COPD and environmental risk factors other than smoking

13. Occupation

Author : P N Lee
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1. Methods

1.1 Papers identified

The procedures used were broadly as described in "COPD and risk factors other than smoking. 1. Identifying Relevant Papers". An initial stage, aimed at identifying which risk factors other than smoking were prospective candidates for more detailed literature searches, identified 38 "Step 1" papers, many of which were general review papers. A number of these papers indicated that various occupations were implicated in COPD, and a MEDLINE literature search was then conducted using the search terms (COPD or chronic bronchitis or emphysema) and (occupation or dust or fumes or asbestos or mining or coal or iron or steel or textile or grain or mill or weld or silica or endotoxin or cadmium or isocyanate or vanadium or oxides of nitrogen or sulphur dioxide). This identified 1763 papers. After inspecting the abstracts 210 papers were obtained. After rejecting a number of papers as not in fact being relevant, this review was based on relevant Step 1 papers and relevant later obtained papers. In view of the large number of papers already available, it was thought unnecessary to consider papers not in English or to study reference lists of obtained papers to find more literature on the subject. Nor was it thought necessary to look within official government mortality statistics by occupation (e.g. [1]) as these would generally not take smoking into account.

The papers obtained were divided into those which considered COPD risk in relation to occupation as a whole (though often citing conclusions for specific occupations), those which considered risk in relation to one of 22 specific occupational groups, and those which considered risk in relation to any of a varied list of less often studied occupations. The occupational groups are sometimes defined by job done and sometimes by agent exposed to, and there are overlaps between a number of the categories.

1.2 Summarizing the data

Relevant papers are of four types:

A. General review papers on occupation, either specific to COPD or considering COPD in some detail;
B. Papers providing direct evidence relating COPD to an occupation or an agent of interest;
C. Papers providing evidence relating COPD to a range of occupations or agents; and
D. Review papers considering the relationship of COPD to a specific occupation or agent of interest.

Section 2 presents relevant quotations from selected papers of type A.

Sections 3 to 23 then present findings for each of 21 occupations or agents:

3. Dust, gases and fumes
4. Asbestos exposure
5. Shipyard workers
6. Coal mining
7. Gold mining
8. Iron mining
9. Uranium mining and milling
10. Foundry workers
11. Welders
12. Metal workers
13. Carbon black workers
14. Exposure to silica
15. Farming
16. Poultry workers
17. Textiles and cotton
18. Woodworkers
19. Brick workers

20. Cement workers
21. Painting
22. Paper and pulp
23. Transport workers

For each section, papers of types B, C and D are considered first in chronological order. For each paper, a paragraph is presented summarizing the main features of the study design and results relevant to COPD. At the end of the section, where relevant, reference is made to papers of type A, citing conclusions relating to the occupation or agent.

Section 24 then very briefly mentions other occupations, where only one publication relevant to COPD is available, and no attempt is made to interpret the data.

Finally, section 25 discusses some of the problems in assessing the relationship of COPD to occupation, and then presents conclusions relating to each of the occupations and agents considered, and overall for occupation.

1.3 Abbreviations used

COPD	chronic obstructive pulmonary disease
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
FEV_1/FVC	the ratio of FEV_1 to FVC
OR	Odds ratio
RR	relative risk; also used for the hazard ratio
95% CI	95% confidence interval. Note that statements such as OR = 2.0, 1.2-3.3 or RR = 1.6 (1.0-2.6) are often used to indicate the OR or RR and its 95% CI
PMR	proportional mortality ratio. This is expressed relative to 100
SMR	standardized mortality ratio. This is expressed relative to 100

2. General review papers

16 of the papers identified are reviews that relate wholly or partly to occupation [2-17]. Relevant sections from some of these are listed below:

Garshick *et al* (1996)[6]

"The studies reviewed in this article indicate the association of occupational exposure to a variety of organic and inorganic dusts and various gases and fumes with chronic bronchitis and decrements in FEV_1. Usually an obstructive pattern was noted, although in some occupations a similar decrement in FVC was noted. The effect of smoking on chronic bronchitis, respiratory symptoms, and FEV_1 was usually additive, although workers exposed to cotton dust in one study demonstrated an interaction between exposure and smoking, as did a study of a general population sample. In coal workers, exposure to dust in younger workers resulted in a greater decline in lung function than if the exposure occurred in older workers. Studies in coal miners and grain workers further suggest that occupational standards in effect are not sufficient to protect the working population from adverse effects."

Silverman and Speizer (1996)[14]

"To summarize, a variety of occupational exposures has been suggested as risk factors for the development of COPD. Occupational dust and fumes in general have been associated with the development of COPD, and several specific dusts and fumes are likely risk factors for COPD. The magnitude of the effects appears to be significantly less important than the effect of cigarette smoking."

Nurminen and Karjalainen (2001)[11]

In an article estimating the proportion of deaths related to occupational factors in Finland, the authors estimated a figure of 12% for COPD. Reference was made to increased risks from dust, coal mining, welding, silica and farming.

Viegi and di Pede (2002)[16]

"A careful review of the literature demonstrates that approximately 15% of both asthma and COPD is work related, and that new agents causing asthma or COPD, as well as a lack of the preventative efficacy of information gathered so far, are still being reported. It definitely supports the concept that in a new classification of risk factors for COPD occupational exposure to dusts, chemicals, and gases should be considered an established, or supported by good evidence, risk factor."

Pauwels and Rabe (2004)[12]

"Sufficiently intense occupational exposure to dust, gases, or fumes is associated with an increased risk of developing COPD, independent of cigarette smoking, but the effects of occupational exposure and cigarette smoking are additive. Both inorganic and organic dust exposure can accelerate the decline in FEV_1."

Balmes (2005)[2]

"The biological plausibility of the capacity of occupational exposures to irritating dusts, gases, and fumes to cause chronic obstructive pulmonary disease (COPD) is high. Epidemiological evidence from both worker cohort and community studies supports an increased risk of COPD associated with such exposures. The occupational contribution to the burden of COPD is sufficiently great that preventive interventions are warranted."

Devereux (2006)[5]

"Intense prolonged exposure to dusts and chemicals can cause COPD independently of cigarette smoking, though smoking seems to enhance the effects of such occupational exposure to increase the risk of developing COPD. About 20% of diagnosed cases of COPD are thought to be attributable to occupation; in lifelong non-smokers this proportion increases to 30%. Exposure to noxious gases and particles – such as grain, isocyanates, cadmium, coal, other mineral dusts, and welding fumes – have been implicated in the development of chronic airflow obstruction. Thus, a full

chronological occupational history should be taken, as relevant occupational exposures are often missed by clinicians."

There are also a number of papers that consider results for a range of occupational categories[18-24]. Their results are considered in the following sections along with the substantial number of papers that concern specific occupations or exposures.

3. Dust, gases and fumes

Sixteen specific studies of workers exposed to dust, gas or fumes were identified, as well as four specific reviews and two general occupational studies which provided relevant results. It should be noted that studies relating to a number of specific occupations with exposure to dust, gas and/or fumes, such as miners (sections 6 to 9), metal workers (section 12), and those exposed to silica (section 14) are considered in other sections. The papers considered here generally relate either to studies that relate endpoints to some overall index of exposure to dust, gas and/or fumes or studies of some rarer specific occupations not considered elsewhere where the comparison is between workers exposed and unexposed to dust, gas and/or fumes.

Dosman *et al* (1980)[25] compared 90 lifetime nonsmoking grain elevator workers exposed to grain dust with 90 age-matched nonsmoking control subjects in the same area of Canada. The prevalence of chronic bronchitis was higher in nonsmoking workers (23.1%) than in the nonsmoking controls (3.3%) ($p<0.01$). FEV_1/FVC did not vary between the two groups, though the grain workers had evidence of greater airflow obstruction, based on flow rates.

Becklake (1985)[26] published a review entitled "Chronic airflow limitation: its relationship to work in dusty occupations." Among points made were that "In most, though not all studies, there were higher prevalences of bronchitis and lower average ventilatory function in exposed compared to nonexposed or less exposed workers", "in addition to implicating a variety of mineral dusts (including silica, abrasives, coal, and iron), grain dusts, exposures to a variety of gases, and heat were also shown to affect FEV_1 decline over time" and, based on pathology studies, that "The results support the view that exposure to coal mining dust increases a man's risk of developing emphysema."

Awad el Karim *et al* (1986)[27] compared 100 men working in a flour mill in the Sudan with 30 control men of a similar age range working in distillation. Prevalence of chronic bronchitis was significantly higher in the workers exposed to flour dust ($p<0.05$) and FEV_1 ($p<0.01$) and FVC ($p<0.001$) were significantly lower before and after shift. In the exposed group there was also a significant ($p<0.01$) drop in FEV_1 and FVC from before shift to after shift.

In a large cross-sectional study of some 16000 men and women in France by Krzyzanowski and Kauffmann (1988)[28] subjects were asked whether they were exposed to dust, gases or chemical fumes at work in their current or previous occupations. After adjusting for age, smoking, education and social class, ever exposure was associated with an increased OR for chronic bronchitis in men (1.53, 95% CI 1.27-1.85) and women (2.09, 1.41-3.12). After adjusting for the same variables plus also height and air pollution, exposure was associated with a non-significantly decreased FEV_1, a significantly ($p<0.05$) increased FVC and a significantly ($p<0.001$) decreased FEV_1/FVC in men. In women exposure was associated with a reduced FEV_1 and FVC, with no material difference in FEV_1/FVC, but none of these relationships were significant.

Krzyzanowski and Jedrychowski (1990)[29] studied 1132 men and 1598 women in Poland in 1968, and then again 5 and 13 years later. Prolonged occupational exposure to dusts (i.e. reported at baseline and 5 years later) was associated with an increased risk of chronic bronchitis incidence in those initially free of the symptom, after adjustment for significant factors selected from age, smoking, socioeconomic status and education. This was evident in women (OR 2.1, 1.3-3.4) and in men aged 41-50 (2.6, 1.5-4.6) but not in men aged 19-40 (1.2, 0.8-2.0) or men aged 51-60 (0.7, 0.2-2.6). (For the three age groups combined I estimate an OR of 1.5, 1.1-2.2.)

Xu *et al* (1992)[30] investigated the effects of dusts and of gases/fumes in a study of 3606 adults aged 40 to 69 in China. Both exposures were estimated on a three point scale (low, moderate, high). After adjusting for age, sex, area

of residence, smoking, coal stove heating and education, a one point increase in each exposure was significantly associated with chronic bronchitis (ORs 1.14, 1.05-1.24 for dusts and 1.12, 1.01-1.23 for fumes). The effect seemed to be restricted to high exposure. Among subjects who did not report using coal stove heating, dust exposure was a significant predictor for FEV_1. There was also a significant decrease for FEV_1 and FVC with increased gas/fume exposure. Current and former smokers "appeared more susceptible to the effect of dusts than never smokers."

Oxman *et al* (1993)[31] carried out a systematic review of the evidence on occupational (inorganic) dust exposure and COPD. Studies were included if dust exposure was measured quantitatively and relationships with the outcomes of interest were calculated with adjustment at least for smoking and age. Only 13 reports derived from four cohorts of workers met their inclusion criteria. Three of the cohorts were of coal miners and one of gold miners. The authors concluded that "occupational dust is an important cause of COPD, and the risk appears to be greater for gold miners than for coal miners. One possible explanation of the greater risk among gold miners is the higher silica content in gold mine dust."

In 1998 Forastiere *et al*[19] reported on a cross-sectional study of 1226 US women aged 55+ in which frequency of a physician diagnosis of chronic bronchitis or emphysema was compared in those exposed or unexposed occupationally to dust, gas, vapours or fumes after adjustment for age and smoking. No increase was seen, with the OR 0.8(0.5-1.5). Nor was any increase seen in smokers or in nonsmokers.

Simpson *et al* (1998)[32] carried out a cross-sectional study in the UK of 1032 workers in nine different industries with exposure to inorganic dusts. Personal exposures to dust and endotoxin were measured. Prevalence of chronic bronchitis ranged from a high of 15.5% in 84 poultry workers to 0% in 34 animal feed workers. After adjusting for smoking and ethnic group, increased exposure to dust or endotoxin was associated with a significantly

($p<0.001$) higher prevalence rate of work related chronic bronchitis (symptoms were considered work-related if they improved on holidays or days away from work).

Donato *et al* (2000)[33] carried out a cross-sectional study of 1497 men and women in an area of Italy with a high density of iron and steelworking factories. Subjects were asked whether they had occupational exposures to dust, fumes or gases. In males, self-reported COPD (chronic bronchitis or emplysema/asthma) was associated with exposure (OR 2.3, 1.4-3.7) after adjustment for smoking. No relationship was seen in women. FEV_1 and FVC were not associated with occupational exposure.

Schenker (2000)[34] published a review of "Exposures and health effects from inorganic agricultural dusts." He noted that "Exposures to inorganic (mineral) dusts among farmers and farm workers may be substantial" and concluded that "It is plausible that agricultural exposure to inorganic dusts is causally associated with chronic bronchitis, interstitial fibrosis, and chronic obstructive pulmonary disease, but the independent contribution of mineral dusts beyond the effects of organic dusts remains to be determined."

In a general population survey in 14 industrialized countries involving 13,253 subjects aged 20 to 44 reported in 2001, Zock *et al*[24] reported no clear relationship of lung function to occupational exposure to vapours, gas, dust or fumes in smokers, ex-smokers or never smokers. An association with chronic bronchitis was evident in current smokers.

Trupin *et al* (2003)[35] carried out a cross-sectional analysis of 2061 US residents aged 55-75 and assessed occupational exposure during the longest-held job both by self-reported exposures to vapours, gas, dust or fumes and through a job exposure matrix. After adjusting for age, sex, race and smoking, COPD, as defined by self-reported physician diagnosis of chronic bronchitis, COPD or emphysema, was significantly related to self-reported exposure (OR 2.0, 1.6-2.5) and to matrix exposure probability (ORs 1.0; 1.4 [1.1-1.9] and 1.6

[1.1-2.5] for low, intermediate and high exposure). These associations were somewhat strengthened by a more restrictive definition of COPD, excluding those with chronic bronchitis only.

Bergdahl *et al* (2004)[36] followed a cohort of 317,629 Swedish male construction workers from 1971 to 1999, using a job exposure matrix to estimate whether or not a man was exposed to inorganic dust, gases and irritants, fumes and/or wood dust. After adjusting for age and smoking, and in comparison to an internal control group of "unexposed" construction workers, there was an increased mortality from COPD among those with any airborne exposure (RR 1.12, 1.03-1.22), with risk elevated for those exposed to inorganic dust (1.16, 1.05-1.28), gases and irritants (1.18, 0.98-1.41) and fumes (1.22, 1.14-1.42) but not wood dust (0.77, 0.53-1.07). These increases were more pronounced in never smokers, e.g. for any airborne exposure, the RR was 2.11 (1.43-3.00).

Moshammer and Neuberger (2004)[37] followed up 3260 Austrian workers for 50 years. Half of them had been exposed at work to (non-fibrous) particulates, while the non-exposed workers were matched for age, year of initial check-up and smoking status at the start of observation. Based on 141 deaths from COPD, the age-adjusted RR in relation to exposure was 1.82 (1.30-2.56).

Girod and King (2005)[38] published a paper entitled "COPD: a dust-induced disease?" They noted that "Various reports have demonstrated the importance of small airway inflammation in the development of airflow limitation and progression of COPD" and proposed that "the pathogenesis of COPD mirrors a chronic inhalational dust-induced disease." This review is predominantly concerned with pathology rather than epidemiology and among other things suggests that smoking-related COPD may result from exposure to the inorganic dust aluminium silicate or kaolinite, a common component of clay soils.

Matheson *et al* (2005)[39] carried out a cross-sectional study in Australia, involving 1232 subjects. A job exposure matrix was used to classify subjects as exposed or not exposed to biological dust, mineral dust or gases and fumes. These three exposures were then related to chronic obstructive bronchitis, emphysema and COPD, separately for each sex, with adjustment for age and smoking status. No significant relationships were seen in men, with ORs for COPD 1.49 (0.63-3.51) for biological dust, 0.88 (0.37-2.06) for mineral dust and 1.19 (0.49-2.92) for gases and fumes. More evidence of a relationship was seen in women, with ORs 7.43 (2.07-26.7) for biological dust, 1.79 (0.60-5.29) for mineral dust and 2.37 for gases and fumes (0.85-6.60). However, there was no relationship to length of exposure, with all analyses for COPD showing weaker relationships for those exposed for 13+ years than for those exposed for 1-12 years.

Sunyer *et al* (2005)[40] followed up 4079 men and 4461 women aged 20-45 years in 14 European countries from 1988 to 2002. Subjects were classified as having no, low or high exposure to biological dust, mineral dust, gas and fumes, or any of these. After adjustment for age, height, BMI, length of follow up and smoking there was no significant relationship in males between decline in FEV_1 or incidence of new cases of airway obstruction and any of the indices of exposure. In females, however, decline in FEV_1 was significantly ($p<0.05$) greater in those with high exposure to biological dust or to mineral dust. The prevalence of chronic phlegm at baseline increased with increasing exposure to mineral dust and to gas and fumes in both sexes. However changes in chronic phlegm were unrelated to the exposures. The authors note that "the same results were obtained for chronic bronchitis (results available on request)" but it is not totally clear that this relates to these specific results for chronic phlegm. However, the authors do conclude that "Occupational exposures to dusts, gases, and fumes occurring during the 1990s are associated with incidence of chronic bronchitis, although these did not impair lung function in a population of relatively young age."

Jaén *et al* (2006)[41] studied 576 subjects in Spain. Occupational exposures were assessed by direct questions on ever having worked in a dusty

job or in a job with exposure to gas or chemical fumes, and also via a job exposure matrix. Respiratory symptoms associated with chronic bronchitis were noted to be more prevalent in exposed subjects, particularly among never smokers. 15 or more years of exposure to dust, fumes or gases was associated with a non-significantly reduced FEV_1 (-80, -186 to +26 ml) and a significantly reduced FEV_1/FVC (-1.7, -3.3 to -0.2 ml), after adjustment for sex, age, height and smoking.

LeVan *et al* (2006)[42] carried out a cross-sectional study in Singapore involving 52325 subjects. Exposure to dust (from cotton, wood, metal, minerals or asbestos) was associated with an increased risk of chronic bronchitis (OR 1.26, 1.01-1.57) after adjustment for age, sex, dialect and smoking. However, no significant association was seen for exposure to smoke (from welding, coal burning, wood burning, other; OR 1.07, 0.83-1.28) or for exposure to vapours (from a variety of sources; OR 0.93, 0.71-1.22).

Zhong *et al* (2007)[43] carried out a cross-sectional study in China involving 25627 subjects. COPD was defined by post-bronchodilator FEV_1/FVC <70%. In an analysis adjusted for area, sex, age, education, BMI, smoking, kitchen ventilation, use of biomass for cooking or heating, pulmonary problems in childhood and a family history of pulmonary disease, occupational exposure to dusts, gases or fumes was associated with an OR for COPD of 1.20 (1.04-1.39).

In a general review of "Occupational exposures: evidence for a causal association with chronic obstructive pulmonary disease" Becklake[4] considered evidence from community-based studies, longitudinal studies of lung function, pathology studies and cohort mortality studies. She considered that the evidence reviewed, "according to accepted criteria for establishing causality, leaves little doubt that occupational exposure to dust and/or to dust and fumes may be causally implicated in the genesis of COPD."

In a general review of "Occupationally induced airways obstruction," Garshick *et al*[6] separate the evidence into studies of mineral dust exposure (coal mining, gold mining, other mining, asbestos, other), organic dust exposure (grain dust, cotton dust), and exposures to gases and fumes. They consider that "The studies reviewed in this article indicate the association of occupational exposure to a variety of organic and inorganic dusts and various gases and fumes with chronic bronchitis and decrements in FEV_1. Usually an obstructive pattern was noted, although in some occupations a similar decrement in FVC was noted. The effect of smoking on chronic bronchitis, respiratory symptoms, and FEV_1 was usually additive."

4. Asbestos exposure

Six studies, all cross-sectional, have provided evidence relating asbestos exposure to COPD.

Kilburn *et al* (1985)[44] studied 71 women who had worked in US shipyards before 1961. Comparisons were made with smoking specific groups of women in another study in Michigan, with a national population sample, and with wives of shipyard workers. Prevalence of chronic bronchitis in the shipyard workers was 50% higher than in the wives of shipyard workers, a difference that does not appear to be statistically significant. Age and height adjusted FVC and FEV_1 were lower than the reference population in current, former and never smokers, though only the difference for FEV_1 in former smokers was significant. (An overall smoking-adjusted comparison was not presented.)

In a further study of US shipyard workers, Kilburn *et al* (1986)[45] studied 417 shipyard workers in Los Angeles and their families. In both sexes, and in all smoking groups, prevalence of chronic bronchitis in the shipyard workers was much higher than a Michigan reference population and somewhat higher than in spouses and siblings of shipyard workers of the same sex. Nonsmoking shipyard workers had normal lung function. FVC and FEV_1 was less than predicted in male shipyard workers who had ever smoked, but did not differ between those with no asbestosis and those with a fine irregular opacity with a profusion of 1/0, but was decreased in those with higher profusion scores. The authors noted the higher prevalence of chronic bronchitis and airway obstruction in families of shipyard workers, but considered that they wee not explained by cigarette smoking or asbestos exposure and tentatively ascribed them to long-term exposure to ambient air pollution in Los Angeles.

Hunting and Welch (1993)[46] studied the relationship of fibreglass and asbestos exposure to lung disease in 333 sheet metal workers with 20 or more years in the trade. In a multiple regression analysis of risk factors for chronic

bronchitis, adjusted for smoking, 10 years asbestos exposure was associated with an OR of 1.51 (95% CI 1.08-2.10), and high fibreglass exposure with an OR of 2.28 (1.07-4.86). In an analysis of obstructive lung disease, based on pulmonary function test results, no significant relationship with years of asbestos exposure was seen.

Algranti *et al* (2001)[47] carried out a study of 828 former asbestos-cement workers in Brazil. Prevalence of chronic bronchitis increased with increasing latency time from first exposure, the increase being evident in current, former and never smokers. FVC and FEV_1 decreased across increasing profusion of asbestosis with an added effect of pleural thickening, and also with increasing latency time from first exposure to asbestos.

Seldén *et al* (2001)[48] studied 130 Swedish dolomite workers potentially exposed to tremolite asbestos. In fact, tremolite asbestos concentrations were generally below the limit of detection (<0.3 fibres/ml). No clear relationships of respiratory symptoms or lung function to dolomite dust or tremolite asbestos were seen.

Huuskonen *et al* (2004)[49] studied 600 smoking construction workers in Finland with an asbestos-related lung disease. The authors noted that "emphysema was more common when workers had asbestosis or were heavily exposed to asbestos (insulators), but due to confounding factors the causative role of asbestos in emphysema needs further study."

Though the studies provide little information on the most relevant endpoints (COPD mortality, doctor diagnosed COPD or GOLD definition based on lung function), they generally show that asbestos exposure, or increased asbestos exposure, is related to an increased risk of chronic bronchitis or emphysema or reduced lung function. The exception was a study of Swedish dolomite workers where exposure to asbestos was stated to be "generally low or even very low". That there is a relation between asbestos exposure and airflow obstruction is consistent with a review by Garshick *et* al[6] who cite additional evidence from other studies. The results described in this

section should be considered along with those for shipyard workers (see next section).

5. Shipyard workers

Four publications relate to three studies on the relationship between working in shipyards and COPD.

In 1989, Cotes *et al*[50] reported on cross-sectional analyses of 607 UK shipyard workers. Comparisons were made between welders or caulker/burners and those that did not involve welding or burning. After allowing for age and current smoking, work as a welder or caulker/burner was associated with an increased risk of chronic bronchitis (RR 2.8, 95% CI 1.4-5.5). Among the welders and caulker/burners who smoked, the RR was related to the average fume exposure. Among those who had ever smoked, FEV_1 was reduced in relation to fume exposure.

The next year, Chinn *et al*[51] reported on an average 7.2 year follow-up of the shipyard workers. Mortality was related to age, level of lung function and smoking, but not to trade as a welder or caulker/burner. The trade was related to increased breathlessness over the follow-up period and to decline in FEV_1 but not to development of chronic bronchitis.

Gennaro *et al* (1993)[52] studied 657 white male shipyard workers in Italy. After adjusting for smoking, chronic bronchitis was higher in those who had worked for more than 20 years compared to those who had worked less (OR 2.03, 1.17-3.52). Duration of employment was also associated with an increased risk of obstruction (normal FVC, low FEV_1/FVC, OR 1.20, 0.73-1.97), restriction (low FVC, normal FEV_1/FVC, OR 2.58, 1.44-4.60) and mixed impairment (low FVC and FEV_1/FVC, OR 2.52, 1.15-5.53). Compared to metal-workers, the group with "the lowest exposure to lung toxins", four job categories were independently associated with restriction (gas welders, arc welders, masons and insulators).

Krstev *et al* (2007)[53] followed to 2001 the mortality of 4702 US shipyard coast guard workers employed in 1950-1964. Compared to general population death rates for the relevant state (Maryland), the SMR for emphysema in men, based on 36 deaths, was 144 (101-199). Only one

emphysema death was seen in women (expected 0.7). In men, those employed for 10 or more years in the shipyard had a lower SMR 118 (64-198) than those employed for less long (167, 103-253), and risk was unrelated to whether or not they had been exposed to potentially hazardous substances in the shipyard.

6. Coal mining

Sixteen studies of specific groups of miners, one general review of the effects of coal mining and one general occupational study provide information on the relationship of coal mining to COPD.

Fairman *et al* (1977)[54] studied 1438 surface coal miners in the USA. The abstract states that "Increased prevalence of chronic bronchitis with increasing exposure [to surface mine dust] was found in all smoking categories", but the actual data presented (in Table 5 of the source) do not actually seem to demonstrate this. Age and height adjusted FVC in smokers declined significantly ($p = 0.0001$) with increasing years of mining, but no significant relationships were seen in exsmokers or never smokers, or for FEV_1 in any smoking group.

Rom *et al* (1981)[55] studied 242 US underground coal miners with mean age of 56 years and a mean of 29 years in the coal-mining industry. The prevalence of chronic bronchitis was 57%, with smoking and years of coal mining additive factors. Increasing exposure to coal dust (measured by years of mining) was not associated with changes in lung function.

Ruckley *et al* (1984)[56] examined the lungs of 450 British coal miners *post-mortem* for signs of dust-related fibrosis and emphysema, with estimates of cumulative exposure to respirable mine dust available for 342 of them. The proportion of subjects with emphysema increased from 47% in men with no palpable dust lesions to 83% in those with massive pulmonary fibrosis. The chance of finding centriacinar emphysema in those with massive fibrosis increased significantly ($p<0.025$) with increasing exposure to coal dust in life. The authors concluded "that the association observed between exposure to respirable coal dust and emphysema in coal miners indicates a causal relationship. However, because it can be demonstrated only for men whose lungs show some dust-related fibrosis, it is suggested that the extent and nature of such fibrosis may be a crucial factor in determining the presence of centriacinar emphysema."

Miller and Jacobsen (1985)[57] compared mortality up to the end of 1979 in 26363 miners from 20 collieries in England and Wales who were surveyed between 1953 and 1958 with that of men in the same regions. After allowing for age there was an association, significant at $p<0.001$, between increasing exposure to dust and mortality from bronchitis or emphysema.

Lloyd *et al* (1986)[58] compared the respiratory health of 458 coal miners in Wales with 228 nearby telecom workers of similar age. The frequency of chronic bronchitis was much higher in the miners (31% v 5%), a difference evident in ever smokers and never smokers. The proportion with an FEV_1 less than 80% of predicted was also greater in miners (20% v 10%, $p<0.05$), a difference again evident in both smoking groups.

Soutar and Hurley (1986)[59] used the same population as Miller and Jocobsen[57] to study the relationship between dust exposure and lung function in miners and exminers examined in 1953 to 1958 and then again 22 years later. FEV_1, FVC and FEV_1/FVC at follow-up was found to be inversely related to exposure to respirable dust after allowing for other factors, even in men without pneumoconiosis. This effect was equivalent to a loss of 228 ml FEV_1 for an exposure of 300 gh/m^3, a "moderately high exposure for this group." Ex-miners who had given up smoking had an even more severe effect of dust exposure, equivalent to a loss of 940 ml FEV_1.

Seixas *et al* (1992)[60] reported results of a study of 1185 US coal miners who had started mining in or after 1970 when comprehensive exposure regulations first came into effect. Statistically significant associations between cumulative exposure and decreased FVC, FEV_1 and FEV_1/FVC were observed after adjusting for age, smoking and other potential confounders. Cumulative exposure was also significantly associated with the prevalence of chronic bronchitis and with the prevalence of FEV_1 and FEV_1/FVC less than 80% predicted. The authors concluded that "exposures to respirable coal mine dust present in U.S. mines since 1970 continue to affect respiratory health in underground miners."

Kuempel *et al* (1995)[61] carried out a mortality analysis to 1979 of 8878 male US coal miners examined in 1969 to 1971. A significant ($p<005$) relationship was reported between mortality from chronic bronchitis or emphysema (as either an underlying or contributory cause) and increasing cumulative exposure to respirable coal mine dust, after adjusting for age and smoking. In fact, the RRs for dust categories II to VI were all substantially elevated relative to the baseline, but did not show any particular dose-related pattern (1, 3.07, 2.89, 4.20, 4.97, 3.58). The authors concluded that "Miners exposed at or below the current U.S. coal dust standard of 2 mg/m^3 over a working lifetime, based on these analyses, have an elevated risk of dying … from chronic bronchitis or emphysema."

Lewis *et al* (1996)[62] carried out a cross-sectional study of the effect of occupation on lung function based on 1286 British coal miners with no x-ray evidence of pneumoconiosis and 567 men living in the same area who had never worked in the mining industry or in any other dusty occupation. There was a significant mean effect of mining on FEV_1 after adjustment for age, height and smoking of -155 ml (-74 to -236 ml), with the effect stronger in younger men.

Love *et al* (1997)[63] carried out a cross-sectional study of 1249 current workers at nine opencast coal mines in the UK. Measure of personal exposure to respirable dust and quartz were taken, and used to classify subjects into five broad groups of exposure. Frequency of chronic bronchitis was influenced by years worked in dusty jobs outside opencast mining, but not by time spent in occupations within the industry. Lung function on average was close to predicted values and showed no relationship to time worked in dusty jobs within or outside opencast mining.

Meijer *et al* (1997)[64] studied mortality up to 1991 in 3790 Dutch coal miners examined between 1952 and 1963. Compared to the Dutch national male population, the SMR for COPD was 179, based on 186 deaths, with the excess risk diminishing with period of death. The excess risk of COPD was

only evident in those who had diminished FEV_1 (<70%) at initial examination, and was unrelated to duration of exposure.

Beeckman *et al* (2001)[65] compared subsequent respiratory symptoms and mortality in 310 US coal miners who had shown high rates of FEV_1 decline during previous mine surveys (cases) and 324 miners who had relatively stable lung function (controls). After adjustment for age and smoking, the cases had a significantly 3.2 fold greater risk of dying from COPD over the period from when lung function was determined (ending in 1988) to the end of the follow-up period (1997). The cumulative incidence of self-reported bronchitis and emphysema was also significantly increased in the survivors.

In the review by Cohen and Velho in 2002[66] entitled "Update on respiratory disease from coal mine and silica dust," there are sections relating coal mine dust to chronic bronchitis, emphysema and lung function declines. Evidence from 13 studies was considered, a number described above, and it was clear that the authors regarded the data as clear and consistent.

In the case-control study in Italy involving 131 COPD cases and 298 controls without respiratory diseases, which was reported by Mastrangelo *et al* in 2003[22], the OR adjusted for age and smoking was a nonsignificant 5.5 (95% CI 0.4-72.1) in miners (compared to office workers). The miners would presumably have been mainly coal miners.

Isidro Montes *et al* (2004)[67] followed up a cohort of 2579 coal miners in Spain at regular intervals over a 20 year period. Comparisons were made between men who had carried out rock work, coal extractors and other workers. Dust levels in the rock workers and coal extractors were similar, but silica levels in the rock workers were much higher. Rock workers had a greater frequency of accelerated FEV_1 decline (FEV_1 less than 85% of the baseline after adjustment for time between measurements) and frequency of FEV_1 <80% predicted than the other two groups. After adjustment for smoking, and compared to the other two groups combined, rock work was

associated with RRs of 1.49 (1.01-2.22) for accelerated FEV_1 decline and 1.43 (0.80-2.54) for FEV_1 <80% predicted. The authors note that "Chronic bronchitis was significantly associated with tobacco consumption with regard to dose-response significance and with the kind of work, in which the trend test borders on significance," but do not give fuller details.

Sichletidis *et al* (2004)[68] compared four groups of workers in Greece in an investigation of the effect of environmental pollution of lignite workers and living in the Eordea valley, a tectonic trench where the topography obstructs free air circulation leading to stagnation of air pollutants. Four groups of men were studied, (A) 199 lignite mine workers living in the Eordea valley, (B) 214 lignite mine workers living outside the valley, (C) 101 office workers living in a city in the valley and (D) 145 cattle breeders living outside the valley in a region "without pollution." The average ages of the four groups were 38.7, 37.2, 42.1 and 52.3. Rates of chronic bronchitis were 26.8%, 24.8%, 17.9% and 10.6%. The authors state that "The prevalence of chronic bronchitis in mine workers (groups A and B) and Ptolemaida residents (group C) is statistically far higher than that of the control group (P<0.001)," but the C-D difference is not significant at all according to my calculations. Adjustment for smoking confirmed the higher rate in the lignite miners, but did not appear to show any clear effect of residence on chronic bronchitis rates. There were no differences between the four groups in FEV_1, FVC or any other lung function measurements, differences noted being in the upper airways (e.g. severe nasal obstruction).

Naidoo *et al* (2005)[69] carried out a *post mortem* study of 3167 South African coal miners autopsied from 1975 to 1997 and having exposure duration information. Relationships between exposure and outcome were conducted on a subset of 745 for whom smoking history was available. In a model adjusted for smoking but not age, there was a significant relationship of exposure duration to emphysema, with ORs of 1.0, 2.2 (1.2-3.9) and 3.4 (1.9-5.9) for, respectively, low, medium and high exposure duration. However, when age, which was highly correlated with exposure duration, was adjusted

for, the association disappeared, with ORs now 1.0, 0.8 (0.5-1.7) and 1.2 (0.6-2.,1). The study is limited by the lack of reliable data on extent of exposure and by the lack of data on smoking for so many of the miners. It should be noted that there were 117 cases of emphysema in the 725 with smoking history available (16.1%) as against 85 cases in the remaining 2442 with no smoking history (3.5%), indicating that absence of smoking data was highly non-random.

Bertrand *et al* (2007)[70] carried out a study in 354 miners in France investigating the respiratory effects of exposure to diphenylmethane diisocyanate- (MDI) based resins and of exposure to ureaformol- and formophenolic- (UF) based resins. 5.6% of miners exposed to MDI had acute symptoms, but the 20 affected had no increase in chronic bronchitis or decrease in FEV_1 or FVC compared to those unaffected by MDI or UF. 22.6% of the miners exposed to UF had acute symptoms. The 80 affected had a significant age-, smoking- and dust-adjusted increase in chronic bronchitis (RR 2.57, 1.07-6.16), but no significant reductions in FEV_1 or FVC. The paper does not provide any simple comparisons of workers exposed and unexposed to MDI or to UF.

In a general review of "Occupationally induced airways obstruction" Garshick *et al*[6] include a section on coal mining, with subsections on chronic bronchitis, airflow obstruction and pathology. They noted that "Pulmonary function and respiratory symptoms have been extensively studied among coal miners in relation to measurements of dust exposure. Exposure to coal dust may result in chronic bronchitis and chronic airflow obstruction unrelated to simple coal workers' pneumoconiosis or to progressive massive fibrosis."

The review by Balmes[2] of the "Occupational contribution to the burden of chronic obstructive lung disease" listed coal among the "agents that cause chronic bronchitis," though only citing one or two references as examples.

7. Gold mining

Seven relevant publications were identified, five in South Africa and two in Australia.

Wyndham *et al* (1986)[71] followed 3971 white male South African gold miners from 1970 to 1979. The SMR for chronic respiratory diseases was significantly elevated at 166 (95% CI 108-243). In a case-control analysis, the 26 deaths from chronic respiratory diseases in men with at least 85% of their service in gold mining were each matched with four controls born in the same year as the case and who survived the case. Cumulative dust exposure had a significant effect on risk after adjustment for amount smoked.

Becklake *et al* (1987)[72] carried out an autopsy study of 44 cases of emphysema and 42 controls without emphysema from among male South African gold miners aged 51 to 71 years who had died during 1980 and 1981. After adjustment for age and smoking, working more shifts in high dust was shown to be a strong and independent predictor of emphysema.

In the same year Holman *et al*[73] carried out a cross-sectional survey of 1363 men employed in a Western Australian gold mine. After adjustment for age and smoking habits, there was a strong relationship of time spent in underground mining to risk of MRC chronic bronchitis on its own, or in conjunction with reduced FEV_1/FVC or FVC. Surface miners did not have any clear excess risk compared to those who had never mined.

In 1991 Cowie and Mabena[74] reported on a cross-sectional study of a working population of 1197 black male South African gold miners. "Three distinct pulmonary disorders could be discerned: silicosis-associated pulmonary dysfunction with dyspnea on effort; chronic airflow limitation, which was related to the duration of underground exposure; and a chronic bronchitic symptom complex, which reflected the intensity of dust exposure in the workplace." These conclusions were drawn from analyses that took smoking into account.

Musk *et al* (1992)[75] reported on a study of 208 nonsmoking Western Australian underground gold miners. After adjusting for age, duration of employment was associated with an increased prevalence of chronic bronchitis and a reduced FEV_1 and FVC, though none of these associations quite reached significance at $p<0.05$.

Another study of nonsmoking gold miners was reported from South Africa by Hnizdo *et al* in 1994[76]. Necropsies of 242 miners were studied. Cumulative silica dust exposure was not significantly related to the degree of emphysema found at necropsy.

Reid and Sluis-Cremer (1996)[77] reported results for longer, 20 year, follow-up for the same cohort of white South African gold miners considered earlier by Wyndham *et al*[71]. Of 4925 miners alive and working in 1970 and then aged 39 to 54, 2032 had died by 1989. The SMR for COPD, based on 176 deaths, was estimated as 189 (162-219), with significant excesses seen for various more specific causes contributing to this total including bronchitis and chronic obstructive airways disease, but not emphysema. A case-control analysis, based on COPD decedents and controls who had worked for a least 85% of their total service in the gold mine showed a significant association with cumulative dust exposure after adjustment for smoking.

Some further evidence supporting the relationship of gold mining to COPD can be found in the review paper by Garshick *et al*[6].

8. Iron mining

Studies have been reported in France and Sweden. In the study in France, Pham *et al*[78] re-examined 871 iron-ore mine workers, five years after an original cross-sectional survey had found a higher smoking-adjusted prevalence of chronic bronchitis in workers exposed to the effects of nitrous gases and dusts than in non-exposed workers. The follow-up analysis "showed that development of respiratory symptoms was more frequent and decline in lung function accelerated in the 5-year interval among underground workers who were still active as compared to those retired."

In 1988 Jörgensen *et al*[79] reported results of a 17 year follow-up study of a group of 240 Swedish iron ore miners originally examined in 1967. Based on the 167 workers followed up, no excess chronic bronchitis or decreased lung function was seen in underground workers compared to surface workers.

In 2004 Hedlund *et al*[80] compared 114 previous or current Swedish male iron ore miners with 2472 population controls. After adjustment for age, smoking and a family history of asthma, the miners had an increased risk of physician-diagnosed chronic bronchitis. The excess was particularly evident in nonsmokers.

Two years later Hedlund *et al*[81], in a study of 206 ex-iron ore miners in Sweden and 4560 population controls, reported a significant increased risk of physician-diagnosed chronic bronchitis in the miners, after adjustment for age, smoking and a family history of asthma. The authors contrasted the persistence of symptoms in ex-miners with the improvement in symptoms after quitting smoking.

9. Uranium mining and milling

Two reports[82,83], both from the Colorado Plateau in the USA, present evidence on mortality in relation to working with uranium.

The earlier report, by Roscoe in 1997[82] followed 3238 white male uranium miners from 1960 to 1990. Significantly increased SMRs were noted for emphysema (250, 95% CI 190-320) and chronic obstructive respiratory diseases other than emphysema or pneumoconiosis (280, 220-350).

The 2004 report, by Pinkerton *et al*[83] followed 1484 men employed in 7 uranium mills from 1940 to 1998. A significantly increased SMR was noted for emphysema (196, 121-299) but not for unspecified chronic bronchitis (91, 11-328). The increase for emphysema was "higher among workers hired prior to 1955 when exposures to uranium, silica and vanadium were presumably higher."

10. Foundry workers

Eight studies of foundry workers were identified as well as one general occupational study which presented relevant results.

Kärävä *et al* (1976)[84] carried out a study in Finland involving the 1000 foundry workers with the longest exposure time from a sample of 20 foundries. Subjects with high dust exposure were compared with subjects with lower exposure within smoking categories. Chronic bronchitis rates were higher in the more exposed group, significant in smokers but not in nonsmokers. High dust exposure was not associated with a significant reduction in FEV_1 or FVC; indeed for FEV_1 in nonsmokers and for FVC in smokers it was associated with a significant increase.

Silverstein *et al* (1986)[85] carried out a proportional mortality analysis of 278 deaths in US male hourly workers employed for at least 10 years at a gray iron foundry, comparing with national rates for males. A significant age standardized PMR was noted for emphysema (285, 95% CI 158-512), based on 10 cases, and for all non-malignant respiratory deaths (177, 122-256), based on 25 deaths. The excesses were evident in both smokers and nonsmokers.

Andjelkovich *et al* (1990)[86] reported on a retrospective cohort mortality study conducted among 8147 men and 627 women employed in a US gray iron foundry between 1950 and 1979, and involving more than 1700 deaths occurring in a 35-year period. In white men the SMR was almost significantly elevated for emphysema (162, 98-253) but was only slightly elevated for all diseases of the respiratory system (110, 83-142). In non-white men the SMRs were 126 (46-175) for emphysema and 87 (63-117) for the wider category. The authors also present a meta-analysis of data from 16 studies, which together give an overall observed/expected ratio of 1.4 based on a total of 1441 deaths from emphysema, but no excess for the wider category. Based on their own study, the authors also report non-significant positive trends in emphysema mortality with time since hire, but not with duration of foundry employment. The authors argue that the excess risk of emphysema in

the foundry workers may have been due to smoking, data for which were not available.

In another paper two years later based on the same study[87], Andjelkovich *et al* carried out SMR analyses by work area. They note that the pattern of excesses, with the greatest increases seen in finishing and in general service and maintenance, is similar for emphysema and lung cancer and they argue that variations in smoking habits between work areas may be the explanation. In support of their view, the authors cite analyses for lung cancer showing no relationship with length of time employed – an increase in those with a very short period of employment suggesting that the increased risk came before beginning work.

A further paper based on the same study in 1995[88] compared a sub-cohort of 3929 formaldehyde foundry workers with both the US population and with 2032 unexposed workers. In the SMR analysis the excess for emphysema was greater for unexposed workers (230, 115-441) than for those exposed to formaldehyde (128, 47-278). Exposure was also not associated with any increased risk in analyses within the cohort after adjustment for smoking.

Ostiguy *et al* (1995)[89] carried out a cross-sectional and follow-up (seven year) survey of 494 long-term workers in a Canadian copper refinery who were exposed to metal dusts and foundry fumes. Prevalence of COPD (FEV_1 <80% predicted) was not associated with the cumulative work-years at the plant or with any type of work at the plant. This was despite exposures to asbestos that produced pleural plaques, as well as the exposures to metal dusts and foundry fumes.

Kuo *et al* (1999)[90] studied 583 male workers from 50 iron foundries in Taiwan, comparing those who worked in four occupations: administrative, after processing, moulding and furnace. Furnace workers had the highest prevalence of chronic bronchitis. After adjusting for age, height and smoking there was a significant decrease based on work duration in FVC and FEV_1 for

furnace and moulding workers compared to the other two occupations. The authors concluded that "Prolonged exposure to free silica, and smoking habits, can result in respiratory abnormalities among foundry workers."

In the case-control study in Italy involving 131 COPD cases and 298 controls without respiratory diseases, which was reported by Mastrangelo *et al* in 2003[22], the OR adjusted for age and smoking was 12.0 (1.3-108.0) in foundry workers (compared to office workers), with some evidence of an increase in risk with length of exposure.

Mendonça *et al* (2007)[91] described a study in Brazil involving a total of 598 male workers in six foundries with sand moulding operations. Length of service was significantly associated with prevalence of chronic bronchitis, after adjustment for smoking, BMI and pneumoconiosis (but not age, which was highly correlated with length of service). Length of service was not, however, significantly associated with abnormal lung function.

11. Welders

Eleven studies specifically of welders were noted as well as two other general occupational studies which reported results for welders. Some welders would also be included in the studies of metal workers considered in section 12.

In a mortality study of 1059 white male welders employed between 1943 and 1973 in three US plants, Polednak (1981)[92] found a non-significant excess of deaths of emphysema (SMR 221, 95% CI 81-482, based on 6 cases) and of all diseases of the respiratory system (133, 71-227, n = 13), as compared to US white male death rates. Mortality did not vary materially in subgroups exposed or unexposed to nickel oxides. Nor was mortality related to length of work as a welder.

Sjögren and Ulfvarson (1985)[93] carried out a study in Sweden of 64 aluminium welders, 46 stainless steel welders and 149 railroad track welders, comparing them to non-welding industrial and railroad workers. Lung function was unaffected in any of the welding groups studied, but all groups showed a significantly higher frequency of chronic bronchitis symptoms than the comparison groups. A relationship seen between respiratory symptoms and level of ozone in aluminium welders was significant but one with chromium level in stainless steel workers was not. There was no evident relationship with the total particulate concentration in railroad welders.

Groth and Lyngenbo (1989)[94] carried out a cross-sectional study in Denmark comparing respiratory symptoms in 2660 welders (mainly shipyard welders) and a control group of 881 electricians. The welders showed a significantly ($p<0.01$) higher incidence of chronic bronchitis (21% vs 9%), which could not be explained by age, smoking or other airpolluting substances. A dose-response relationship was found between symptom prevalence and exposure to welding fumes.

In a study in Turkey reported in 1995, Özdemir *et al*[95] compared 110 welders with 55 controls from the same companies who were of similar age

and socioeconomic status and with no occupational dust or gas exposure. Chronic bronchitis was much more common in the welders (30% vs 11%), a difference which could not be explained by smoking. FVC and FEV_1 were significantly lower in welders, though this difference was only significant in smokers. Chronic bronchitis and pulmonary function was not significantly affected in those who had worked as a welder for less than 20 years.

In the occupational study in New Zealand published in 1997 by Fishwick *et al*[18] 1609 subjects completed a respiratory questionnaire. Compared to the professional, administrative and clerical service group, ORs (adjusted for age, sex and tobacco smoking) for welders, solderers and electronic processors were 1.5 (0.3-9.4) for chronic bronchitis and 0 for chronic bronchitis with airway obstruction, based on, respectively, 2 and 0 cases in this occupational group.

Bradshaw *et al* (1998)[96] carried out a cross-sectional study of respiratory symptoms and lung function in New Zealand involving 62 current welders and 75 non-welders at the same sites. In a multivariate analysis including age, smoking and race, total exposure to welding fumes for more than 10 years was associated with an OR for chronic bronchitis of 9.5 (1.3-69[*]), with the OR for 4-10 years 2.1 (0.3-15.5). FEV_1 and FVC were noted to be significantly lower in workers with a work-related respiratory symptom, but lung function seems not to have been studied directly in relation to exposure to welding fumes.

Sobaszek *et al* (1998)[97] compared respiratory symptoms and lung function in 134 stainless steel welders working in France and 252 blue-collar workers of similar age, height and duration of employment. Chronic bronchitis was increased in the welders (7.7% vs 3.8%) but not significantly. There was no significant difference between welders and controls in pulmonary function values. Although the authors reported a decrease in age-

[*] The upper 95% confidence limit is given as 1.9, which is not possible. It appears to be a typographical error for 69.

adjusted spirographic values after 25 years of welding activity, this was not significant for FEV_1.

In a follow-up of the New Zealand population considered earlier[96], Erkinjuntti-Pekkanen *et al* (1999)[98] reported a two-year follow-up among 54 welders and 38 non-welders. A relationship between chronic bronchitis and welding was noted (24.1% in welders vs 5.3% in non-welders, p = 0.02). Although no overall differences were noted between the two study groups in changes of pulmonary function, the authors did observe that welders who smoked and welders working without local exhaust ventilation or respiratory protection had an increased risk of accelerated decline in FEV_1.

Steenland (2002)[99] reported a mortality follow-up to 1998 of male mild-steel welders and non-welders employed at one of three US plants which began operation in the 1950s. The welders were not exposed to asbestos (as in shipyard welders) or to nickel or chromium (present in stainless steel). In the welders, the SMR, compared to the US population, was elevated, significantly for emphysema (194, 103-332) but not for bronchitis (127, 19-267) or other non-malignant respiratory diseases (112, 75-162), the last category being primarily non-specific COPD. However, similar excesses were seen for non-welders; emphysema 174, 110-261, bronchitis 195, 63-456 and other non-malignant respiratory diseases 103, 74-138, so no specific effect of mild-steel welding was evident. More detailed results by duration of exposure and latency were only reported for lung cancer.

In the case-control study in Italy involving 131 COPD cases and 298 controls without respiratory diseases, which was reported by Mastrangelo *et al* in 2003[22], the OR adjusted for age and smoking was 6.4 (1.6-25.5) in welders (compared to office workers), with a significant association noted with length of exposure.

In a study in Turkey in 2005, Fidan *et al*[100] compared 51 welders who had worked for at least five years and 31 control workers free of exposure to welding fumes and hazardous dusts. After adjustment for age and smoking,

the OR for chronic bronchitis was 4.78 (1.30-17.54). No significant effect of welding on FEV_1 or FVC was seen, but there was a significant reduction ($p = 0.002$) in the FEV_1/FVC ratio and in parameters of forced expiratory flow.

Hammond *et al* (2005)[101] compared rates of respiratory symptoms and COPD in three groups of car workers, 234 body welders, 116 paintshop workers and a control group of 357 assembly workers. Although welders had a significantly higher risk of respiratory symptoms than painters or assembly workers in age, race and smoking adjusted analyses, and significantly more improvements in symptoms on weekends or vacations, no significant increase in the adjusted OR was noted for COPD in welders.

Luo *et al* (2006)[102] carried out a study in Taiwan of four groups of males, 41 auto-body spot welders, 76 arc welders, 71 office workers and 59 assemblers without welding exposure, the last two groups being considered as a control group. Spot welders had reduced FVC and FEV_1, but only that for high exposure for FVC was significant. FVC and FEV_1 were not affected in arc welders, though significant reductions in PEFR were noted.

The review by Balmes[2] of the "Occupational Contribution to the Burden of Chronic Obstructive Lung Disease" listed welding fumes among the "agents that cause chronic bronchitis", though not citing specific references in support.

An earlier review by Nurminen and Karjalainen[11] was similarly unhelpful, citing a review by Becklake[4] as showing "little doubt that occupational exposure to … welding fumes plays an important role in the genesis of chronic obstructive pulmonary disease", when the Becklake review merely talks about fumes and not welding fumes.

12. Metal workers

Apart from the studies of foundry workers and welders noted in the previous two sections, nine studies of metal workers were also identified, as well as four other general occupational studies which reported results for metal workers.

Beaumont and Weiss (1980)[103] carried out a mortality study of 8679 members of a US metal trades union during the period 1950-1976. Compared to US men of comparable age and race, the risk of death from non-malignant respiratory diseases was increased (SMR 125 based on 146 deaths, $p<0.01$). The increase was greater (SMR 160, $p<0.01$) for mortality occurring at least 20 years after first employment and it was also related to cumulative exposure. Detailed results were not reported by subcategories of non-malignant respiratory diseases, but it was noted that burners using an oxyacetylene torch had an increased risk of emphysema (7 observed, 2.25 expected, $p<0.01$). Significant increases for all non-malignant respiratory diseases were noted in four of the eight job categories studied (welders, shipfitters, burners and boilertmakers).

Armstrong and Kazantzis (1985)[104] carried out a nested case-control study among three cohorts of cadmium workers in the UK. 276 workers who had died of bronchitis and emphysema were compared to up to three controls per case matched on date of birth and plant and alive at the time the case died. Mortality from bronchitis and emphysema was associated with high levels of exposure to cadmium fume and with duration of exposure.

In 1989, Scotti *et al*[105] compared two groups of industrial workers in Italy, 733 exposed and 1041 not exposed to the "specific risks of the iron and steel industry." The prevalence of chronic bronchitis and functional impairment was significantly related to exposure after adjustment for age and smoking.

Bogadi-Šare (1990)[106] compared 106 workers in Croatia exposed to stainless steel dust and 80 workers unexposed to irritant pollutants at work.

There was no greater prevalence of chronic bronchitis in the exposed groups, but lung function was significantly lower in both smokers and nonsmokers.

Kolarzyk *et al* (1992)[107] carried out a 16.5 year follow-up study in Poland of 65 men working in a coking plant and a control group of 34 men in a cold rolling mill working "in favourable hygienic circumstances." Although there was no significant difference in diagnosed COPD between the two groups, a faster decline of FEV_1 and VC was noted in the coking plant.

The same year, Rastogi *et al*[108] carried out a study in India involving 580 workers in the brassware industry and a reference group of 131 workers of similar socio-economic status unexposed to a dusty environment. While an increased risk of chronic bronchitis in the exposed workers was not statistically significant, there was a significantly increased smoking-adjusted risk in relation to increased time of working in the grinding, soldering and brass ingot making operations.

In the occupational study in New Zealand published in 1997 by Fishwick *et al*[18] 1609 subjects completed a respiratory questionnaire. Compared to the professional, administrative and clerical service group, ORs (adjusted for age, sex and tobacco smoking) for metal and electrical workers (other than welders, solderers and electronic processors) were 1.7 (95% CI 0.9-3.1) for chronic bronchitis and 1.8 (0.5-6.6) for chronic bronchitis with airway obstruction, based on, respectively, 16 and 3 cases in this occupational group.

Hobbesland *et al* (1997)[109] carried out a mortality analysis of 14730 male ferroalloy workers in Norway employed for at least 6 months in 1933-1990. Overall mortality from all non-malignant respiratory diseases or from bronchitis, emphysema or asthma was not increased compared to age- and year-specific national rates. However, there was a significant increase in mortality from bronchitis, emphysema or asthma in men with at least 3 years work in ferrosilicon/silicon-metal plants, with a significant increase per unit of amorphous silica exposure.

Lubin *et al* (2000)[110] followed 8014 white male workers employed for a year or more prior to 1957 at a US copper smelter from 1938 to 1989. The SMR, compared to the US national population, was 156 (142-212) for all non-malignant respiratory diseases, based on 455 deaths, and 173 (141-212) for emphysema, based on 93 deaths. There was no relationship, within the cohort, between risk of emphysema or of all non-malignant respiratory diseases and increasing exposure to inhaled airborne arsenic.

In 2000, Tüchsen and Hannerz[23] estimated age standardized COPD hospitalization ratios for various occupational groups compared to Danish national rates for age 20-59 for 1981-1993. A significantly elevated risk was seen in workers in the iron and metal industry in both males (ratio = 158) and females (ratio = 153). This association was not significant after controlling for social group.

In a general population survey in 14 industrialized countries involving 13,253 subjects aged 20 to 44 reported in 2001, Zock *et al*[24] reported no clear relationship of lung function or chronic bronchitis to metal working.

In the case-control study in Italy involving 131 COPD cases and 298 controls without respiratory diseases, which was reported by Mastrangelo *et al* in 2003[22], the OR adjusted for age and smoking was a nonsignificant 1.4 (0.4-4.6) in metal workers (compared to office workers).

Sorahan and Esmen (2004)[111] studied a cohort of 926 male nickel-cadmium battery workers in England employed for a year or more prior to 1975, with mortality followed up to 2000. Compared with England and Wales mortality rates by age and period, a significantly increased risk of mortality was noted for all non-malignant diseases of the respiratory system (SMR 142, 109-182 based on 61 deaths). No more detailed breakdown of deaths within this category was presented. There were no significant trends in mortality by year of hire or period from commencing employment and, in an internal

analysis, no significant trends in mortality by cumulative exposure to cadmium.

In his review of the "Occupational Contribution to the Burden of Chronic Obstructive Pulmonary Disease", Balmes (2005)[2] includes "metals : osmium, vanadium and welding fumes" in a table of "some agents that cause chronic bronchitis".

13. Carbon black workers

Surveys have been carried out of European and North American carbon black workers. In 1993 Gardiner *et al*[112] reported on a study of 3086 employees in 18 plants in 7 European countries. Symptoms of chronic bronchitis were found to be increased, and lung function decreased in relation to increasing indices of current exposure to carbon black dust, after adjustment for age, smoking and previous hazardous exposure.

In 2003, Harber *et al*[113] described a similar study of 1755 workers in 22 North American plants. After adjustment for age, sex, race and smoking there was a significant relationship of cumulative carbon black exposure to reduced FEV_1 but not clearly to other lung function variables. Recent exposure was unrelated to lung function. Heavy cumulative exposures were also associated with a small increase in chronic bronchitis in nonsmokers, but there was no significant association in smokers.

14. Exposure to silica

Nine papers, six describing specific studies and three reviews, have provided evidence relating silica to COPD.

Ng *et al* (1992)[114] carried out a study in Singapore of 85 rock drilling and crushing workers in a granite quarry with a high level of exposure to silica dust, 154 quarry maintenance and transport workers with low dust exposure and an external comparison group of 148 postal workers with no granite dust exposure. The highly exposed group showed a significant increase in age-adjusted prevalence of chronic bronchitis, evident in both smokers and nonsmokers. After allowing for the effects of age, height, race and smoking, the highly exposed quarry workers showed an average 5% lower FEV_1, FVC and $\%FEV_1/FVC$ when compared with the other groups, a difference evident both in current smokers and nonsmokers.

Meijer *et al* (2001)[115] studied 144 concrete workers from two factories in the Netherlands and a control group of 110 office workers of similar age, weight and length of employment. No statistical differences in chronic respiratory symptom prevalence was seen between the two groups. No difference was seen in FVC or FEV_1 but a 2% lower FEV_1/FVC ($p = 0.02$) was seen in the concrete workers, independent of smoking habits and a history of allergy.

In the review by Cohen and Velho in 2002[66] entitled "Update on respiratory disease from coal mine and silica dust", there is a section entitled "Silica exposure and lung function impairment and obstructive lung disease". This starts by pointing out that "the data on silica exposure and chronic obstructive lung disease comes from a series of studies of South African gold miners" (see also section 7), concluding that "silica dust seems to be a more potent toxin than coal mine dust in causing COPD". Cohen and Velho also cite evidence from gold miners and silica-exposed granite workers showing resulting declines in FEV_1.

Merget *et al* (2002)[116] published a review of the "Health hazards due to the inhalation of amorphous silica." Tables are presented summarizing evidence on amorphous (non-crystalline) silica from epidemiological studies, case reports and animal studies. The review notes that "Occupational exposure to crystalline silica dust is associated with an increased risk for pulmonary diseases such as silicosis, tuberculosis, chronic bronchitis, chronic obstructive pulmonary disease (COPD) and lung cancer" and that "The major problem in the assessment of health effects of amorphous silica is its contamination with crystalline silica." It states that "Epidemiological studies do not support the hypothesis that amorphous silicas have any relevant potential to induce fibrosis in workers with high occupational exposure to these substances, although one study disclosed four cases with silicosis among subjects exposed to apparently non-contaminated amorphous silica. Since the data have been limited, a risk of chronic bronchitis, COPD or emphysema cannot be excluded."

Romundstad *et al* (2002)[117] followed the mortality from 1962 to 1966 of 2562 men working in one of three silicon carbide smelters in Norway. There were 45 deaths from asthma, chronic bronchitis or emphysema as against 20.4 expected from national age-specific rates (SMR 220, 95% CI 160-300). There were indications of a positive association between cumulative exposure to total dust and mortality from these three causes combined, which became clearer after restricting the analyses to workers employed for more than three years. Additional analyses suggested that smoking did not act as a confounder.

Calvert *et al* (2003)[118] carried out a case-control analysis based on death certificates from 1982 to 1995 in 27 US states comparing 94922 COPD deaths with 474564 deaths whose certificate did not mention the disease of interest or any of several diseases reported to be associated with crystalline silica exposure. The controls were matched 5:1 to each case on sex, race, state, age and period of death. Subjects were classified into four groups (low or no, medium, high, super high) of crystalline silica exposure based on their

occupation. A conditional logistic regressional analysis showed a significant trend ($p<0.001$) in risk of COPD with ORs of 1.02 (0.99-1.04), 1.29 (1.25-1.33) and 1.47 (1.30-1.66) for, respectively, medium, high and super high exposure relative to low or no exposure.

Hnizdo and Vallyathan (2003)[119] carried out a review of the epidemiological and pathological evidence relating COPD to occupational silica dust exposure. The authors noted that "Occupational exposure is an important risk factor for chronic obstructive pulmonary disease (COPD), and silica dust is one of the most important occupational respiratory toxins", and concluded that "The evidence surveyed suggests that chronic levels of silica dust that do not cause disabling silicosis may cause the development of chronic bronchitis, emphysema, and/or small airways disease that can lead to airflow obstruction, even in the absence of radiological silicosis."

Brown and Rushton (2005)[120] carried out a mortality study to 2001 of 2703 workers employed for at least one year in one of seven UK silica sand producing quarries. Compared with national mortality rates, COPD mortality was not increased in men (SMR 80.6, 49.9-123.2) and no COPD deaths were seen in women. There was no significant excess death rate from non-malignant respiratory disease in any of the seven quarries, and no association with level of cumulative respirable crystalline silica.

Oliver and Miracle-McMahill (2006)[121] carried out a study of airway disease in 317 US highway and tunnel construction workers exposed to silica. A logistic regression analysis is presented in which prevalence of chronic bronchitis is related to age, smoking status, whether the worker tunnelled or mined, whether the worker broke through slurry walls, whether the worker carried out chipping caisson overpour, present trade (six categories), months at site and years at usual job. These analyses are presented in two ways – unadjusted (one variable at a time) and adjusted (considering all the variables simultaneously). The adjusted analyses seem hopelessly unstable, due to highly correlated variables, both as regards time and job. For example, the

model shows a reduced risk of chronic bronchitis for the variable tunneled/mined (OR 0.26), and a highly increased risk (OR 25) for present trade as a tunnel worker. Also, the analyses for present trade use labourer as a reference group, despite it being clear that this group has a substantial proportion of subjects being involved in work activities involving silica exposure, including a higher proportion than any other group for the activity "chipping caisson overpour". Although the authors conclude that "Tunnel construction workers exposed to respirable crystalline silica and cement dust are at increased risk for airway disease. Extent of risk varies by trade and work activity", the analyses presented seem almost uninterpretable.

The review by Balmes[2] of the "Occupational Contribution to the Burden of Chronic Obstructive Lung Disease" listed silica and silicates among the "agents that cause chronic bronchitis", although not citing specific references in support or discussing the difference between the effects of crystalline and amorphous silica.

15. Farming

Twenty-one studies of specific groups of farmers, three general reviews of the effects of farming and six general occupational studies provide information on the relationship of farming to COPD.

Heller *et al* (1986)[122] compared 428 male farmers and farm workers in different regions of England and Wales with 356 control men working in the same areas in industries not known to be associated with an occupational lung disease. The prevalence of chronic bronchitis, adjusted for age, smoking, social class and area, did not differ between the two groups. The farmers had non-significantly higher FEV_1 and FVC, however, but significantly lower FEV_1 given FVC.

Vohlonen *et al* (1987)[123] carried out cross-sectional and follow-up surveys of 12056 farmers in Finland. In analyses adjusted for age, sex, smoking and atopy, prevalence and annual incidence of chronic bronchitis varied significantly by task ($p<0.001$). Thus, prevalences were 12.9% for swine tending, 8.9% for cattle tending, 5.8% for poultry tending and 5.3% for plant cultivation. When detailed characteristics of the work were investigated, the methods of grain handling and drying were considered by the authors to be the most important factors for predisposing farmers to chronic bronchitis and farmer's lung.

Iversen *et al* (1988)[124] carried out a study of 1685 farmers in Denmark. In an analysis adjusted for age and smoking, those who worked with pigs had an OR of 1.53 (1.10-2.36) for chronic bronchitis compared to those who did not work with pigs.

Dalphin *et al* (1989)[125] compared 250 dairy farmers in the Doubs area of France with 350 control administrative workers matched for sex, age, height and smoking habits. The dairy farmers had an increased prevalence of chronic bronchitis (OR 2.13, 95% CI 1.11-4.07) and significantly reduced FVC ($p<0.01$) and FEV_1/FVC ($p<0.001$). Results for FEV_1 were not presented.

Chen *et al* (1991)[126] studied 1633 residents of a town in Canada, looking in detail at the joint effects of grain farming and smoking on lung function and on the prevalence of chronic bronchitis. There were no effects of grain farming on FVC or FEV_1 in either sex or on FEV_1/FVC in men, but in women FEV_1/FVC was markedly reduced in heavy smoking grain farmers, leading to a significant main effect (p=0.006) and interaction (p=0.001) in their analyses. Chronic bronchitis rates in grain farmers were generally higher than in non-farmers, given smoking habits and sex, particularly in women, but no overall test of the effects of grain farming was presented.

In a further study of dairy farmers in the Doubs area of France, Dalphin *et al* (1993)[127] compared 197 male dairy farmers with chronic bronchitis and 163 without. No relationship was seen between chronic bronchitis and plant dust exposure assessed by quantification of barn threshing and cattle foddering.

In a study in France, Nejjari *et al* (1996)[128] studied the determinants of chronic bronchitis in a sample of 2406 subjects aged 65 years or over. In a multivariate analysis adjusting for age, sex, smoking, education, history of asthma and digitalis intake, farm workers had an increased prevalence compared to white collar workers (OR 1.70, 1.12-2.54).

In the occupational study in New Zealand published in 1997 by Fishwick *et al*[18] 1609 subjects completed a respiratory questionnaire. Compared to the professional, administrative and clerical service group, ORs (adjusted for age, sex and tobacco smoking) for farmers and farm workers were 0.9 (0.2-3.6) for chronic bronchitis and 3.1 (0.3-29.6) for chronic bronchitis with airway obstruction, based on, respectively, 2 and 1 cases in this occupational group.

In a third study from the Doubs region of France, Mauny *et al* (1997)[129] reinvestigated in 1995 113 barn-drying farmers and 231 traditional-drying farmers studied originally in 1990. The initial results had suggested that barn-drying fodder may protect dairy farmers from lung function

impairment. The follow-up results confirmed the original observations, with barn-drying farmers having a lower prevalence of chronic bronchitis (4 v 10%, $p<0.05$) and slightly higher FEV_1 ($p=0.06$) and FEV_1/FVC ($p<0.01$) than traditional-drying farmers, after adjustment for age, smoking, altitude and cumulative exposure. However no difference was seen between the groups of farmers in decline in lung function over the period.

Melbostad *et al* (1997)[130] carried out a study of 8482 farmers and spouses in Norway. Work-related factors of importance for chronic bronchitis were full-time versus part-time farming, involvement in livestock production and occupational exposure to dust outside agriculture. The combinations of the work exposure factors were significant and showed a 2- to 3-fold increase in risk, with combinations with smoking showing up to a 6-fold increase.

In a further study from the Doubs region of France, Dalphin *et al* (1998)[131] compared a sample of 265 dairy farmers and 149 non-exposed administrative workers. Prevalence of chronic bronchitis, adjusted for age, sex and smoking, was much higher in the dairy farmers (OR 11.8, 1.4-97.1). There was no significant difference in FEV_1 or FVC between the two groups, but a reduction in FEV_1/FVC ($p<0.025$).

In 1998 Forastiere *et al*[19] reported on a cross-sectional study of 1226 US women aged 55+ in which frequency of a physician diagnosis of chronic bronchitis or emphysema in various occupational groups was compared to that in managers, professional and administrative occupations after adjustment for age and smoking. Those working in farming, forestry and fishing had an OR of 1.9 (0.8-4.8) based on 7 cases in that occupational group.

Kirkhorn and Garry published a review in 2000[132] entitled "Agricultural lung diseases." This presents information on the large number of exposures that may be relevant, including inorganic and organic dusts, allergens, endotoxins, microorganisms, toxic gases and pesticides, and the variety of types of lung condition that may result. References are cited associating chronic bronchitis with working with animals (including swine),

working in grain production, and with endotoxin exposure. The authors conclude that "It is clear that present-day agricultural exposures to dusts and gases are associated with acute and chronic respiratory diseases and syndromes."

In 2000, Tüchsen and Hannerz[23] estimated age standardized COPD hospitalization ratios for various occupational groups compared to Danish national rates for age 20-59 for 1981-1993. Male farmers had a significantly elevated risk (SHR = 115) but women working in agriculture had a significantly reduced risk (SHR = 49). In men the increase diminished over time.

Danuser *et al* (2001)[133] described a study of 1542 Swiss farmers. Farmers were subdivided into seven groups (crop, pig, pig/cattle, cattle, poultry, and mixed farmers, and working in small farms). Compared to the final group, the prevalence of chronic bronchitis, adjusted for age and smoking, was increased in crop farmers (OR 2.32, 1.03-5.23) but not in other groups. There was also a significant increase (2.61, 1.01-6.76) in those who spent >4 hours in animal confinement buildings as compared to those who spent 0-1 hours. For 1-4 hours the OR was 2.08 (0.87-4.96).

Kimbell-Dunn *et al* (2001)[134] carried out a study of 1706 farmers in New Zealand. After adjusting for sex and smoking, the prevalence of chronic bronchitis was significantly increased in those involved in hay handling (OR 1.6, 1.1-2.3) and in those working with horses (1.6, 1.1-2.5) but not in those working with pigs, with poultry, with stored grain or with grain crops compared to farmers not working in any of these. In other analyses chronic bronchitis was associated with growing barley (1.8, 1.1-2.9) and working with oats as a crop (2.1, 1.2-3.8).

In a general population survey in 14 industrialized countries involving 13,253 subjects aged 20 to 44 reported in 2001, Zock *et al*[24] reported no clear relationship of lung function to working in agriculture. However, an association with chronic bronchitis was seen, more evident in smokers.

In 2002 Hnizdo *et al*[20] estimated risk of COPD (FEV_1/FVC <70%, FEV_1 <80% of predicted) for subjects aged 30-75 by occupational group based on NHANES III, conducted in the USA in 1988 to 1994. Adjustment was made for age, sex, race, BMI, smoking, education and SES, and comparison was made to office workers. Two years later the same authors[21] also presented similar analyses but for airflow obstruction (FEV_1/FVC <75%, FEV_1 <80% of predicted) and by race. For workers in agriculture the OR for COPD was 1.5 (0.8-2.7) for all subjects and 0.8 (0.2-2.8) for never smokers. The ORs for airflow obstruction were 1.2 (0.6-2.3) in Caucasians, 2.0 (1.0-4.4) in African-Americans and 3.1 (1.4-6.9) in Mexican-Americans.

Linaker and Smedley (2002)[135] published a review paper entitled "Respiratory illness in agricultural workers." This includes a short section which is reproduced below.

> "**Chronic obstructive airways disease**
>
> It is not clear whether chronic obstructive airways disease should be regarded as an occupational disease of farmers. Agricultural exposures to organic and inorganic dusts, gases and fumes can cause irritation and inflammation of the airways. In theory, prolonged exposure might lead to chronic airflow limitation through airway obstruction or loss of elastic recoil in damaged parenchyma. Cross-sectional surveys using standardized symptom questionnaires (Medical Research Council, American Thoracic Society) to ascertain chronic bronchitis have found prevalence rates of 7-26% among various farming populations. In some studies, symptom rates have been higher among farmers who work with confined animals as compared with farmers using non-confinement methods or non-farming controls, but others have found similar symptom rates in all groups. In studies that adjusted for smoking status, some found an increased rate of symptoms of chronic bronchitis in farmers. The association between work in farming and impaired (obstructive) lung function has

been variable. Several studies have found no significant reduction of lung function in farming populations compared with controls, despite increased symptom rates. Overall, there is no excess mortality from chronic bronchitis in farmers compared with the rest of the working population in the UK, although this is likely to be confounded by a low prevalence of smoking in farmers."

A number of the references cited by Linaker and Smedley (not shown) are publications described above.

Another review the same year by Omland[136] is entitled "Exposure and respiratory health in farming in temperate zones – a review of the literature." This contains sections on chronic bronchitis and on lung function, each sub-divided into cross-sectional studies and longitudinal studies. He concludes that "chronic bronchitis is frequent and data suggests that it is work related in farmers" and that "… pig farming, and animal production are common risk factors for chronic bronchitis …". He also considers that "FEV_1, and FEV_1/FVC seems to be reduced in farmers, and longitudinal studies indicate an increased annual loss in FEV_1 in farmers, especially in pig farmers."

Radon *et al* (2002)[137] summarize results from the European Farmers' Project, a cross-sectional study of nearly 8000 farmers in seven centres in Denmark, Germany, Switzerland, the UK and Spain. Compared to the population of the European Community Respiratory Health Survey, animal farmers had a significantly higher prevalence of symptoms of chronic bronchitis. The major risk factor for respiratory symptoms was shown to be ventilation of the animal houses and greenhouses.

In yet another study in the Doubs area of France, Chaudemanche *et al* (2003)[138] evaluated 215 dairy farmers and 110 controls in 1994 and again in 1999. In 1999 analyses the prevalence of chronic bronchitis was higher ($p=0.013$) and FEV_1/FVC lower ($p<0.025$) in the dairy farmers after adjustment for age, sex and smoking, but FEV_1 and FVC did not significantly

differ between the groups. Over the five year follow-up period the annual decline in FEV_1/FVC, but not in FVC or FEV_1, was significantly ($p<0.025$) greater in farmers.

In the case-control study in Italy involving 131 COPD cases and 298 controls without respiratory diseases, which was reported by Mastrangelo *et al* in 2003[22], the OR adjusted for age and smoking was 15.1 (3.2-71.6) in farmers (compared to office workers), with a significant association noted with length of exposure.

Monsó *et al* (2003)[139] carried out a study comparing 7188 farmers in Europe and 1839 in California. Chronic bronchitis was more prevalent in Europe (12.2%) than in California (4.4%). Compared to unexposed farmers, and after adjustment for age and smoking, prevalence of chronic bronchitis was significantly elevated in swine farmers (OR 1.22, 1.03-1.43), rabbit farmers (1.68, 1.13-2.50), grain farmers (1.42, 1.21-1.67), oil plant farmers (1.49, 1.22-1.81) and cotton farmers (1.67, 1.22-2.27). It was also significantly associated with toxic pneumonitis, working inside animal confinement buildings and working inside a greenhouse.

Monsó *et al* (2004)[140] carried out a study of 105 never smoking animal farmers working inside confinement buildings. 18 had COPD according to the GOLD criteria. Exposure to total dust and to endotoxins in total dust were determined by personal samples, and measurements of various indoor air contaminants were made in the workplaces. After adjustment for age, sex, and type of farming, the prevalence of COPD showed a significant relationship to total dust (OR 6.60, 1.10-39.54 for 4^{th} quartile v 1^{st} and 2^{nd} quartiles combined). There was also some relationship with endotoxins, significant in crude, but not in adjusted, analyses.

Blair *et al* (2005)[141] reported results of a study in the USA of 52393 private pesticide applicators and 32345 spouses of farmers. There were a total of 2055 deaths over a 5 year follow-up period. Compared to general population mortality rates in the relevant states, the SMR for COPD was very

low for both the private applicators (20, 10-30) and for the spouses (30, 20-70). SMRs were generally low for these populations for most causes, the authors commenting that "Several factors may contribute to the low mortality observed in this population, including the healthy worker effect typically seen in cohorts of working populations (which may decline in future years), a short follow-up interval, and a healthier lifestyle manifested through lower cigarette use and an occupation that has traditionally required high levels of physical activity."

Schenker *et al* (2005)[142] describe results from a population-based survey of 1947 California farmers. After adjusting for age, smoking and sex, those with high dust exposure had a "borderline significant" increased odds of chronic bronchitis (OR 1.8, 0.9-3.7). There was no relationship of chronic bronchitis to farm type.

In yet one more study from the Doubs region of France, Gainet *et al* (2007)[143] re-evaluated in 1998 157 dairy farmers and 159 controls first studied in 1986. In 1998 the prevalence of chronic bronchitis was higher in the farmers than in the controls (OR 2.22, 1.09-4.53), after adjusting for age, sex and smoking. FVC ($p<0.025$), FEV_1 ($p<0.001$) and FEV_1/FVC ($p<0.001$) were all significantly lower in the farmers. Over the 12 year follow-up period the decline in FEV_1 and in FVC was similar in both groups, but dairy farming was associated with a significantly ($p<0.001$) greater reduction in FEV_1/FVC. Decline in FVC was accelerated in dairy farmers working in traditional farms and those currently foddering.

Lamprecht *et al* (2007)[144] carried out a population based sample of 2200 adults aged 40 years and over in Austria. Non-reversible airways obstruction was defined as a post-bronchodilator $FEV_1/FVC < 0.70$. Ever having worked in a farm for three months or more was significantly associated with airways obstruction. For COPD GOLD stage I or higher the OR was 1.5 (1.1-2.0) and for stage II or higher it was 1.8 (1.2-2.7), the latter estimate being unchanged when adjustment for sex, age and smoking was carried out.

Valcin *et al* (2007)[145] used data for 21541 nonsmoking women in the US Agricultural Health Study to evaluate occupational risk factors for chronic bronchitis. ORs were adjusted for age, state and related agricultural exposures. "Applying manure and driving combines were independently associated with chronic bronchitis. Off-farm job exposures associated with chronic bronchitis were organic dusts, asbestos, gasoline, and solvents. Five pesticides were associated with chronic bronchitis after multivariate adjustment and sensitivity analyses: dichlorvos (OR = 1.63, 95% CI = 1.01, 2.61), DDT (OR=1.67, 95% CI = 1.13, 2.47), cyanazine (OR = 1.88, 95% CI = 1.00, 3.54), paraquat (OR = 1.91, 95% CI = 1.02, 3.55), and methyl bromide (OR = 1.82, 95% CI = 1.02, 3.24)."

In a general review of "Occupationally induced airways obstruction" Garshick *et al*[6] include sections on grain dust and on agricultural and farm workers; other organic dusts. They note that "Studies in … grain workers … suggest that occupational standards in effect are not sufficient to protect the working population from adverse effects." No clear conclusions are reached for farmers.

16. Poultry workers

Three studies are considered, two from Croatia and one from Sweden. In the first study in Croatia, reported in 1994, Zuskin *et al*[146] compared 57 female workers employed in the processing of poultry food and 51 non-exposed control workers of similar age. Prevalence of chronic bronchitis was much higher in the poultry workers (26% v 4%), as was prevalence of other chronic respiratory symptoms.

The next year the same group[147] also reported a higher prevalence of chronic bronchitis in 343 poultry workers in Croatia than in 200 controls with a similar age, smoking habit and duration of employment. Prevalence increased with increasing years exposed. Lung function was also significantly impaired in the poultry workers, particularly in workers with a longer duration of exposure.

Rylander and Carvalheiro[148] studied 42 nonsmoking poultry workers in Sweden and 40 nonsmoking controls. The poultry workers were slightly older but there was no significant difference for years worked. In the poultry workers FEV_1 (but not other lung function variables) was significantly lower and symptoms related to chronic bronchitis were significantly higher. The authors noted that "Endotoxin levels in the poultry buildings exceeded those earlier suggested as the threshold value for airways inflammation."

17. Textiles and cotton

Six studies of textile workers were identified as well as three more general occupational studies which presented relevant results, and one review of the respiratory effects of long-term exposure to cotton dust.

In 1982 Beck *et al*[149] described a 6-year follow-up study of a cohort of 383 white active and retired US cotton textile workers and of a control cohort of 277 white men and women who had not worked in a cotton textile mill. The frequency of all respiratory symptoms studied, including chronic bronchitis, was substantially higher in the cotton workers, and loss of FEV_1 over the 6 year period was significantly greater. These differences were evident in both sexes and in smokers and nonsmokers.

Fishwick *et al*[150] conducted a cross-sectional study of 1057 white cotton and man-made fibre spinning mill operatives in the UK. After adjustment for age, sex and smoking, increasing time worked in the waste room was associated with a significant reduction in FEV_1 and FVC. "Current and retrospective cotton dust exposures did not appear as predictor variables in the regression analysis although in a univariate analysis, FEV_1 was reduced in those operatives exposed to high dust concentrations assessed by personal and work area sampling."

In 1997 Niven *et al*[151] reported a study in the UK comparing 2168 cotton textile workers and 863 workers exposed to man-made fibre textiles. After adjustment for sex, age, smoking and race, the cotton textile workers were significantly more likely to suffer from chronic bronchitis, and prevalence was also associated with increasing cumulative exposure to cotton dust. The diagnosis of chronic bronchitis was associated with a small but significant decrement in lung function.

In the same year Zuskin *et al*[152] described a study in Croatia of 135 textile dyeing workers and 103 non-exposed control workers. The frequency of all respiratory symptoms, including chronic bronchitis, was substantially higher in the textile dyeing workers in both smokers and nonsmokers.

Ventilatory capacity was significantly reduced in the exposed population and was also lower after than before the morning shift.

Christiani *et al* (2001)[153] carried out a 15 year follow-up study in China of 447 cotton textile workers and a control group of 472 silk textile workers. Testing occurred four times during the period. More workers in the cotton group consistently reported symptoms than in the silk group. After adjustment for age, sex and smoking, the cotton workers had small, but significantly greater annual declines in FEV_1 and FVC than did the silk workers. Longitudinal change in FEV_1 in cotton workers was significantly related to years worked in the mills and to high levels of endotoxin.

In a general population survey in 14 industrialized countries involving 13,253 subjects aged 20 to 44 reported in 2001, Zock *et al*[24] reported no clear relationship of lung function to working in textiles. However, an association with chronic bronchitis was seen, more evident in smokers.

In 2002 Hnizdo *et al*[20] estimated risk of COPD (FEV_1/FVC <70%, FEV_1 <80% of predicted) for subjects aged 30-75 by occupational group based on NHANES III, conducted in the USA in 1988 to 1994. Adjustment was made for age, sex, race, BMI, smoking, education and SES, and comparison was made to office workers. Two years later the same authors[21] also presented similar analyses but for airflow obstruction (FEV_1/FVC <75%, FEV_1 <80% of predicted) and by race. For workers in textile mill products manufacturing the OR for COPD was 2.2 (95% CI 1.1-4.2) for all subjects and 3.1 (0.4-28) for never smokers. The ORs for airflow obstruction were 2.0 (1.0-3.9) in Caucasians, 1.2 (0.5-3.1) in African-Americans and 7.2 (1.3-40.1) in Mexican-Americans.

In the case-control study in Italy involving 131 COPD cases and 298 controls without respiratory diseases, which was reported by Mastrangelo *et al* in 2003[22], the OR adjusted for age and smoking was 7.2 (1.3-41.1) in cotton textile workers (compared to office workers), with a significant association noted with length of exposure.

Wang *et al* (2003)[154] report further results, relating to respiratory symptoms, from the 15 year follow-up study in China reported earlier by Christiani *et al*[153]. Byssinosis was only reported in the cotton workers and incidences of chest tightness, chronic bronchitis, cough and dyspnoea were stated to be more common and persistent in the cotton workers than in the silk workers, though the difference for chronic bronchitis was quite slight, and not significant. In the cotton workers chronic bronchitis was significantly less common in those workers who had left the mills and in relation to years since last worked, these analyses being adjusted for age, sex, smoking and years worked. Relationships to cumulative exposure to endotoxin and to dust were only evident for byssinosis and not for other respiratory symptoms.

The same year Christiani and Wang[155] published a short review of "Respiratory effects of long-term exposure to cotton dust." That review leans heavily on the results from the 15 year follow-up study in China[153,154]. They note that "The precise etiology of airway disease caused by cotton dust and other organic dusts remains to be determined. However, increasing evidence indicates that cotton dust *per se* is not the causal factor, but dust contaminated with endotoxin is most likely the causative agent of byssinosis."

In an earlier general review of "Occupationally induced airways obstruction" Garshick *et al*[6] include a section on cotton dust. They note that "exposure to cotton dust is associated with symptoms of chronic bronchitis that tend to coexist with byssinosis" and that the available pathologic studies "do not suggest that cotton dust exposure results in pathologic evidence of emphysema. The changes described are those of chronic bronchitis."

18. Woodworkers

Six studies of woodworkers were identified as well as four more general occupational studies which presented relevant results.

Liou *et al* (1996)[156] carried out a study in Taiwan involving 82 workers from 12 wood mill plants and 262 office workers in a shipyard as the comparison group. In smokers, respiratory symptom prevalence did not differ between the two groups, but in nonsmokers the incidence of chronic bronchitis and some other symptoms was greater in the wood mill workers. "After adjustment for age, sex, height, and smoking status, all parameters of pulmonary function were significantly lower in exposed workers than in controls and showed a declining trend with increasing exposure levels classified by job titles."

Robinson *et al* (1996)[157] carried out a proportionate mortality analysis based on 27,362 members of the US Carpenters' Union who died in 1987-1990. Compared to national age-, sex- and race-specific mortality for the years of the study, significantly raised mortality was noted for emphysema (114, 102-128) in white males. A similar excess was seen for construction carpenters and wood products carpenters, but no trend was evident by number of years in the Union.

In the occupational study in New Zealand published in 1997 by Fishwick *et al*[18] 1609 subjects completed a respiratory questionnaire. Compared to the professional, administrative and clerical service group, ORs (adjusted for age, sex and tobacco smoking) for woodworkers were 0.5 (0.1-5.3) for chronic bronchitis and 0 for chronic bronchitis with airway obstruction, based on, respectively, 1 and 0 cases in this occupational group.

Lipscomb and Dement (1998)[158] studied lung diseases in 1989-1992 in a cohort of 10,938 active union carpenters. There were 51 cases coded as chronic bronchitis, 22 from emphysema, 90 from chronic obstructive airway disease and 511 from bronchitis unspecified as acute or chronic. No association with years in the union or type of work was seen for unspecified

bronchitis, and no results were given for emphysema. Rates were nonsignificantly higher in relation to longer time in work for chronic bronchitis and for chronic obstructive airway disease.

In 1999, Mandryk *et al*[159] reported on a study in Australia of 197 workers (virtually all male) in four sawmills, one wood chipping mill and five joineries. Maintenance workers at the woodworking sites (who would not normally have wood dust exposure) were used as controls. The woodworkers of all types had markedly lower FEV_1 and FVC than the controls after adjustment for age, sex and smoking. Woodworkers also had a markedly higher adjusted prevalence of chronic bronchitis.

The next year, the same authors[160] studied a total of 87 workers from three green and two dry sawmills in Australia as well as an undefined group of 30 controls. The green mill workers had significantly higher rates of chronic bronchitis than either the dry mill workers or the controls in the green mill workers. Significant dose-response relationships were found between lung function and personal exposures to dust, endotoxin, glucan, fungi and gram negative bacteria.

In 2000, Tüchsen and Hannerz[23] estimated age standardized COPD hospitalization ratios for various occupational groups compared to Danish national rates for age 20-59 for 1981-1993. No increased risk was seen overall in wood and wood products workers.

In a general population survey in 14 industrialized countries involving 13,253 subjects aged 20 to 44 reported in 2001, Zock *et al*[24] reported no clear relationship of lung function to working with wood. However, an association with chronic bronchitis was seen, more evident in smokers.

In the case-control study in Italy involving 131 COPD cases and 298 controls without respiratory diseases, which was reported by Mastrangelo *et al* in 2003[22], the OR adjusted for age and smoking was 4.4 (95% CI 1.1-17.7) in wood carpenters (compared to office workers).

Friesen *et al* (2007)[161] studied the relationship between COPD and other diseases to various exposure indicators in a population of 26,847 sawmill workers in Canada employed between 1950 and 1995. There was limited evidence of a relationship between COPD hospitalizations and non-specific particulates. However, there was a roughly monotonic relationship with increasing wood dust exposure, with the slope significant.

19. Brick workers

Two studies specifically of brick workers are considered, one from South Africa and one from the USA. One of the more general occupational studies also provides information.

The study reported by Myers and Cornell in 1989[162] concerned 268 brick workers in South Africa. Regression analysis showed that exposure to dust was significantly associated with an increased prevalence of respiratory symptoms, including chronic bronchitis, and with reduced lung function. Smoking generally had less of an effect than dust and was not significantly associated with reduced lung function.

In the case-control study in Italy involving 131 COPD cases and 298 controls without respiratory diseases which was reported by Mastrangelo *et al*[22], the OR adjusted for age and smoking was 6.5 (95% CI 1.1-37.0) in refractory brick workers (compared to office workers), with a significant association noted with length of exposure.

Salg and Alterman, in 2005[163], reported a proportionate mortality study of members of the International Union of Bricklayers and Allied Craftworkers, with comparison made with US age, sex and race specific data for the study period (1986-1991). The proportion of white male members dying from emphysema (PMR 133) was significantly increased, and a nonsignificant increase in mortality from chronic and unspecified bronchitis (PMR 130) was also seen. Deaths among non-white men, and particularly women, were much lower, and did not show significant relationships.

20. Cement workers

Three cross-sectional studies of cement workers were identified, each in a different country. The first, reported by Fell *et al* in 2003[164], was conducted in Norway and concerned 119 workers currently or formerly exposed to Portland cement dust and 50 workers from a nearby control plant. Prevalence of COPD and symptoms, and also lung function, was similar for exposed workers and controls and there was no relationship with extent of exposure. The authors, who include a brief summary of 15 previous studies, many with limitations, concluded that their findings "do not support the hypothesis that cement dust exposure has a negative impact on lung function or gives an increase in respiratory symptoms."

In the same year, based on a study in Pakistan involving 50 healthy male cement mill workers and 50 healthy male control subjects matched on age, height, weight and socioeconomic status, Meo[165] claimed that "Exposure to cement dust causes interstitial lung disease, pleural thickening and chronic bronchitis in cement mill workers." However, the conclusion for chronic bronchitis was based on only one case in the workers, as against none in the controls!

In 2005 Mwaiselage *et al*[166] described a study in Tanzania of 120 workers exposed to cement dust and 107 controls. After adjustment for age, pack-years of smoking and education, exposed workers had much higher rates than controls of chronic bronchitis and other respiratory symptoms, with rates significantly related to the level of dust exposure. The prevalence of COPD (chronic bronchitis and air flow obstruction) was also much higher in the exposed group, and increased with cumulative dust exposure.

The review by Balmes[2] of the "Occupational Contribution to the Burden of Chronic Obstructive Lung Disease" listed Portland cement among the "agents that cause chronic bronchitis", though not citing specific references in support.

21. Painting

Four cross-sectional studies of painters were identified as well as two other more general occupational studies which presented results for painters.

In the occupational study in New Zealand published in 1997 by Fishwick *et al*[18] 1609 subjects completed a respiratory questionnaire. Compared to the professional, administrative and clerical service group, ORs (adjusted for age, sex and tobacco smoking) for spray painters were 3.3 (95% CI 0.8-14.8) for chronic bronchitis and 14.4 (1.9-72.7) for chronic bronchitis with airway obstruction based on, respectively, 3 and 2 cases in this occupational group. No excess was noted for other painters.

In the case-control study in Italy involving 131 COPD cases and 298 controls without respiratory diseases, which was reported by Mastrangelo *et al* in 2003[22], the OR adjusted for age and smoking was 4.7 (1.3-16.4) in painters (compared to office workers), with a significant association noted with length of exposure.

In 2004 Glindmeyer *et al*[167] reported results of a cross-sectional study of 240 US painters spraying polyurethane enamels. After adjusting for smoking and asthma symptoms, the extent of respirable paint aerosol and respirable isocyanate aerosol was associated with significant reductions in FEV_1 and other lung function measurements. There was some trend towards the prevalence of GOLD criteria COPD increasing with cumulative respirable aerosol exposure, but this was not significant.

In the study of car workers by Hammond *et al* in 2005[101] previously reported in section 11 (welders), no significant elevation was noted in paint shop workers in any respiratory symptom studied compared to the reference group of assembly workers. However, there was a significant increase in physician reported COPD, with an OR of 4.11 (1.36-12.43) after adjustment for age, race, smoking, sex and a family history of a respiratory condition. (Note that the ORs are as given in the source table, though they are cited as 3.73, 1.27-11.00 in the text and abstract of the paper.)

In 2005 Kaukianen *et al*[168] described a questionnaire study on 1000 Finnish construction painters and 1000 carpenters. After adjustment for age, smoking and atopy, the prevalence of chronic bronchitis was significantly higher in the painters, and was also associated with the duration of exposure.

In 2007 Pronk *et al*[169] reported on a study involving 581 subjects working in various spray-painting industries in the Netherlands. After adjustment for age, sex, smoking and atopy, exposed workers had a significant increase in various respiratory symptoms, including "COPD-like symptoms", as compared to office workers.

22. Paper and pulp

Five studies of paper or pulp mill workers were identified as well as one general occupational study which presented some relevant results.

Thorén *et al* (1989)[170] identified, from death and burial registers in the parishes around a paper mill in Sweden, 33 men who had died with asthma, COPD or respiratory cancer and 228 referents who had died from non-malignant, non-respiratory diseases. Based on records at the mill, subjects were classified according to whether or not the men had worked in the mill. Compared to the referents, the OR adjusted for age, for asthma or COPD was estimated as 3.8 (95% CI 1.2-12.0), similar to the crude OR of 3.9. For COPD only, based on 5 cases, the crude OR can be estimated as 2.6 (0.4-15.8).

Two years later the same group (interestingly with first author K Torén not K Thorén)[171] reported on a similar study around two further paper mills in Sweden. Here the age adjusted OR for asthma or COPD was estimated as 0.8 (0.3-2.1) based on 19 cases (12 exposed) and 325 referents (225 exposed). Results were not given for COPD only and could not be calculated. It is noted that the dust levels in the present mills were below 3 mg/m^3, much lower than in the earlier study where they often exceeded 10 mg/m^3.

In a study in India reported by Srivastava *et al* in 1992[172] 30 subjects engaged in maintenance and repair of moulds used for producing watermarks on paper were studied, along with 27 control subjects employed in the canteen of the same mill. Three of the exposed subjects were found to have emphysema, as against none of the controls, a difference which was noted to be significant at $p<0.1$ (though it does not appear to be!).

In a study in Croatia by Zuskin *et al* in 1998[173] 101 workers in the paper recycling industry were compared with 87 unexposed workers of similar age. Significantly higher prevalence of all chronic respiratory symptoms, including chronic bronchitis, were seen in the exposed workers, after adjustment for smoking. Exposure was a highly significant predictor of FEV_1.

In a general population survey in 14 industrialized countries involving 13,253 subjects aged 20 to 44 reported in 2001, Zock *et al*[24] reported no clear relationship of lung function to working with paper. However, an association with chronic bronchitis was seen, more evident in smokers.

Henneberger *et al* (2005)[174] compared 245 bleachery workers from three pulp mills where ozone was used and 80 comparison workers from two adjacent paper mills. Subjects were classified as having or not having peak exposures to ozone and/or ClO_2/SO_2, a peak exposure occurring if it resulted in acute respiratory symptoms. After adjustment for sex, age, smoking, atopy and peak irritant exposures that occurred before the follow-up, an increased risk of chronic bronchitis was seen in those with peak exposures to both irritants or to ClO_2/SO_2 only, but not in those with peak exposure to ozone only.

There is also the study of Jaakkola *et al* (2007)[175] based on a sample of 342 office workers in Finland exposed to carbonless copy paper, paper dust or fumes from photocopiers and printers. The authors note in the abstract an association between chronic bronchitis and exposure to carbonless copy paper but this was not nearly statistically significant regardless of which factors were adjusted for.

23. Transport workers

Three studies of transport workers and four of the general occupational studies have reported evidence relating working in transport to COPD.

Guidotti (1992)[176] obtained death certificates for 216 members of an Amalgamated Transit Union Local in Canada and compared the distribution of deaths with that of men in the province. After standardizing for age and year of death the PMR for COPD was 176 (97-321).

In the same year Gupta *et al*[177] compared 108 workers in a railway workshop in India with 45 controls of similar socio-economic profile. The prevalence of MRC chronic bronchitis was 9% in the controls and 17% in the workers, rising to 33% in those with a duration of exposure exceeding 10 years, a trend I estimate as significant at about p=0.01, though not age-adjusted.

In the occupational study in New Zealand published in 1997 by Fishwick *et al*[18] 1609 subjects completed a respiratory questionnaire. Compared to the professional, administrative and clerical service group, ORs (adjusted for age, sex and tobacco smoking) for transport and storage workers were 1.8 (95% CI 0.8-4.0) for chronic bronchitis and 1.5 (0.1-15.9) for chronic bronchitis with airway obstruction, based on, respectively, 9 and 1 cases in this occupational group.

In 2000, Tüchsen and Hannerz[23] estimated age standardized COPD hospitalization ratios for various occupational groups compared to Danish national rates for age 20-59 for 1981-1993. In men an increased risk in taxi and bus drivers and also in other drivers was significant before but not after adjustment for social group. Female transportation workers had an elevated risk even after controlling for social group.

Fleming and Charlton (2001)[178] used data from the UK General Practice Morbidity Survey in 1991/1992 to compare prevalence of COPD according to whether or not they worked in occupations with high exposure to

vehicle exhaust fumes. For employed persons, the prevalence ratio for COPD in the exposed group (112, 99-125) almost significantly exceeded that for all employed persons (100) after adjusting for age and smoking habit.

In 2002 Hnizdo *et al*[20] estimated risk of COPD (FEV_1/FVC <70%, FEV_1 <80% of predicted) for subjects aged 30-75 by occupational group based on NHANES III, conducted in the USA in 1988 to 1994. Adjustment was made for age, sex, race, BMI, smoking, education and SES, and comparison was made to office workers. Two years later the same authors[21] also presented similar analyses but for airflow obstruction (FEV_1/FVC <75%, FEV_1 <80% of predicted) and by race. For workers in transportation and trucking the OR for COPD was 1.2 (0.8-2.0) for all subjects and 2.0 (0.3-1.5) for never smokers. The OR for airflow obstruction was 1.7 (0.9-3.2) in Caucasians, 1.0 (0.5-1.8) in African-Americans and 3.3 (1.2-9.2) in Mexican-Americans.

In the case-control study in Italy involving 131 COPD cases and 298 controls without respiratory diseases, which was reported by Mastrangelo *et al* in 2003[22], the OR adjusted for age and smoking was a nonsignificant 0.8 (0.1-5.4) in truck drivers (compared to office workers).

24. Other occupations

The searches also identified another 24 publications, each considering one occupation. Increased risk of chronic bronchitis (and other respiratory symptoms), decreased levels of FEV_1 (and other measures of lung function), and/or increased mortality from COPD, chronic bronchitis or emphysema were noted for:

(1) workers exposed to sulphur dioxide in Sweden[179];

(2) plumbers and pipefitters in the USA[180];

(3) jute processing workers in China[181];

(4) animal food processing workers in Yugoslavia[182];

(5) workers exposed to cork dust in Spain[183];

(6) polyurethane foam producers in the USA[184];

(7) confectionery workers in Croatia[185];

(8) industrial arts teachers in Sweden[186];

(9) fishermen in Denmark[187];

(10) construction operating engineers in the USA[188];

(11) marine engineers in Norway[189];

(12) rice-granary workers in China[190];

(13) workers in the heavy clay industry in the UK[191];

(14) tunnel workers in Norway[192];

(15) mail carriers in Croatia[193];

(16) refractory ceramic workers in Europe[194];

(17) heavy and highway construction workers in the USA[195];

(18) women working indoors in Iran[196];

(19) workers in the soft tissue producing industry in Germany[197];

(20) asphalt workers in Europe[198];

(21) coke oven workers in China[199];

(22) workers exposed to lignite dust in Greece[200]; and

(23) horse trainers in New Zealand[201];

but not for:

(24) workers in Greece processing dried tobacco leaves[202].

25. Discussion and conclusions

25.1 Problems in assessing the relationship of COPD to occupation

There are great problems in assessing the relationship of COPD to occupation. One is the huge size of the literature. Time constraints have meant that our literature search has clearly been seriously incomplete. As described in section 1, the papers were obtained by relatively simple MEDLINE searches and then inspecting abstracts to identify apparently relevant papers, limiting attention to those in English. No attempt has been made to get further papers and it is clear from many of the papers obtained that there are additional relevant references. However, the number of papers considered in this review, over 200, is substantial and it is hoped that they give a good insight into the available material.

Another problem is the wide range of occupations and exposures involved. Twenty-one different groupings are considered in sections 3 to 23, with section 24 mentioning, but not evaluating, a further twenty odd occupations for which only one relevant publication was found and it was considered not possible to reach any reliable conclusions. Some of section 3 to 23 relate to specific occupations, such as coal mining, and some to specific exposures, such as silica. The sections chosen seemed useful for classifying related papers together, but inevitably there is some overlap between sections. For example, while section 3 concerns dust, gas and fumes, and mainly concerns studies which have made an attempt to calculate some overall exposure index, a number of the other sections concern workers with exposure to dusts, gases and/or fumes.

A further issue is that, in a number of occupations, exposure to the putative agent may have decreased dramatically over time, and that inferences drawn from studies conducted long ago may not necessarily apply to more recent studies, where exposures are low. This applies particularly to industries where known respiratory diseases other than COPD have been clearly associated with exposure and have led to legislation limiting exposure. These include coal miners (pneumoconiosis), asbestos workers (asbestosis), cotton textile workers (bysinnosis) and farmers (farmer's lung).

For a number of occupations it should also be realised that the nature of the exposure varies by study or region, and that for some occupations there are a wide variety of potential exposures. Farming is a particular problem here, as risk of COPD (if any) may vary by whether animals or crops are farmed, the type of animal, the type of crop, the type of job on the farm, etc.

Information on risk of COPD in relation to occupation may be collected in a number of ways. As in the reports relating COPD to other risk factors, the endpoints considered vary. Attention has been limited mainly to the following four broad types:

(i) questionnaire-derived chronic bronchitis, typically assessed using the Medical Research Council or American Thoracic Society questionnaires, e.g. "Cough and chronic expectoration for 3 months of the year for at least two consecutive years";

(ii) doctor-diagnosed chronic bronchitis, emphysema or COPD, whether reported by the subject or derived from medical records;

(iii) relevant lung function variables, FEV_1, FVC or FEV_1/FVC; and

(iv) mortality from COPD, chronic bronchitis or emphysema.

Endpoints will be discussed in more detail in the overview report on the whole project on COPD and risk factors other than smoking, but for the moment it should be noted that criteria for diagnosis have changed materially over time.

The types of study which provide relevant data also vary, with different types having different weaknesses and problems of interpretation. Studies which follow an occupational cohort for a number of years, and compare observed mortality from a range of specific causes with that expected from national or regional age-specific reference rates, are open to two particular sources of bias. One is the "healthy worker effect"; - in the absence of any specific occupational effect, the SMR of a working population is likely to be less than 100, simply because it excludes those who are unfit to work, who are likely to have above average mortality. Another source of bias may be confounding by smoking. Workers in some occupations may have an

above (or below) average proportion of smokers and available reference rates are often not smoking-specific to allow correction for this.

A different type of problem arises in studies which follow the mortality of a representative population sample, comparing rates by type of occupation. A study may estimate risks for a large number of occupational groups (relative to some defined "unexposed" control group – e.g. office workers) and for a large number of causes of death, only reporting RRs that are significant at some defined confidence level. This means that evidence on the extent of the relationship of a disease of interest (here COPD) to an occupation of interest may be lost. This is a form of publication bias, so that the available data overestimates the strength of the relationship.

In this type of study, and also in studies which compare an occupational group with a specified control group (e.g. coal miners with administrative workers in the same mine), there is the assumption that the control group is actually unexposed. While workers in the specified control group may have no (or very little) exposure to the specific agent (or agents) to which the occupational group is exposed, they may have exposure to other agents which might cause the same response.

While there are always problems in the design, conduct and interpretation of epidemiological studies, those associated with occupational epidemiology studies seem especially extensive. Nevertheless, it seems possible to draw some conclusions for the occupations and exposures considered in this report.

25.2 Conclusions for specific occupations and exposures

Dust, gas and fumes Section 3 mainly concerns the relationship between COPD and overall indices of exposure to dust, gas and fumes, many of the more specific exposures being considered in later sections. However, section 3 also includes results for some more specific exposures not considered elsewhere. Overall, results from 18 studies and four specific reviews are summarized. There is a consistently reported association of overall exposure

to dust, gas or fumes with increased chronic bronchitis prevalence, and a number of studies, though not all, report reduced lung function. Limited evidence from two mortality studies is consistent with this. There is also some evidence of effects on chronic bronchitis and FEV_1 in workers exposed to grain or flour dust.

Asbestos exposure The relationship of asbestos exposure to asbestosis, mesothelioma and lung cancer has been extensively studied. However, only six studies were found that related asbestos exposure to COPD, none relating asbestos exposure to COPD mortality. The studies, considered in section 4, generally show that asbestos exposure is related to an increased risk of chronic bronchitis, and reduced lung function, though a study of Swedish dolomite workers exposed to tremolite asbestos[48] did not.

Shipyard workers Section 5 considers four studies of shipyard workers. The overall evidence of an effect of shipyard work was inconclusive, but some of the studies indicated a higher risk of COPD in welders (see also section 11).

Coal mining Section 6 considers evidence from 17 studies and one general review. While it has long been known that working in coal mines can result in pneumoconiosis, it is also clear that coal mining substantially increases risk of COPD. This is apparent from a number of mortality studies, with increases in chronic bronchitis prevalence and reductions in FEV_1 consistently reported. These results typically relate to underground mining, but one study of opencast miners[63] found no association with chronic bronchitis prevalence or lung function.

Gold mining Section 7 reports on seven studies, five in South Africa and two in Australia. The evidence is consistent that gold mining is associated with an increased risk of chronic bronchitis and reduced lung function, but seems inconclusive regarding its role in emphysema.

Iron mining Of the four studies considered in section 8, increased chronic bronchitis and/or reduced lung function in iron miners was seen in three.

While the evidence is not as strong or extensive as for coal mining or gold mining, it seems consistent with risk of COPD being increased in miners.

Uranium mining and smelting Section 9 considers two mortality studies, both from the Colorado Plateau. Both report significant about 2-fold increased risks of emphysema and one with a similarly increased risk of other COPD.

Foundry workers Section 10 summarizes evidence from nine studies. There is consistent evidence of increased mortality from COPD in foundry workers, a detailed study in the USA[86-88] finding that the increase is mainly regarding emphysema. Apart from a study in a Canadian copper refinery[89], prevalence of chronic bronchitis was consistently increased and lung function decreased in relation to foundry work.

Welders The evidence considered in section 11 comes from 13 studies. While there is consistent evidence that welders have a high prevalence of chronic bronchitis, reduced lung function has not been clearly demonstrated. A mortality study of US welders[99] reported an increased SMR for emphysema but not other COPD in mild-steel welders, though a similar excess was seen for non-welders at the same plants.

Metal workers Apart from the studies of foundry workers and welders considered in the two previous sections, section 12 considered 13 other studies presenting results for metal workers. These relate to a wide variety of metals, including cadmium, iron and steel, stainless steel, brass, ferroalloy and copper, and it is likely that any risk varies with type of metal and type of job. Many of the studies were mortality or case-control studies and the great majority of these reported an increased risk of COPD. Most of these did not separate risk by subcategory, but those that did indicated an increased risk of emphysema. Limited evidence on lung function is consistent with a reduction associated with metal work.

Carbon black workers Section 13 considers two studies, both large. One[112] based on 18 European plants found an association of exposure to

carbon black dust with increased chronic bronchitis and reduced lung function, but the other[113], based on 22 North American plants, was less clear, though it did find a significant reduction in FEV_1.

Exposure to silica The evidence in section 14 comes from six specific studies and three reviews. One of the reviews[66] points out that much of the evidence on silica comes from miners (see section 7), and notes that "silica dust seems to be a more potent toxin than coal mine dust in causing COPD". Another review[116], on amorphous silica, notes that while the evidence of an effect of crystalline silica dust risk on COPD is clear, the data on amorphous silica are limited and inconclusive. The data on chronic bronchitis prevalence and lung function considered in section 14 are very limited, but there are three relevant mortality studies. Although one study found no increased COPD risk in silica sand quarry workers[120], clear excesses were seen in silicon carbide smelters[117] and in occupations with high crystalline silica exposure[118].

Farming Section 15 considers 27 studies relevant to risk of COPD as well as three general reviews. Many of these are cross-sectional studies and investigate the relationship of chronic bronchitis prevalence to type of job within the farm, with increased prevalence noted most often in relation to working with pigs and working in confinement buildings. While a series of studies in the Doubs area of France have noted a higher risk of chronic bronchitis in dairy farmers compared to office workers, and some other studies have reported higher risks in grain farmers, in animal farmers and in general farm workers, others have not. Data on lung function are similarly inconsistent. One COPD case-control study[22] reported a very high OR of 15.1 (95% CI 3.2-71.6) for farm workers compared to office workers, but limited mortality data do not suggest any clear increase in risk. The data are extremely difficult to summarize, but suggest that some aspects of farm working may be associated with an increased risk of COPD.

Poultry workers The three studies considered in section 16 are all consistent with working with poultry being associated with increased chronic bronchitis or reduced lung function.

Textiles and cotton Ten studies considered in section 17 relate to textile and cotton workers. Although it has long been established that working with cotton can cause bysinnosis, an allergic reaction leading to breathing difficulties, the evidence summarized is also quite consistent that exposure to cotton dust can lead to chronic bronchitis and reduced lung function, though one review[6] considered that the evidence does not suggest a role of cotton dust exposure in emphysema. The evidence regarding an effect of textiles other than cotton is limited and inconclusive.

Woodworkers Section 18 summarizes evidence from 10 studies. The evidence appears to be conflicting, with a number of studies reporting an association with COPD-related endpoints, sometimes strong, and other reporting no association. Variation in results may, of course, depend on the type of wood used and the levels of dust involved.

Brick workers The limited evidence considered in section 19 is all consistent with an effect of exposure to brick dust. This fits in with the data from section 3.

Cement workers The evidence considered in section 20 is limited, and inconsistent. One of the papers cited[164] is an extensive review which concludes that an effect of cement dust exposure has not been demonstrated, but other studies (e.g.[166]) have claimed a relationship.

Printing The evidence considered in section 21, from six studies, is somewhat limited but is suggestive of a relationship of painting, particularly spray painting, to COPD.

Paper and pulp Section 22 summarizes evidence from six studies of paper or pulp mill workers. A clear association with COPD risk has not been established.

Transport workers The seven studies considered in section 23, each conducted in a different country and with a variety of occupations included, suggest the possibility of a relationship between working in transport (or with a high exposure to vehicle exhaust fumes) and risk of COPD.

Other occupations Section 24 lists 24 publications each considering an occupation/exposure not considered earlier. The fact that the great majority of them report a significant increased risk of one or more endpoints relevant to COPD is consistent with an occupational role in the aetiology of the disease. However, the limited amount of material precludes a confident conclusion for any specific one, though some add to the evidence that occupational dust exposure is a cause of COPD.

25.3 Overall conclusions

The data relating occupation to COPD are particularly difficult to summarize and evaluate. It is clear that occupation does play a role, with exposure to a number of sources of dust, gas and fumes likely to play a part. The strongest evidence of increased risk comes for miners (clearest for coal mining and gold mining). Other occupations and exposures for which the evidence is quite strong include foundry work, welding and metal work generally, and exposure to asbestos, silica and brick dust. There are a number of other occupations where limited evidence suggests a possible effect on COPD risk.

There have been a few attempts to estimate the occupational contribution to the burden of COPD. The population-attributable risk for COPD has been estimated as 15-20%[2], 19.2%[20] and 12%[11], though clearly such estimates have considerable uncertainty.

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