

# **APPENDIX 1**

**CONTRIBUTION TO THE EVIDENCE-BASE FOR HSE'S  
STRATEGY ON OCCUPATIONAL RESPIRATORY  
DISEASE (EXCLUDING ASTHMA)**

**CHRONIC OBSTRUCTIVE PULMONARY DISEASE  
(COPD)**

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## CONTENTS

	Page No
Executive Summary .....	1
1. What is Chronic Obstructive Pulmonary Disease (COPD)?.....	4
2. Mortality Statistics for Great Britain .....	5
3. Morbidity statistics for Great Britain.....	6
3.1 COPD in Underground Coalworkers .....	6
4. Economic Costs of COPD .....	6
5. Causes of COPD – toxicological considerations? .....	7
5.1 Cigarette smoking .....	7
5.2 Coalmine dust .....	7
5.3 Crystalline silica.....	9
5.4 Other mineral dusts .....	10
5.5 Organic dusts .....	10
5.6 Gases .....	11
5.7 Conclusions.....	11
Table 2. Substances with potential to cause occupational respiratory disease (excluding asthma and respiratory tract cancers).....	12
6. Evidence on the extent of work-related COPD in the general population.....	14
6.1 Conclusions from the American Thoracic Society .....	15
6.2 Additional evidence on the extent of work-related COPD from studies not covered by the American Thoracic Society Review (2003) .....	16
6.21 Findings on the association between COPD and employment from the United States population-based Third National Health and Nutrition Examination Survey (Hnizdo et al 2002) .....	16
6.22 A study of the occupational burden of COPD in the US .....	17
(Trupin et al 2003). .....	17
6.23 A study of respiratory symptoms and occupation in Doetinchem in the Netherlands (Vermeulen et al 2002). .....	19
6.3 Conclusions concerning the evidence for work-related COPD .....	21
References.....	23

## **Executive Summary**

Chronic obstructive pulmonary disease (COPD) is a progressive disease that causes much human suffering and has a considerable economic impact on society. It can have both occupational and non-occupational causes. The disease usually encompasses chronic bronchitis and/or emphysema. The condition is not fully reversible in that only partial relief may be obtained with treatment. The British Thoracic Society estimates that the annual treatment costs to the NHS amount to about £500 million. The wider societal costs including working days lost and productivity losses are not known but could be substantial. COPD is currently the fourth leading cause of death worldwide and is the only chronic disease on the increase in industrialised countries (European Lung White Book 2003). It is predicted that by the year 2020 it will be the third leading cause of death responsible for 6 million deaths worldwide. The British Thoracic Society estimates that there are 600,000 diagnosed cases in the UK, although it notes that there are likely to be many additional undiagnosed cases. COPD is given as the underlying cause of death on about 30,000 death certificates per year in the UK; again it is possible that the death certificate data underestimate the true extent of COPD-related mortality.

Cigarette smoking is the main cause of COPD. However, occupational exposure to dusts, gases and fumes can cause COPD independently of cigarette smoking, and can increase the risk of developing COPD in those who smoke. Given that COPD is so prevalent, if occupational exposures produce even a small increased risk of COPD, this could amount in absolute terms to large numbers of people with work-related COPD (i.e COPD that has been caused or made worse by work).

There are a number of difficulties surrounding the ability to determine the proportion of COPD in the UK population that is caused or made worse by work. One reason for this is that for an individual worker with COPD who smokes, it may not be possible to discriminate between the relative roles of cigarette smoking and occupational exposures in causing the condition.

Hence work-related cases tend not to be picked up and routinely reported via occupational health surveillance schemes. However, on a larger-scale, it is possible to assess the impact of work-related COPD on society by comparing the prevalence of COPD in occupationally exposed and non-exposed populations. Any excess of COPD found in the exposed group (after correcting for smoking and other confounders) is the “attributable risk” due to the exposure. If the proportion of exposed workers in the general population is known or can be estimated, the “population attributable risk” (PAR) % can be determined.

The American Thoracic Society (ATS) has recently estimated that as much as 15% of all cases of COPD are work-related. The PAR of 15% is based on an analysis of ten large-scale general population studies conducted in the United States, France, Spain, Norway, the Netherlands, Northern Italy, China and New Zealand. It is also supported by a few additional studies published too recently to have been included in the ATS analysis. None of these studies were conducted in the UK. Nonetheless, it is concluded that the 15% PAR estimate from the ATS is more likely than not to be broadly representative of the situation in the UK, particularly considering that much of the supporting evidence derives from studies in Northern European countries where the pattern of industrialisation is likely to be similar to that in the UK.

The emerging evidence indicates that there could be at least 90,000 cases of work-related COPD in the UK. Given the long latency for the development of clinically relevant COPD (in the region of 15–20 years), this implies that the causal occupational exposures for these cases would have occurred around the 1960-1980s. It is uncertain whether or not patterns of industrialisation in the UK and workplace standards of control for airborne contaminants have changed over the last 20-30 years to an extent such that the population attributable risk of work-related COPD might be expected to decline in the future.

From the large-scale population studies that inform on work-related COPD, the substances that have been reported as causing the highest risks of work-

related COPD include crystalline silica, glass fibre, sawdust, automobile exhaust, solvents, ammonia, nitrogen oxides, sulphur dioxide, metal fumes and anhydrides. Occupational groups most at risk include construction and mining, food processors, cleaners, spray painters, rubber, leather, plastics/synthetics manufacture, textile mill workers and laboratory technicians. These substances/occupations are of current occupational relevance in the UK.

Overall, the pattern of evidence appears to support the possibility that the public health and socio-economic impact of work-related COPD in the UK is likely to be highly significant, and that work-related COPD should be regarded as a priority for action within HSE's strategy on occupational respiratory disease (excluding asthma).

## **1. What is Chronic Obstructive Pulmonary Disease (COPD)?**

COPD is a disease that encompasses chronic bronchitis and/or emphysema. There is some overlap between chronic asthma and COPD. Certain patients with chronic asthma develop relatively fixed, non-reversible airways obstruction, in a very similar manner to COPD patients. Indeed, some authorities believe that chronic asthma is a risk factor for the development of COPD. The GOLD (Global initiative for Chronic Obstructive Lung Disease) definition of COPD is as follows (GOLD 2003):

*COPD is a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.*

The signs and symptoms of COPD include chronic cough and sputum production, and shortness of breath. The diagnosis is confirmed by spirometry. The GOLD criteria for diagnosis are the presence of a postbronchodilator FEV1 <80% of the predicted value in combination with an FEV1/FVC ratio <70%. There can be a lack of correlation between the presence of symptoms and the degree of airflow limitation. In some individuals there can be quite a marked decline in pulmonary function before symptoms develop. However, workers with a history of dust, noxious gas or fume exposure who are clearly symptomatic but with normal spirometry should be regarded as being at increased risk of developing COPD.

COPD is not usually diagnosed until midlife when the condition is already moderately advanced. It would be very unusual for COPD to be diagnosed in someone <40 years old. In severe cases of COPD the ability of the lungs to exchange oxygen and carbon dioxide is impaired and this compromises cardiovascular/metabolic function.

## 2. Mortality Statistics for Great Britain

In Great Britain, COPD is given as the underlying cause of death on 30,000 death certificates per year (Table 1).

**Table 1. Annual number of deaths from COPD**

	England and Wales		Scotland		Total
	Males	Females	Males	Females	
1980	18100	7291	1724	727	27842
1981	17587	7309	1616	760	27272
1982	18582	8018	1753	892	29245
1983	18299	7958	1707	817	28781
1984	18937	8488	1708	863	29996
1985	20850	10093	1690	961	33594
1986	20148	9755	1681	980	32564
1987	18372	9246	1570	915	30103
1988	18817	9932	1536	953	31238
1989	19733	10647	1711	1214	33305
1990	17902	10080	1493	1062	30537
1991	18213	10833	1550	1026	31622
1992	17469	11133	1493	1068	31163
1993	17540	11401	1650	1344	31935
1994	15457	10520	1391	1112	28480
1995	16581	11678	1499	1292	31050
1996	15462	11411	1416	1270	29559
1997	15478	11740	1468	1297	29983
1998	15197	11761	1426	1412	29796
1999	15692	12554	1494	1648	31388
2000	14098	11486	1514*	1495*	28593*
2001	13878*	11817*	1461*	1527*	28683*

\* *Coded using ICD-10*

Source: EMSU Mortality Databank – compiled from death statistics from the Office for National Statistics and the General Register Office for Scotland.

Note: There is no set of ICD codes universally accepted as representing COPD. The mortality data above refer to ICD-9 codes 490-496 (labelled 'Chronic Obstructive Pulmonary disease and Allied' within ICD-9, which includes Bronchitis, Emphysema, Asthma, Bronchiectasis, Extrinsic Allergic Alveolitis and Chronic Airways Obstruction, not elsewhere classified). For the year 2001 (2000 and 2001 for Scotland) data are coded to ICD-10 and codes J40 to J47 have been used (labelled 'Chronic Lower Respiratory diseases' – which includes the same disease categories as above). Over time the number of deaths coded to ICD-9 code 496 (Chronic Airways Obstruction, not elsewhere classified) in Great Britain increased from 4654 in 1980 to 10176 in 1990, and 25281 in 1999. This means that by 1999 most of the deaths were being coded to 496. There is a large reduction in the number of cases coded to 491 (Chronic Bronchitis) over the same period suggesting that over time more deaths have become attributed to the more general category of Chronic Airways Obstruction.

Table 1 shows that in 1980, there were almost three times as many deaths in men as in women from COPD. However, over the last 20 years the number of deaths in men has steadily fallen, but this has been balanced by an increase in the number of deaths in women, such that by 2001 the numbers of deaths from COPD in men and women are about the same. Changes in trends of cigarette smoking undoubtedly account for much of this changing pattern of

mortality, but it is conceivable that changes in employment patterns with an increasing number of women in the workforce may also be a factor. Note that although the number of deaths from COPD in men and women in the UK is the same in absolute terms, because of the larger numbers of women in older age groups, the age-adjusted death rates for COPD remain markedly higher for men than women, which might argue for an occupational causation (European Lung White Book 2003). The European Lung White Book cautions that mortality statistics are likely to underestimate the true extent of COPD-related mortality, as it may not necessarily be given as the main or contributory cause of death on death certificates.

### **3. Morbidity statistics for Great Britain**

It is difficult to determine the prevalence of COPD in the population because by the time the disease is diagnosed it is usually moderately advanced. Furthermore, it seems likely that much COPD goes undiagnosed, as symptoms may be attributed in some of those affected as being due to ageing or lack of fitness (Price and Duerden 2003). The British Thoracic Society estimates that there are 600,000 diagnosed cases of COPD in the UK. However, they caution that this figure could represent the 'tip of the iceberg' due to lack of awareness of symptoms among the general population. A study by Dickinson *et al* (1999) of randomly selected individuals aged 60 – 74 years from a general practice register in Lincolnshire found that there were 2.69 "true" cases of COPD for each diagnosed case, with an overall prevalence of 6.2% undiagnosed COPD.

#### **3.1 COPD in Underground Coalworkers**

Coalworkers are the only occupational group in Great Britain for which there are statistics on the incidence of COPD. Chronic bronchitis and/or emphysema) became subject to compensation under the Industrial Injuries Scheme in 1993, but only for coalworkers with a history of 20 years underground work and a specified degree of lung disablement (it is assumed in this document that most if not all of these compensated cases of chronic bronchitis and/or emphysema in coalminers represent COPD). In the years that followed after 1993, many thousands of British coalworkers received compensation, reflecting the backlog of cases that had accumulated prior to this scheme. In recent years, the annual incidence of claimants has fallen to a few hundred per year. There were 475 successful compensation cases in 2002. However, the decline in the coalmining industry in Great Britain and there are currently only about 6000 underground workers. Therefore, although the available evidence suggests a relatively high risk of COPD associated with coalmine dust, this industry sector is now too small to make a significant public health impact on the scale of COPD in Great Britain.

### **4. Economic Costs of COPD**

One recent review stated that in 1996-97, the NHS spent more than £818 million on the treatment of COPD (Price and Duerden 2003). The British

Thoracic Society estimated that the costs to the NHS for COPD treatment amount to £500 million annually. However, the wider societal costs including lost working days and productivity losses are potentially much greater. In the European Union member states, it has been estimated that productivity losses due to COPD amount to €28.5 billion annually (European Lung White Book 2003).

## **5. Causes of COPD – toxicological considerations?**

Large-scale epidemiological studies have attributed about 15% of COPD cases in the general population to workplace exposures to dusts, gases and fumes. If this is correct, then it would mean that currently there are 90,000 work-related cases of COPD in the UK. What could have caused this occupational ill health? A useful starting point might be to briefly consider the toxicological characteristics of known causes of COPD.

### ***5.1 Cigarette smoking***

Cigarette smoking is the main cause of COPD. Cigarette smoke is a complex mixture of particles and gases. No one component of cigarette smoke has been identified as the single aetiological agent for COPD development. Rather, it is likely that the particulate and gaseous components of cigarette smoke each have a different role, acting at different sites (alveolar or bronchial) to elicit different toxicological responses that contribute to COPD development. Interestingly, it is well recognised that only a certain proportion of cigarette smokers ever develop clinically significant COPD, suggesting that genetic factors predisposing to sensitivity or resistance play a key role in determining disease outcome. Might this also apply to other causes of COPD?

Inhaled cigarette smoke contains high concentrations of nitrogen monoxide, up to 1000 ppm (data cited by Mercer et al 1995), as well as lesser amounts of nitrogen dioxide. There is very widespread occupational exposure to these gases albeit at substantially lower concentrations (see Table 2). Could this be a potential cause of work-related COPD? This is discussed below (see section 5.6).

The nitrogen oxides are only one of many irritant gases present in cigarette smoke that have the potential to cause acute and chronic inflammatory responses throughout the respiratory tract. Again, it needs to be considered whether or not this potential can translate into a risk of COPD under conditions of occupational exposure to these gases (see section 5.6).

### ***5.2 Coalmine dust***

The evidence for a causal association between coalmine dust and COPD is probably stronger than for any other industrial substance. However, this is not because there is something particularly hazardous about coalmine dust compared to other mineral dusts. It seems to be a consequence of the fact that dust exposures have tended to be far higher in coalmining compared to

most other industries (such high exposures producing substantial risk). Also, coalminers tend to provide relatively stable populations that are more likely to remain in the same occupation over a working lifetime and hence are more amenable to epidemiological investigation than is the case with many other occupational groups.

Coggon and Newman Taylor (1998) provide an excellent review of the evidence for the ability of occupational exposure to coalmine dust to cause chronic bronchitis and emphysema. Indeed, since 1993, chronic bronchitis/emphysema have been prescribed diseases for coalworkers in the UK and are also prescribed diseases in Germany. In 2002, 475 British coalworkers received compensation.

The review by Coggon and Newman Taylor describes the evidence for an excess of COPD deaths in British coalminers. They observe that there is no excess of lung cancer deaths in coalminers indicating that the excess of COPD deaths is unlikely to be seriously confounded by cigarette smoking.

Coggon and Newman Taylor present various lines of evidence for coalmine dust as a cause of COPD including a discussion of the pathological evidence from autopsy studies for an excess of emphysema in coalminers that is predominantly centrilobular in location.

These authors explain that the influx of neutrophils to the sites of coal dust accumulation in the lungs leads to the release of enzymes (including elastase) powerful oxidants and free radicals, plausible mediators of tissue injury leading to emphysema. The results of a study by Rom (1991) are cited, in which bronchoalveolar lavage fluid (BALF) was analysed from 17 coalminers (non-smokers or ex-smokers) and 12 non-smokers and 6 current smokers (all non-miners). The results showed a higher proportion of neutrophils and an increased neutrophil elastase activity in the miners compared with either the smoking or non-smoking control groups. Similar findings were obtained in a study in rats exposed to  $10 \text{ mg.m}^{-3}$  of coal dust for 52 days (Brown and Donaldson 1989).

HSE notes that there is other supporting evidence implicating a role for neutrophil activity in coalmine dust-induced emphysema. Under normal physiological circumstances, dust particles are cleared from the lungs by the action of alveolar macrophage cells. These mobile cells phagocytose particulate matter encountered in the airspaces; the particle-laden cells then move by amoeboid action towards the bronchioles for subsequent clearance via the mucociliary escalator.

Experimental studies in animals show that the capacity of the alveolar macrophages to clear particles can be exceeded in the presence of an excessive lung burden of dust. This condition is referred to as "overload". In the laboratory rat, a laboratory species particularly sensitive to the effects of overload, overload begins with a dust burden of 1 mg per gram of lung. The "overloaded" macrophages send out cytokine signals causing a further influx of macrophages and *neutrophils* to the sites of dust deposition, and this leads

to the start of an inflammatory and granulomatous response (see IEH Report 1999). Observations show that overload leads to an accumulation of dust in the pulmonary interstitium and the lung-associated lymph nodes. In one autopsy study of retired US coalworkers, the average lung dust burden was 70 mg per dry gram of lung, and for coal dust alone was 45 mg per dry gram of lung (Kuempel et al 1997). Investigations indicated there had been a complete cessation of lung dust clearance in these cases (overload).

Coggon and Newman Taylor also note that there is overwhelming evidence for an impairment of pulmonary function in coalminers, consistent with the observed excess mortality from COPD. They note a lack of correlation between the symptoms of bronchitis and the degree of pulmonary function deficit in coalminers, but generally it is well recognised that there is a lack of correlation between symptoms and decrements in FEV1 (GOLD 2003). From all the available studies on the relationship between coalmine dust exposure and pulmonary function deficit, Coggon and Newman Taylor felt that the study by Soutar and Hurley (1986) provided the most reliable estimate of risk. The results of this study on over 4000 British coalminers suggest a decline in FEV1 of 0.76 ml per  $\text{ghm}^{-3}$  exposure to respirable dust. Assuming a typical working year is 1740 hours, this would equate to a loss of FEV1 of 104 ml after a 40 year working lifetime exposure to a respirable dust concentration of  $2 \text{ mg.m}^{-3}$  (8-hr TWA) [HSE calculation]. This loss in FEV1 would be over and above that due to ageing and smoking.

### **5.3 Crystalline silica**

Crystalline silica (mainly encountered in the form of quartz) is one of the most aggressive mineral dusts in terms of its ability to cause lung damage, and yet, perhaps because of the emphasis on silicosis, it has not been widely considered as a potential cause of COPD. However, there is pathological evidence in both humans and animals for the ability of crystalline silica to cause emphysema (NIOSH 2002). Radiographically, small emphysematous spaces are frequently seen close to large silicotic masses (Weill et al 1994). There is pathological evidence of emphysema from autopsy studies of silica-exposed workers (Hnizdo and Vallyathan 2003). A recent review of the evidence on crystalline silica and COPD by these authors led to the claim that crystalline silica can cause COPD even in the absence of radiological evidence for silicosis. This appears consistent with the review of coalmine dust by Coggon and Newmann Taylor that notes evidence for COPD in coalminers even in the absence of pneumoconiosis. Hnizdo and Vallyathan note that there is more emphysema in gold miners than in coalminers, which is believed to reflect the fact that there is generally higher exposure to crystalline silica in goldmining.

As detailed in a further recent review (NIOSH 2002) there is also evidence for an accelerated decline in FEV1 in silica-exposed workers, again supporting the view that crystalline silica has the potential to cause COPD. However, the evidence for a decline in FEV1 appears patchy and inconsistent, and there is no comprehensive review of the available data on this subject. The evidence surrounding the exposure-response relationship for silica-induced decrements in FEV1 has not been thoroughly evaluated at the time of writing this

document. However, 15 years daily exposure to  $0.3 \text{ mg.m}^{-3}$  (8-hour TWA) of respirable crystalline silica is predicted to lead to a 20% risk of developing silicosis as defined by Category 2/1+ on the International Labour Organisation scale (HSE Phase 1 Review 2002). In the study on which this risk estimate was based, this category of radiographic change was associated with a 250 ml deficit in FEV1 (Buchanan et al 2003).

Crystalline silica is specifically toxic to alveolar macrophage cells, the cells responsible for removing inhaled particulates from the alveolar airspaces. *In vitro* studies also show that the surface of crystalline silica particles is cytotoxic, capable of causing lysis of cell membranes and hence cell death (HSE Phase 1 Review 2002). The deposition of crystalline silica particles in the lungs causes an influx of neutrophils and an acute inflammatory response; aggregates of macrophages at the sites of silica deposition instigate a granulomatous response eventually leading to silicotic nodule formation. The influx of neutrophils in acute inflammatory responses to crystalline silica provides a plausible basis for emphysema development.

#### **5.4 Other mineral dusts**

A few examples and HSE's experience in assessing them are picked out below for illustration purposes.

Trupin et al (2003) cite literature noting that "dusty trades" have been linked to chronic bronchitis since the 19<sup>th</sup> century. A mortality study of workers in "dusty trades" showed a statistically significant increase in the number of deaths from chronic bronchitis when compared with mortality rates for other white males in the United States (Amandus et al 1991). In an HSE review of kaolin (English china clay), a study of UK workers was identified that showed 40 years exposure to  $2.5 \text{ mg.m}^{-3}$  respirable dust would lead to a loss in FEV1 of 220 ml (Standring et al 1994). This suggests an increased risk of COPD. There is exposure to kaolin dust in quarries and potteries; the UK is the world's leading exporter of kaolin. Other mineral dusts with suggestive epidemiological evidence for an increased risk of COPD are included in Table 2.

#### **5.5 Organic dusts**

Some organic dusts encountered in the workplace seem particularly toxic to the lungs perhaps because of contamination with endotoxin that can induce both acute and chronic inflammation in the alveolar airways. Occupational exposure to grain dust has been shown to cause chronic bronchitis and COPD (HSE EH64 C16). An accelerated decline in lung function and an increased prevalence of chronic cough and phlegm has been reported in workers exposed to wool process dust (HSE EH64 C57). Cotton dust causes airway inflammation leading to byssinosis, a condition that appears to have an immunological component. However, this can lead to fixed airways obstruction in a proportion of affected individuals becoming indistinguishable from COPD (HSE EH64 C44). The toxicological mechanisms whereby organic dusts lead to lung inflammation and airways obstruction are complex, but as

noted above, endotoxin contamination is likely to play an important role. There are relatively few workers currently exposed to cotton and wool process dust in the UK.

## **5.6 Gases**

Evidence from studies in experimental animals (rabbits, rats and dogs) shows that prolonged inhalation exposures to nitrogen dioxide and nitrogen monoxide can induce emphysema at concentrations of <2 ppm (IPCS 1997, Mercer et al 1995, Azoulay et al 1977, Hyde et al 1978). Nitrogen dioxide is a reactive oxidising gas that causes lipid peroxidation and thereby damages cell membranes in the lungs leading to inflammation. Nitrogen dioxide also impairs the action of the cilia that line the bronchial airways and hence slows down the action of the mucociliary escalator. Nitrogen dioxide is also thought to be specifically toxic to alveolar macrophage cells; these cells are involved in lung defense mechanisms (IPCS 1997). The toxicological mechanisms whereby nitrogen monoxide causes emphysema are not fully elucidated. Nitrogen monoxide molecules contain an unpaired electron and hence have free radical properties that confer chemically reactive properties. Nitrogen monoxide is less water-soluble than nitrogen dioxide and is known to have effects on the endothelial cells of the pulmonary capillaries. The study by Mercer et al (1995) showed that low exposures to nitrogen monoxide caused the development of small holes in the alveolar walls (fenestrae) that were suggested to represent early stages in emphysema development.

There are claims within the secondary scientific literature that continued exposure to ammonia, ozone and sulphur dioxide can cause chronic bronchitis (Parkes 1994 pp 240), but there does not appear to be a strong body of documented evidence. This authoritative source claims that prolonged exposures to any irritant, gaseous or particulate, can cause bronchitis and mucous gland hyperplasia.

## **5.7 Conclusions**

Three general types of occupational exposure situation entailing repeated inhalation exposure to airborne substances merit attention or concern as prospective causes of work-related COPD:

- (i) Irritant gases at concentrations eliciting an inflammatory/tissue damaging response.
- (ii) High concentrations of dust, sufficient to produce overload, as exemplified by coalworkers' pneumoconiosis.
- (iii) Particulates with significant cytotoxic potential, at levels at which such cytotoxicity would be predicted to manifest itself, eg some workforces exposed to respirable crystalline silica.

It is clear that there have been many such occupational exposure situations in the past. This gives support from the standpoint of plausible toxicological mechanisms, for current inheritance of a substantial burden of work-related COPD.

**Table 2. Substances with potential to cause occupational respiratory disease (excluding asthma and respiratory tract cancers).**

<b>Substance</b>	<b>Sources of occupational exposure/uses</b>	<b>Health effects</b>
Acetaldehyde	Food industry as flavour & fragrance ingredient. Chemical intermediate. In UK, 500-1500 workers exposed in flavour & fragrance industry but many 1000s exposed via vehicle exhausts and hot processing of plastic.	Upper respiratory tract irritation with possibility of chronic inflammation.
Acetic anhydride	Production of plastics, pharmaceuticals, dyes, fragrances, explosives and food additives. Laboratory workers.	Severe irritation of airways and lung damage.
Aluminium metal dust	Explosives, paints, vehicle construction	Pulmonary fibrosis, pneumonitis
Aluminium oxide dust	Aluminium refining. Manufacture of pharmaceuticals, optical glass, absorbents and drying agents, polishes, refractories, ceramics. Used as a filler for rubber and plastics.	Pulmonary fibrosis, pneumonitis
Ammonia	Agriculture Fertiliser and chemical manufacture, mirrors, refrigerant, wastes, laboratory reagent.	Single exposures can cause sensory irritation and inflammation of respiratory tract epithelium. Potential for COPD with long-term exposures.
Cement dust	Cement manufacture Construction	Impaired pulmonary function. Irritation of airways. Chronic cough.
Chlorine	Chemical industry. Bleaching, water treatment, disinfection. Paper, textiles.	Respiratory tract irritation and inflammation.
Chlorine dioxide	Flour milling. Bleaching agent. Biocide/sterilant.	Respiratory tract irritation. Impaired lung function.
Coalmine dust	Mining	Pneumoconiosis and COPD.
Cotton dust	Textile industry	Byssinosis COPD
Dimethylamino-ethanol	Manufacture of organic flocculants, ion exchange resins, catalyst in manufacture of polyurethane foams, surface coatings. Potential for several 1000s UK workers to be exposed when industrial surface coatings are applied.	No good human evidence but animal evidence shows irritation of respiratory tract (substance is corrosive).
Ethyl and methyl cyanoacrylate	Adhesives. Many 1000s of UK workers likely to be exposed.	Respiratory tract irritation.
Grain dust	Docks, mills, farms, animal feeds.	Chronic bronchitis Accelerated decline in FEV1
1,6-	Manufacture of nylon used in textiles,	Upper airway

Hexanolactam (dust and vapour)	carpeting, cable insulation. Production of film, coatings, synthetic leather and as a curing agent for polyurethanes.	irritation.
Hydrogen fluoride	Petrochemical industry. Etching, surface treatments, metal pickling.	Irritation and inflammation of upper airways.
Hydrogen chloride	Chemical manufacture, cleaning and etching agent. Water treatment, food processing.	Irritation and inflammation of upper airways
Kaolin	Quarries (UK is world's largest exporter) Pottery & Ceramic manufacture, pharmaceuticals.	Accelerated decline in FEV1. COPD
Methyl methacrylate And other acrylates	Manufacture of cast acrylic sheet, resins, surface coatings, moulded and extruded products, medical and dental appliances. Many 1000s of workers exposed in the UK.	Respiratory tract irritation.
Nitrogen dioxide	Welding fume Diesel engine exhaust emissions – garages, mining. Nitrate and fertiliser manufacture. Many 1000s exposed.	Single exposures can cause sensory irritation. Long term low level exposures can cause emphysema (experimental animal evidence)
Nitrogen monoxide	Welding fume Diesel engine exhaust emissions Nitrate and fertiliser manufacture Hospital intensive care units. Many 1000s exposed.	Long term low level exposures can cause emphysema (experimental animal evidence)
Ozone	Welding. Water purification. Bleaching of foods and textiles. Reactant in the chemical industry. Photocopiers. Many 1000s exposed.	Irritation, cough, breathlessness, dyspnoea.
Phosgene	Chemical industry. Manufacture of dyestuffs, polycarbonates and pharmaceuticals. Generated when volatile organochlorine compounds come into contact with flames or hot metal.	Pulmonary oedema
Pulverised fuel ash	Power stations. Civil engineering, Land reclamation, grout, ready mix cement. Several 1000s exposed.	Chronic bronchitis
Respirable crystalline silica	Mines, quarries, foundries, heavy clay industry, industrial sand industry, ceramics and pottery, stonemasonry. In excess of 100,000 workers exposed on a daily basis.	Silicosis COPD
Sulphur dioxide	Foundries, foodstuffs, textiles, paper	Single exposures can cause sensory irritation and inflammation. Decreases in FEV1. Long-term repeated exposures may cause chronic pathological changes in respiratory tract epithelium.
Talc	Roofing, foundries, rubber industry. Filler in paints and plastics. Lubricant, cosmetics,	Accelerated decline in FEV1.

	pharmaceuticals.	Fibrosis
Welding fume	Welding	Chronic bronchitis Increased risk of lobar pneumonia
Wool process dust	Textile industry	Chronic bronchitis Accelerated decline in FEV1

## **6. Evidence on the extent of work-related COPD in the general population**

There are a number of difficulties surrounding the ability to determine the proportion of COPD in the UK population that is caused or made worse by work. For example:-

- The only occupational group in the UK for which there are any statistics on the prevalence of COPD is underground coalworkers.
- Many cases of COPD are undiagnosed because some individuals attribute their symptoms to ageing or to lack of fitness and do not seek a clinical diagnosis.
- Although there are the GOLD criteria for the definition and diagnosis of COPD, there may be differences in the criteria used to diagnose COPD among individual clinicians, and also differences in the criteria used for the “epidemiological” definition of COPD in large-scale community studies. These differences add to the uncertainties in estimation of the extent of work-related COPD in the general population.
- For an individual worker with COPD who smokes, it may not be possible to discriminate between the relative roles of cigarette smoking and occupational exposures in causing the condition. Hence work-related cases tend not to be picked up or reported via occupational health surveillance schemes.

However, bearing in mind the difficulties noted above, it is possible to broadly estimate the proportion of work-related COPD in the population by comparing the incidences of COPD in occupationally exposed and non-exposed populations. After correction for age and cigarette smoking, any excess incidence of COPD found in the exposed group is the “attributable risk” due to the exposure. If the proportion of exposed workers in the general population is known or can be estimated, the “population attributable risk” (PAR) % can be determined.

There are a number of large-scale epidemiological studies that have either determined a PAR for work-related COPD, or have amassed sufficient information to allow a PAR to be calculated. The studies are often based on questionnaire or telephone surveys, and rely on self-reports of occupation/exposures, respiratory health and smoking history. However, many studies include pulmonary function testing to provide objective

information in addition to the respiratory health questionnaires, and some use a validated job-exposure matrix to help categorise the probability of occupational exposures to dusts, gases and fumes in a semi-quantitative fashion. There are a number of differences in the design and methods applied in different studies that can make it difficult to compare findings.

Differences between studies include the age-ranges of the individuals sampled; COPD becomes increasingly prevalent with increasing age and some studies focus on the 55-75 year age range but other studies include much younger individuals. There are also some differences between studies in the criteria for determination of COPD status. Some studies were not specifically designed to investigate work-related COPD but nonetheless yielded relevant information. For example, the French PAARC (Pollution Atmospherique et Affection Respiratoires Chroniques) study of 16,000 adults was designed to investigate the impact of air pollution on respiratory health. Households headed by manual workers were excluded in order to avoid significant occupational exposure. Nonetheless, analysis of the findings from this study (Krzyzanowski and Kauffman 1988) revealed that occupational exposures of relatively low intensity encountered in non-industrial workplaces may constitute a non-negligible risk to respiratory health. In fact, from the information presented in this study, the American Thoracic Society calculated a PAR for work-related COPD of between 13-16%.

### ***6.1 Conclusions from the American Thoracic Society***

Recently, the American Thoracic Society (ATS) published an analysis of ten large-scale epidemiological studies conducted in the United States, France, Spain, Norway, the Netherlands, Northern Italy, China and New Zealand. The French study was the analysis of the PAARC study note above. These studies either determined a PAR for work-related COPD or presented sufficient information to allow a PAR to be calculated. The analysis of the ATS led to the conclusion that around 15% of the total burden of COPD in the general population is work-related.

Among the studies reviewed by the ATS, increased risks of airflow obstruction were associated with self-reported occupational exposures to quartz, glass fibre, sawdust, automobile exhaust, solvents, ammonia, nitrogen oxides, sulphur dioxide, metal fumes and anhydrides. Occupations with increased risks for COPD included construction and mining, bakers, food processors, cleaners, spray painters, plastics and rubber workers, and laboratory technicians.

None of the large-scale epidemiological studies included in the ATS analysis were based in the UK. However, particularly as a number of the studies were conducted in Northern European countries it seems reasonable to suppose that the 15% estimate for work-related COPD would represent a realistic ballpark figure for the UK.

## **6.2 Additional evidence on the extent of work-related COPD from studies not covered by the American Thoracic Society Review (2003)**

A number of studies that inform on the extent to which occupational exposures cause or contribute towards the development of COPD that were published too recently to have been included in the ATS review are detailed below. These studies are illustrative of the epidemiological methods used to determine the proportion of COPD in the population that is work-related.

### **6.21 Findings on the association between COPD and employment from the United States population-based Third National Health and Nutrition Examination Survey (Hnizdo et al 2002)**

*Summary: The results of this study indicate that the attributable fraction of work-related COPD in the population due to occupational exposures is 19.2%, and for never smokers, is 31.1%.*

The study comprised an analysis of data derived from the Third National Health and Nutrition Examination Survey in a representative sample of the general US adult population conducted from 1988 to 1994. The aim of the analysis was to explore the association between COPD and employment by industry and occupation. COPD was defined epidemiologically as FEV1/FVC <70% and FEV1 <80% of predicted values. The analysis was based on 9,823 subjects aged 30-75 years who underwent lung function tests and completed a questionnaire. The latter included detailed questions on smoking history, as well as on occupation. Odds ratios for COPD were determined for both industry sector and occupation, adjusted for the effects of age, sex, body mass index, smoking status, pack-years of cigarettes smoked, race/ethnicity, education and economic status. Because of large numbers and low prevalence of COPD, office workers were used as the baseline category against which other occupational groups were compared. Occupations were grouped according to the size of the odds ratio for COPD into high- and low-risk groups. In these groups, the trend with duration of employment was assessed using office workers as an “unexposed” comparison group.

Results showed that of the 9,823 subjects with valid lung function tests, 693 (7.1%) were identified as having COPD. Among these, 156 subjects had a physician’s diagnosis of emphysema and 438 had a physician’s diagnosis of chronic bronchitis. Perhaps surprisingly, subjects without a physician’s diagnosis had poorer lung function values than those with, consistent with the view that much COPD goes undiagnosed. When the results were analysed in terms of non-occupational risk factors for COPD, age was clearly a major factor; the percentage of all subjects aged 30-39 years with COPD was 1.9%; 6.7% (40-49 yrs); 13.1% (50-59 years) and 17.5% (60-75 yrs). Half of the total study population comprised never-smokers, and although the population prevalences of COPD were lower than in smokers, there were still cases of COPD among the never-smokers. For example, there were 833 never smokers aged 60-75, among whom the percentage with COPD was 6.9%.

Of the 9,823 subjects in the study, 295 who never worked were excluded from the calculations of odds ratios for COPD according to industry and occupation. When industry sector was analysed as a risk factor for COPD, 14 industries were identified as having increased odds ratios compared to the office workers. However, the lower 95% confidence interval for these odds ratios exceeded 1 for only four of these industry sectors which were:- rubber, plastics leather manufacturing (OR 2.5; 95% CI 1.4-4.4), textile mill products manufacturing (OR 2.2; 95% CI 1.1-4.2), armed forces (OR 2.2; 95% CI 1.2-3.9), and food products manufacturing (OR 2.1; 95% CI 1.1-4.1).

The total estimated working population of the US aged 30-75 years was 110,300,000. Of these, 6.9% (7,652,390) were estimated to have COPD. The number of cases attributable to employment was determined as 1,467,290, giving an attributable fraction of 19.2%. For never smokers, the estimated working population was 46,490,000, of whom, 1,131,840 (2.4%) were estimated to have COPD. The attributable fraction of work-related COPD in never smokers was estimated as 31.1%.

The authors gave their views on the strengths and weaknesses of this study. The strengths included reliable lung function data, a large sample size, and varied industrial exposures. The limitations were that the survey was not designed to be representative of US employment patterns, thus potentially missing some high risk work; there may have been some misclassification of exposure; and the cross-sectional design has limitations for determining causal relationships.

## 6.22 A study of the occupational burden of COPD in the US

(Trupin et al 2003).

*Summary: The results of this study indicate that a considerable proportion of COPD in the population is work-related. A PAR of 20% was determined based on the longest held job, but after adjustment using a job exposure matrix the PAR came down to 9%. The results show that the excess risk of COPD from the combined effects of cigarette smoking and occupational exposure is nearly twice what would be expected if the risks were simply additive. The weaknesses of the study are that it was relatively small-scale being based on 2061 subjects; data on COPD was determined from a self-reported physicians diagnosis with no independent confirmation by spirometry; the response rate for eligible subjects was only 53% and the potential for bias is uncertain; the cross-sectional design is limited for determining causal relationships. The strengths lie in the detailed reporting of the methods and clear analyses of results; as it is a recent study the findings will be more representative of current working conditions and smoking prevalences than earlier studies. The PAR estimates from this study are consistent with the conclusions from the ATS review.*

This study was based on a telephone survey of a randomly selected sample of US residents aged 55-75 years. The sample was constructed from three

cohorts. The first cohort was a random sample of 48 US states; the second and third samples were drawn from geographical areas that were known “hot-spots” for high rates of COPD based on national COPD mortality data. In the third sample (n= 110), only subjects with a physician’s diagnosis of a COPD condition or asthma were included. Of those eligible subjects (55-75 years) who were available for interview, the combined response rate was 53% leading to a final sample size of 2061. The same questionnaire was administered to all participants regardless of the cohort of origin. Information was obtained on occupational exposures to vapours, gases, dusts and fumes (VGDF) for all jobs held during the subjects’ working life. Also, a job exposure matrix developed for the European Community Respiratory Health Survey was applied. This takes into account duration of employment in the longest held job and across all jobs for which the subject reported exposure. The matrix led to specific occupations being categorised as having a low, intermediate, or high probability of dust exposure. Information on smoking, demography and socio-economic status was also obtained.

The statistical analyses were performed twice; once with a more comprehensive definition of COPD (termed ‘any COPD’, this was based on a self-reported physicians diagnosis of chronic bronchitis, emphysema or COPD), and once using a narrower definition (excluding chronic bronchitis). Subjects with asthma alone were included in the general population reference group.

The results showed that there were 377 individuals who reported a physicians’ diagnosis of at least one COPD, of whom, 288 reported chronic bronchitis and 144 emphysema. There were 140 respondents reporting COPD who also had a diagnosis of asthma. There were 129 reporting a diagnosis of asthma but not COPD.

Interestingly, the authors noted that there appeared to be a greater degree of work disability associated with COPD compared with asthma. Only 19% of respondents reporting COPD were employed at the time of interview compared with 30% of those reporting asthma alone, and 31% of those reporting no chronic airways disease. Half of those with COPD reported exposure to VGDF during their longest held job, compared with 42% of those with asthma alone and 32% of those with no chronic airways disease. Among the 189 subjects with chronic bronchitis alone, 42% reported VGDF exposure, and 57% of the 188 subjects reporting a diagnosis of COPD or emphysema reported VGDF exposure. Analyses using the job exposure matrix revealed that those reporting COPD were the most likely to be employed in either intermediate or high probability exposure occupations.

Based on self-reported diagnoses of COPD (regardless of asthma diagnosis), VGDF exposure during the longest held job was associated with a two-fold increase in the risk of COPD (OR 2.0, 95% CI 1.6-2.5). The PAR of COPD for self-reported exposure was 20% (95% CI 13-27%). When using the job exposure matrix, the PAR (combined for intermediate and high probability of exposure) was 9% (95% CI 3-15%).

When a narrower definition of COPD was used to exclude the 189 subjects with chronic bronchitis alone, the adjusted OR for self-reported occupational exposure rose slightly to 2.6 (95% CI 1.8 – 3.5) and the PAR was 31%. Using the job exposure matrix, the ORs for intermediate and high exposures were 1.5 (95% CI 1.04-2.2) and 1.9 (95% CI 1.2 3.2) respectively. The combined PAR was 13% (95% CI 3-22%).

Since occupational exposures may have affected cigarette smokers and non-smokers differently, the joint associations of cigarette smoking (ever smoked versus never smoked) and self-reported occupational exposure with COPD were examined using the definitions with and without chronic bronchitis. The results showed that the joint association between smoking and occupational exposure was greater than would be expected with a strictly additive relationship. The unadjusted probability of any COPD among those with neither exposure was 0.08; among those with occupational exposure alone it was 0.10 (therefore the excess risk is 0.02); among those with smoking exposure alone it was 0.19 (excess risk is 0.11); and among those with both exposures it was 0.32 (excess risk 0.24). In an additive relationship, the excess risk of COPD for the combination of smoking and occupational exposure (compared to neither exposure) would be approximately equal to the sum of the excess risks for smoking alone and occupational exposure alone. However, the excess risk for those with both smoking and occupational exposure was almost twice that of a purely additive relationship.

Similar findings were obtained when the same analysis was conducted for the narrower definition of COPD. The authors' discussion identified certain strengths and weaknesses with this study. One source of uncertainty was the reliance placed on a self-reported physician's diagnosis of COPD unconfirmed by spirometry. They noted that other studies suggest this may lead to an underestimate of the true prevalence due to lack of access to medical care and underdiagnosis. The potential for misclassification of exposure was discussed, and the potential for recall bias whereby affected individuals may be more likely to recall their past exposures. However, it was felt that the job exposure matrix was not prone to this bias, and its use reaffirmed the association between exposure and disease.

6. 23 A study of respiratory symptoms and occupation in Doetinchem in the Netherlands (Vermeulen et al 2002).

*Summary: This study was based on identifying individuals with self-reported symptoms of chronic bronchitis, and such cases may not necessarily have COPD. However, it is included in this appendix because it is likely that individuals with chronic bronchitis are at increased risk of developing COPD, and hence the findings of this study are considered to be of relevance to the aims of this document. The results of this study showed that employment in the 'construction', 'metal', 'rubber, plastics and synthetics' and 'printing' industries was positively associated with chronic bronchitis symptoms. There was evidence for increasing risk with increasing duration of employment in these industries. The weaknesses of the study include the relatively small*

*scale, being based on only 1104 subjects; data on respiratory symptoms was obtained via a self-reported questionnaire, with no supporting spirometry data. The cross-sectional design is not ideally suited to the identification of causal relationships. However, the study is relatively recent and therefore may be more representative of current working and smoking patterns than earlier studies.*

This was a cross-sectional study of the general population in a small industrial town in the Netherlands (Doetinchem). Subjects were from the Dutch Monitoring Project on Risk Factors for Chronic Diseases (MORGEN). The study was based on a random sample of 1104 subjects aged 20-59 years. The subjects completed a self-administered questionnaire on respiratory symptoms, smoking habits, socio-economic status, and sectors of industry and occupation in which respondents had worked for more than one year. Both asthma and bronchitis symptoms were investigated but only the details relating to bronchitis will be presented here. Bronchitis was defined as a positive answer to at least one of the following questions: 'Do you cough daily for more than 3 months a year?', 'Do you bring up phlegm daily for more than 3 months a year', 'Have you had episodes in the last 3 years in which you coughed and brought up phlegm which lasted for more than 3 weeks?', and 'Have you had attacks of shortness of breath while walking on a flat terrain at normal speed with other people?'

A total of 274 subjects (24.8%) reported one or more asthma or bronchitis symptoms. As controls, 274 subjects were selected from the asymptomatic subjects and were frequency matched for age and sex at group level. The relation between occupational history and bronchitis symptoms was investigated taking account of socio-economic status and smoking history in a multiple logistic regression analysis. Analyses based on the longest held occupation revealed increased risks for bronchitis symptoms in the 'construction' (OR = 3.38; 95% CI 1.02-11.27), 'metal' (OR = 3.17; 95% CI 0.98-10.28), 'rubber, plastics and synthetics' (OR = 6.52; 95% CI 1.26-53.80), and 'printing' industry (OR = 3.96; 95% CI 0.85-18.48).

For the industries with statistically significant associations with bronchitis and asthma symptoms ( $p < 0.1$ ) the regression analyses were repeated based on the total occupational histories with inclusion of time related variables such as duration and time since first employment. In the 'metal' and 'rubber, plastics and synthetics' industry, the odds ratios increased significantly with increasing duration of employment, however, statistical significance was not achieved. Time since first employment showed a less clear relationship with bronchitis symptoms compared to duration of employment.

The majority of subjects in the 'rubber, plastics and synthetics' category were employed in one rubber tyre manufacturing factory. A large-scale exposure assessment had been performed in this factory at the end of the 1980s revealing a mean inhalable dust concentration of  $1.5 \text{ mg.m}^{-3}$ . However, exposures in the inner tube department and among technical services personnel were higher at  $17.3$  and  $4.2 \text{ mg.m}^{-3}$  respectively (presumably 8-hr TWAs although time periods for air sampling not stated). The high dust

exposures were mainly caused by excessive use of talc to prevent tacking of uncured profiles.

Working in the metal industry was associated with both symptoms of asthma and bronchitis. Exposures in this industry include metal dust and fume, welding fume, crystalline silica and isocyanates. The authors commented upon the observed association between bronchitis symptoms and working in the printing industry; they felt it was unclear what the main risk factors would be, although it was noted that exposures to irritative solvent vapours and paper dust would occur.

Individuals from this population smoked less often than was common in the 1960s and 70s. Of the men and women, 38.5% and 28.6% respectively were current smokers and similar proportions were former smokers. Although smoking is a key risk factor for bronchitic symptoms, adjusting for smoking (as well as for age, sex and socio-economic status) in this study generally had a minimal effect on the risk estimates for industries and occupations suggesting the the observed effects could be primarily accounted for by occupational exposures.

### **6.3 Conclusions concerning the evidence for work-related COPD**

There is a strong and consistent body of evidence from a number of large-scale epidemiological studies indicating that occupational exposures to dusts, gases and fumes make a substantial contribution to the population burden of COPD. The American Thoracic Society (ATS) estimates that about 15% of all cases of COPD in the general population are work-related. In epidemiological terms, this fraction of 15% is known as a “population attributable risk” (PAR). The PAR estimate derives from an analysis of 10 large-scale studies conducted in the United States, France, Spain, Norway, the Netherlands, Northern Italy, China and New Zealand. Similar estimates were derived from two well-reported studies in the US published too recently to have been included in the ATS analysis. A further study in an industrial town in the Netherlands adds support to the view that occupational exposures add substantially to the population burden of chronic respiratory disease.

None of these studies was conducted in the UK, but the 15% estimate seems more likely than not to be broadly representative of the situation in the UK. One reason for this conclusion is that the substances identified which have the highest risks for work-related COPD seem relevant to the UK e.g quartz, glass fibre, sawdust, automobile exhaust, solvents, ammonia, nitrogen oxides, sulphur dioxide, metal fumes and anhydrides. Occupations with increased risks for COPD included construction and mining, food processors, cleaners, spray painters, plastics and rubber, leather and plastics/synthetics manufacturing, textile mill workers, and laboratory technicians.

There is no sign from any of the individual studies that the PAR estimate of 15% could be “worst-case”, in fact the opposite is more likely. This is because none of the studies of this subject deliberately focused on high risk occupational groups, and in fact one study specifically excluded households

where the head of the house was a manual worker. Another reason for considering that the 15% estimate is not likely to be “worst-case” is that a strong view emerges from the literature that much COPD goes unrecognised and undiagnosed.

Another reason to consider that the 15% estimate is likely to be representative for the UK is that it derives from findings in a number of developed countries, including some northern European countries, and it seems unlikely that there would be major systematic differences in the patterns of industrialisation in the UK compared to these other countries. It also seems unlikely that there would be major differences in occupational hygiene standards such that occupational inhalation exposures would be markedly higher or lower in the UK compared to other industrialised countries.

The question might arise as to whether differences in the pattern of cigarette smoking in different countries might render the 15% PAR for work-related COPD irrelevant to the UK. The prevalence of smoking is known to have declined among males in the UK over the last 20 years, and to have increased among women. Smoking status is clearly an important consideration throughout all the population studies on work-related COPD. However, all of the available studies informing on work-related COPD have taken full and detailed account of smoking status and so differences in smoking prevalences in different countries seem unlikely to have been able to bias the PAR estimate of 15%.

One conclusion to emerge from the available studies is that as the prevalence of cigarette smoking declines in the population, the proportion of COPD due to occupational exposures will increase. Thus, although a decline in cigarette smoking should lead to a reduction in the incidence of COPD in the population, the proportion of cases that are work-related will increase. In non-smokers with COPD, a large-scale study in the United States found that the proportion due to workplace exposures to vapours, dusts, gases and fumes was 31.1%.

One very recent study conducted in the US included an analysis of the interaction between cigarette smoking and occupational exposures to vapours, gases, dusts and fumes on the risk of COPD. The results indicated that the combined effects from cigarette smoking and occupational exposure are more than would be expected from a simply additive relationship. The results suggested a doubling in the excess risk of COPD compared to what would be expected if the combined effects of smoking and occupational exposure were simply additive. However, this was not a particularly large-scale study and confirmatory evidence from other studies would be useful.

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