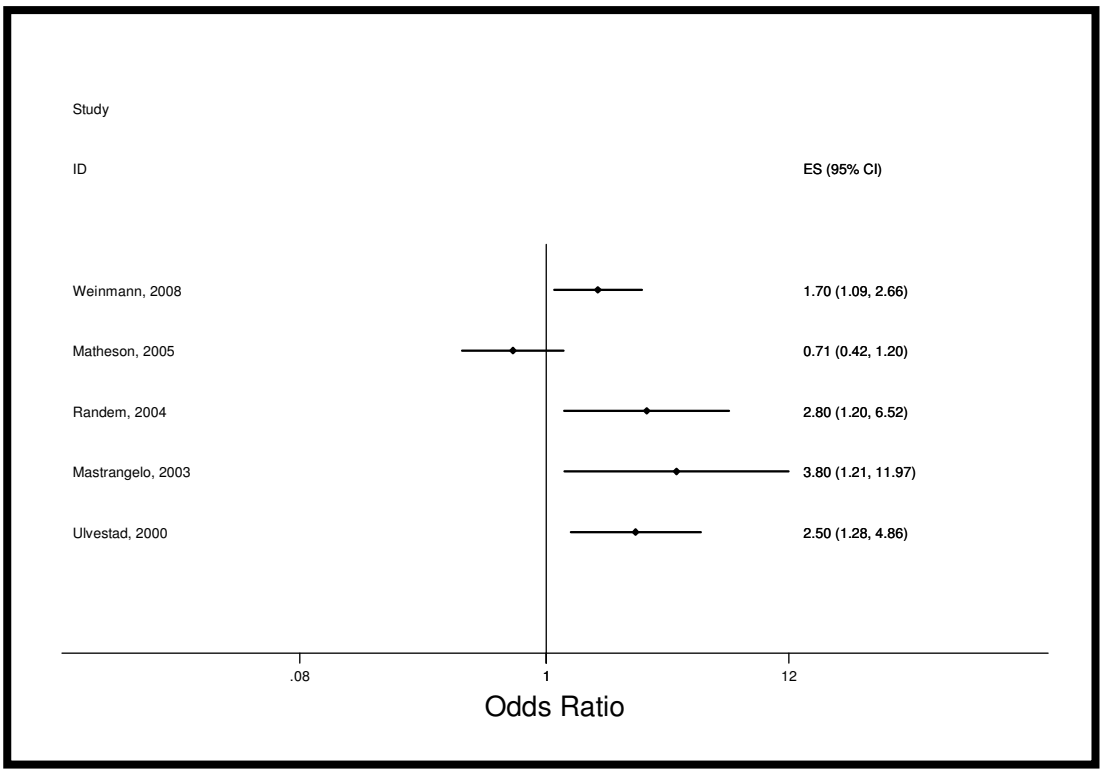
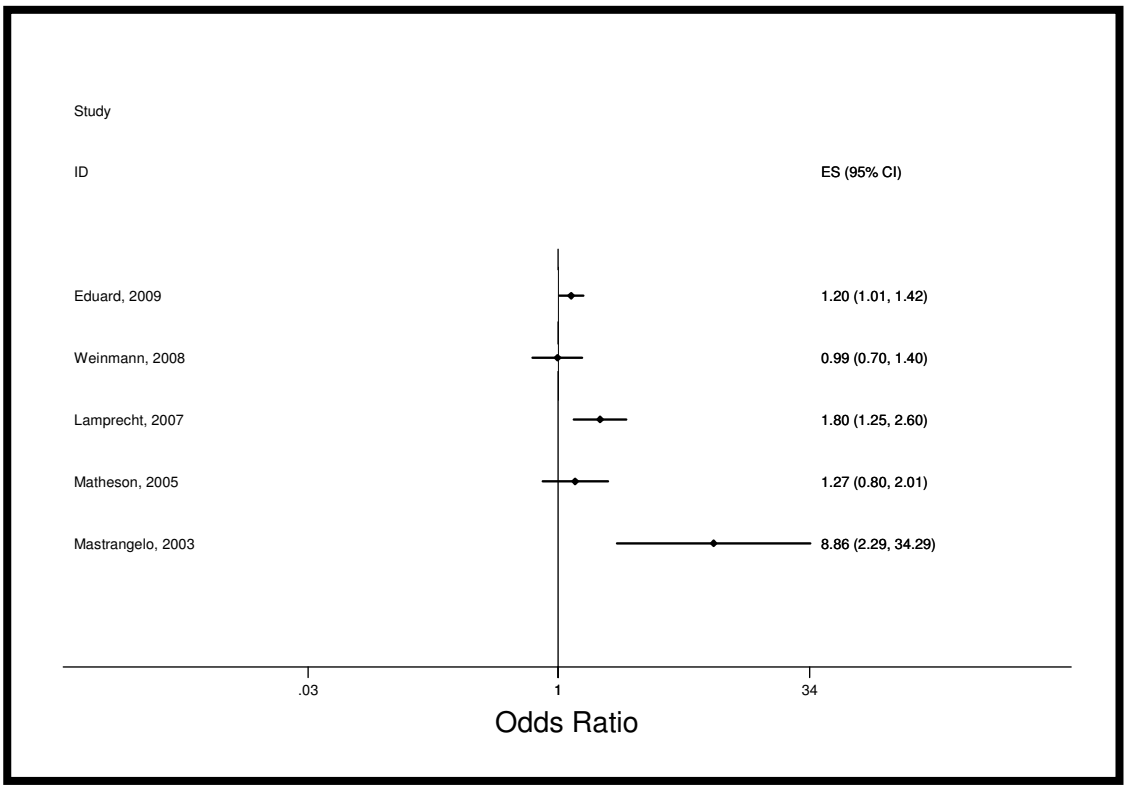


Figure 3 Forest plot of the association between exposures expressed as organic dust exposure and COPD (I+ and II+) in studies with calculated OR and 95% CI.



Biological plausibility and experimental data

COPD is a heterogeneous disease with diverse involvement of both large and small airways and (in relation to emphysema in particular) lung parenchyma. Several pathological pathways are thought to be involved. An abnormal inflammatory response in the lungs to toxic particles and gases inhaled from tobacco smoke, air pollution and occupational exposure is thought to be the central event in the pathogenesis of COPD (107). However, the pathophysiological mechanisms that link the inflammatory response in the lung with accelerated loss in FEV_1 are not satisfactorily explained, and might also involve factors related to genetic factors, to immune regulation, and to mechanisms related to cellular repair and the resolution of inflammation (108).

Smoking is the main risk factor for COPD and has been the exposure most studied. Smoking induces an inflammatory response in the lung in all smokers but only in some will the inflammation intensify and continue despite quitting smoking, suggesting a genetic contribution in the pathogenesis (109). Most of the evidence for smoking being a specific risk factor for COPD is based on longitudinal epidemiological studies demonstrating a dose-response relationship between smoking and decline in lung function. These studies have analysed for the effect of smoking as such and have not assessed the effect of the more than 400 constituents identified in tobacco smoke. The effect of smoking is not fully understood (19) and COPD induced through tobacco smoke exposure

might therefore be a non-specific response to inhaled irritants in subjects with an increased susceptibility. In one sense, cigarette smoke could be considered as mimicking an occupational exposure to a complex mixture of gases and particles. There are published data that show pathological similarities in the COPD "phenotype" associated with tobacco smoke exposure and occupational exposure to particles and gases. Smoking-induced COPD is characterised pathologically by the development of emphysema, chronic bronchitis and small airways disease in varying degrees in different individuals. The effect of occupational exposure is less studied but published data supports an association between emphysema and occupational exposure to cadmium (69) and to a lesser extent to coal (110) and silica (111). Likewise, exposures to cadmium, coal, endotoxin, and silica in animal models have caused emphysema (112). The autosomal-recessively inherited polymorphism of α1-antitrypsin deficiency is a genetic disorder clearly associated with emphysema and COPD. Tobacco smoke is the major cause of a classical gene-environment interaction in this condition leading to COPD in these subjects. However, studies published during the last 10 years have shown an increased risk of chronic cough, lower FEV_1, and lower FEV_1/FVC among subjects with phenotype Pi*Z and occupational exposure, an association independent of tobacco smoke (113,114).

During the last two decades multiple epidemiological studies have been published supporting pathways through which COPD can be caused by exposures other than smoking such as occupational exposure to dust, smoke, vapour, and gases. Data from the NHANES III study in the USA using post bronchodilator spirometry to diagnose COPD (FEV_1/FVC <0.70) have revealed a prevalence of COPD among non-smokers of 6.6%. These data suggest that about 25% of COPD cases in USA were in never-smokers (115) but this result may partly be due to misclassification in older subjects (12). Similar findings have been observed from other parts of the world (24). This further adds to an understanding of the importance of exposures other than smoking in the aetiology of COPD. In summary, both observationally and experimentally, a causal relationship between occupational exposure and COPD is biologically plausible.

Dose-response data from selected industries

A source of evidence for tobacco smoke as a risk factor for COPD comes from several longitudinal epidemiological studies demonstrating a dose-response relationship. Likewise, during the last two decades a substantial number of longitudinal studies focusing on specific occupational exposures and COPD or airways obstruction have found a dose-response relationship. These include cotton textile (75,76), jute processing (78), farming (82), grain and animal feed (83), wood workers (86), welding (60), foundry work (66), coal mining (61,62,116-118), hard rock mining (119,120), tunnel drilling (121), and non-mining industrial dust (55). The uniform findings of a dose-response relationship despite the diversity of exposures add to the evidence that occupational exposure from dust, smoke, vapour, and gas are risk factors for COPD.

Tobacco smoke and occupational exposure: a matter of coherence

In most studies that have assessed the relationship between occupational exposure and obstructive lung disease, the confounding effect of tobacco smoke exposure is handled by strategies of matching, adjusting, controlling or stratifying the data. Few studies present data about the magnitude of the lung function loss arising upon simultaneous exposure to tobacco smoke and occupational exposure to dust, gases and vapour. Table 3 lists studies where the magnitudes of annual loss in FEV_1 attributed to tobacco smoke exposure and to occupational exposure have been separately assessed.

Table 3 Annual loss in FEV_1 by smoking and occupational exposure

Exposure/occupation	**Annual loss in FEV_1 by**	
	Occupational exposure	Smoking
Coal miners in UK (122,123)	4-8 ml	11 ml
Coal miners in USA (117)	7 ml	9 ml
Industrial workers in Paris (55)	8 ml	11 ml
Silica in different countries (124)	4 ml	7 ml
Steel workers in USA (60)	5 ml	9 ml
Metal smoke in Norway (53)	4 ml	7 ml
Wood dust in Denmark, females (86)	4 ml	8 ml

Based on similar findings the ATS review from 2003 (21) evaluated the magnitude of the effect of occupational exposures to be consistent with that of cigarette smoke, suggesting an equivalent effect of occupational exposure to that of moderate tobacco smoke exposure (125). It was not possible to relate the annual fall in lung function to the occupational exposure due to insufficient information about the smoking intensity of exposure from the studies. There is a general assumption that exposure to dust, vapour, gases, and fumes in Danish industry has decreased during the last two decades but few published data confirm a real reduction. Wood dust exposure in the furniture industry has experienced a substantial drop in exposure of 6-8%/yr from 1988 to 2004 (126) whereas measurements of welding fume in 1987 and 2004 in metalworkers did not confirm a reduction in exposure (127).

The association between the risk of COPD and exposures to tobacco smoke and occupational exposure to VGDF have been analysed in studies from USA from the same group in San Francisco (30,31,91). Trupin et al. found that the adjusted OR for COPD increased from 1 among subjects exposed to either smoke or occupational exposure to 2.4 (95% CI 0.9-6.1) in subjects only occupationally exposed, and to 7.0 (95% CI 3.6-13.7) in subjects with only smoke exposure, and to 18.4 (95% CI 9.3-36.4) in subjects smoke and occupational exposed (91). A similar finding from another population was published by Blanc et al, where the adjusted OR for COPD for the

combined exposure was 18.7 (95% CI 11.6-30.0). These data indicate a more than additive effect of simultaneous exposure to tobacco smoke and occupational exposure to VGDF (31). A study of 67 subjects with COPD and 1652 referents found the combined effect of exposure to smoke and VGDF had a smaller OR of 8.5 (95% CI 3.8-18.8) than the studies above, but in this study the referents included both non-smokers and smokers with cumulated exposure <10 pack-years (30). This might explain the lower risk estimate for the combined effect of exposures.

Another study from the USA of 5,335 subjects aged 34 to 67 years was analysed for the effect of occupational exposure from dust and fume exposure among subjects with mild COPD (FEV_1/FVC <0.70, FEV_1 between 55 and 90% of predicted). All were smokers. During the five years follow-up, for each year of occupational exposure to fume was associated with a 0.25% reduction in post bronchodilator FEV_1% predicted (50).

Published data suggest that (i) the contribution to COPD risk of occupational exposure to VGDF is of a magnitude falling within the range of risk associated with common cigarette smoking intensities (e.g. less than heavy smoking but more than very light smoking), (ii) the combined effects of smoke and occupational exposure may be more than additive and (iii) occupational exposure to fume adds to the burden of obstruction in smoking subjects with mild to moderate COPD.

Strengths and limitations

COPD is a disease that develops over a long period of time before it is diagnosed and for which it is not possible clinically to separate occupational COPD from COPD due to smoking or other causes. The disease might exist for many years without clinical symptoms or with minor symptoms that are not recognized as signs of disease, but rather as a consequence of increasing age. The major scientific studies looking at occupational COPD are of an epidemiological nature, with varying study designs. These studies share a common strategy to compare the prevalence or incidence of COPD among subjects exposed and unexposed both in population-based cross-occupational studies and in industry specific studies. There are some inherent underlying methodological problems in this situation. The long latency period increases the risk for incorrect information regarding early exposure: mild cases of COPD will not be recognized due to few or none symptoms and selection of healthy subjects more than subjects with less good health into exposed trades (healthy worker effect) and staying in the job (healthy survivor effect) will introduce bias. These methodological errors will all tend to mask a true association between exposure and disease.

The major advantage of analysing for prevalence or incidence of COPD from industrial exposures in cohort studies is that the estimate of exposure can be of high quality, although misclassification and confounding can not be excluded. In longitudinal studies the error of inter-individual spirometric measurements is substantially reduced since the proband is its own control, thus increasing the chance of a correct measurement of change due to the occupational exposure.

Longitudinal studies are able to predict a decline in lung function more precisely than cross-sectional studies which tend to overestimate the fall (16,128,129).
A great advantage in using population-based cross-occupational studies for analysing the prevalence or incidence of COPD is the avoidance of selection bias. However, the information about exposure may be scanty and might include recall bias. Introducing JEM approaches avoids a possible differential misclassification but introduces a risk for non-differential misclassification with a consequent underestimation of the true effect of exposure.

This document emphasizes standard spirometric criteria for COPD and does not systematically consider chronic bronchitis. Different COPD populations defined on the basis of FEV_1/FVC alone may be heterogeneous with respect to etiological risk factors and clinical progression of disease, including disability risk. Moreover, chronic asthma in adults cannot be differentiated confidently from COPD based on spirometry alone, even with bronchodilator administration. Nonetheless, this heterogeneity is likely to be far greater using a broader definition of COPD that also subsumes chronic bronchitis. At the same time, we also recognize the potential limitations of an over-narrow definition of COPD and do assess, in that context, studies in which COPD is based in whole or in part on a clinical definition of disease (such as report of a physician's diagnosis) or where emphysema has been studied pathologically (130).

The non-uniform definition of COPD in the studies introduces possible misclassifications and limits the comparison of the prevalence/incidence of COPD between the studies. In most of the studies, especially the older studies, there is no information about post bronchodilator spirometry for subjects with FEV_1/FVC ratio <0.7. In these studies subjects with asthma might wrongly be diagnosed as patients with COPD introducing a misclassification. As stated previously (12) the GOLD criterion using a fixed FEV_1/FVC of <0.70 will overestimate obstruction in older or male subjects, while among the young or female subjects GOLD criteria will tend to underestimate the true prevalence because FEV_1 /FVC falls with aging (131,132). Defining COPD solely on the criterion of FEV_1/FVC <0.7 is no longer accepted in the European Respiratory Journal (12).
The misclassification will mostly influence the estimate of the proportion of ill subjects rather than skew the association between disease and exposure. The inhomogeneous definition of COPD does not seem to differentiate the relation to exposure supporting a rather robust effect of the exposure to the outcome.

Of all the selected studies designed to include quantitative exposure measurements only nine have addressed COPD or FEV_1/FVC <0.70 as outcome. Of these, one study examined coke oven workers exposure (63), one study analysed tunnel workers exposure (68), two focused on wood workers exposure (85,86), one measured grain dust (84), two looked at farming exposure (79,81), one described organic dust exposure (35), and one study estimated risk of COPD between different occupations (36). Associations between exposure or occupation and COPD only described in a

single study is obviously insufficient to argue for any quantitative boundaries in the length of duration or intensity of exposure necessary to increase the risk of COPD (35,36,63,68,84).

Two studies (85,86) have assessed for an association between wood dust exposure and COPD or FEV_1/FVC <0.70. The data are too diverse and sparse to define any lower limit of exposure associated with increased risk of COPD.

The data describing farming exposure (79,81) does not have the quality, uniformity, and strength to speculate in exposure characteristics more precise associated with risk of COPD.

Based on a detailed analysis of the present studies we have to conclude that there are insufficient exposure data for an in depth evaluation of a detailed estimate of any increased risk in relation to the nature, severity/scope and duration of the exposures.

The quality of the selected articles has been systematically evaluated by the working group and those selected have all been evaluated as studies with low risk of confounding/bias/chance. This procedure does not totally exclude the chance of misleading data but the chance of this will be low.

Conclusion

The articles included were evaluated in detail using the ERS proposed extraction sheet with information of study design and population, measurement of exposure, level of exposure, duration of exposure, quality of the exposure description, quality of the outcome, limitation (confounding/bias), quality of results, key findings, grading of the study (2++ very low risk of confounding/bias/chance, 2+ low risk of confounding/bias/chance, 2 – high risk of confounding/bias/chance). In all 68 articles were included of which 59 articles were original cohorts or populations and nine papers described additional findings from a previous selected cohort or population. All articles were graded with a quality of 2+ or 2++. Using the criteria described by the Danish Working Environmental Research Fund for an association (exposure – disease) and in accordance with the evaluation the working group concluded that there is a strong evidence (+++) for a causal association between various types of physical and chemical exposures at work and chronic obstructive pulmonary disease (COPD).

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Appendix

A. Abbreviations

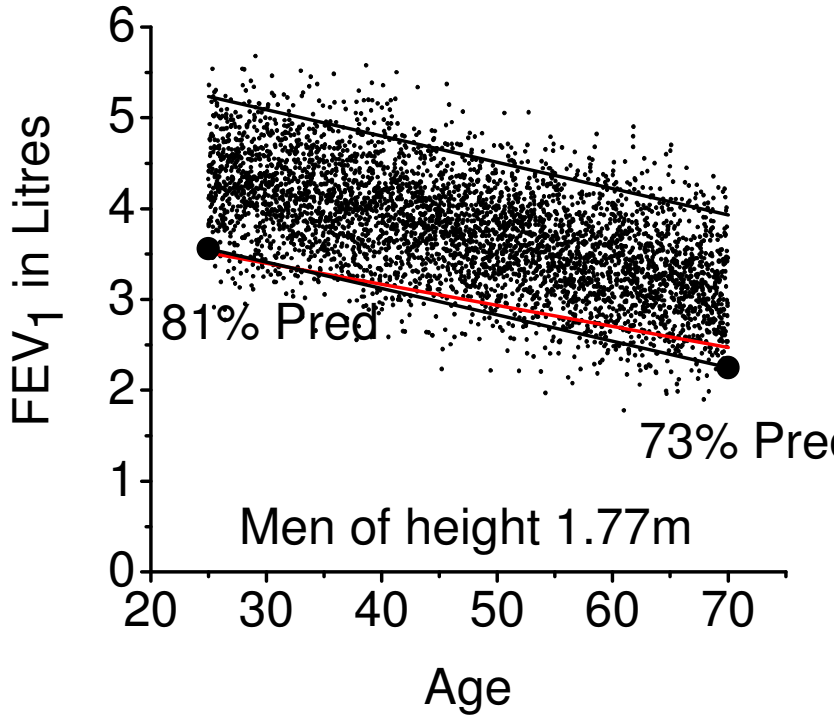
ALOHA (JEM)	Modified version of the ad hoc JEM
AOD	Airway Obstructive Disease
ATS	American Thoracic Society
BHR	Bronchial Hyper Reactivity
BMI	Body mass index
BMRC	British Medical Research Council
BOLD	Burden of Obstructive Lung Disease
BTS	British Thoracic Society
CI	Confidence Interval
CNSLD	Chronic Non-Specific Lung Disease
COPD	Chronic Obstructive Pulmonary Disease
DALY	Disability-Adjusted Life Year.
ECCS	European Conference on Complex Systems
ECRHS	European Community Respiratory Health Survey
ERS	European Respiratory Society
ETS	Environmental tobacco smoke
FEV_1	Forced expiratory volume in one second
FRC	Functional Residual Capacity
FVC	Forced vital capacity
GM	Geometric mean
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HR	Hazard Ratio
JEM	Job Exposure Matrix
LLN	Lower limit of normal
(M)MRC	(Modified) Medical Research Council
MSHA	Mine Safety and Health Administration
NHANES	National Health and Nutrition Examination Survey
OEL	Occupational exposure limit
OR	Odds Ratio
PAF	Population attributable fraction
PAR	Population attributable risk
PEF	Peak expiratory flow
PLATINO	The Latin American Project for the Investigation of Obstructive Lung Disease
PP	Percent of predicted
PR	Prevalence Ratio
RR	Relative Risk
RSD	Residual standard deviation
RV	Residual Volume
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SR	Standard residuals
TCDD	2,3,7,8-Tetrachlorodibenzo-p-dioxin
TLCO	Transfer factor for carbon monoxide
TLC	Total lung capacity
TWA	Time-Weighted-Average
VC	Vital Capacity
VGDF	Vapour, Gases, Dust and Fume

B. How best to express abnormal spirometry

Since the early 1960s lung function tests have tended to use the method of percent of predicted (PP) to express deviation from predicted. This practice makes the assumption that the effect of disease progression on lung function is proportional to the predicted value. The latter value being obtained from prediction equations usually based on data from healthy subjects who have no symptoms or disease and who have not been smokers. For FEV_1 and FVC the predicted values are based on the subject's sex, age and height. It has been estimated that if all the known factors influencing lung function are taken into account then about 30% of the total variance is still unaccounted for which will relate to genetic and other factors (133).

A predicted value has quite wide confidence limits. For men the range of the 90% confidence limits for values predicted by ECCS equations (2) span 1.68 L and for women this is 1.25 L. Thus a man born with a low growth trajectory for his lungs may have normal lung function for him that is only 70% of his predicted value. This range of scatter around the mean predicted value is in absolute terms the same for subjects with small predicted values and those with large predicted values. This means the LLN for someone with a larger FEV_1 is at a higher percent of the predicted value than that for someone with a lower predicted FEV_1 value as shown in Figure 4. The percent of predicted value can therefore be misleading when estimating whether a lung function index is normal or not.

Figure 4 Scatter plot of random data for FEV_1 for men all of height 1.77m with the upper and lower 90% confidence limits shown as black lines and the line corresponding to 80% of predicted mean value shown in red. The lower limit of normal for a man aged 25 and 70 are shown as ● symbols with their values in percent of predicted.



In the past a 'rule-of-thumb' of 80% of predicted being the cut off value to define abnormality has been applied. This is approximately true for some people for FEV_1 but is not true for all subjects or for other indices. The best means for presenting the subject's results are as standardised residuals (SR): where FEV_1SR = (Recorded FEV_1 - Predicted FEV_1)/ RSD (133). The RSD is the residual standard deviation for the regression equation used (also known as standard error of the estimate). All indices are now presented in the same units and the LLN is at minus 1.645 for the usual 5 percentile limit. Table 4 shows the lower limit of normal values for several lung function indices for a given subject with values expressed as absolute values as percent of predicted and as SR. It can be seen that the percent of predicted values corresponding to the LLN cover a wide range from 69% to 85% according to the index.

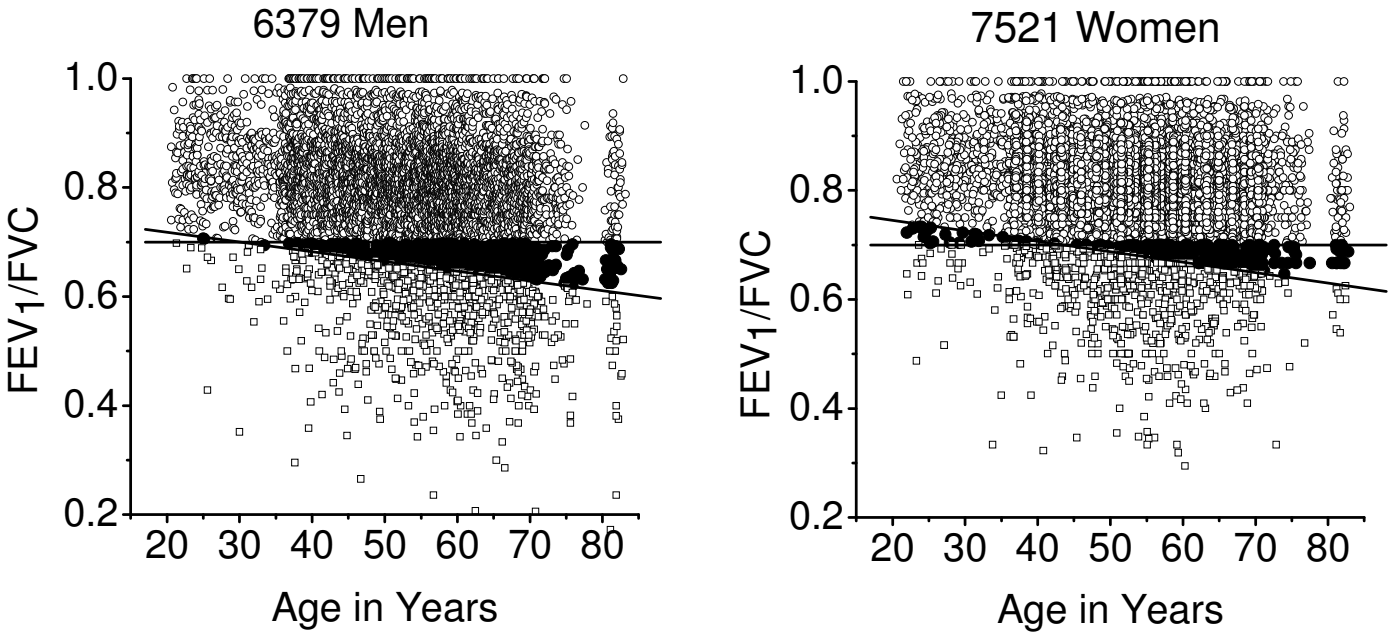
Table 4 The lower limits of normal (LLN) for various lung function indices for a man aged 50 year and of height 1.75m expressed as absolute values, as percent of predicted and as standardised residuals.

	Absolute	%Predicted	SR
FEV_1 L	2.746	76.6	-1.645
FVC L	3.426	77.3	-1.645
FEV_1/FVC	0.66	84.9	-1.645
PEF L/s	6.769	77.3	-1.645
FRC L	2.468	71.4	-1.645
RV L	1.488	68.8	-1.645
TLC L	5.751	83.3	-1.645
RV/TLC	0.24	73.2	-1.645
Tlco mmol/min/kPa	7.793	77.1	-1.645

It is not possible for anyone to memorise or know what the lower limit of normal is going to be for each index and for every individual since the range of values varies with the age, sex and height of the subject. Patterns of lung function abnormality can easily be identified from SR values but not from PP values. An alternative suggestion has been made with regard to the LLN for FEV_1/FVC that this should be set at a constant value of 0.7 for all subjects in order to try to make things easier (11,134). However, for FEV_1/FVC it has been shown that in over 50 datasets of normal lung function the FEV_1/FVC values diminish with age (135) and so the LLN will also be lower in the elderly compared with younger subjects. Thus using a constant LLN of 0.7 for FEV_1/FVC means that some younger subjects, especially women, who truly have airflow obstruction (value below the true LLN) will be missed by the 0.7 threshold and so this single value limit will not identify true disease in these subjects. Conversely, in older subjects many will be called abnormal by the constant 0.7 value when in fact their values are above the conventional LLN from population studies. This is shown in Figure 5 where subjects plotted between the two lines are either false negatives if they are to the left of the cross over point or false positives if they are to the right. The cross over point is at an older age in women so that these errors in diagnosing true airflow obstruction are dependent on age and sex. Several publications have now shown this to be true

(131,136) and it has recently been suggested that using a constant 0.7 lower limit to determine the presence of airflow obstruction might not be compatible with good clinical practice because of this clinical prejudice based on age and sex (12).

Figure 5 Plot of lung function data for FEV_1/FVC for men on the left and women on the right from a large population survey. A horizontal line shows the cut off for 0.70 and a diagonal line shows the lower limit of normal from the ECCS equations (2). Subjects as open circles are normal by both criteria and as open squares are abnormal by both criteria. Data as ● are either false negatives if they are to the left of the cross over of the two lines or false positives if they are to the right of the cross over point.



Thus the recommendation from the ERS and ATS for assessing lung function abnormalities is to use the method of standardised residuals and lower limits of normal should be defined using this method so that values of -1.645 and +1.645 are at the lower and upper confidence limits (13). These limits are used when dealing with patient data since the a priori probability of the result being abnormal is high. If a study is being undertaken on a normal population, for example in a screening program of asymptomatic people, then the 95% confidence limits of -1.96 and +1.96 might be more appropriate to use to minimise the number of false positive results obtained. This latter strategy could be suggested for studies in occupational settings since the subjects are mostly normal with a low a priori probability of having abnormal lung function. Longitudinal data are preferred so one can identify individuals with unacceptably large declines in function irrespective of where their values are with regard to normal ranges.

C. COPD data extraction sheet

As an analytic tool for evaluation of the articles, the working group used a modified data extraction sheet from The European Respiratory Society (ERS):

ERS Task Force: **Management of work-related COPD** **Proposal for data extraction sheet**

Key question: _____
Bibliographic citation
First author: _____
Title:_____
Journal year; number:pages:_____

Study design:
□ metaanalysis □ systematic review
□ cohort study □ case-control study □ cross sectional study
□ survey □ longitudinal follow-up of cases
□ descriptive study of disease register (reporting/surveillance scheme) /occupational statistics
□ case series □ case report
□ economic analysis □ Other, specify:_____

Selection of **study population**/patients:
□ convenience sample □ consecutive sample □ random selection
□ not reported □ Other, specify:_____

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

Comparison group: □ yes □ no □ not applicable □ do not know
characteristics (age, sex, country,…): _____

Response rate: _____% □ not reported
Sample size: n = _____
of which number with occupational COPD: n=_____(_____%)

Measurement of **exposure**
□ industry □ occupation □ task □ self-reported agents
□ group measurement in the workplace
□ individual measurement in the workplace
□ other, specify: _____

level of exposure: □ specified: unit (e.g. mg/m^3, ppb): _____
minimum: _____maximum: _____
mean/median: _____
□ not specified □ low □ moderate □ high □ various

duration of exposure: _____

Is the exposure adequately described? □ yes □ yes, partly, □ no, □ no mention, □ not applicable, □ do not know

Measurement of **outcome** (e.g. occupational COPD/work-related COPD)
□ questionnaire
□ symptoms, quality of life, frequency of exacerbations
□ lung function measurements
□ BHR
□ other, specify:_____

Is the outcome adequately described? □ yes □ yes, partly
□ no □ no mention
□ not applicable □ do not know

Was the measurement of the outcome sound? □ yes □ yes, partly
□ no □ no mention
□ not applicable □ do not know

Limitations:
Data probably **confounded**? □ yes □ yes partly
by □ smoking □ other,specify:_____
□ no □ not applicable □ do not know

Data probably **biased**? □ yes □ yes partly
□ misclassification of exposure
□ misclassification of disease
□ selection of study population
□ other, specify:_____
□ no □ not applicable □ do not know

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:_____

Grading of the study (revised SIGN criteria)
Meta analysis or systematic reviews of RCTs / RCT with risk of bias
□ 1++ High quality/ very low risk □ 1+ Well conducted/low risk □ 1- /high risk
Case-control or cohort studies with risk of confounding, bias, or chance / review
□ 2++ very low risk / high quality systematic reviews of case-control or cohort studies
□ 2+ low risk □ 2- high risk
□ 3 Non-analytic studies □ 4 Expert opinion

D. Evidence model

The working group used the evidence model recommended by the Danish Working Environment Authority (29):

Degree of evidence of a causal association between an exposure to a specific risk factor and a specific outcome.

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.

E. Evidence Table 1: Population-based studies

Exposure	Study design	Population	Outcome	Measure of association	Reference
• **Cross-sectional studies**					
Vapours, gas, dust, or fumes. Questionnaire or JEM defined.	Case-control study.	n=1,843/1,719 (1,709/1,652 referents). Age 55-75 yrs.	COPD diagnosed: by a physician, excl. chronic bronchitis or GOLD II+	**Physician** (n=1,843) Self-reported; Significant OR 2.1 (95% CI 1.4-3.0) and PAF of 25%. JEM; Non significant. **GOLD II+** (n=1,719) Smoking (non-sm/smoke) exposure (yes/no): Non-sm/yes; Non significant. Smoke/no; Significant OR 4.9 (95% CI 2.3-10.4). Smoke/yes; Significant OR 8.5 (95% CI 3.8-18.8).	P.D. Blanc 2009 (30)
Dusty/dirty jobs. Questionnaire or JEM defined.	Ecological analysis.	n=19,094 (referents; range 15-93%). Age at follow-up ≥40 yrs.	COPD: GOLD II+	Significantly increased prevalence per 10% increase in exposure; 0.8 (95% CI 0.3-1.3) p=0.003.	P.D. Blanc 2009 (32)
Vapours, gas, dust or fumes. Questionnaire or JEM defined.	Case-control study.	n=1,044 (302 referents). Age 40-65 yrs.	COPD: GOLD II+	Self-reported; Significant OR 2.13 (95% CI 1.55-2.93) and PAF of 31%. JEM high; Significant OR 2.33 (95% CI 1.45-3.72) and PAF of 14%.	P.D. Blanc 2009 (31)

Exposure	Study design	Population	Outcome	Measure of association	Reference
Mineral dusts, metal dust and fumes, organic dusts, irritant gases or vapours, sensitizers, organic solvents, diesel exhaust, and ETS. Expert defined JEM.	Case-control study.	n=744 (356 referents). Age ≥ 45 yrs.	COPD diagnose and FEV_1/FVC <LLN or COPD based on an algorithm developed for the study based on ICD9 MD diagnosis and medications.	Overall (except ETS); Significant OR 1.5 (95% CI 1.1-2.1) and PAR of 24%. Mineral dust; Significant OR 1.7 (95% CI 1.1-2.7) and PAR of 9% Irritant gases and vapours; Significant OR 1.6 (95% CI 1.2-2.2) and PAR of 21% Diesel exhaust; Significant OR 1.9 (95% CI 1.3-3.0) and PAR of 12%	S. Weinmann 2008 (33)
Dust, fumes or gases. Questionnaire defined.	Cross-sectional study.	n=576 (159 referents) Age 20-70 yrs.	FEV_1/FVC%	Significant reduced in exposed ≥15 yrs. compared with non-exposed -1.7% (95% CI -3.3 - -0.2)	Á. Jaén 2006 (34)
Biological dust, mineral dust, gases and fumes. Questionnaire defined.	Two phased cross-sectional study.	n=1,213 (550-814 referents). Age 45-70 yrs.	FEV_1/FVC <0.70 ± symptoms.	Biological dust; Significant OR 3.19 (95% CI 1.27 – 7.97) Mineral dust; Non significant OR Gases and fumes; Significant OR 2.81 (95% CI 1.01 – 7.77) Generally higher risk in females than males.	M.C. Matheson 2005 (35)
17 occupation categories and 17 industry categories. Questionnaire defined.	Cross-sectional study.	n=9,120 (2,175 referents). Age 30-75 yrs.	FEV_1/FVC <0.75 and FEV_1 <0.8	Caucasians; PAF of 21.0% African-Americans; PAF of 23% Mexican-Americans; PAF of 54.4%	E. Hnizdo 2004 (37)
Vapours, gas, dust, or fumes. Questionnaire defined.	Cross-sectional study.	n=14,855 (approx. 8,393 referents). Age 20-44 yrs.	COPD: GOLD I+	Non significant.	R. de Marco 2004 (38)

Exposure	Study design	Population	Outcome	Measure of association	Reference
16 occupation categories. Record defined.	Case-control study.	n=429 (72 referents). Age ≥45 yrs.	FEV_1 <0.8	Biological dust; Significant OR 8.86 (95% CI 2.29-34.3) Gas/vapour/fume; Significant OR 5.83 (95% CI 1.82-18.6) Mineral dust; Significant OR 3.80 (95% CI 1.21-12.0)	G. Mastrangelo 2003 (39)
14 occupation categories and 16 industry categories. Questionnaire defined.	Cross-sectional study.	n=9,495 (2,277 referents). Age 30-75 yrs.	COPD: GOLD II+	Work by occupation in all ethnic groups: Armed forces; Significant OR 2.0 (95% CI 1.1-3.6) Freight/stock/material handlers; Significant OR 2.2 (95% CI 1.3-3.7) Overall PAF 15.1% and among never smokers 25.6%	E. Hnizdo 2002 (36)
Gases, dusts, or fumes. Questionnaire defined.	Case-control study.	n=517 (450 referents). Median age 57 yrs.	COPD: GOLD II+	Significant OR 1.79 (95% CI 1.12-2.85) and PAR of 29.6%.	G.K. Mak 2001 (40)
Fumes, gases, vapour, or dust. Questionnaire defined.	Cross-sectional study.	n=1,132 (774 referents). Age 22-44 yrs.	FEV_1/FVC ≤0.75 + symptoms	Ever exposed to VGDF significant OR 3.13 (95% CI 1.07 – 9.12)	D. Fishwick 1997 (41)
Dust. Questionnaire defined.	Cross-sectional study.	n=1,191 (300 referents). Age 64-97 yrs.	COPD: FEV_1/FVC ≤0.65 or clinical findings.	Dust exposure and lower social class; Significant OR 2.3 (95% CI 1.1-4.8) and PAR of 19.6% Other combinations; Non significant.	R. Isoaho 1994 (42,43)
Dusts and gases/fumes. Questionnaire defined.	Cross-sectional study.	n=1,094 (530 referents). Age 40-69 yrs.	FEV_1	Dust exposure; Significant deficit in FEV_1, p<0.05	X. Xu 1992 (44)

Exposure	Study design	Population	Outcome	Measure of association	Reference
Asbestos, quartz, wood dust, metal gases (chromium, nickel, platinum), aluminium production and processing, welding, and soldering. Questionnaire defined.	Two phased cross-sectional study.	n=706 (431/497 referents). Age 18-73 yrs.	COPD: GOLD II+	Overall non significant. Persons >50 yrs; Exposed to asbestos; significant OR 2.8 (95% CI 1.1-7.3) Exposed to quartz; significant OR 3.7 (95% CI 1.2-11.0).	P.S. Bakke 1991 (45)
Dusts, chemicals and/or fumes, and not specified exposures. Questionnaire defined.	Cross-sectional study.	n=1,635 (1,218 referents). Age 18-64 yrs.	COLD: emphysema and/or chronic bronchitis or Spirometry: FEV_1/FVC <0.7 or FEV_1 <0.7	COLD: Males, overall; Significant OR 2.31 (95% CI 1.10-4.86). Spirometry: Males, overall; Significant OR 1.45 (95% CI 1.03-2.05).	G. Viegi 1991 (46)
Dusts and gases or fumes. Questionnaire defined.	Two phased cross-sectional study.	n=8,515 (4717 referents). Age 25-74 yrs.	FEV_1/FVC <0.6	Dust; Significant OR 1.68 (95% CI 1.18-2.40). Dust, males; Significant OR 1.62 (95% CI 1.17-2.23). Dust, females; Non Significant. Fumes; Non Significant. Dust and fumes; Significant OR 1.57 (95% CI 1.10-2.24).	R.J. Korn 1987 (47)
Occupational exposure or working in high-risk industry. Questionnaire defined.	Cross-sectional study.	n=1,195 (518 referents). Age ≥18 yrs.	Airways obstructive disease (AOD) grade 2: Physician-confirmed AOD or FEV_1/FVC <0.8 or FEV_1 <0.75.	Significantly increased prevalence in exposed compared with referents 38.6% compared with 32.8%, p<0.01.	M.D. Lebowitz 1977 (48)

Exposure	Study design	Population	Outcome	Measure of association	Reference
• **Longitudinal studies**					
Welder smoke, gases or chemical irritants. Questionnaire defined.	Longitudinal study; 10 yrs.	n=2,017 (937 referents). Age 18-58 yrs.	COPD: GOLD II+	Occupational exposure; Significant OR 2.62 (95% CI 2.02-3.41) Smoking; Significant OR 1.75 (95% CI 1.27-2.41) Interaction smoking-occupational exposure; Significant OR 2.51 (95% CI 1.97-3.20)	B. Boggia 2008 (49)
Fume and dust. Questionnaire defined.	Longitudinal study; 5 yrs.	n=5,335 (3846 referents). Age at baseline 34-67 yrs.	FEV_1	Fume exposure in men compared with referents: Significantly associated with 0.25% reduction per yr of post bronchodilator FEV_1.	P. Harber 2007 (50)
Biological dust, mineral dust, gas and fumes. Questionnaire defined.	Longitudinal study; mean 8.9 yrs.	n=6,481(approx. 2,823 referents). Age 20-45 yrs.	FEV_1/FVC <0.7	No significant difference in RR.	J. Sunyer 2005 (51)
Occupation based on 7 groups. Questionnaire defined.	Longitudinal study; 10 yrs.	n=1,109 (183 referents). Age at baseline 36-67 yrs.	COPD: FEV_1/VC <0.70 and FEV_1 <0.8 or FEV_1/FVC <0.70	Non significant but borderline results: Manual workers; OR 1.78 (95% CI 0.80 – 3.97) Low educational level; OR 1.73 (95% CI 0.98 – 3.04)	A. Lindberg 2005 (52)
Asbestos, quartz, ammonia, chlorine, nitrous gas, ozone, sulphur dioxide, aldehydes, anhydrides, diisocyanates, and metals (chromium, nickel, and platinum). Questionnaire defined.	Longitudinal study; 20-25 yrs.	n=911(518 referents). Age at baseline 22-54 yrs.	FEV_1/FVC <0.65	Only significant in high asbestos exposure compared with referents, p<0.05.	S. Humerfelt 1993 (53)

Exposure	Study design	Population	Outcome	Measure of association	Reference
Dusts, variable temperature, high humidity, or chemicals. Questionnaire defined.	Longitudinal study; 13 yrs.	n=1,769 (1481-1670 referents). Age at baseline 19-70 yrs.	COPD: FEV_1 <0.65 or FEV_1 decline.	Decline in FEV_1: Males exposed to dust; Significant decline in FEV_1 -6.1 ml/yr compared with referents, p<0.05. Males exposed to chemicals; Significant decline in FEV_1 -6.0 ml/yr compared with referents, p<0.05. Females exposed to variable temperature; Significant decline in FEV_1 -6.1 ml/yr compared with referents, p<0.05. COPD: Non significant	M. Krzyzanowski 1986 (54)
Dust, gases and heat. Questionnaire defined.	Longitudinal study; 12 yrs	n=556 (177 referents). Age at baseline 30-54 yrs.	FEV_1 slope (ml/yr)	Overall significant for at least one occupational hazard compared with referents, p≤0.01. Dust; Significant dose-response relation, p≤0.01.	F. Kauffmann 1982 (55)

F. Evidence Table 2: Inorganic exposures and occupational cohort studies

Exposure	Study design	Population	Outcome	Measure of association	Reference
• **Welding**					
Spot and arc welders. Air sampling	Cross-sectional study.	n=247 (130 referents). Age 22-56 yrs.	FEV_1/FVC <0.75	Non significant. Borderline linear trend (p=0.08) to FEV_1 decline and spot welding.	J.J. Lou 2006 (57)
13 job categories in shipyard workers. Questionnaire defined.	Cross-sectional study.	n=657 (174 referents). Mean age 45.7 yrs.	Obstructive pulmonary function: Normal FVC and low FEV_1/FVC Mixed pulmonary function impairment: Low FVC and low FEV_1/FVC	Obstructive pulmonary function: No significant association with job title. Mixed pulmonary function: No significant association with job title. Significant OR 2.52 (95% CI 1.15-5.53) for >20 yrs exp. compared with <20 yrs exp. for mixed impairment.	V. Gennaro 1993 (58)
Dust and fumes of stainless steel welding. Defined by work place.	Cross-sectional study.	n=186 (80 referents). Mean age exposed 38.5 yrs referents 36.9 yrs.	FEV_1/FVC ratio	Significant lower FEV_1/FVC ratio; Smokers: 79.2% compared with referents 84.4%, p<0.05. Non-smokers: 80.4% compared with referents 92.8%, p<0.01.	A. Bogadi-Šare 1990 (59)
Dust exposure in steelworkers. Record (steel corporation) defined.	Longitudinal study; 4-9 yrs.	n=475 (internal referents). Age at baseline 20-61 yrs.	FEV_1/FVC ratio	Significant change in FEV_1/FVC ratio of -0.03%/yr, p=0.02.	M. Wang 1996 (60)
• **Coal**					
Coal mine dust. Questionnaire defined.	Longitudinal study; → 16 yrs.	n=977 (internal referents). Mean age at follow-up 39.9 yrs.	FEV_1/FVC ratio	FEV_1/FVC ratio change in significant association to mean exposure, p=0.02.	N.S. Seixas 1993 (61)

Exposure	Study design	Population	Outcome	Measure of association	Reference
Coal miners. Personal respirable dust samples. Cumulative exposure, mg/m^3-yr: low exp <11; moderate exp 11 – 20; high exp >20	Longitudinal study; 15-18 yrs.	n=1,185 (internal referents with the lowest cumulative exposure). Mean age 40 yrs.	FEV_1/FVC <0.8	Per increment of 1 mg/m^3-yr: OR 1.05 (95% CI 1.01-1.09) 20 mg/m^3-yr: OR 2.5	N.S. Seixas 1992 (62)
• **Coke**					
Coke oven workers. Personal air sampling BSF (benzene soluble fraction). Cumulative exposure, µg/m^3- yrs: low exp. <630, moderate exp.630-1,713, high exp. ≥1,714	Cross-sectional study.	n=923 (211 referents). Mean age exposed 34.6 - 37.9 yrs referents 35.7 yrs.	COPD: GOLD II	Moderate exposure: Significant OR 4.00 (95% CI 1.80-8.89) High exposure: Significant OR 8.22 (95% CI 3.76-17.97)	Y. Hu 2006 (63)
• **Asphalt**					
Asphalt worker. Exposure monitoring study.	Cross-sectional study.	n=259 (195 referents) Mean age exposed 37 yrs referents 40 yrs.	COPD: FEV_1/FVC <0.7	Significant OR 2.8 (95% CI 1.2-6.5).	B.G. Randem 2004 (64)
• **Silica**					
Dust and silica. Personal air sampling (range of dust and silica 0.08-2.67 mg/m^3 and 0.0003-0.186 mg/m^3, respectively).	Cross-sectional study.	n=254 (110 referents). Mean age exposed 35.9 yrs referents 35.5 yrs.	FEV_1/FVC ratio COPD: FEV_1/FVC ≤LLN	Significant lower FEV_1/FVC ratio in exposed compared with referents, p=0.02 No significant association between exp. and COPD.	E. Meijer 2001 (65)
Silica exposure in foundry workers. Questionnaire defined.	Longitudinal study; → 13 yrs.	n=815 (internal referents). Mean age 58.7 yrs.	Abnormal FEV_1/FVC ratio; - <0.70 if age <60 yrs. - <0.65 if age ≥60 yrs.	Significant relationship with increasing cumulative silica exposure, p=0.03. - No association in nonsmokers - Significant trend in smokers p=0.01.	V.S. Hertzberg 2002 (66)

Exposure	Study design	Population	Outcome	Measure of association	Reference
• **Cement**					
Cement dust. Personal sampling (range total dust 0.4-53.7 mg/m^3, respirable dust 0.0-2.3 mg/m^3, α-quartz ≤0.06 mg/m^3).	Cross-sectional study.	n=169 (50 referents). Mean age exposed 69.3 yrs referents 66.8 yrs.	COPD: GOLD II+.	No significant association between exp. and COPD.	A.K.M. Fell 2003 (67)
• **Tunnel work**					
Tunnel workers. Personal samplings: - Total dust 3.6 mg/m^3 (GM) - Respirable dust 1.2 mg/m^3 (GM) - α-quartz 0.034 mg/m^3 (GM) - Oil mist 0.5 mg/m^3 (GM) - NO_2 0.5 ppm (peak value).	Cross-sectional study.	n=417 (205 referents). Mean age exposed 41 yrs referents 40 yrs.	FEV_1/FVC <0.7.	Significant OR 2.50 (95% CI 1.31-4.96). Significant association between FEV_1/FVC <0.7 and workers employed 10-20 yrs compared with workers employed <10 yrs OR 2.56 (95% CI 1.13-6.32).	B. Ulvestad 2000 (68)
• **Cadmium**					
Cadmium workers. Static and personal sampling (range 34-600 µg/m^3). Cumulative exposure, µg/m^3-yrs: low exp. <400 moderate exp. 401-1,600 high exp. ≥1,600	Cross-sectional study.	n=189 (92 referents).	FEV_1/FVC ratio	Significant lower FEV_1/FVC ratio compared with referents, p<0.001. Significantly associated with 'year started exposure' (pre-1951, 1951-1970, post-1970) -0.29%/(µg/m^3)/yr; p<0.001. Not significantly associated with cumulative exposure.	A.G. Davison 1988 (69)

Exposure	Study design	Population	Outcome	Measure of association	Reference
• **Glass bangle**					
Glass bangle workers Personal dust sampling and air sampling.	Cross-sectional study.	n=347 (127 referents). Mean age exposed 30.9 yrs referents 30.6 yrs.	FEV_1/FVC ratio	Significant lower FEV_1/FVC ratio 78% compared with referents 81%, p<0.001.	S.K. Rastogi 1991 (70)
• **Bleach**					
Bleach workers. Questionnaire defined.	Longitudinal study; mean 3.4 yrs.	n=232 (54 referents). Mean age 43.7 yrs.	FEV_1/FVC <LLN	Significant prevalence ratio in: Pre-baseline ozone gassings; PR 4.3 (95% CI 1.2-15.7). Pre-baseline and interval ozone gassings; PR 5.5 (95% CI 1.1-28.0).	A.J. Mehta 2005 (71)

G. Evidence Table 3: Organic exposures and occupational cohort studies

Exposure	Study design	Population	Outcome	Measure of association	Reference
• **Cotton**					
Cotton spinning mill workers. Static air samplings of dust (range; 0.04-3.23 mg/m^3). Personal air samplings of dust (range; 0.14-24.95 mg/m^3).	Cross-sectional study.	n=1043 (<430 internal referents). Mean age; exposed 33-44 yrs referents 31-37 yrs.	FEV_1	No significant relation to FEV_1 deficit.	D. Fishwick 1996 (72)
Ex-cotton textile workers. Questionnaire defined.	Cross-sectional study.	n=886 (431 referents). Age 45-74 yrs.	FEV_1	Men: Non significant. Women: Significant deficit in FEV_1 compared with referents, $p<0.05$.	P.C. Elwood 1986 (73)
Cotton textile workers. Mean (SD) dust exposure 19.3 (13.3) mg/m^3/yr.	Longitudinal study; 20 yrs.	n=825 (417 referents). Mean age at baseline; exposed 37.1 yrs referents 36.1 yrs.	FEV_1	15 yrs follow-up: Significant decline in FEV_1 -9.7 ml/yr (95% CI -16.77- -2.63) compared with referents. 20 yrs follow-up: Non significant.	X. Wang 2008 (74)
Cotton textile workers. Area samplings of dust. Mean (SD) cumulative dust exposure µg/m^3-yrs: Yarn manufacturing 2,445 (3,253) Slashing and weaving 6,091 (5,870)	Longitudinal study; 5 yrs.	n=1,817 (464 referents). Mean age; exposed 39.3 yrs referents 36.5 yrs.	FEV_1	<u>Yarn manufacturing:</u> Significant annual decline in FEV_1 16.20 ml/yr per 100 µg/m^3 average cotton dust exposure	H.W. Glindmeyer 1991 (75)
Cotton textile workers. Questionnaire defined.	Longitudinal study; 6 yrs.	n=660 (277 referents). Age at baseline ≥45 yrs.	FEV_1	Men: Significant decline in FEV_1 -42 ml/yr compared with referents -25 ml/yr, p=0.02. Women: Significant decline in FEV_1 -30 ml/yr compared with referents -14 ml/yr, p=0.001.	G.J. Beck 1982 (76)

Exposure	Study design	Population	Outcome	Measure of association	Reference
• **Flax**					
Ex-flax workers. Questionnaire defined.	Cross-sectional study.	n=1,896 (1,267 referents). Age 40-74 yrs.	FEV_1	Men: Significant deficit in FEV_1 compared with referents, $p<0.05$. Women: Significant deficit in FEV_1 compared with referents, $p<0.01$.	J.H. Elwood 1986 (77)
• **Jute**					
Jute processing. Area sampling (mean range 1.4 – 64.6 mg/m^3).	Longitudinal study; 5 yrs.	n=75 (25 referents). Mean age; exposed 40.0 yrs referents 38.5 yrs.	FEV_1	Men: Significant decline in FEV_1 -90.0 ml/yr compared with referents -32.9 ml/yr, $p<0.01$.	Z. Liu 1992 (78)
• **Farming**					
Farming. Personal sampling: interquartile range for dust 0.24-1.6 mg/m^3.	Cross-sectional study.	n=4,735 (21% referents, crop farmers). Mean age 49 yrs.	COPD: FEV_1/FVC <LLN	Overall livestock farming: Significant OR 1.4 (95% CI 1.1-1.7) for COPD. Organic exposure: Significant OR 1.2 (95% CI 1.0-1.4) for COPD for a 10-fold increase of exposure level.	W. Eduard 2009 (79)
Farming. Questionnaire defined.	Cross-sectional study.	n=1258 (970 referents). Median age 57 yrs.	COPD: GOLD II+	Significant OR 1.8 (95% CI 1.2-2.8) for COPD GOLD II+.	B. Lamprecht 2007 (80)
Indoor air contaminants in animal confinement buildings. Personal air sampling (interquartile range 2.3-9.4 mg/m^3).	Cross-sectional study.	n= 76 (referents, 1st and 2nd quartile exposure). Mean age 45.1 yrs.	COPD: GOLD II+	High dust exposure (4th quartile): Significant OR 6.60 (95% CI 1.10-39.54) for COPD GOLD II+. Significant dose-response relationship.	E. Monsó 2004 (81)
Dairy farmers. Medical file defined.	Longitudinal study; 6 yrs.	n=328 (138 referents). Age at baseline 20-60 yrs.	FEV_1	Significant decline in FEV_1 compared with referents, $p=0.03$.	J. Dalphin 1998 (82)

Exposure	Study design	Population	Outcome	Measure of association	Reference
• **Grain**					
Grain processing and animal feed industry. Personal dust samplings (range 2 – 20 mg/m^3).	Longitudinal study; 5 yrs.	n=140 (referents, no and low exposure). Mean age at baseline 37.7 yrs.	FEV_1	Estimated for a 40 yrs old non-smoker: High compared with low dust exp: 58.2 compared with 35.8 ml. annual decline in FEV_1, p<0.05.	W. Post 1998 (83)
Grain dust. Personal air sampling (range 0-95.59 mg/m^3).	Longitudinal study; 6 yrs.	n=159 (<38 referents, low exposure). Mean age 42.7 yrs.	FEV_1/FVC <0.7	High exposure: Significant OR 3.09 (95% CI 1.35-7.07) for obstruction.	M. Bachmann 1991 (84)
• **Wood**					
Wood dust. Personal air sampling (mean dust concentration 3.82 mg/cm^3).	Cross-sectional study.	n=297 (152 referents). Mean age; exposed 32.27 – 34.92 yrs referents 33.69-33.77 yrs.	FEV_1/FVC <0.7	Significantly lower FEV_1/FVC in exposed compared with referents, p<0.01. Significant lower FEV_1/FVC in exposed employed ≥10 yrs compared with exposed employed <10 yrs, p<0.01.	M.H. Shamssain 1992 (85)
Wood dust. Personal air sampling Median (range) 3.75 (0-7.55) mg*yr/m^3.	Longitudinal study; 6 yrs.	Male: n=1,031 (104 referents). Mean age at baseline 39 yrs. Female: n=316 (131 referents). Mean age at baseline 38 yrs.	Decline in FEV_1, FEV_1/FVC; New onset cases of FEV_1/FVC<0.70	Males: No significant decline in FEV_1, FVC, FEV_1/FVC or increase in new onset of COPD in relation to exposure. Females: Dose-response relationship between exposure and % annual decrease in FEV_1; An additional difference of -14.50 ml/yr and -27.97 ml/yr for medium and high exposed respectively. New onset COPD: 11% in fourth quartile of cumulative dust exposure, compared with 4% in first quartile of cumulative dust exposure, p = 0.08	G. Jacobsen 2008 (86)

Exposure	Study design	Population	Outcome	Measure of association	Reference
Wood dust. Personal air sampling mg/m^3 GM (GSD) Inhalable dust: 1.45 (2.7)	Longitudinal study; 3.5-4.2 yrs.	n=1,164 (internal referents) Mean age at baseline 39-41 yrs.	Decline in FEV_1, FEV_1/FVC	No significant decline in FEV_1, FEV_1/FVC, in relation to inhalable wood dust. Residual particulate matter significant associated with annual decline in FEV_1 (milling and plywood sawmill) and FEV_1/FVC (milling) for the respirable dust fraction.	H.W. Glindmeyer 2008 (87)
• **Paper**					
Soft–paper dust. Dust sampling, GM mg/m^3: Respirable dust: 4.9 Total dust: 5.8	Cross-sectional study.	n=94 (48 referents). Mean age; exposed 35.7 yrs referents 42.6 yrs.	FEV_1	Significant deficit in FEV_1 compared with referents, $p<0.05$.	D. Heederik 1987 (88)
• **Rubber**					
Rubber fumes and dust. Personal air sampling (mean dust exposure 2.0 mg/m^3). Mean cumulative dust 32.5 mg/m^3-yrs.	Cross-sectional study.	n=139 (69 referents). Mean age; exposed 37.1 yrs referents 35.5 yrs.	FEV_1/FVC ratio	Significantly lower FEV_1/FVC ratio in exp. compared with referents, 80 compared with 82%, $p<0.05$. Cumulative dust exposure significantly associated with FEV_1/FVC ratio -0.04%/mg/m^3*yr; $p<0.001$.	E. Meijer 1998 (89)
Rubber workers. Environmental samples.	Longitudinal study; 1 yr.	n=233 (141 referents). Age >24 yrs.	FEV_1/FVC ratio (cross-sectional) FEV_1 (longitudinal)	Decline in FEV_1/FVC ratio: Non significant. In multiple regression: Exposure time (yrs) was significant to predict one year loss in FEV_1, $p<0.001$.	L.J. Fine 1976 (90)

Exposure	Study design	Population	Outcome	Measure of association	Reference
• **Endotoxin**					
Farming. Personal sampling: interquartile range for endotoxin 19,000-63,000 EU/m^3.	Cross-sectional study.	n=4,735 (21% referents, crop farmers). Mean age 49 yrs.	COPD: FEV_1/FVC <LLN	Significant OR 1.2 (95% CI 1.0-1.5) for COPD for a 10-fold increase of exposure level.	W. Eduard 2009 (79)
Indoor air contaminants in animal confinement buildings. Personal air sampling (interquartile range 282.2-2,203.0 units/m^3).	Cross-sectional study.	n= 76 (referents, 1st and 2nd quartile exposure). Mean age 45.1 yrs.	COPD: GOLD II+	Non significant.	E. Monsó 2004 (81)
Cotton textile workers. Mean cumulative endotoxin exposure 48,479.5 EU/m^3/yr.	Longitudinal study; 20 yrs.	n=825 (417 referents). Mean age at baseline; exposed 37.1 yrs referents 36.1 yrs.	FEV_1	Endotoxin exposure not related to annual decline in FEV_1.	X. Wang 2008 (74)
Grain processing and animal feed industry. Personal samplings of endotoxin, mean (3 – 177 ng/m^3).	Longitudinal study; 5 yrs.	n=140 (referents, no and low exposure). Mean age at baseline 37.7 yrs.	FEV_1	Annual decline in FEV_1 estimated for a 40 yrs old non-smoker: High endotoxin exposure; Non significant.	W. Post 1998 (83)