Epidemiological studies of the relationship between occupational exposures and chronic non-specific lung disease

Dick Heederik

Stellingen

Recent gepubliceerde onderzoeksresultaten, gebaseerd op in het verleden blootgestelde populaties, laten geen eenduidig antwoord toe op de vraag hoe groot het risico op CARA is voor de tegenwoordig beroepsmatig aan luchtverontreiniging blootgestelde populatie in Nederland.
(Dit proefschrift)

De uitspraak dat effecten van een beroepsmatige stofblootstelling op de luchtwegen zich vooral bij rokers manifesteren is een grove generalisatie en niet in overeenstemming met onderzoeksresultaten.
(Jacobsen M. Smoking and disability in miners. Lancet 1980; ii: 740)

Preventieve maatregelen met het doel CARA ten gevolge van een beroepsmatige blootstelling aan luchtverontreiniging te voorkomen zijn nu al mogelijk op basis van recent verzamelde blootstellingsgegevens en bestaande grenswaarden voor luchtverontreiniging op de arbeidsplaats.

Een MAC-waarde voor endotoxinen, gebaseerd op acute longfunctieveranderingen, moet op korte termijn worden overwogen gezien de consistentie in de onderzoeksresultaten.
(Palchak RB et al. Airborne endotoxin associated with industrial scale production of protein products in gram-negative bacteria. Am Ind Hyg Assoc J 1988; 49:420-421)

Voordat men in de epidemiologische onderzoekzoekspraktijk overgaat op de door K.R. Popper voorgestelde procedures om hypothesen te toetsen moet meer aandacht aan de critici van Popper, waaronder P. Feyerabend, worden gegeven.
(P. Feyerabend. Science in a free society. Schocken Books, New York, 1978)

De slechte karakterisering van een beroepsmatige blootstelling in veel epidemiologische studies is het gevolg van een verwaarloosbaar kleine inbreng van arbeidshygiënische principes.
(Checkoway H, JM Dement, DP Fowler, RL Harris, SA Lamm & TJ Smith. Industrial hygiene involvement in occupational epidemiology. Am Ind Hyg Assoc J 1987; 48:515-523)

Indien de verzameling en beoordeling van longfunctiegegevens in de bedrijfsgezondheidszorg niet op een gestandaardiseerde wijze plaatsvinden, kunnen deze tienduizenden metingen per jaar beter achterwege blijven.

Smith karakteriseert epidemiologisch en toxicologisch onderzoek respectievelijk als 'exposure poor, species right', 'exposure satisfactory, species wrong'. Het waardeoordeel 'the score poor plus right wins over satisfactory plus wrong' geeft de plaats van de epidemiologie ten behoeve van risicoanalyses duidelijk aan.
(Smith AH. Epidemiologic input to environmental risk assessment. Arch Env Health 1988; 43: 125-127)

De uitspraak van Kroes "Casuïstisch en epidemiologisch onderzoek hebben in verband met het opstellen van advieswaarden relatief weinig betekenis" is volstrekt onjuist gezien de veelvuldige toepassing van epidemiologische gegevens bij de onderbouwing van milieu- en arbeidshygiënische grenswaarden.
(Kroes R. Normstelling voor chemische verbindingen. In: Stumpel ARJ, R van den Doel. Medische milieukunde. Bohn, Scheltema & Holkema. Utrecht /Antwerpen 1989, p.171)

De bevinding dat een grote opzichtige postzegel op een antwoordenvelop van een postenquête tot een statistisch significant verhoogde respons leidt, kan een nieuwe impuls geven aan het werk van de ontwerpafdeling van de PTT.
(Choi, BCK, AWP Pak, JT Purdham. Effects of mailing strategies on the response rate and time in a questionnaire among nurses. Seventh International Symposium on Epidemiology in Occupational Health, Tokyo, 1989)

Autouitlaatgassen zijn milieuhygiënisch gezien pas schoon als ze aangewend kunnen worden voor de interieurventilatie van de auto.

Stellingen behorend bij het proefschrift:
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18 april 1990

EPIDEMIOLOGICAL STUDIES OF
THE RELATIONSHIP BETWEEN OCCUPATIONAL EXPOSURES AND
CHRONIC NON-SPECIFIC LUNG DISEASE

Promotoren: dr. K. Biersteker, hoogleraar in de gezondheidsleer, meer in het bijzonder de milieuhygiëne en de tropische gezondheidsleer

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Dirk Johannes Jacobus Heederik

EPIDEMIOLOGICAL STUDIES OF THE RELATIONSHIP BETWEEN OCCUPATIONAL EXPOSURES AND CHRONIC NON-SPECIFIC LUNG DISEASE

PROEFSCHRIFT
ter verkrijging van de graad van
doctor in de landbouw- en milieuwetenschappen,
op gezag van de rector magnificus,
dr. H.C. van der Plas,
in het openbaar te verdedigen
op woensdag 18 april 1990
des namiddags te vier uur in de aula
van de Landbouwuniversiteit te Wageningen

Omslagfoto's met toestemming van:

Museum Historische Landbouwtechniek te Wageningen
Openlucht Museum te Arnhem

"... the canker of industrial diseases gnaws at the very root of our national strength."

John Simon, PP.XXVII (1862) 'Fourth Annual Report of the Medical Officer to the Privy Council, for 1861', pp.31-2.

Voor P.J.L. Heederik Sr.

ABSTRACT

EPIDEMIOLOGICAL STUDIES OF THE RELATIONSHIP BETWEEN OCCUPATIONAL EXPOSURES AND CHRONIC NON-SPECIFIC LUNG DISEASE

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Dirk Johannes Jacobus Heederik

In this thesis the relationship between occupational exposures, lung function and Chronic Non-Specific Lung Disease is studied. The study comprises an epidemiological analysis of data from the British Pneumoconiosis Field Research among coal miners and an analysis of data gathered in the Zutphen Study, a Dutch general population study.
These findings point to a few general conclusions. Occupation and occupational exposures are clearly related to respiratory symptoms and reductions in lung function. The relationship between smoking and CNSLD incidence appeared to be a stronger one than the relationship between occupation, occupational exposures and CNSLD incidence. However, considerable odds ratios and relative risks were found for specific exposures and some occupations. The etiological fraction for occupational exposures with CNSLD incidence is estimated to be 10-30% for the Zutphen Study. Relationships found argue for new studies among recently exposed populations. No evidence for a relationship between occupational exposures and total mortality was found. The relationship with CNSLD mortality after allowing for smoking habits and age is less clear. Studies with more detailed exposure information and larger statistical power are needed to elucidate the relationship between occupation and CNSLD mortality.

Key words: occupational exposures, lung function, lung disease, CNSLD, COLD

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TABLE OF CONTENTS

1. INTRODUCTION

Asthma, bronchitis and emphysema, collectively called Chronic Non-Specific Lung Disease (CNSLD), form an important public health problem in the general population. In the Netherlands CNSLD is the fifth most common cause of death. Approximately 5.5% and 2.2% respectively, of men and women who died in 1985 had CNSLD as primary cause of death. For 6.6% of the men and 2.4% of the women CNSLD was mentioned on the death certificate as secondary cause of death (CBS, 1985).

Morbidity statistics, however, reflect the impact of CNSLD on public health more clearly then mortality statistics do. Because of improved medical treatment techniques CNSLD leads to death only for a small minority of those with CNSLD. Many CNSLD patients are to some extent disabled because of their disease. Approximately 5% of all sickness spells which lead to absence from work for men and 9% for women respectively were caused by CNSLD in 1984 (CBS, 1985). The true percentage is probably higher as for 71% of sickness absence cases the reason is unknown. Sickness absence because of CNSLD lasts approximately four times longer than absence due to all causes together. Van der Lende et al. (1975a+b) estimated the prevalence of CNSLD for which medical treatment is necessary as 8-15% for Dutch males aged 15-64 and 5% for Dutch females in the same age range. In a recent report, the costs of treatment of CNSLD patients by physicians and hospitals plus the costs of absence from work due to CNSLD were estimated at 1.000 million Dutch guilders per year (Van Mölken et al., 1989). This brings CNSLD among the diseases with a high financial burden for society.

Among the determinants of CNSLD, smoking is considered the most important. Other environmental factors like outdoor, indoor as well as occupational air pollution, have also been studied. Smoking is widespread among the general population, and it is known to be a strong determinant of lung disease like lung cancer and CNSLD. The universality of smoking habits, and the widely accepted evidence of their role in the development of airway disease have tended to overshadow the role of other environmental pollutants such as occupational exposures (Becklake, 1985). In addition to this, other factors might explain the limited attention

given to the role of occupational exposures in the development of CNSLD. These other reasons include (Smith, 1987; ACGIH, 1988; Becklake, 1988, 1989a+b):

- the absence of powerful longitudinal epidemiological studies of occupationally exposed workers;
- the focus on workforce based studies, which are sensitive to selection biases such as the 'Healthy Worker Effect', instead of community based studies;
- the paucity of statistical and epidemiological techniques for assessing the contribution of more than one risk factor in the development of diseases with a multifactorial etiology;
- the presence of specific lung disease such as pneumoconiosis and tuberculosis leading to increased 'noise levels' in epidemiological studies of CNSLD;
- the absence of precise and valid techniques and strategies to measure occupational pollutants.

Although several studies point to a role of occupational exposures in the development of CNSLD, there is still no agreement on the magnitude of the effects of occupational exposures. In the case of coalworkers, perhaps the best studied occupationally exposed population, some authors have expressed the opinion that airflow limitations resulting from an occupational exposure are of minor degree and not sufficient to impair lung function and disable the worker unless he is a smoker also (Morgan, 1978, 1986; Anonymous, 1980; Parkes, 1982; Abrams, 1984). Others disagree and argue that clinically relevant decreases in lung function could result from a lifetime exposure to coalmine dust (Seaton, 1983a+b, 1984; Becklake, 1985, 1988, 1989a+b; Bates, 1987; Hurley & Soutar, 1986; Kauffmann & Anessi, 1987; Soutar, 1987; Marine et al., 1988). Some studies suggest that lung function decreases associated with occupational exposure to e.g. dusts can be of the same order as decreases from smoking (Elmes, 1981; Seaton, 1983a; Marine et al., 1988). This is questioned by others (Anonymus, 1980; Cochrane, 1983; Morgan, 1978, 1983, 1986; Oldham, 1984).

So, the contribution of occupational exposures to the incidence of CNSLD is still not known (Becklake, 1985; Whittenberger, 1985; NHLBI, 1987;

WHO, 1989). It has been estimated that the overall contribution of occupation to CNSLD is small compared to the contribution of smoking (WHO, 1985; Elmes, 1981). If this is so, strategies to prevent the development of CNSLD should primarily aim at the elimination of smoking. Others argue that specific occupational exposures can make a considerable contribution to the development of CNSLD and conclude that preventive strategies should aim at the reduction of both smoking and these occupational exposures (Jacobsen, 1980; Marine et al., 1988). Specific information on the role of occupational exposures in the development of CNSLD could contribute to the development of scientificly based preventive strategies instead of sweeping generalisations on relative contributions of factors such as "smoking" and "occupational exposures" (Jacobsen, 1980; Becklake, 1985, 1988, 1989a+b; Marine et al., 1988; WHO, 1989).

This research was carried out to investigate the contribution of occupational exposures in the development of CNSLD. In the following chapters literature on the evidence of a relationship between occupational exposures and CNSLD will be reviewed and special issues in current occupational epidemiologic research will be highlighted. Special emphasis will be put on occupational exposure assessment, because this part of occupational epidemiologic research in the field of lung disease has not been given the attention it deserves according to recent reviews (Checkoway et al., 1987; Smith, 1987; ACGIH, 1988). Due to the incompleteness of evidence for a relationship between occupational exposures and CNSLD several issues remain to be studied. Some of these will be adressed in our own data analysis.

The historical background of epidemiological research into CNSLD will be described in chapter 2, followed by a chapter on methodological issues in exposure-response modeling in occupational epidemiology (chapter 3). Thereafter recent epidemiological evidence of the relationship between occupational exposures and CNSLD will be discussed in chapter 4.

For our own analyses, data from two large longitudinal studies were used. First, data were used from coal miners exposed to dust and surveyed in the British Pneumoconiosis Field Research of the National

Coal Board (Fay, 1958). These data allowed the study of the influence of estimation error of the exposure on exposure-response relationships, because detailed exposure information was available and monitoring strategies were known in great detail. Estimation error of the exposure might be one factor which contributes to lack of clarity in the discussion on the relative contribution of several exposures, such as occupational exposures and smoking to respiratory changes. Therefore an attempt is made in Chapter 5 to estimate this error in a particular epidemiological study and disattenuate the regression coefficients of lung function change on the cumulative dust exposure. Second, data were used from the Zutphen Study, the Dutch contribution to the Seven Countries Study (Keys et al., 1967). In this general population-based follow-up study CNSLD morbidity was assessed at regular intervals and causes of death were registered. The occupation of the participants was recorded on several occasions.

The aims of the analyses of the Zutphen Study were to contribute new information on the relationship between occupational exposures and CNSLD by:

- the analysis of data of the Zutphen population with 25 years of follow-up on morbidity and (cause-specific) mortality. The maximum duration of follow-up of the general population studies published so far is only half as long. Follow-up studies are limited to lung function data. Long-term effects of occupational exposures on respiratory health might therefore be investigated in this study in more than one respect. For the analysis of the CNSLD morbidity data an alternative approach was also used. The design of the Zutphen morbidity study made an analysis of CNSLD incidence data possible, besides the more conventional analysis of prevalence data.
- the use of other indices of occupational exposures in the analysis then applied in most general population-based studies described so far. In most studies self-reported specific exposures were used. Non-differential misclassification might therefore have occurred. In the Zutphen Study other exposure indices were used of which at least one, the occupational title, is believed to be less sensitive to non-differential misclassification. Apart from the occupational title, specific exposures were generated with a Job Exposure Matrix. For specific

exposures as generated with the Job Exposure Matrix the validity is unknown but suspected to be variable. Therefore this technique was used in addition to the occupational title only.
- the evaluation of the effect of changes in occupation on the relationship between occupation and CNSLD. This was possible because the occupational title was registered repeatedly.

Specific analyses comprised:
- a cross-sectional analysis of the relationship between occupational exposures and respiratory symptoms (Chapter 6).
- a longitudinal analysis of the relationship between occupational exposures and CNSLD incidence (Chapter 7).
- a longitudinal analysis of the relationship between occupational exposures, lung function, and CNSLD incidence, CNSLD mortality and total mortality (Chapter 8).

In the final chapter results of these analyses and their implications will be discussed.

2. HISTORICAL BACKGROUND

2.1. Chronic bronchitis and emphysema

The first clinical descriptions of chronic bronchitis originate from the beginning of the nineteenth century by Badham (Colley, 1985), but it took more than a century before more attention was paid to the study of this disorder. At the beginning of this century, bronchitis was a major cause of death and disability in Britain. From those days on, bronchitis was called the "British disease" because of the high mortality rates in certain urban areas in Britain compared with other countries. In those days, the effect of cigarette smoking, which is now considered to be a main cause of bronchitis and emphysema, can hardly have influenced the mortality figures. The amount of tobacco smoked at that time was only about one-tenth of what became the average consumption in the forties and most persons smoked pipe tobacco and cigars (Gilson, 1970; Elmes, 1981). Interest in the study of chronic bronchitis and emphysema grew after the mortality from other respiratory diseases such as tuberculosis and pneumonia had decreased strongly after the second world war in Britain, as in other western countries (Elmes, 1981). In The Netherlands for instance, age-adjusted mortality rates from tuberculosis showed a steady decline from 15-20 between 1910-1920 to less than 2.5 per 10,000 inhabitants in 1950 and to a negligible figure afterwards (CBS, 1985). A detailed comparison of trends in respiratory disease mortality over the last 80 years is given by Elmes (1981). He showed that (1) exposure to infective agents, (2) social factors such as population density and nutrition (3) exposure to air pollution such as cigarette smoke and (4) inherited susceptibility are the four most important causes of lung disease. At the beginning of this century, infective agents played an important role in the development of chronic bronchitis. Bronchial infections lead to damage to bronchioles and alveolar tissues and had fatal consequences in terminal patients with severe obstructions. Infections could be treated with antibiotics since the late 1940s. In The Netherlands differences in secular trends of total infectious disease mortality and mortality because of upper respiratory infections during the pre world war II and post-war period have been found, which are at least partially attributable to the introduction of antibiotics

(Mackenbach & Looman, 1988). Elmes (1981) also showed that lung cancer and chronic bronchitis are the two diseases causing the main burden of lung disease these days.

There always had been considerable disagreement about the definitions of chronic bronchitis and emphysema. British researchers tended to stress the importance of chronic bronchitis as a potentially serious progressive disease, and a major cause of death and disability, while American researchers regarded the disorders as a relatively unimportant inflammatory process in the bronchial tree, which was accompanied by persistent cough. They focussed more strongly on emphysematic processes in the lung which they found to be the most important determinant of non-malignant respiratory morbidity and mortality (Colley, 1985). Major progress was made at a Ciba Guest Symposium in 1959 (Ciba, 1959). At this symposium chronic bronchitis, emphysema and asthma were defined. Chronic bronchitis was defined as chronic mucous expectoration. Emphysema was defined as loss and widening of the terminal bronchioles and alveoli, and the diagnosis had to be based on anatomical evidence. Asthma was defined as a reversible functional airflow limitation. In The Netherlands, the term CNSLD, Chronic Non-Specific Lung Disease was introduced as a general term, to cover all three diseases (Gezondheidsraad, 1966). CNSLD, or the Dutch equivalent CARA (Chronische Aspecifieke Respiratoire Aandoeningen), was considered to be present in case of chronic or of episodic productive cough, or chronic or periodic shortness of breath, in absence of other diseases such as tuberculosis, lung cancer, pneumoconiosis, and fibrotic diseases of the lung.

The term 'CNSLD' was especially used by those who accepted the "Dutch hypothesis" which assumes that individual susceptibility in the form of hyperreactive airways or atopy is a key factor in the development of bronchitis, asthma and emphysema (Orie et al., 1961; Colley, 1985). They defined chronic bronchitis as a clinical syndrome characterised by cough, phlegm production, with a fluctuating course and in most cases accompanied by an airflow obstruction. The "British hypothesis" proposed that an environmental exposure, like smoking leads to inflammation and phlegm production. Environmental factors such as smoking were the major determinants of both bronchitis and emphysema, and these were seen as

independent disorders. Asthma was regarded to be independent of both emphysema and bronchitis. To characterise an irreversible airflow limitation, irrespective of whether it was caused by bronchitis or emphysema, the term Chronic Obstructive Lung Disease (COLD) was proposed. In the following years, further reports on the classification of these diseases were published by the World Health Organisation and the American Thoracic Society (WHO, 1961; ATS, 1962). In 1965, the British Medical Research Council (BMRC) published its report on the definition and classification of these diseases for clinical and epidemiological purposes (BMRC, 1965). The Council introduced the terms, simple chronic bronchitis, chronic or mucopurulent bronchitis and chronic obstructive bronchitis, which were defined as:

- chronic simple bronchitis: chronic or recurrent increase in the volume of mucoid bronchial secretion sufficient to cause expectoration;
- chronic mucopurulent bronchitis: chronic bronchitis in which the sputum is persistent or intermittently mucopurulent when this is not due to localised bronchopulmonary disease;
- chronic obstructive bronchitis: chronic bronchitis in which there is persistent widespread narrowing of the intrapulmonary airways, at least on expiration, causing increased resistance to flow.

At the beginning of the sixties, little was still known about the early stages of the disease process of bronchitis. The follow-up study by Fletcher et al. (1976) of British manual workers shed new light upon the relationships between smoking, lung function, and respiratory symptoms. Their results suggested that neither mucus hypersecretion nor bronchial infections cause a rapidly progressing airflow limitation. Both were caused by smoking, but they appeared to be separate entities with different underlying mechanisms. These findings were confirmed by other researchers (Bates, 1973; Kauffmann et al., 1979). As a result of this, Fletcher (1978) noted that there is no longer the wide agreement on definition of bronchitis and emphysema as there was in the sixties. For example, the term chronic obstructive bronchitis may be too general as it could now be used to cover peripheral airways obstruction, small airways disease and emphysema (Colley, 1985). However, a generally accepted substitute for the term chronic bronchitis, and its different conditions, still does not exist (Bates, 1979).

In more recent reviews, chronic bronchitis and emphysema are diseases often regarded as a result of different, independently operating, processes, like hypertrophy of the mucous glands in the large airways, alterations of physical properties of the lung as in aging, morphological changes in the small airways, and loss of alveoli. The individual reactions vary, and the expression of these processes in terms of a clinical picture depends on the relative importance of these factors in a specific individual and on the presence of complicating airway infections in later stages of the diseases (Bates, 1979). However, these recent insights did not overrule the discussion on the British and Dutch hypothesis. Some still regard the discussion as open, which is illustrated by recent publications on the relationships between airway responsiveness, atopy and chronic obstructive lung disease (Weiss & Speizer, 1984; Sparrow et al., 1988; O'Connor et al., 1989).

2.2. Asthma

Asthma is a functional disorder characterised by widespread partial narrowing of the airways which varies in severity, is reversible, either spontaneously or as a result of treatment, and is not due to cardiovascular disease (Ciba, 1959). If asthma is caused by an agent in the industrial environment, the term occupational asthma is used (Parkes, 1982; Gee, 1984; Chan-Yeung & Lam, 1986). The mechanism of disease is often immunological, and it has been pointed out that atopic individuals tend to develop an asthmatic allergy more readily than non-atopic individuals. However, non-atopics can become sensitised too (Chan-Yeung & Lam, 1986). Because of the allergic background in asthma, different types of asthmatic reactions have been described. A distinction is made between immediate (within 10-20 minutes), late (after 4-8 hours), delayed (12-24 hours) and dual reactions (combination of immediate and late reaction). In the work environment, with complex exposure patterns, the obstruction observed also behaves in a more complex way than in a laboratory setting, and can be overlooked because of its nature. Many allergens in the industrial environment have been identified and among them are small molecules such as isocyanates and organic dusts which originate from animals and plants. An overview of dusts and chemicals

which have been shown to cause asthma in the work environment is given by Parkes (1982) and Chan-Yeung & Lam (1986). Most surveys estimate that 2-6% of the adult population has asthma, although criteria for the diagnosis of asthma and populations studied may differ (WHO, 1989). It is estimated in two studies, from Japan and the United States of America, that 2-15% of adult asthma cases may have an occupational agent as a cause (Salvaggio, 1979; Kobayashi, 1980). Asthma prevalences greater than 30-50% have occasionally been observed among specific occupationally exposed groups like detergent enzyme workers, wood workers and millers, but these prevalences are exceptional (Parkes, 1982; Gee, 1984; Morgan & Seaton, 1984).

2.3. Early studies on the relationship between occupational exposures and CNSLD

In the beginning of this century most evidence of a relationship between occupational dust exposure and bronchitis mortality was based on the national mortality statistics in Britain. Collis (1915) studied the 1911 occupational mortality statistics and concluded that:

> "while the influence of dust in general in the causation of bronchitis may be accepted, certain dusts do not appear to exert such an influence. Thus coal dust.. is not associated with bronchitis."

He was struck by the difference in bronchitis mortality rates for coal workers (death rate of 0.6, 3.5 and 19.5 per 1,000 for men aged 45-54, 55-64, 65 and over, respectively) and other occupational groups (e.g. cotton strippers 2.9, 12.5 and 42.6 per 1,000 for the same age groups). Collis shared the mainstream opinion at the end of the nineteenth century that dust related diseases ceased to exist because of improvements in working conditions, ventilation and shorter working hours (Hunter, 1980).

Haldane analysed the 1921 mortality statistics and found comparable results (Gilson, 1970). He stated that:

> "When we compare the bronchitis mortality of old colliers with that of other men...it appears that the dust cannot on the whole have made much difference."

In those days, cigarette consumption, which is now considered as the main determinant of bronchitis and emphysema, can hardly have influenced the mortality figures. The amount of tobacco smoked in those days was a

fraction of the average consumption in the forties (Gilson, 1970). So other factors than smoking were more suspect as a potential cause of bronchitis mortality.

Information concerning the validity of a diagnosis of bronchitis is not present, so the validity and precision of the statistics used in those days cannot be assessed. However, Arlidge noted already in 1889 confusion about differences between bronchitis, asthma, fibroid pneumonia and consumption (tuberculosis) (Arlidge, 1889). Almost a decade later, the Departmental Committee on Compensation for Industrial Diseases still mentioned problems in distinguishing tuberculosis from other lung disease like pneumoconiosis. There were even discussions about making tuberculosis a compensable industrial disease (HMSO, 1907). Further development of roentgen techniques at the beginning of this century made a more reliable distinction possible although epidemiological details such as precision or validity of the techniques used are unknown (Pancoast et al., 1918).

Although for several European countries mortality figures by occupation are available, a comparison is almost impossible. Heijermans (1926) analysed mortality statistics from England and Wales, France, Germany, The Netherlands and Switzerland of the first quarter of this century. In his conclusions he stresses the incomparability of mortality statistics because of differences in the definition of occupations; the definition of several causes of death; the standardisation procedures; the cut-off of age classes; hygienic circumstances and climate. However, despite these differences he concludes that an increased mortality due to lung diseases existed among workers with dusty occupations such as miners and textile workers.

English mortality statistics in the fifties showed in contrast to the earlier figures an elevated age standardised mortality rate for miners (miners, 733 per million; transport workers 465 per million and agricultural workers 263 per million). The reason for this change over the years is not completely clear, but several explanations have been suggested. Mechanisation of mining started at the beginning of the century and took till the fifties. This resulted in higer exposure

measure the extent to which the disease in any individual was due to his occupation;

- Epidemiological data from the Registrar General were subject to biases. First, it was pointed out that death certificates tend to contain information on a man's longest held or original job. Therefore mortality figures on the number of coal face workers with bronchitis, tend to be inflated. Second, industrial migration might distort conclusions drawn on the basis of statistical information. Third, the committee mentioned again that miners wives appeared to have an increased mortality of chronic bronchitis too, as shown by the Registrar Generals statistics as well as in field studies.

The conclusions of the committee were at the time heavily debated. Initially most arguments against the conclusions of the committee were based on reappraisal of the epidemiological evidence on the relationship between dusty occupations and respiratory symptoms, lung function and mortality (Gough, 1966; McLaughin, 1966; Pemberton, 1966).

But the committee's conclusions were a target for critics for a long time after the presentation of the report also. Oldham (1968) and Gilson (1970) criticised the interpretation of the male/female pattern in mortality over social classes strongly. They showed that the excess death rate in miners could either be interpreted as an additional factor of occupation or as a multiplicative factor between males and females, which is fairly constant over the social classes, poorly related to occupation, but more strongly related to socio-economic factors. Fox and Adelstein (1978) also discussed the analysis of mortality by broad social classes and the use of wives as a standard. They argued that in the female/male comparison one assumes that direct effects of occupation on mortality are not present for women, and indirect influences have to be the same for men and women. The first assumption means that women do not work, are not exposed to occupational hazards or that women occupations are not related to those of their husbands. The second assumption means that the "way of life" is the same for men and women. Both assumptions were strongly criticised because there appeared to be a strong relationship between the occupation of the wife and her husband, and many wives of coal miners were working in dusty occupations in the

textile industry. Way of life, smoking habits and alcohol consumption differed strongly between men and women also and might therefore contribute to differences in mortality between men and women. Fox and Adelstein also concluded that the results of the analysis of mortality statistics have altered the balance of commentaries on occupational mortality:

"... in more recent volumes, emphasis has shifted to the discussion of socio-environmental influences."

Some statements of Fletcher (1958) illustrate this point. Because of the similarities in mortality pattern of men and women he wrote:

"..it must therefore be due to some general environmental rather than occupational influence...".

Because the unskilled workers lived in overcrowded and polluted parts of the cities he suggested that atmospheric pollution might explain these findings. Inadequate medical care and transmission of infections might also play a role of importance. He also mentioned the British habit of sleeping with open windows as a factor to explain the high mortality rates of bronchitis in comparison with other countries (Fletcher, 1963). So, the patterns found in bronchitis mortality were difficult to interpret because of the relationships between male and female mortality rates, the relationships with social class and the degree of urbanisation as reviewed by Goodman et al. (1953) and outdoor air pollution. Episodes of extremely high air pollution during certain meteorological conditions showed that excess mortality could occur. So, the evidence for the involvement of air pollution was becoming stronger, not only because of the observations made during the 1952 London episode, but also because measured exposure levels were in later studies related to various outcomes like mortality, hospital admissions and morbidity in Britain and other countries (Holland & Reid, 1965; Lawther, 1967; Holland et al., 1979, Thurston et al., 1989).

Just before the official introduction of the BMRC questionnaire on respiratory symptoms in 1960, several relatively large scale studies were set up and carried out. Among those population based studies were the Rhonda Fach Study and the Stavely Study of the British Medical Research Council's Pneumoconiosis Research Unit published by respectively Cochrane et al. (1952) and Higgins et al. (1959). These studies were started because mortality and statistics of the Registrar-

General and morbidity statistics of the Ministry of Pensions and National Insurance, suggested that miners and foundry workers were more prone to develop lung diseases than other industrial workers. In 1959 a survey of chronic respiratory disease in Stavely England was carried out, a small industrial town inhabited by a working population which was largely dependent on industry. This study will be presented in greater detail as an example of the methods used in those days. The BMRC investigation was designed to compare the prevalence of chronic bronchitis, and respiratory disability in a sample of miners, foundry workers and other industrial groups. The study population consisted of a random sample of 776 men, stratified in two groups of 25-34 and 55-64 years. The results were presented by a detailed tabular analyses, but a stratification was made only for one or a combination of two variables (occupational group and smoking; occupational group and years of exposure). Exposure monitoring was not performed as part of the survey, so exposure levels encountered are unknown. There appeared to be a clear trend for the respiratory symptoms to increase with increasing smoking habits. Miners and ex-miners had a higher prevalence of respiratory symptoms and a lower $FEV_{0.75}$[2] than those working in non-dusty occupations. All differences were small and statistically non-significant. Only the mean $FEV_{0.75}$ in the younger miners was significantly reduced. The prevalence of breathlessness was significantly associated with increasing number of years spent on the coal shift, accompanied by a fall in $FEV_{0.75}$. Other symptoms were not related to the numbers of years spent on the coal-getting shift, and the authors suggested that a selection effect (of workers with highly exposed jobs, changing to lower exposed jobs in the mines) might explain these findings. Indications that such processes might be present were not given.

In a nine year follow-up study of the same population the prevalence of respiratory symptoms was higher and lung function was lower in miners and ex-miners, and in men exposed to chemical fumes than in men who had worked only in non-dusty jobs. During the nine-years 102 men had died. The mortality among miners was not significantly elevated compared to

[2] In the original article lung function was expressed as the 'indirect Maximum Breathing Capacity' which was calculated by multiplying the $FEV_{0.75}$ with 40

those in non-dusty occupations. It is noteworthy that the miners in the higher age category who were seen in 1959 and 1966, had the highest initial $FEV_{0.75}$ and the steepest slope of function decline. The annual decline in the three-quarter second FEV_1 was greater in the smokers than in non-smokers. Change in function was not clearly related to occupation. Therefore the authors concluded that the results suggested once again, that smoking is a more important factor in the development of respiratory disability than occupation. In a comparison with a Danish population after ten years of follow-up it was found that the Stavely population had a markedly higher mortality of respiratory disease which, however, could not be explained by differences in smoking habits between the two populations (Cole et al., 1974), but might be attributable to differences in occupational exposures. The Rhonda Fach as well as the Stavely study were the basis of mortality follow-up studies later on (Higgins et al., 1968; Cochrane et al., 1979, Cochrane & Moore, 1980a+b; Foxman et al., 1986). No clear-cut relationships were found between occupation and CNSLD or total mortality in these follow-up studies.

At the time of these studies and shortly thereafter, several surveys were carried out in Britain, Northern Ireland, Federal Republic of Germany, the United States of America, Canada, and South Africa among coal miners, foundry men, textile and flax workers. In total more than 100 studies were undertaken which are summarised by the Deutsche Forschungsgemeinschaft (DFG, 1978), and have been reviewed by several authors (Enterline, 1967; Gilson, 1970; Higgins, 1973; DFG, 1978). Most of the studies were cross-sectional, and dust exposed workers were compared to non-exposed workers. Generally a higher prevalence of bronchitis was found in workers in dusty occupations, and their lung function was lower, even after stratifying for smoking. However, there was no consistency in the relationships between years underground, or years at the coal face and symptom prevalence or lung function. Higgins (1973) was reluctant to ascribe the results found to dust alone, also because bronchitis symptoms prevalence nor lung function were related to simple pneumoconiosis. The degree of pneumoconiosis was considered as a surrogate measure of exposure because it was closely correlated with the mass of dust found in the lung at autopsy. Morgan (1978) argued that this apparent discrepancy of the absence of a relationship between pneu-

moconiosis and bronchitis symptoms and lung function decreases is probably explained by the fact that emphysema and bronchitis are two independent disease processes, and that each process is related to a different particle fraction in the work environment. The larger particles are more likely to cause airways dysfunction, and the smaller deposit in the alveolar region and cause parenchymal damage and pneumoconiosis. Miller and Jacobsen (1985) argued that although there is a clear relationship between dust exposure and pneumoconiosis, it is merely a probabilistic relationship described by statistical properties, instead of a deterministic relationship. A deterministic relationship implies that those who developed pneumoconiosis would be the same as those who develop an airflow reduction, which is usually not seen. They thus explained the poor performance of degree of pneumoconiosis as surrogate exposure variable in the analysis of determinants of CNSLD.

2.4. In conclusion

The question whether the higher prevalence of productive cough, the lowered lung function, and the high mortality from bronchitis among miners and other occupational groups was related to their dusty occupation, socio-economic factors or air pollution became one of increasing complexity over the years. Generally speaking one would argue that the information on mortality from bronchitis present in those days, and the techniques used to analyse the data were inadequate to make a precise estimate of the respective effects of occupation, smoking, environmental pollution and social class on CNSLD mortality and morbidity.

The absence of an exposure-response relationship in most of the cross-sectional lung function studies has not been debated explicitly in the literature. However, because most of the studies conducted in the earlier days were cross-sectional, the healthy worker effect may have played an important role. Recent insights in exposure assessment strategies show that in many cases surrogate exposure measures like the "years underground" or "years at the coal face" , which were used in the early studies, are useful only in a restricted number of situations and often lead to negative findings (Rappaport et al., 1988). In the early lung

function studies, with cross-sectional designs and simple statistical techniques, the detection of an occupational exposure effect was an important methodological problem, because its relative contribution next to other factors then such as smoking and environmental pollution to bronchitis symptoms or airflow obstruction, had to be established.

Another confounding phenomenon might be the high prevalence of pneumoconiosis in most coal worker and foundry worker populations. For instance, the follow-up of the Stavely cohort, described by Foxman et al. (1986), showed that 36% of the miners had pneumoconiosis, compared to 22% of the foundry men and 13% of the mixed worker populations. How far these observations influenced the bronchitis prevalence figures or mortality findings, because of competitive risks, similarities in symptoms, a healthy worker effect or a limited validity of the diagnosis is unclear and not discussed in the literature. Soutar (1987) concluded that, because of the limitations of the early lung function studies, comparison of prevalence of disease in large populations of workers in dusty and non-dusty occupations are invaluable in identifying and quantifying possible health problems. Such studies may raise suspicion, but they cannot conclusively demonstrate that the dust is responsible for disease.

In the next chapters methodological issues in establishing exposure-response relationships will be discussed and results of more recent studies will be reviewed.

3. OCCUPATIONAL EXPOSURE AND CNSLD: METHODOLOGICAL ISSUES[1]

3.1. Introduction

The amount of the agent at a specific site in the human body, or the dose (the product of concentration and time) is seldom known or estimable in an epidemiological setting, therefore the term exposure is preferred (WHO, 1983). In most epidemiological studies only the external exposure, the concentration of an agent in air, water, soil, or food, can be measured. However, although the internal exposure, uptake and dose at target organs are generally unknown, estimates can sometimes be made by taking biological and physical aspects of uptake and distribution of an agent into consideration. For instance, penetration and deposition of particles in the lung depends on physical characteristics such as particle size and lung geometry. Based on knowledge about penetration and deposition of particles in the airways, particle size selective sampling techniques have been developed which approximate dust deposition in specific regions of airways and lungs. This example shows that estimation of the exposure is to a great extent determined by the health effects studied. Exposure measurement strategies set up to relate occupational exposures to health effects are described by the term 'health endpoint dependent exposure assessment'. In this chapter, requirements of the measurement strategy as determined by the health endpoint are illustrated briefly by examples from the literature. In addition, various exposure measurement and estimation techniques used in epidemiological studies are presented and discussed.

3.2. Exposure assessment dependent on health endpoint

Roach (1966, 1977) showed in his early work, that the burden of an agent in the lung depends strongly on its half life in the human body. If the effect of the agent is proportional to the body burden and the agent

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[1] Part of this chapter has been presented to the International Workshop on 'Retrospective exposure assessment for occupational epidemiologic studies', March 1990 and will be published in the Scand J Work Env Hlth

involved is an irritant with a short half life, the risk of an effect in the airways is best described by the maximal peak exposure, with a sampling time less than the half life. If the agent requires a long period to act and its half life is very long, sampling can best be done over a prolonged period. The so-called 'cumulative exposure' which is the product of concentration in the environment and exposure time is the best approximation of dose in these circumstances. For agents with an indirect or delayed action the relationship between exposure and effect becomes more complex.

Esmen (1984) extended this work and tried to include information about more complex disease processes, in a study of occupational exposure to toluene di-isocyanate known to cause occupational asthma. He assumed that the concentration in the lung needed to exceed a certain level before sensitisation occurred. He concluded that the measurement strategy necessary to establish the risk of sensitisation might be too complex to be applicable in practice, because sensitisation may occur after one episode of massive exposure or may occur after a long-term low exposure. This implicates that the response is independent of the total dose received. The specific exposure pattern might be the main determinant of response and a significant measurement effort would be required to establish exposure patterns for each worker exposed. Smith (1985) was able to estimate silica dose and the resultant mass of fibrotic tissue in humans instead of simple cumulative exposure. The study population worked in a silicon carbide factory and was exposed to silica dust. He calculated the actual alveolar dose with a model in which he entered the long-term exposure to silica in the air, allowing for different jobs over the years, and the retention of silica as a function of inhalation, clearance by alveolar macrophages and other clearance parameters. Most of the parameters were estimates derived from animal experiments. The estimated mass of fibrotic tissue correlated highly with the opacities on X-rays, read according to International Labour Organisation (ILO) procedures. Peto et al. (1982) showed for mesothelioma that mesothelioma death rates appear to be proportional to some function of time from first exposure and to cumulative exposure. Time from first exposure determined the risk strongly because this variable was an approximation of the time necessary for an asbestos fibre to migrate to the pleura.

This was later confirmed by Sullivan et al. (1988). For lung cancer in asbestos workers the excess risk appears to be proportional to the cumulative asbestos exposure only (Peto, 1978).

The penetration of particles into the lung depends upon their physical properties (size, form, density and aerodynamic diameter) and the dimensions of the airways and lungs. Mechanisms responsible for deposition of particles are sedimentation, impaction, interception and diffusion (Lippmann et al., 1980). As a result of particle properties and the architecture of the lung, deposition of particles of different aerodynamic diameters occurs in different regions. Basically, three regions are distinguished: the nasopharyngeal region, the tracheobronchial region and the alveolar region. On the basis of deposition characteristics the "respirable dust fraction" was defined in the sixties and gravimetric sampling techniques to measure this fraction were developed (Vincent & Mark, 1981). Respirable particles, with an aerodynamic diameter less than 7 micrometer, deposit mainly in the alveolar region and form a biologically relevant dust fraction which was shown to determine the risk on pneumoconiosis (Vincent & Mark, 1981). The International Standard Organization (ISO) (1983) and the American Conference of Governmental Industrial Hygienists (ACGIH) (1985) have proposed new criteria for aerosol measurement. They defined dust fractions which are relevant for risk assessment for larger particles which deposit in the upper and lower airways. The ISO defined the dust fraction which can enter the human body through the nose or mouth (inspirable dust fraction) and distinguished within the inspirable dust fraction the extra thoracic fraction, the tracheobronchial fraction, and the alveolar fraction. Stimulated by these reports, new generations of samplers are emerging for both environmental and personal monitoring purposes. However, they have not yet been applied at large scale in epidemiological studies (Vincent & Mark, 1988).

An interesting development is the prediction of the concentration of a gas at a specific region of the respiratory tract. For ozone, models have been developed which predict the tissue dose in the airways as a function of the average ozone concentration in the airspace of the lung at a certain distance from the trachea, the radius of the airways, the

average air velocity, the effective dispersion, and the ozone flux from air to lung surface (Menzel, 1987; Miller & Overton, 1989). Such models can be used to predict the ozone dose in a particular region, dependent of environmental ozone concentrations and breathing patterns.

It is obvious that knowledge of the disease process should influence environmental monitoring strategies. These considerations are generally seen as a new development in occupational epidemiology and occupational hygiene which might mark a period of closer coorporation between these two fields of science (Checkoway et al., 1987; Smith, 1987; ACGIH, 1988). Physical considerations lead to the concept of size selective sampling in the sixties and the definition of the respirable dust fraction. More recently other dust fractions, for coarser particles have been defined. Till now, disease related considerations have not much influenced exposure measurement and estimation techniques in occupational CNSLD epidemiology. So far, it is still assumed that for CNSLD epidemiology, the cumulative exposure is an acceptable characterisation of the exposure to describe exposure response relationships. There is a considerable amount of empirical evidence which shows that this assumption is a defendable one (Soutar, 1987). However, several studies indicate that for certain pollutants which are able to cause asthma, like toluene-di-isocyanate, peak concentrations of the air pollutant determine the effect more strongly than longterm average concentrations (Diem et al., 1982).

3.3. Characterisation of exposure

3.3.1. Introduction

In occupational epidemiological studies several methods are being used to characterise the exposure of the population under study. Several authors provide a hierarchy of exposure characterisation methods for use in epidemiological studies (Vihma, 1981; Checkoway et al., 1987):

- **specific exposure**
  - quantitative characterisation of exposure
  - qualitative estimation of exposure

  - presence in specific jobs, tasks
  - presence in specific environment
- **occupational title**
- **occupational status**
- **department**
- **sector of industry**

The characterisation of specific exposures, depicted on top of the hierarchy, is the most detailed method which can be applied to derive exposure-response relationships. All the other methods are not exposure specific, meaning that they are based on other variables such as social status, income, and type of industry. The occupational title (OT) or occupational category for instance, represents at its best a defined profile of exposures. However, exposures of workers within the same OT, but who work in different departments or factories may differ, which is another limitation of the OT. Despite its limitations, the OT has been applied in epidemiological studies with considerable success in the past for instance in the rubber industry (Monson, 1980). The other classifications are based on socio-economic status or industrial administrations. These classifications are often used for registry based epidemiological studies and contain virtually no information on occupational exposures.

These different classifications will be discussed briefly in the following paragraphs. Aspects of validity (lack of systematic error) and precision (lack of random error) of these classifications will be discussed also. Quantitative measures of precision and validity have been described in the literature (WHO, 1982). An estimate of precision of some measurement can be obtained if repeated measurements made by the same or another observer are present. This allows the calculation of a coefficient of variation for continuous exposure variables or the percentage of agreement or a Cohens Kappa (Fleiss, 1981) for categorical variables. To establish the validity of a test, the same population has to be measured with a criterion technique too. Then the sensitivity and specificity of the test can be calculated in comparison with the results from this criterion test.

3.3.2. Specific exposures

Practically the most ideal situation in occupational epidemiology exists when personal exposure data are present with multiple measurements over longer exposure periods. Examples of such detailed exposure information are given by studies among workers exposed to ionizing radiation in nuclear power plants and other nuclear facilities. Personal monitoring can be done permanently during work hours because personal dosimetry is a technically simple method for this particular exposure. Estimates of exposure to different types of ionizing radiation can be derived also. The exposures can be expressed as doses from external sources to various parts of the body or the entire body, the skin of the entire body and extremities. As a result of this, detailed exposure information exists which allows calculation of cumulative exposures for each person separately. Different cross-classification can be made for special subgroups of workers with specific exposure patterns. Applications of such detailed strategies can be found in various sources in the literature (Gilbert & Marks, 1979; Gilbert, 1982; Tolley et al., 1983; Radford & Renard, 1984; Beral et al., 1985)

More often strategies are applied in which the exposure is measured for subgroups of workers. Such procedures result in a considerable reduction of measurement effort, because only a sample of workers has to be monitored. This is favorable when sampling techniques are time consuming and expensive to apply. Early descriptions of such strategies have been given by Oldham & Roach (1952) and Ashford (1958). They described the statistical background of the measurement strategies applied in the British 'Pneumoconiosis Field Research'. Colliery populations were divided into homogeneous subgroups on the basis of their occupation, place of work, and shift and the basic sampling unit was the so called "man-shift". This meant that dust exposure measurements were taken for a random sample of all workers employed during a certain shift. Time exposed was measured for all workers based on colliery records. The cumulative exposure was calculated as the product of the exposure measured for a certain occupational group and the time exposed. The sampling effort was allocated to certain man-shifts based on several factors like the standard deviation in exposure for that particular

homogeneous subgroup, the labor turnover of a group, and the number of men belonging to the group. An underlying assumption of this sampling strategy is that the exposure of an individual worker is supposed to be indistinguishable from the shift average of the whole group. Surveys in different occupational exposed populations have shown that considerable inhomogeneity between workers may exist (Rappaport, 1985; Heederik et al., 1986; Kromhout et al., 1987). Most important reasons for this inhomogeneity are small differences in work practice and environmental conditions, and an inappropriate definition of the subgroup. The latter may for instance occur when a broad definition of a subject's function or job is used while workers with the same job or function perform slightly different tasks. The magnitude of the inhomogeneity depends on the specific situation. The composition of so-called homogeneous subgroups can be made on the basis of information on a subject's job, or by some estimation technique.

Strategies as described above are seldom applied, and monitoring of occupational exposures is seldom done routinely. If the exposure is frequently monitored the purpose is more often to establish if certain treshold limit values are exceeded. The data which result from such compliance strategies have a limited value for epidemiological purposes because their aim is not to characterise the exposure of members of the study population, but they are generally conducted to identify the worker with the highest risk of exposure (Boleij et al, 1987; Rappaport, 1988). This explains why even for large and elaborate cohort studies, which have been conducted in past decades, the exposure information gathered by the occupational hygienists has sometimes been of little use for an epidemiological study.

A specific problem in occupational cohort studies is the introduction of new monitoring techniques during the study. Examples of this problem have been discussed for occupational asbestos exposures (Dement et al., 1983), but many other examples can be found in the literature. In a retrospective cohort study among asbestos textile workers exposure monitoring data from 1935 to 1975 had to be used. Sampling was done with different techniques based on the measurement of number of particles per unit of air, gravimetric techniques measuring mass of dust per unit of

air, and modern elaborate scanning electron microscopical techniques which quantified the number of fibers per unit of air for different boundaries of aspect ratios of the fibers. For epidemiological mortality studies, conversion factors between these techniques had to be established before a cumulative exposure could be calculated, introducing considerable estimation error.

Exposures at the workplace are often approximately log normally distributed (Oldham, 1953, Esmen & Hammad, 1977) although deviations can occur because of specific tasks performed or because workers avoid high exposure which cause an irritant sensation (Smith et al., 1978). The range of the log-normal distribution is large, even for workers who perform the same task daily (Oldham, 1953; Esmen & Hammad, 1977; Esmen, 1984; Heederik et al., 1986; Kromhout et al., 1987). The difference between the lowest and highest exposure experienced over several days can be a factor 10 to 30. The number of measurements necessary to be able to distinguish personal exposures between several workers can therefore be considerable.

When no quantitative actual exposure information is available different techniques can be used which lead to some form of a qualitative exposure estimate. The three main methods to derive such estimates are:

- questionnaires to establish the presence of current or previous occupational exposures. This technique is mainly used for retrospective exposure estimation and applied in case-control studies;
- qualitative exposure estimation procedures, in which the exposure is estimated by observers in a work place investigation. These procedures are often described as "semi-quantitative methods" and are used in prospective, as well as retrospective studies;
- estimation of the exposure by means of a Job Exposure Matrix, which in essence is a database containing information on occupations, industries and exposures connected to a specific combination of occupation and industry. The Job Exposure Matrix is mainly used for retrospective studies.

In the next paragraphs these techniques will be described in greater detail.

3.3.3. Questionnaires

In many studies questionnaires have been used to obtain an estimate of a person's occupational exposure. Generally such questionnaires are meant to obtain a full occupational history based on a categorisation for job titles or types of industry. Several studies have found good agreement between self-reported occupational histories and employer records or governmental records of such information (Jonathan et al., 1957; Keating et al., 1950; Mosel & Cozan, 1952; Goldstein et al., 1971; Pershagen & Axelson, 1982; Siematycki et al., 1981; Baumgarten et al., 1983). In most of these studies, there was more than 80% agreement between the different sources of information, although the maximal time period involved was only 13 years. A specific problem is coding the occupational and industrial history. The number of different occupations and industries is high and differences between industries and occupations often seem marginal. Therefore coding has to be done by instructed personnel. Although there is limited information on the performance of coding personnel, validity and precision are probably poor. In a recent study in eight European Community countries it was shown that the percentage of agreement for repeatedly coding the occupational status (comparable to the socio-economic status) was 70% (Cohens Kappa 0.65), and somewhat higher for coding a specific industrial occupation (Cohens Kappa 0.70). For coding the industrial occupation there appeared to be specific clusters of disagreement in occupations involved in handling of metal goods, engineering and vehicle industry. The validity of coding occupational status was poor to moderate if a shortened instruction was used compared to a standard instruction (Cohens Kappa 0.37-0.52) (Rona & Mosbech, 1988, 1989).

Although categorisations of the occupational history can be useful, information on exposure cannot usually be obtained from them. Several researchers have therefore developed questionnaires which contain a list with specific exposures, or questions referring to known health hazards on the workplace, that can simply be confirmed or denied (ALA, 1983; Rosenstock et al., 1984). Rosenstock et al. (1984) showed that occupational exposures assessed with a self-completed questionnaire had 75% sensitivity and 70% specificity and a positive predictive value of 83%

when the exposures obtained with the questionnaire were compared to the estimates of an occupational hygienist for the different jobs. However, Bond et al. (1988) showed that in a retrospective study respondents recalled only 2.6% of the chemicals they had ever worked with during their employment period in a chemical plant, illustrating that recall was poor.

3.3.4. Qualitative exposure estimation

Qualitative exposure estimation is the process of estimating a subject's exposure on a ranking scale or quantitatively on the basis of present knowledge on e.g. tasks performed, and processes applied. This method is often applied because it is simple, comprehensive and efficient and because it leads to a reduction in measurement effort when applied in combination with strategies in which the exposure is actually measured (Kromhout et al., 1987). The aim of qualitative exposure estimation procedures is to classify a population in a number of more or less homogeneous exposure categories. This categorisation is done on the basis of criteria which refer to the level of exposure (a), the duration of exposure (b), and the frequency of exposure (c). It is clear from earlier paragraphs that relevant values of level, duration, and frequency depend on the health endpoint under study. Several examples of qualitative exposure estimation procedures have been published in which the estimates were generated by different subjects like workers (doPico, 1982; Rom et al., 1983; Kromhout et al., 1987; Hertzman et al., 1988), occupational hygienists (Blum et al., 1980; Rosenstock et al., 1984; Kromhout et al., 1987), plant supervisors (DeFonso & Kelton, 1976; Wald et al., 1984), chemists (Gerin et al., 1985) or so-called occupational health teams (Woitowitz et al., 1970).

Qualitative exposure estimation methods can result in a ranking of the exposure. This was confirmed by several studies in which the exposure estimates were compared to (bio-)monitoring data (Kromhout et al, 1987; Hertzman et al., 1988), but great care has to be taken when they are actually used. The agreement between exposure measurements and estimates, and between different estimators is not perfect. Kromhout et al.

(1987) compared different estimators and found that the agreement between different estimators in five factories, expressed as Cohen's Kappa, was highest between the occupational hygienists, and lower for all other combinations of estimators (employees, supervisors and occupational hygienists). The agreement was, however, never higher than 0.50, indicating a moderate to poor agreement. It has also been shown that in many cases, exposure categories are not homogeneous, which means that considerable differences can exist within an exposure category. It has also been found that distributions of the exposure of several exposure categories often overlap (Heederik et al., 1986; Kromhout et al., 1987). The usefulness of this method to characterise occupational exposure therefore seems limited and depends on the specific situation encountered.

3.3.5. Job Exposure Matrices

A Job Exposure Matrix (JEM) is a data base which enables the researcher to generate specific occupational exposures for a certain job in a certain sector of industry. A matrix has a two dimensional structure, with industry specific occupational groups or jobs on one axis, and specific exposures on the other axis. The first JEM was developed by the National Cancer Institute in the United States of America as an alternative to self-reported exposure information or an estimated exposure based on a workplace visit (Hoar et al., 1980; Hoar, 1983). The motives for using a JEM are clearly expressed in the following:

> "(..) Ideally, to study health effects of occupational exposures, one would like to have accurate quantitative and qualitative information that was objectively recorded at the time of exposure. Slightly less ideal would be exposure information that was recorded and reported after the exposure but before any adverse health effect was diagnosed. Self reported exposure information after diagnosis of an illness would be next best, followed by proxy-reported exposure information after diagnosis.
> Although analyses of occupational hazards are most powerful when subjects are grouped by exposure, this inability of people to directly relate their exposure histories has caused most studies to be traditionally based on job title and industry.
> In general job titles alone are poor surrogates for exposure information. A single title may refer to occupations in different industries with very different exposures. Also, similar exposures may occur in jobs with dissimilar titles or in different industries. Misclassification of exposure status reduces the power of an analysis and dilutes risk estimates. In response to this problem, several researchers developed job exposure matrices, which are cross-classifications of industry specific job titles with agents to

which persons in the jobs are exposed. The job exposure matrix allows researchers to translate job and industry data into exposure data" (Hoar et al., 1983).

Since the development of this matrix in the US, several other matrices have been developed in other countries like Great Britain, Italy (Malcaluso et al., 1983), and Sweden (Plato et al., 1988) with industry and calendar period specific matrices as the latest development (Kauppinen & Partanen, 1988). For this study, the British matrix developed by Coggon et al. (1984) and Pannett et al. (1985) has been used, and will therefore be described in greater detail. The British matrix is based on the three digit code of the General Registrars Classification of Occupations of 1966 with 211 occupational units and subunits (GRO, 1966) and the four digit code of the Standard Industrial Classification, which describes 355 industrial units and subunits. (CSO, 1968). The two classifications resulted in too many combinations of occupations and industries. Therefore occupations and industries were grouped in 669 combinations with a similar exposure profile. These 669 combinations are linked to 50 occupational exposures, which are given in appendix 3. Some exposures were added to these 50 agents because they were known to be related to occupational diseases. The matrix distinguishes four levels of exposure: high, intermediate, low and no exposure and these levels are defined as:

high a high proportion of workers is heavily exposed

moderate a small proportion of workers is heavily exposed or a high proportion of workers is lightly exposed

low a small proportion of workers is lightly exposed

none exposures trivial or do not occur.

The exposure information is classified by a trained occupational hygienist and based on present knowledge published in handbooks, reviews etc. The pro's and con's of the use of matrices are clearly discussed by Pannett et al. (1985), and some important problems mentioned are that:

- selection of agents included is often arbitrary;
- inclusion of broad categories is sometimes necessary because single chemical compounds cannot be distinguished within one occupational group;
- the effect is determined by the biological route which is difficult to implement;

- cut off points of grades of exposure are arbitrar;
- validation has not been done but is necessary;
- there is a need to included patterns in the exposure over time.

The US matrix has indirectly been validated by a reanalysis of a case-control study of bladder cancer (Hoar et al., 1980). Originally, the occupational exposure was characterized by an interview. The odds ratios for exposure to aromatic amines generated with the JEM, with bladder cancer were higher than the original ones published by Cole et al. (1972), because some misclassification had apparently disappeared and because exposed workers were grouped over the different sectors of industry. However, Coggon et al. (1984), had an opposite experience with the use of a JEM in a reanalysis of a case-control study of lung cancer. In the original study, exposure information was obtained by a postal questionnaire. For four exposures: asbestos, chromate, oils and inhalable polycyclic aromatic carbohydrates an exposure-response relationship was found. However, this relationship was stronger in the initial study and they therefore concluded that a direct estimate of the exposure on the basis of information on industry and job is preferable above the use of a JEM.

The validity of job exposure matrix estimates has been studied directly only in two small scale surveys in the Netherlands (De Haan, 1989; Kromhout & Heederik, 1989). In the first survey in the construction industry, exposure estimates of the US JEM were compared with field survey results of the Occupational Health Service in the construction industry (BG Bouw) and with exposure estimates of three occupational hygienists familiar with the construction industry. Only 13 to 38% of the exposures generated by the job exposure matrix were mentioned in the survey reports or estimated by at least one of the hygienists. Exposures mentioned by the hygienists or in the survey reports were generally also generated by the job exposure matrix, suggesting that false positive errors were especially likely to occur. There were indications that if specific exposures were grouped in broader categories, such as 'dusts' or 'solvents', estimates using the matrix improved compared to those of the hygienists. Kromhout & Heederik (1989) compared results of the US and the British matrix for the occupations held in 1960 for participants of

the Zutphen study. They found that the agreement between the two matrices was low for most of the specific exposures. Only for wood dust a Cohens Kappa of 0.9 was found. For the other exposures it was generally lower than 0.5 indicating moderate to poor agreement.
The initial optimism about exposures estimated with a job exposure matrix seems not justified in the light of these results. The study of validity of exposures generated with job exposure matrices deserves therefore more attention. Hinds et al. (1985) warn against the use of JEMs in other countries than the country for which they were developed, because of differences in industrial development and legislation leading to qualitative as well as quantitative differences in exposure.

3.4. The influences of misclassification of exposure

In epidemiology non-differential and differential misclassification are distinguished. Both are forms of information bias (Rothman, 1986). Differential misclassification of the exposure in this context means that the misclassification is dependent on the health effect. For instance, when more misclassification is present in a group of diseased persons than in the control group differential misclassification is present. In case of non-differential misclassification, the misclassification is independent of the health effect.

The influences of these forms of misclassification have been discussed in the epidemiological literature (e.g. Copeland et al., 1977; Greenland, 1980; Tockman, 1982; Flegal et al., 1986; De Klerk et al., 1989). Differential misclassification of the exposure can lead to under as well as overestimation of the effect of exposure on health, dependent on the type of study and the exact form of differential misclassification. Generally, non-differential misclassification of exposure leads to underestimation of the effect of exposure on the health parameter studied. Several factors may lead to misclassification in occupational studies (Ulvarsson, 1983; Kauppinen, 1988b):

- only part of the occupational history is known;
- job description is inaccurate;
- non-occupational exposures are present;

- exposure categories are not homogeneous with regard to exposure;
- overlap in exposure categories is present;
- other exposure routes are omitted (skin);
- sampling techniques used lead to bad estimates of personal exposure

Although both forms of misclassification have received some attention in occupational and environmental epidemiology, most attention in occupational epidemiology has been given to non-differential misclassification due to large variations in time and space of the air pollutant concentration in the work place. For an individual worker, large differences in concentrations of an air pollutant in time and space lead to a large intra-individual or day-to-day variation in exposure. If only a limited number of personal samples is taken to estimate his personal exposure, the estimation error of his mean exposure is large. It has been shown that this imprecision in exposure estimates for a worker based on a limited number of samples taken might result in a considerable bias of the exposure response relationship (Armstrong and Oakes, 1982; Ulvarsson, 1983). The bias that occurs in a regression analysis if a dependent variable measured on a continuous scale is regressed on an imperfectly measured exposure variable can be described by the ratio λ of the within- and between subject (intra- and interperson's) variability in exposure:

$$b = \beta(1 + \lambda)^{-1}$$

where

b = expected value of the empirical regression coefficient of a dependent variable Y on an independent variable x which is an imperfect measure of the independent variable X,

β = the true regression coefficient of Y on X,

$\lambda = \sigma^2_e/\sigma^2_t$,

σ^2_e = within subject variance,

σ^2_t = between subject variance.

If for instance λ=1, the empirical regression coefficient underestimates the true coefficient by 50 percent. The statistical background has

been recognised before and is referred to as attenuation (Cochran, 1968; Snedecor & Cochran, 1980). If repeated exposure measurement on an individual are present, an analysis of variance is possible to estimate the intraperson and interperson components of variance. Occupational hygiene surveys showed that for exposed populations λ's in the order of 0.2 to 6.0 are possible (Esmen, 1984; Rappaport, 1985; Heederik et al., 1986; Kromhout et al., 1987), suggesting that in certain extreme situations an underestimation of the true relationship between Y and X of more than 500% is possible. Liu et al. (1978) showed that the bias in the regression coefficient of Y on X can be reduced by performing repeated measurements on the same subjects so that a better estimate of the mean exposure for each person will be derived.

3.5. Measuring CNSLD in epidemiologic studies

In epidemiological studies of CNSLD two classes of methods have been applied and further developed; questionnaires to register respiratory symptoms and spirometry. Other tests, like closing volume, diffusion capacity and hyperreactivity have been developed since then. They have not generally been used in epidemiological studies (Chang-Yeung et al., 1985) and will not be discussed here.

3.5.1. Questionnaire

In the earlier studies, a large inter-observer variation was found in studying the prevalence of cough, phlegm, and chest tightness (Cochrane et al., 1951). Because the recognition of chronic bronchitis depended on the symptoms experienced by a person, a need existed for standardised procedures to register symptoms. In the 1950's a standardised questionnaire was developed by the British Medical Research Council (BMRC). In its first form, it was published in 1960 (BMRC, 1960). Tape recorded interviews with patients were supplied to train and test interviewers. This questionnaire was revised at regular intervals, and has been generally accepted since its introduction. Several other nations like the USA (ATS, 1969) and international organisations like the European

Committee on Coal and Steel (ECCS, 1967) adopted the BMRC questionnaire after minor changes to make it more suitable for use in other populations or for other research purposes. Later, a self-administred questionnaire was developed. In the Netherlands a shortened version of the BMRC questionnaire is often used (Biersteker et al., 1974). Shortened versions, and self administered versions have also been developed in other countries (Lebowitz & Burrows, 1976; Mittman et al., 1979). The questionnaires enable the researcher to register respiratory symptoms as cough, phlegm, breathlessness and wheezing, that are associated with bronchitis and asthma.

During the 1950's and 1960's much effort was put into studies to establish the reproducibility and validity of the questions referring to phlegm production. Extensive reviews of these early years of the questionnaire can be found in Samet (1978a) and a World Health Organisation publication (WHO, 1982). The validity of the questionnaire was evaluated for phlegm only, by comparing the daily phlegm production with the answers to questions about the amount of phlegm produced each day. These variables correlated well and the expected relationships between phlegm production and prevalence of symptoms and indirect breathing capacity were also present. Other questions have not been validated because of the absence of an independent criterion (WHO, 1982), but show a correlation with the FEV_1 level.

Independent studies showed that the percentage of agreement was between 65% and 90% in the USA, the UK and the Netherlands when the questionnaire was administered twice after time intervals of one to a few month by a trained, experienced observer (Van der Lende et al., 1972; Samet, 1978b; WHO, 1982). Correction of the percentage of agreement for some agreement by chance, by calculation of a Cohen's Kappa would result in a lower agreement compared to these published results. These results show that even with trained interviewers the reproducibility is mostly unsatisfactory low. It is noteworthy that the percentage of agreement of the smoking status has found to be 95-99% in different studies (Fletcher, 1959; Morgan et al., 1964; Holland et al., 1966). Factors which contribute to a low reproducibility are differences between observers (Samet, 1978a; WHO, 1982), inaccuracy of the use of a questionnaire

(Fairbairn et al., 1959), knowledge of the test subject about possible relationships between environmental exposures and CNSLD (Samet et al., 1978b) and psychosocial factors like job satisfaction (Wright et al., 1977). Although not studied in detail, differences in wording and sequence of questions probably contribute also to a low reproducibility.

3.5.2. Lung function

Lung function measurements are widely used in CNSLD epidemiology and it has been shown that persons with respiratory complaints have a reduced lung function compared to asymptomatic persons. The most widely used lung function measurement technique is simple spirometry. This is the measurement of volume change by the measuring device, the spirometer, during defined breathing maneuvers. The volume recorded during a (forced) expiratory maneuver is the (Forced) Vital Capacity ((F)VC). The volume measured in the first second of the maneuver is the Forced Expiratory Volume in one second (FEV_1). The ratio of FEV_1 and FVC, the Tiffeneau-index, is often used.

By calculating the derivative of volume to time, a flow-volume curve can be obtained. From this curve several variables like Maximal Expiratory Flows ($MEF_{x\%}$) at different volumes of the Forced Vital Capacity (x%) can be derived. The Forced Vital Capacity and a Forced Expiratory Volume in one second are the most commonly reported variables. These two variables are the simplest, most repeatable and valid of the various lung function variables which can be measured (WHO, 1982). A reduction of the expiratory flow, sometimes accompanied by a reduction of the (forced) vital capacity, is indicative of an obstructive disorder (reduction of the expiratory flow due to narrowing of the airways). A reduction of the vital capacity with a normal expiratory flow points to a restrictive disorder (reduction of the expiratory volume due to fibrosis, restricted thorax mechanics, etc.). Practical protocols have been developed by the ATS and ECCS concerning standardisation of the spirometer, test procedures, and instructions for both the laboratory assistant as well as for the test subject (Ferris, 1978b; ATS, 1987; Quanjer, 1983). In epidemiological studies, the Peak Expiratory Flow and the Maximal Expiratory Flows at

different percentage of the FVC ($MEF_{x\%}$) have been widely used in the last decade because of the additional information given by these variables, although the intra-person variation is somewhat larger than for FVC and FEV_1.

3.6. The healthy worker effect

The healthy worker effect was probably first described in detail by William Ogle in 1885 in an appendix of the Registrar Generals report on mortality in England and Wales (Ogle, 1885; Weed, 1986). The healthy worker effect refers to the observation that the working population is healthier than the general population. Ogle identified two kinds of selection which are responsible: one working at the time of hire, and the other working during time of employment. The first selectively attracts or rejects new workers depending on physical demands of the job and health selection by occupational physicians, the second forces people to leave industry because their health is too much impaired for the job performed.

Since then numerous studies have been conducted to describe the healthy worker effect in greater detail, of which most pertain to mortality (Fox & Collier, 1976; McMichael, 1976; Vinni & Hakama, 1980; Monson, 1980, 1986; Wen & Tsai, 1982; Koskela et al. 1984; Weed, 1986). These studies have shown that because of these selection processes the mortality of the working population is usually lower than the mortality in the general population. There seems to be a dynamic phase in the healthy worker effect during the first years of follow-up in mortality studies in which the Standardised Mortality Ratio (SMR) increases asymptotic to a plateau value and remains stable thereafter. It is, however, difficult to exactly quantify the healthy worker effect because its magnitude depends on various factors of which latency survival time (Monson, 1986), and to a lesser extend age (McMichael, 1976; Monson, 1986), socio-economic status (Wen and Tsai, 1982; Wen et al., 1983), race (McMichael, 1976), type of work involved (McMichael, 1976), cause of death (Selzer & Jablon, 1974; Enterline, 1975; Fox and Collier, 1976; McMichael, 1976; Monson, 1986), elapsed time period of observation (Fox and Collier, 1976; McMichael,

1976), have been identified. It is noteworthy that for non-malignant respiratory disease the healthy worker effect seems to be relatively strong, leading to an SMR of 60 in a population of white male US rubber workers (Monson, 1986).

Few morbidity studies have adressed the healthy worker effect. Some studies show that those leaving the industry before retirement have a health condition which is worse than those of the same age and with similar smoking habits staying in industry (Chan-Yeung, 1980; Broder & McAvoy, 1981; Enarson et al., 1986; Hurley & Soutar, 1986; Hollander et al, 1988). Hurley & Soutar, (1986) showed that in a group of 199 coal workers who had left the industry before normal retirement age and who had respiratory symptoms during follow-up, a steeper exposure-response relationship between dust exposure and lung function decline was found after correcting for age and smoking habits, than in coal workers who had not left the industry.

In a population of Canadian West-coast grain-workers a reduced prevalence of atopy was found compared to a control group (Chan-Yeung, 1980). During a follow-up study of these grain workers it was found that those who had left the industry during the three year follow-up, had reduced metacholine thresholds compared to those who stayed in the grain industry (Enarson et al., 1986). In another study among Canadian grain workers, exposed workers had less precipitin reactions against grain dust extracts than controls (Broder & McAvoy, 1981). After three years of follow-up it was observed that those who left the grain industry had more respiratory symptoms during the initial survey than those who remained in the grain industry (Broder et al., 1985).

3.7. In conclusion

The theoretical considerations discussed in this chapter show that the methods to study exposure-response relationship in occupational CNSLD epidemiology are still developing. In the past the definition of the respirable dust fraction was an important step forward. This fraction had to be measured when the health risks of dusts were studied of which

the main target was the alveolar region. The usefulness of characterisation of the respirable dust fraction has been proven in pneumoconiosis epidemiology. A recent and important development is the definition of dust fractions of larger particles than those defined as respirable dust because they estimate the deposition of particle dose in the airways. Monitoring strategies dependent on the health endpoint have not emerged yet in CNSLD epidemiology. The choice for a cumulative exposure, which is characterised in most epidemiological CNSLD studies is based on empirical evidence only. Knowledge about disease processes has not been applied so far.

Misclassification of the exposure occurs when exposure is estimated rather than measured, and also because of errors in sampling and analysis when exposure is measured. In addition misclassification arises when the personal exposure is estimated from stationary sampling, because large variability of air concentrations of a pollutant in time and space often exists. This poses specific problems for the researcher, because this misclassification might lead to considerable underestimation of the exposure-response relationship. Procedures for the characterisation of the exposure have generally not been standardised. In contrast considerable effort has been put into standardisation of the registration of respiratory symptoms and the measurement of lung function. This stresses the need for improved exposure classification procedures and monitoring strategies.

The healthy worker effect is considered a selection bias operating in almost all epidemiological studies. Although no quantification of this effect has been made, several studies show that those in industry are healthier than those out of the industry, when they have comparable age and smoking habits. Those leaving the industry have a health condition which is worse than those who remain in industry. There are some indications that for CNSLD the healthy worker effect is somewhat stronger than for other health endpoints. It is generally accepted that the healthy worker effect leads to an underestimation of exposure-response relationships, but as stated before, the magnitude of the underestimation is unknown and depends on factors which are specific for the population under study.

4. RECENT EVIDENCE OF A RELATIONSHIP BETWEEN OCCUPATION AND CNSLD

4.1. Introduction

Most discussions on the evidence of a relationship between occupation and CNSLD involve chronic bronchitis and emphysema but not asthma. This reflects the difficulties in relating environmental factors to the occurence of bronchitis and emphysema because of the multicausal aetiology of these diseases. Simple clinical tests to connect manifestations of the disease with occupational exposures for the individual are absent. While, in contrast, for asthma the work related nature of reactions observed can be established with specific clinical immunological tests and or clinical provocation tests with the occupational allergen involved. In this review the literature presented therefore pertains to bronchitis and emphysema.

A relationship between occupation and CNSLD has been established in different types of occupational studies. At the beginning of this century most of the evidence of a relationship between occupation and CNSLD was based on mortality statistics in Great Britain as mentioned in chapter 2. During the fifties and sixties, the first cross-sectional population based studies were undertaken mainly in Great Britain, but also in other countries like the United States of America (USA) and the Federal Republic of Germany (FRG). The initial leading role of Great Britain in research is easily explained. The death rates were high compared to other countries. For instance in 1950 the age adjusted death rates for chronic bronchitis were over 60 per 100,000 in England and Wales compared to equal to or less than 15 per 100,000 in the Netherlands, Germany, USA and Canada (Stuart-Harris & Hanley, 1957). Differences in registration of the causes of death or diagnostic procedures existed but could not explain these differences (Fletcher, 1963).

Recent evidence on a relationship between occupational exposures and CNSLD consists of results from general population studies and occupational group studies. The general population studies are in most cases morbidity studies in which respiratory symptoms and lung function were

registered. The occupational group studies were mostly conducted among miners and foundry workers, but later, in the seventies and eighties other occupational groups, like those with an organic dust exposure were studied. Both cross-sectional as well as longitudinal morbidity studies were performed. Elaborate studies were conducted like the Pneumoconiosis Field Research among coal workers in Britain and the Research Program on Chronic Bronchitis among various dust exposed groups in the Federal Republic of Germany. Some case-control studies among emphysema patients have been conducted also. Only a limited number of mortality studies have been published.

The main emphasis in this chapter will be given to general population studies. Results of occupational group studies among miners will be summarised because this is perhaps the best studied occupational group. Discussions on severity of airway obstructions and magnitude of the relationship between dust exposure and CNSLD are often focussed on this population.

4.2. Recent general population studies

Several studies among the general population started in the sixties and seventies. Originally, the majority of those studies was not designed to answer questions concerning the relationship between occupation or occupational exposures and lung disease. The aims were often more general; the study of the natural history of lung disease and identification of determinants of the disease or disease processes in general. In these studies the statistical analysis was often elaborate and multivariate techniques as multiple regression analysis for lung function studies and logistic regression analysis for respiratory symptom prevalence studies were used. This made it possible to treat several independent variables simultaneously in the analysis, and to adjust for confounding effects of smoking, age and in the case of lung function studies standing height also. The studies will be presented in chronological order of appearance of relevant publications.

Lebowitz (1977a) reported results of the Tucson Epidemiologic Study. The Tucson Epidemiologic Study on Obstructive Lung Disease is a longitudinal study of a random sample of Anglo-whites living in Tucson, Arizona, USA. For this study, more then 3800 persons from 1655 families were enrolled between 1971 and 1972 who have had yearly examinations and interviews. Extensive personal, medical and occupational histories were taken. Occupational history was recorded during an interview. The study subjects were asked to provide a complete list of all jobs they had ever had. They were also asked if they had ever had an occupational exposure to any of a list of inhalants and if they had worked in an industry known to be associated with an exposure to dusts, fumes or gases. Of the 1195 males ever employed, 56.6% had one or more occupational exposures and 35% was a current smoker or had ever smoked. Very few females had an occupational exposure, and this group was not further analysed. For the specific exposures the product of intensity on a three point scale (1=low, 2=intermediate, 3=high) and years of exposure was calculated. The difference in respiratory symptom prevalence between persons with less than 30 'exposure intensity years', and persons with more than 30 'exposure intensity years' was calculated. Most exposures were positively related to respiratory symptom prevalence. Especially persons with a high 'exposure intensity' for silica, fiber glass, fumes and solvents and persons in the construction industry had a statistically significant higher prevalence for chronic productive cough, attacks of wheezing and dyspnea. They had an abnormal lung function more often (FVC < 75% of reference value or FEV_1/FVC < 80%).

In another publication on this study, the relationships between several socio-environmental factors (like occupation) and respiratory symptoms were described (Lebowitz, 1977b). No significant correlation was reported between the various respiratory symptoms or reported diagnoses with a dichotomous SES index, after allowing for age, smoking and gender. Further analyses revealed significant correlations between income, education, occupation, and various respiratory symptoms. Income and education were inversely related to most symptoms and respiratory diseases. Occupation was analysed as a four level variable ((semi) professional workers; managers, professionals, clerical workers, sales men; (semi-) skilled workers; unskilled and domestic workers). The relationship of

occupation with respiratory symptoms and diseases was weaker than for income and education.

Kauffmann et al. (1979, 1982) published results of a 12-year follow up of 556 men aged 30-54 in 1960, who were working at that time in the surrounding industries of Paris. They were mainly involved in the mechanical engineering industry, chemical industry (paint production), printing industry and food processing industry (flower milling). The occupational exposures were recorded after a workplace visit at the start of the study by an occupational physician or engineer. The dust exposure was estimated on a four point scale, the exposure to gases on a two point scale. The annual rate of decline of FEV_1 was calculated as the difference in lung function between 1960 and 1972. The FEV_1 decline was significantly related to an occupational exposure to mineral dust as well as grain dust. The decline was greater for those higher exposed. There were indications that exposure to heat had an effect on change in FEV_1, independently of the effect of dust exposure on lung function decline. It is noteworthy that no relationship between dust exposure and lung function was found for the 1960 cross-sectional data. The authors concluded, after a graphical analysis of lung function level in 1960 and consecutive change, that a self selection effect seems to be present among the exposed, in such a way that the persons in better health remained higher exposed. This was illustrated by an initially higher lung function with a steeper decline in the years that followed among the exposed compared to unexposed persons.

Rasmussen (1985) studied the level of FEV_1, MMEF[1] and slope of Phase III of the single breath nitrogen test in 1270 men categorised as cement factory workers, farmers, other blue collar workers and white collar workers. White collar workers had on average higher FEV_1 and MMEF compared to the other occupational groups. No differences in slope of phase three were observed between occupational groups although differences existed between the various categories of smoking habits. It was concluded that smoking habits had a different effect on the respiratory system as compared to occupational exposures, because a relationship between

[1] Maximal Mid Expiratory Flow

smoking and the slope of phase III was found, which was not found for occupational exposures.

Korn et al. (1987) published results of the Six Cities Study in the USA. They studied 8,515 white adults whose occupational history was taken by interview. Based on this information, the total years of exposure to dust, gases or fumes was calculated per job and the total years of exposure for each subject. The respiratory symptoms were registered with a version of the ATS questionnaire. An index of Chronic Obstructive Pulmonary Disease (COPD) was defined as a Tiffeneau index (FEV_1/FVC) smaller than 0.6. This was used as a dichotomous outcome variable in the multiple logistic regression analysis. The same statistical technique was used for the analysis of the respiratory symptoms. A number of 3568 (41.9%) persons of this population had never smoked, 3028 were current smoker (35.6%), 1919 were ex-smoker (33.5%). Of all men, 45% reported an occupational dust exposure and 47% reported an exposure to fumes or gases. Fewer females reported such exposures (19% dust, 16% fumes or gases). The adjusted odds ratio's of respiratory symptoms (cough, phlegm, wheeze and breathlessness) for subjects exposed to dust ranged from 1.3 to 1.8 for respectively past and current exposure. For exposure to fumes or gases the odds ratios ranged from 1.3 to 1.6. There were significant positive trends for wheezing and phlegm production with increasing duration of exposure. The COPD-index had a significantly elevated odds ratio of 1.5 with dust exposure. Current smokers did not appear to be more susceptible to the effect of dust or fumes on symptoms than never smokers. Those who had never smoked but had been exposed to dust had higher symptom prevalences than current smokers not exposed to dust. No significant interactions were found for smoking and occupational exposure with respiratory symptoms and lung function. Gender did not modify the relationships found between occupational exposures and respiratory symptoms, but men with an occupational dust exposure had a higher COPD prevalence than women.

Prediletto et al. (1987) studied a general population sample of 3289 persons (men and women) in an unpolluted area of Northern Italy. The analyses conducted was restricted to those who were full time employed (n=1635), aged 18 over. Information on occupational exposures was

registered by questionnaire. Different exposed groups were distinguished; those with an exposure to dust only (iron dust, wood dust, rock wool dust) (95 males, 5 females), those with an exposure to dust and chemicals such as solvents, acids, gases, insecticides (96 males, 5 females) and those with an exposure to chemicals or gases only (126 males, 69 females). The remaining 710 males and 508 females were considered to have no occupational exposure. Although the results were not presented in great detail, the conclusion of the authors was that in a rural unpolluted area, subjects with an occupational exposure showed lower lung function and higher prevalence of symptoms then unexposed controls.

Krzyzanowski and Kauffmann (1986, 1988) recently published results of the analysis of the relationship between a moderate occuptional exposure and respiratory symptoms and lung function among 16,000 adults of the large French "Pollution Atmosférique et Affections Respiratoires Chroniques" (PAARC) Study. The adults were from households 'not headed' by manual workers and the occupational exposures present were therefore assumed to be only moderate. In a questionnaire, 34% of the 8692 men and 23% of the 7772 women reported some exposure to dusts, gases or fumes. No details were given on the different occupational groups which were part of this population. However, analysis by occupational groups of at least 20 persons did not reveal any statistically significant differences between exposed and non-exposed workers within an occupational group. Only for male and female bakery workers, exposed workers had a higher symptom prevalence for dyspnea (men only), wheezing (men and women), and cough (women only). A statistical significant increase in prevalence was found for chronic cough, (OR 1.4 men, 1.4 women) chronic bronchitis (OR 1.5 men, 2.1 women), dyspnea (OR 1.4 men, 1.6 women) and wheezing (OR 1.6 men, 1.7 women) among males and females exposed to dusts, gases and/or fumes after correction for age, smoking habits, socio-occupational class, education and air pollution level in a multiple logistic regression analysis. A reduction of the $FEV_1/FVC\%$ and $MMEF^1/FVC\%$ was seen for the exposed, after adjustment for standing height, age, smoking habits, socio-occupational class, education, and

[1] Maximal Mid Expiratory Flow

air pollution level in a regression analysis. FVC was significantly elevated among the exposed males (+ 400 ml). The FEV_1 did not differ significantly between exposed and unexposed, but was lower among the exposed (- 51 ml men; - 171 ml women). The models chosen for respiratory symptoms contained several independent variables (educational level; occupational exposure; socio-economic class; outdoor air pollution level) which might be highly correlated, leading to unprecise estimates of regression coefficients. However, the authors concluded that occupational exposures of relatively low intensity encountered in the non-industrial work places may constitute a non-negligible risk for respiratory health.

Recently the results of a survey among a 1.8% random sample of 4992 inhabitants of the South-west coast of Norway were published (Gulsvik et al., 1988). The study comprised a self-administered questionnaire with items on occupational exposures (dust or gases, asbestos, quartz), and respiratory symptoms. Of this sample 89.5% returned their questionnaire. Of the responders, 41% were non-smokers, 20% ex-smokers and 39% smokers. Ten percent of the responders had a history of hay-fever, and they were defined as being atopic. An exposure to dust or gases, asbestos and quartz was reported by 28%, 5% and 4% respectively. The relationships between morning cough, cough during the day, chronic cough, phlegm when coughing, chronic cough for three weeks, breathlessness on exercise, attacks of breathlessness and wheezing with the independent variables were studied. Smoking was significantly related to all respiratory symptoms. After allowing for age, smoking habits and atopy status, those with an occupational exposure to gases or dust had an odds ratio of 1.8 for most of the respiratory symptoms compared to those without exposure.

Krzyzanowski et al. (1986, 1988) reported results of the Cracow Study after thirteen years of follow-up. The Cracow Study is a longitudinal study focussed at chronic obstructive lung diseases in Cracow, Poland and is based on a random sample of residents of the city, aged 19 - 70 during the first survey in 1968. The group was followed and surveyed again in 1973 and 1981. In the first publication the authors presented results of an analysis of factors that contributed to loss of ventilatory function over time and incidence of COPD. Incident COPD

cases were defined as persons with a baseline FEV_1 greater than 70% of the reference value (at the first survey), and a subsequent change over 13 years to a level smaller than 65% of the reference value. Of the men 30%, 27%, 12%, and 25% had a occupational exposure to dust, variable temperature, high humidity and chemicals respectively, as registered during an interview. For females these percentages were 13, 9, 6, and 11% respectively. Among men the occupational dust exposure was related to 13 year FEV_1 decline. In women such a relationship was found for variable temperature. The COPD incidence was not significantly related to occupational exposures. The second paper mentions slightly different population sizes. In 696 men and 983 women who had an age between 19-60 at the first survey, the relationship between change in lung function (FVC and FEV_1) over the 13 year period and occupation was analysed. During the three surveys information was gathered by interview on occupational exposures to dusts, variable temperature, chemicals and irritating gases. It was shown that an exposure to variable temperatures had the strongest relationship with the decline in lung function, after correcting for confounding variables e.g. age, height and smoking habits. The effect of dust was smaller than the effect of variable temperature on lung function decline, but formed an important determinant of lung function decline in subgroups of pottery workers and workers in the building materials industry. The magnitude of the effects of the occupational exposures on lung function decline were similar as those of smoking. The group exposed to occupational factors was smaller than the population of smokers.

The results of the population studies are summarised in table 4.1.

Table 4.1. Result of an analysis of the relationship between occupational exposures, respiratory symptoms and lung function in general population studies

country	subjects	health endpoint	type of study	exposure characterisation	exposures related to health endpoint	quantification of results	reference(s)
USA	1195 men 1519 women	symptoms, spirometry X ray	cross-sectional	interview	specific exposure dusts, glass fibers construction industry production industry sector	elevated symptom prevalence with occupational exposure no OR's given reduced FVC and FEV_1/FVC	Lebowitz, 1977a+b
France	556 men	FVC, FEV_1	longitudinal 12 year follow-up	walk through, estimation for 30 exposures	dusts, gases, heat	increased FEV_1 decline for exposed	Kauffmann et al, 1982
Denmark	1270 men	FEV_1, MMEF slope Phase III	cross-sectional	interview	occupational groups exposed to dust, variable temperature, physical excretion	reduced FEV_1 and MMEF level for exposed	Rasmussen, 1985
Poland	759 men 1065 women	FVC, FEV_1 COPD incidence[b]	longitudinal 13 year follow-up	interview[c]	variable temperature (women), dusts (men)	increased FEV_1 decline for exposed	Krzyzanowski et al., 1986
USA	8515 men	symptoms COPD prevalence[a]	cross-sectional	interviewer with questionnaire	dusts, fumes, gases	dust OR 1.3-1.6 gas or fumes 1.33-1.4	Korn et al., 1987
Italy	1635 working men and women	symptoms lung function	cross-sectional	questionnaire	dusts with fumes and chemicals	elevated symptom prevalence with occupational exposure no OR's given	Prediletto et al., 1987
France	8692 men	symptoms FVC, FEV_1	cross-sectional	interview[d]	dusts, fumes, gases	men:OR 1.4-1.6 women: OR 1.4-2.1	Krzyzanowski & Kauffmann, 1986, 1988
Poland	696 men 983 women	FVC,FEV_1	longitudinal 13 year follow-up	interview[e]	variable temperature, dusts, chemicals	increased FEV_1 decline for exposed	Krzyzanowski et al., 1988
Norway	4992 men & women	symptoms	cross-sectional	interview	dusts & gases	OR approx. 1.8 for all symptoms with occupational exposure to dusts and gases	Gulsvik et al., 1988

[a] prevalent cases defined as persons with a FEV_1/FVC ratio <0.6
[b] incident cases defined as persons with a baseline $FEV_1 \geq 0.70$ reference, and change over 13 years to < 65% of reference value
[c] yes/no exposure only
[d] manual workers not included in the analysis
[e] stratified to years of exposure

In almost all these studies the characterisation of the occupational exposure was relatively poor. Exposures were generally self-reported and registered during an interview or based on questionnaire information. Only in one study, the occupational exposure was estimated by an occupational physician or occupational hygienist. In this study carried out by Kauffmann et al. (1982), the workplace was visited and a walk through survey was completed. The exposures implicated were measured on a two point scale (yes/no exposure) or graded in three to four categories. Although the definitions of an occupational exposure vary between the studies, the presence of any occupational exposure varied between approximately 25-60% for all males under study and 8-20% for females. In a few studies a relationship with years of exposure was present (Lebowitz, 1977a; Korn et al., 1987).
In all these studies relationships were found between occupational exposures and respiratory symptoms or lung function changes. The magnitude of the odds ratios of the occupational exposure to dusts, fumes and or gases in the studies with respiratory symptomes as health endpoint are comparable between the studies and vary from 1.3 to 2.1. Exposure to dust or to dust, gases or fumes, and in two case an occupational exposure to cold were significantly related to symptoms or lung function changes. The relationship between occupational exposures and respiratory symptoms was in some cases of the same magnitude as the relationship with smoking. There was no evidence for a statistically significant interaction between the occupational exposures and smoking in any of the studies. The relationships between occupational exposures and the respiratory symptoms were the same for smokers and non-smokers. In the lung function studies the effect of the occupational exposures on lung function decline was also of the same magnitude as the effect of smoking on lung function decline. In all cases the effect of smoking and occupation or occupational exposures was additive.

Korn et al. (1987) discussed possible influences of misclassification of exposure, recall bias or selection bias on the results of their analysis of the Six Cities Study data. Because designs of these general population studies are similar, with respect to population sampling and characterisation of the exposure, their comments are of general interest. They concluded that:

- misclassification of exposure should be random because occupational status of the selected population was comparable to the total population. The effect of this misclassification would lead to a decrease of the magnitude of the relationship between occupational exposures and CNSLD.
- recall bias (overreporting of occupational exposures among those with respiratory symptoms) was unlikely to occur because the aim of their study was not to assess effects of occupational exposure on respiratory symptoms. In addition, relationships between occupational exposures and lung function were also established.
- selection bias towards those with a higher occupationally exposed job was unlikely because a random sample of the population was taken.

Of these arguments the first is probably too optimistic. The similarity of distributions of occupational status between two populations does not necessarily mean that self-reported exposures should show random misclassification. Therefore, more direct evidence of the precision and validity of self-reported exposures is necessary before this conclusion can be supported. It seems, however, unlikely that the similarities in results between the various countries are caused by similar magnitudes of misclassification of the exposure.

Another factor present might be incomplete correction for confounders such as smoking, and socio-economic status resulting in so-called residual confounding bias (Breslow & Day, 1980). Although this effect might be present in some specific studies in which crude characterisations for smoking were used, it is unlikely that it produced the relationships found between occupational exposures and CNSLD in all studies. A strong argument against residual confounding by smoking habits is the fact that significant relationships of the same magnitude between occupational exposures and CNSLD were found for smokers as well as non-smokers in a separate analysis (Korn et al., 1987).

4.3. Recent occupational group studies

Compared to the above described community-based studies, occupational population-based studies have the advantage that the exposure can be

characterized in a more appropriate way. There is only a limited number of exposures under study, and the exposure can therefore be characterized quantitatively. A relatively important drawback is that work-force based studies are relatively sensitive to selection effects like the healthy worker effect.

During recent years, reviews have been published on occupational group studies among various occupational groups. Becklake (1985) reviewed most of the population-based studies among coal workers and foundry workers which had been undertaken since the beginning of the seventies. She showed that in most of the cross-sectional studies there was no consistency in the magnitudes of the relationship between dust and lung function and/or respiratory symptoms, and the relationship between smoking and lung function and/or respiratory symptoms. This might be related to differences in factors such as duration of exposure, and treatment of the exposure variables, but she concluded that a health selection effect was probably the most important explanatory factor. Despite these inconsistencies in magnitude of effects, most of the cross-sectional studies demonstrated an effect of exposure on lung function which is confirmed by longitudinal lung function studies, case-control studies based on pathologically confirmed emphysema and mortality studies.

Most of the longitudinal lung function studies were conducted among coal miners, foundry workers and more recently grain workers also. The overall picture that arises from the studies among coal miners and foundry workers is similar. Higher exposed workers have a steeper decline in lung function, and in several independent studies, especially among British miners exposure-response relationships between cumulative coal dust exposure and lung function decline have been established. Most of the evidence comes from the British Pneumoconiosis Field Research (Fay, 1958). The primary aim of this study was to obtain information that would lead to formulation of new dust standards. It had to be established ".. what environmental conditions should be maintained if miners are not to be disabled by the dust they breath". Therefore medical surveys were conducted at approximately five year intervals at 24 coal mines spread over Britain. Later surveys took place at ten of the initial 24

coal mines. Individual miners' exposure to dust has been measured throughout the periods of the study and earlier exposures have been estimated.

Soutar (1987) compared the results of recently published studies in exposure-response relationships among miners. He showed that the effect of coal dust on lung function (FEV_1) ranged from 60 - 80 ml per 100 gh/m^3 dust exposure in four independent cross-sectional studies among British currently employed coal miners and ex-miners (Rogan et al., 1973; Gauld et al., 1985; Soutar & Hurley, 1986). This is comparable with the effect found in longitudinal studies among British coal miners (Love & Miller, 1982; Heederik & Miller, 1988). Although in other studies in the US and South Africa only surrogate measures for the exposure were used instead of cumulative coal dust exposure, inverse relationships between exposure and lung function were published, with comparable magnitudes of the effect of dust on lung function (Becklake, 1985). There is some evidence that the effect of coal dust exposure is a mixed obstructive restrictive effect, although the structural defect, responsible for the restriction is not known (Soutar, 1987). Recently strong evidence was published by Marine et al. (1988), which supports the hypothesis that mixed coal dust exposure is related to a clinically relevant decrease in FEV_1 independent of smoking. They defined four respiratory indices: FEV_1 < 80% predicted; chronic bronchitis; chronic bronchitis with FEV_1 < 80% predicted, and FEV_1 < 65% predicted. For all four indices a dust related increase in prevalence was found after allowing for smoking in a group of 3380 British coal miners. There was no evidence that smoking potentiated the effect of dust exposure. This means that in most cases the effects of dust and smoking on lung function were not multiplicative. At intermediate and high dust exposures the prevalence of these indices in non-smokers approached the prevalence in smokers exposure. The authors concluded that dust exposure as well as smoking can cause clinically relevant respiratory disfunction. Preventive strategies should therefore aim at both smoking and coal mine dust exposure.

These findings in field surveys, both cross-sectional and longitudinal are confirmed by case-control studies among coal worker populations. Several case-control studies, using pathologically confirmed emphysema

patients, showed that emphysema patients have had higher dust exposures than controls and that the contribution of dust exposure to the development of emphysema was independent of smoking. Emphysema was also found among the non-smoking dust exposed coal workers (Lamb, 1976; Leigh et al., 1982; Cockcroft et al., 1982; Ruckley et al., 1984; Becklake et al., 1987). Only a very limited number of studies among coal miners did not show a relationship between occupational dust exposure and CNSLD. Therefore the positive studies form powerful evidence that exposure to coal dust can cause a disabling chronic bronchitis.

In the Federal Republic of Germany (DFG, 1978) a large scale survey with standardised methods has been performed in several dusty industries. The survey was part of a research program initiated by the Health and Safety Directorate of the Commission of the European Communities. A population of approximately 6700 persons from the coalmining industry, steelworks, heavy engineering works, cement works, asbestos industry, ceramic and refractory works industry was studied. Each worker completed a modified BMRC respiratory questionnaire including questions on smoking habits and an occupational history. A clinical examination, X-ray, measurement of FVC, FEV_1 were part of the study also. In each factory (dust)exposures were measured. For the analysis workers were classified in three exposure categories (low, moderate, high). In the lower age-group (20-35 year) dust exposure resulted in similar rates of increase in bronchitis symptoms as moderate smoking ($\leq$ 10 gram tobacco/day). In the other age groups (35-55 and > 55 years) the effect of dust exposure was less than the effect of smoking but larger than the effect of dust in the younger workers. Comparisons between industries showed that coalminers were most heavily affected, probably because they had the highest dust exposure. These results showed that effects of dust on lung function can be found in other dusty industries than mining also.

For many other exposures the evidence is less extensive and generally limited to cross-sectional studies and very few longitudinal work force based studies. Grain dust is an important example, and the results found among grain workers are illustrative for experiences with wood dust, textile dust and organic dust in agricultural studies like those encountered in swine confinement buildings (Smid & Heederik, 1988; Rylander et

al., 1989). For instance, evidence of an effect of grain dust on health comes from many cross-sectional but only a limited number of longitudinal lung function studies. These studies have been conducted during the last two decades. Most studies showed a marked decrease in lung function among grain workers in cross-sectional studies and an accelerated decrease in lung function in longitudinal studies. However, designs of these studies were simple, exposure characterisation consisted only of a few measurements and there was thus very limited evidence for an exposure-response relationship. The interpretation of the results is complicated because sensitisation against grain dust has also been described, resulting in occupational asthma and extrinsic allergic alveolitis of which the occurrence is dependent on the exposure level and the types of grain involved (Smid & Heederik, 1989).

4.4. In conclusion

Recent studies clearly point to a relationship between occupational exposures and respiratory symptoms and lung function. The general population studies which have been conducted in various countries all point in the same direction. Exposure information is in this type of study, however, scarce and often self reported. Misclassification of the exposure and responder bias probably occur and might lead to biased estimates of the contribution of occupational exposures to the development of CNSLD. Occupational group based studies show that exposure-response relationships have been established for a limited number of occupational exposures, especially in coal workers. For other occupational groups the evidence is less definite, although effects of exposure on lung function observed in cross-sectional studies, for instance among grain workers are generally consistent. Studies of those who leave the industry, or studies of those who enter the industry and are surveyed within a year from initial exposure show that selection effects are present and lead probably to an underestimation of exposure-response relationships (see chapter 3).

The evidence reviewed showed also that respiratory symptoms, airway obstructions and emphysema are related to occupational dust exposures in

the absence of cigarette smoke. Significant relationships exist between occupational exposures and respiratory symptoms or lung function decreases after correction for smoking habits. No statistically significant interaction terms between occupational exposures and smoking were observed, suggesting an additive effect of both factors on respiratory health.

5. WEAK ASSOCIATIONS IN OCCUPATIONAL EPIDEMIOLOGY: ADJUSTMENT FOR EXPOSURE ESTIMATION ERROR[1]

5.1. Summary

Epidemiological studies often estimate the health effects of occupational exposures by multiple regression techniques. The standard theory of regression analysis is based on the assumption that the explanatory variables are known without error, and it has long been known that departures from this assumption will lead to underestimation of the true regression coefficients. In reality, there may be considerable imprecision in the measurement of individuals' exposures to hazards in the workplace, but this is seldom taken into account in analyses. We therefore studied the effect of allowing for imprecision in the exposure estimate with more sophisticated statistical methods, using lung function data from a sample of 348 British miners exposed to mixed coal dust, over an eight year period.

Change in lung function over an eight year period was regressed on the cumulative dust exposure, weight, age and smoking habits. The error in the exposure estimation was assumed to be up to 30% of the total variance of the distribution of the exposure. Adjustment of the regression coefficients of lung function change on dust exposure for the estimation error using linear structural relationships increased the regression coefficient more than threefold compared with those calculated by standard regression analysis. The adjustment led to a change of the coefficients of age as well. These results indicate that a serious underestimation of the relation between lung function change and occupational exposure may occur, which might lead to false interpretations about the relative importance of the occupational exposure as a determinant of disease.

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[1] Presented at the annual meeting of the Dutch Epidemiological Society in 1988
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5.2. Introduction

Cross-sectional epidemiological surveys of British coal-miners have demonstrated an inverse relationship between forced expired volume in one second (FEV_1) and cumulative exposure to respirable mixed coal-mine dust, independent of the presence of pneumoconiosis (Rogan et al., 1973), suggesting that respirable dust exposure might be related to rate of decline of lung function in addition of that attributable to aging and smoking. Results have been consistent with similar studies in other coal mining countries (Reichel & Ulmer, 1978; Hankinson et al., 1977). The relationship between loss of lung function and cumulative dust exposure has been confirmed in longitudinal analyses (Love & Miller, 1982).

There is much concern about the acceptability of health risks which arise from occupational exposures. Discussion on the magnitude of relative risks of smoking and of exposure to coal mine dust on lung function have aroused particularly heated controversy (Morgan, 1986). However, conclusions based on the magnitude of regression coefficients can be misleading if the independent variables in the regression analysis are subject to random estimation error. This type of error leads to a bias towards zero or underestimation of the regression coefficient, often referred to as attenuation (Snedecor & Cochran, 1980). There are many potential sources of error in the estimation of individuals' exposures to dust in the workplace. Sampling schemes based on periodic measurements of occupationally exposed workers will not usually incorporate sufficient allowance for day-to-day variation in concentrations, nor spatial variations away from the sampling points, nor inhomogeneity of occupational groups. Long term variations may be missed if the sampling points or occasions are sparse. The data on individuals' work patterns may not relate exactly to sampling locations, and work histories taken by interview may suffer from faulty recall. Variations in individuals' patterns of breathing, because of differences of work load or lung dimensions may produce differences in the quantities of dust deposited in the lung, even if ambient concentrations are the same.

Estimates of individual exposures may thus be subject to considerable error from any or a mixture of these sources, and the attenuation of the regression coefficient increases with the amount of error in the estimates (Cochran, 1968; Snedecor & Cochran, 1980). In the case of a simple regression with one independent variable measured with error, a simple formula is available to adjust for the error and to provide a "disattenuated" estimate of the regression coefficient. Extensions to adjust for this in the coefficients of other variables in more complicated regression equations, and to allow for error in more than one independent variable, rapidly become algebraically complex (Cochran, 1968). However, such situations are fairly easy to specify as extended regression models using so-called linear structural equations (Everitt, 1984).
We describe here an example of such an analysis, where an estimate of the relationship between mixed dust exposure and lung function was adjusted for estimation error in the exposure.

5.3. Methods

5.3.1. Available survey and exposure data

The data analyzed were from one British colliery studied as part of the National Coal Board's Pneumoconiosis Field Research (PFR) (Hurley et al., 1987). From the records of medical surveys which took place at that colliery in 1970 and 1978, lung function measurements and information on smoking habits were extracted. The highest values from at least two technically satisfactory forced expirations of forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were analysed.

Data on standing height without shoes, age at survey and weight were available. Men were classified as non-smoker (who had never smoked as much as one cigarette a day for a year), ex-smoker, or smoker on the basis of consistent replies at each survey in 1970, 1974 and 1978. Persons who changed their smoking habits during the time of observation, were defined as intermittent smokers. A few workers whose replies were seriously inconsistent were omitted from the analysis.

Estimates of individual workers' exposures to respirable dust in the PFR were based on environmental measurements of concentrations in defined occupational groups, and on records of the amounts of time each man spent working in each of these groups (Hurley et al., 1987). For the period before the start of the PFR, or when men transferred from another colliery, employment histories were obtained by an interview at the medical survey. Exposure estimates were calculated for each miner as the product of respirable dust concentrations and times worked, cumulated over various time periods. The change in lung function was calculated by subtracting the lung function at the first survey from that at the last survey. To exclude possible disturbing effects of lung growth among the younger workers, persons aged 25 or less at the last survey were excluded from the analysis. Suitable data on lung function, smoking and exposure to dust were available for 348 men.

5.3.2. Data analysis

Loss of lung function was initially analyzed by the application of detailed graphical and tabular analysis. Multiple linear regression analysis was used to relate decline in lung function to respirable dust exposure estimates, with adjustment as necessary for age, height, weight and smoking habits. Models with interaction terms between the smoking habits and the exposure variables were tested, as well as models with quadratic and logarithmic expressions for the exposure. Residuals were examined in detail. These analyses were performed with the SAS-Software on a Prime computer (SAS, 1985).

The regression analyses was supplemented and extended by further work using the package LISREL (Jöreskog & Sörbom, 1986), to adjust for the attenuation due to estimation error in the exposure variables. LISREL allows estimation, by maximum likelihood, of coefficients in linear relationships more complex than that of multiple regression; it includes facilities for adjustment of error in some or all of the independent or explanatory variables. This is achieved by supplying some estimate of the error variances of the variables affected. In using LISREL to examine the effects of random errors in the exposure measurements, we

assumed a simple model for the changes in the lung function variables as suggested by ordinary regression analysis (see appendix chapter 5). For example for the change in FVC (dFVC) the model eventually selected was:

$$dFVC=b_0 + b_{1j} + b_2x_2 + b_3x_3 + b_4x_4 + e$$

where b_{1j} is the coefficient of the dummy variable identifying the appropriate smoking group, and x_2, x_3, and x_4 are the variables age, weight and the chosen dust exposure. This was augmented by the equation:

$$x'_4= x_4 + f_4$$

indicating that the exposure variable in the regression equation was not observed, but measured with error f_4. A solution to these simultaneous equations can be obtained provided that information is supplied on the magnitudes of the components of variance of x'_4; that is, on how much of the variation in x'_4 is due to the variation in x_4 in the population, and how much due to the random variation represented by the measurement error f_4.

Little hard information is available on the magnitude of the measurement error variance. Previous published work (Heederik et al., 1986), repeated measurements available of subgroups of coal workers, and discussions with occupational hygienists suggested that an assumption that it may contribute between 20% and 40% of the total variance of the observed cumulative exposures, would not be unreasonable in many studies. The analyses reported below were based on assumptions consistent with these educated guesses.

5.4. Results

Details of the study population are presented in table 5.1.
The cumulative dust exposure estimates are shown separately for the periods up to the 1970 survey and that between the 1970 and 1978 surveys, which is labelled "concurrent" to indicate that it coincides with the period over which the losses in FVC and FEV_1 were calculated.

Table 5.1. General characteristics and dust exposure of men at the end of the follow-up period. Percentages and standard deviations between parentheses (n=348)

	mean	(sd)	n	(%)
age	48.2	(9.0)		
standing height (cm)	170.3	(6.4)		
weight (kg)	75.6	(11.5)		
non-smokers			57	(16.4)
ex-smokers			20	(5.7)
intermittent smokers			60	(17.3)
smokers			211	(60.6)
dust exposure until 1970 (ghr/m^3)	48.4	(26.7)		
concurrent dust exposure	19.3	(11.2)		

These losses in FVC and FEV_1 and the previous and concurrent cumulative exposures are given in table 5.2 grouped according to age and smoking habits. The Pearson correlation coefficient between the previous and concurrent cumulative exposure for respirable dust was 0.22.

Table 5.3 shows the results of fitting regression models for the losses of FVC and FEV_1, in terms of the variables age and weight, and dummy variables expressing membership of the four smoking groups (with non-smokers as the reference). Table 5.4 shows the results of adding either the previous or the concurrent dust exposure to the models in table 5.3. Models which used the logarithms of the exposures fitted better than linear or quadratic terms in the original exposures. As can be seen from table 5.4, the previous exposure made the more significant contribution to the models for both dependent variables, with evidence of a stronger effect on FVC than on FEV_1. Further modelling did not result in better fits than those presented for the models in the tables. The negative signs of the regression coefficients on dust exposure and age (table 5.3) imply an increasing rate of loss in lung function in older men, and additionally in those with a higher dust exposure, adjusted for age (table 5.4). Smokers showed a greater rate of loss than non-smokers and ex-smokers (table 5.3). Intermittent smokers showed even greater losses in function than smokers did.

Table 5.2. Mean FVC and FEV_1 losses over an eight year period and dust exposure according to age and smoking habits

smoking habit	age	<40	40-49	>50	all
non-smokers	n	18	18	21	57
	dFVC	-414	-367	-543	-446
	$dFEV_1$	-416	-356	-400	-391
	PD	14.7	45.8	62.7	42.2
	CD	21.8	21.7	17.5	20.2
intermittent smokers		18	16	26	60
		-263	-825	-898	-688
		-219	-747	-621	-534
		18.2	44.8	60.1	43.4
		21.5	20.3	19.1	20.2
ex-smokers		1	5	14	20
		-250	-470	-375	-393
		-200	-330	-361	-345
		41.2	44.5	51.7	49.4
		27.0	22.4	14.5	17.1
smokers		35	60	116	211
		-304	-553	-544	-506
		-373	-512	-469	-465
		19.0	45.5	64.3	51.4
		19.4	19.7	18.6	19.1
all men		72	99	177	348
		-321	-559	-582	-522
		-343	-512	-474	-458
		18.0	45.4	62.5	48.4
		20.7	20.3	18.2	19.3

n number of observations
dFVC mean change in Forced Vital Capacity (l)
$dFEV_1$ mean change in Forced Expiratory Volume in one second (l)
PD mean previous cumulative dust exposure (ghr/m^3)
CD mean concurrent cumulative dust exposure (ghr/m^3)

Table 5.5. Regression of FVC-change on exposure calculated with LISREL for different reliabilities of the exposure.

Reliability	logarithm previous mixed dust exposure $\hat{\beta}^1$	t-value	age $\hat{\beta}^1$	t-value	logarithm concurrent mixed dust exposure $\hat{\beta}^1$	t-value	age $\hat{\beta}^1$	t-value
1.0	-81.5	-2.3	-8.2	-2.4	-41.0	-1.4	-14.0	-5.6
0.9	-101.0	-2.3	-6.9	-1.8	-45.7	-1.4	-14.1	-5.6
0.8	-131.7	-2.3	-4.9	-1.1	-51.6	-1.4	-14.2	-5.6
0.7	-189.5	-2.3	-1.1	-0.2	-59.2	-1.4	-14.3	-5.6

[1] regression coefficient after allowing for age, weight and smoking habits

Table 5.5 shows that the regression coefficients of lung function on previous and concurrent cumulative exposure increase as reliability decreases (or as error variance increases) in the LISREL model. For the model containing concurrent dust exposure, decreasing the assumed reliability by 30% resulted in a 44% increase in the magnitude of the concurrent dust exposure coefficient, with only a 2% increase in the age coefficients. The results from a similar analysis including previous dust exposure were even more dramatic, with an assumed reliability of 70% resulting in a 233% increase in the exposure coefficient and a 87% reduction in the age coefficient.

The values of the corresponding t-statistics for the statistical significance of previous dust exposure did not increase with the adjusted estimates, indicating that the standard error was increasing along with the estimate. This reflects the increase in residual error which is always traded-off for bias adjustments. However, there was an interesting drop in the magnitude and significance of the age coefficient as these adjustments took place, suggesting that the imperfect measurement of previous exposure was excessively confounded with age when their effects were estimated without adjustment.

Some further modelling showed that the effect of allowing for estimation error was much greater for the exposures before 1966 than between 1966 and 1970 (table 5.6). For all these models, the adjustment for the reliability of the exposures had negligible effect on the coefficients of weight and smoking, which is not shown in tables 5.5 and 5.6. Similar results were obtained in the analysis of change in FEV_1.

Table 5.6. Regression of FVC-change on previous exposure by means of LISREL with different reliabilities of the exposure.

	logarithm of the exposure:			
	before 1966		from 1966 - 1970	
Reliability	$\hat{\beta}^1$	t-value	$\hat{\beta}^1$	t-value
1.0	-51.0	-2.1	-77.0	-2.3
0.9	-66.0	-2.1	-86.4	-2.3
0.8	-91.7	-2.1	-96.7	-2.3
0.7	-151.6	-2.0	-115.0	-2.3

[1] regression coefficient after allowing for age, weight and smoking habits

5.5. Discussion

The purpose of the work reported here was to gain some insight into the effects of errors in the measurement of occupational exposures on estimates of their health effects. This was accomplished using models based on linear structural relationships. The data used were, for convenience, from a single colliery, and originated from less than 350 miners. Nevertheless, multiple regression analyses, of the sort commonly applied to similar epidemiological data, showed a clear effect of mixed coal dust exposure on rate of lung function decline after allowing for smoking, age and weight. The change in FVC showed a more profound effect of dust exposure than the change in FEV_1, and the relationship was stronger with previously accumulated exposure to dust than with that accumulated during the period over which the change was observed. The results were qualitatively similar to those reported by Love and Miller (1982) for FEV_1.

As expected from the theory, the introduction of an adjustment for error in the measurement of individuals' exposures resulted in an increase in the regression coefficient of the dust exposure variable, with the size of the adjustment becoming greater as lower reliability in the exposure was assumed. The largest adjustment was seen for change in FVC with an exposure variable representing exposures before 1966, when the coeffi-

cient after adjustment for an assumed reliability of 70% was three times the unadjusted coefficient.

The effect of the adjustment was strongest on the exposure for the period before 1966, that is the furthest before the observed lung function changes. It is to be expected that these earlier exposure estimates were less reliable than those for the later periods, both because later accumulation of data on times worked was extracted more frequently and more directly from a computerised payroll system, and also because the estimated exposures for the earlier periods include estimates based on the men's recall of employment before they entered the research programme. In addition, it is these exposures which are most highly correlated with age; and the apparent reduction in the importance of the age variable in the adjusted analyses with previous exposure, suggests that measurement error in the exposure variable makes it more difficult, using ordinary regression methods, to disentangle the partial confounding between historical exposure estimates and age. Further work is needed, possibly on other data sets, to identify and disentangle the relative importance of these and other aspects of historical exposures.

We do not underestimate the task of attempting a realistic quantification of the measurement error attached to explanatory variables in epidemiological studies, in order to make the sort of adjustment employed here. An alternative approach to the problem is to characterise individuals' exposures more precisely, but this requires an increase in effort to be sustained throughout the measurement process. The option of making adjustments through techniques such as linear structural equations will often be more feasible in practice. Several computing packages provide solutions to such equations (Everitt, 1984), LISREL being perhaps the most general (Jöreskog & Sörbom, 1986).

Although these findings were based on a small data set, it is clear that they have wider implications. Assessment of the severity of health effects judged from unadjusted regression coefficients may underestimate the strength of the effects, if there is considerable error in the estimation of individuals' exposures. It is possible that statutory limits on such exposures may, in turn, not be sufficiently stringent, although

6. CHRONIC NON-SPECIFIC LUNG DISEASE AND OCCUPATIONAL EXPOSURES ESTIMATED BY MEANS OF A JOB EXPOSURE MATRIX - The Zutphen Study[1]

6.1. Summary

Information gathered in the 'Zutphen Study', the Dutch contribution to the Seven Countries Study that started in the sixties, was used for this study. Of the 1266 men aged 65-84 invited for the 1985 survey, 939 (74%) participated. All participants were interviewed according to the BMRC CNSLD questionnaire by a trained physician. The physician also filled out a questionnaire with questions concerning previous treatments for asthma, bronchitis and emphysema. Exposures were generated by means of a job exposure matrix on the basis of the longest performed job in an industry and grouped in twelve exposure catagories. A logistic regression analysis was performed using the occupational exposures as the independent variables allowing for smoking habits, age and socio-economic status. For the diagnosis by the physician and treatment for emphysema and/or bronchitis, the highest odds ratios with the exposures were found, indicating an adverse effect of the occupational exposures on respiratory health. In contrast, the variable 'ever treated for asthma' had odds ratios smaller than one with most of the exposure variables suggesting a selection effect. In an analysis in which all persons who were ever treated for asthma were excluded, an increase in the odds ratios compared with the first analysis was seen. The relationships between occupational exposures as generated with the job exposure matrix and CNSLD were stronger than those recently reported in the literature.

[1] Revised version of the paper: D. Heederik, H. Pouwels, H. Kromhout, D. Kromhout. Chronic non-specific lung disease and occupational exposures estimated by means of a job exposure matrix - The Zutphen Study. Int J Epidemiol 1989; 18: 382-389

6.2. Introduction

To this point only tobacco smoke is an unquestioned risk factor for the development of chronic non-specific lung disease (CNSLD) (Morgan, 1986). Occupation and its related exposures are generally recognised as potential determinants of CNSLD, but clear cut relationships between occupational exposures and CNSLD have been established only in some closed populations or occupational group studies, carried out so far. In these cases a serious underestimation of the exposure-response relationship might be present because of the healthy worker effect in the exposed population. In the past coal workers, foundry workers, textile mill workers and grain workers have been identified as having an increased risk for developing chronic bronchitis (Morgan & Seaton, 1984). However in general doubt still exists whether occupational exposure aggravates the symptoms in workers with chronic bronchitis or whether occupation can be a real determinant independent from other factors like smoking (Parkes, 1982; Morgan, 1986). Population-based studies are therefore often seen as an alternative approach to overcome selection effects like the healthy worker effect and could give more reliable estimates of the relationship between work related exposures and CNSLD. However, recent examples of population-based studies (Lebowitz, 1977a+b, 1982; Kauffmann et al., 1979, 1982; Krzyzanowski & Kauffmann, 1986; Korn et al., 1987) illustrate a weakness of these studies. Characterisation of the exposure is a cumbersome problem in this kind of studies and the exposure is therefore often only characterized by means of a questionnaire or interview. In cancer epidemiology so-called 'job exposure matrices' are applied for exposure estimation purposes with sometimes promising results.

In order to estimate the importance of occupation as a determinant of CNSLD, this prevalence study was undertaken. Special emphasis was given to the characterization of the exposure using the job exposure matrix methodology to generate specific occupational exposures for each individual.

6.3. Materials and methods

Information for this study was gathered from the 'Zutphen Study', the Dutch contribution to the Seven Countries Study (Keys et al., 1967). This longitudinal study of the relationship between diet, other risk factors and chronic diseases started in 1960 among men aged 40 to 59 in the town of Zutphen. This is an old industrial town in the eastern part of the Netherlands with about 25,000 inhabitants living there at that time. In 1960 a sample of 1,088 men, born between 1900 and 1919, was selected to participate in a longitudinal study. On January 1, 1985 only 555 men of the original sample were still alive. Subsequently in 1985, this group was expanded with a two to three sample of 1075 men from Zutphen in the age range of 65 - 84 years. For the 1985 survey of the expanded cohort, 1,266 men were invited.

Each person was interviewed about previous diseases and examined physically by a trained physician, interviewed about his diet by a dietician, and asked to fill out a questionnaire with items on subjective health symptoms and psycho-social factors. A more detailed description of the purpose and design of the Zutphen study can be found elsewhere in the literature (Kromhout et al., 1982, Kromhout & Oberman de Boer 1986).
The questions which refer to respiratory symptoms were adapted from on the internationally accepted British Medical Research Council questionnaire (BMRC, 1966). These questions were asked by the physician who also performed the physical examinations. The following information was used in the present study (see Appendix chapter 6):

- the presence of respiratory symptoms and other characteristics, including;
  - wheezing (positive answer to question 45);
  - shortness of breath (positive answer to question 47, 48 or 49);
  - cough and sputum (positive answer to question 41 or 42 or 43 or 44a);
  - ever treated for chronic bronchitis and/or emphysema (positive answer to question 46b or 46c);
  - ever treated for asthma (positive answer to question 46a);
- the CNSLD diagnosis by a physician;
- information on smoking habits, expressed as the number of pack years of cigarettes ever smoked (the product of the number of packs of

cigarettes smoked per day and the number of years smoked on a continuous scale), and information about the smoking habits in the year before the study (smoking yes/no). In the calculation of the number of pack years smoked it was assumed that a pack of cigarettes contained 25 cigarettes;

- age;
- socio-economic status (SES) measured as a variable with three categories, was based on information of the respondents on their education; (1) primary school; (2) secondary school, lower level and/or lower technical education (3) secondary school, higher level, professional education on higher levels and university;
- the nature of the longest held occupation;
- the sectors of industry in which a respondent worked for more than one year.

With the last two items, and a British job exposure matrix composed by Pannett et al. (1985) it was possible to generate specific exposures for a specific occupation in a specific sector of industry. This was only done for the longest held occupation and the sector of industry in which this occupation was performed. The information on occupation was coded by one of the authors (HP).

The job exposure matrix is based on the British Registrar General's 1966 classification of occupations and 1968 classification of industries (GRO, 1966; CSO, 1968), implicating that our information on occupation and industry had to be recoded according to the British classifications. The specific exposures as generated with the matrix are graded as no exposure, a low level and a high level exposure. No exposure corresponds to the degree of exposure that might be expected in the unemployed general population. In the version of the job exposure matrix used, a distinction was made between exposures from World War II until 1950 and from 1950 until the present time. For the analysis presented in this article the latter exposure estimates were used. In the data analysis, the low exposure was generally considered as no exposure for reasons explained later. Therefore, a dichotomous exposure variable was created for each exposure, although models with a distinction between no, a low and a high exposure level were also studied.

A separate analysis for all the 50 agents in this matrix could not be performed because quite often the number of persons with a high exposure was low (5-20 persons) or because not all the generated exposures were relevant in relation to occupational lung disease. The specific exposures were therefore grouped into categories with a comparable qualitative exposure for some of the relevant occupational exposures. For instance workers with an exposure to grain dust, textile dusts and wood dust were grouped in an 'organic dust' exposure category and an exposure of the skin to polycyclic aromatic compounds was considered irrelevant. This procedure resulted in twelve exposure groups; fumes, organic dust, mineral dust, heavy metals, organic solvents, heat, cold, working outdoors, adhesives, paint, frequent contact with animals and frequent contact with public. These procedures resulted in the following characterisations of the occupational exposures:

- whether or not the respondent has ever worked in industry;
- the sectors of industry in which individual workers have worked;
- the longest held occupation;
- whether the respondent was a 'blue collar' or 'white collar' worker;
- exposure groups established on the bases of the job exposure matrix;
- whether or not a person was occupationally exposed and in which categories exposed workers were classified (dust, fumes and/or gases).

For the data analysis a logistic regression analysis was used that allows adjustment for confounders. The statistical analysis was performed on a VAX-8600 computer with Statistical Analysis System (SAS, Catmod Procedure). The CATMOD procedure is based on Maximum Likelihood Estimates as described by Schlesselman (1982). The set of confounders was selected by a comparison of the logistic regression models with various combinations of confounders on the basis of the likelihood ratio of the models or the significance of individual variables. Especially for smoking habits different combinations of variables (categorisations, number of cigarettes smoked, pack years smoked) were explored. All odds ratios for the exposures were calculated after adjustment for the relevant confounders. The significance level was calculated by dividing the regression coefficient with the standard error of the coefficient. The social-economic status was only included in models with the more crude exposure variables like, working in the industry (yes/no), being a 'blue

collar worker' (yes/no), and having a specific occupational exposure (yes/no). For the analyses with the finer characterization of the exposure, the adjustment led to unstable regression coefficients, because for several of the exposures the number of exposed persons was too low and/or were highly correlated with other independent variables.

6.4. Results

Of the 1,266 men invited for the 1985 survey, 939 (74%) participated; 109 (9%) were not able to attend the examination because of morbidity, or mortality; 156 (12%) refused to participate; and 62 (5%) did not participate due to various reasons including moving outside Zutphen (Kromhout & Oberman de Boer, 1986). Men who couldn't provide complete information on respiratory symptoms, smoking habits or who were being or had ever been treated for lung diseases like tuberculosis, embolism or lung cancer, were excluded from the analysis. The remaining population consisted of 828 men aged 65-84. Part of the analysis was completed with less then 828 men because of missing information for some of the exposure variables.

Table 6.1. Prevalence of respiratory symptoms, CNSLD diagnosis and treatment in the Zutphen population in 1985 (n=828), percentages in parentheses

CNSLD		positive	
wheezing	(question 45)	182	(22.0)
shortness of breath	(question 47, 48, 49)	78	(9.4)
cough and sputum	(question 41,42,43 and 44a)	70	(8.5)
diagnosis by the physician		78	(9.4)
ever treated for:			
- asthma	(question 46a)	57	(6.9)
- emphysema or chronic bronchitis	(question 46 b+c)	119	(14.4)

The mean age of the population was high; 72 years (s.d. 5.4), and therefore also the pack years of smoked cigarettes; 25.6 (s.d. 23.7). Of the participants 91% had smoked cigarettes, cigars or pipe at some time and

46% of the participants smoked in the year immediately preceding the study. Of the study group 273 (33%) persons had a low, 348 (42%) an intermediate and 207 (25%) a high socio-economic status. The prevalence for the dependent variables is given in table 6.1.

The distribution of the population over the different sectors of industry, professions and specific exposure groups as generated with the exposure matrix is shown in tables 6.2, 6.3 and 6.4. The data show that only 17% of the workers had ever had an occupation in more than one type of industry. This indicates that the migration between industries was low in this population. The odds ratios for the selected confounders were all tested in one model and are given in table 6.5. No difference in the relationship with the dependent variables was seen for persons who smoked cigarettes, cigars or pipes.

Table 6.2. Distribution of the population over the different sectors of the industry and the number of years worked in the specified sector of industry. Standard deviation in parentheses (n=828)

	n	years worked in the sector of industry
food- and tobacco industry	112	27.4 (17.0)
textile, shoe and leather industry	71	25.8 (18.1)
wood- and furniture industry	58	28.6 (18.4)
paper- and paperproducts industry	68	22.1 (17.0)
graphical industry	53	27.3 (19.5)
chemical industry	30	22.3 (14.3)
construction pottery- and glass industry	40	28.2 (18.2)
metal- and metalproducts industry	110	25.5 (18.0)
machinery industry	19	18.2 (13.1)
electrotechnical industry	14	20.5 (16.8)
transport industry	35	23.2 (13.6)
not working in industry	327	- -
no information on industry	54	

Pack years smoked had an odds ratio of approximately 2-3 for a smoker who smoked one pack of cigarettes a day for 50 years for all the symptoms and the diagnosis of the physician except for 'ever treated for asthma' based on the regression coefficient in table 6.5. Persons who

had continued smoking the preceding year had a significantly lower odds ratio for the 'CNSLD diagnosed by the physician' (Odds Ratio=0.53; $p<0.05$), 'ever treated for emphysema or chronic bronchitis' (Odds Ratio=0.63; $p<0.05$), and 'shortness of breath' (Odds Ratio=0.57; $p=0.054$) but a significantly higher odds ratio with 'cough and sputum' (Odds Ratio=2.46; $p<0.05$). Age was positively related to shortness of breath (Odds Ratio=1.06; $p=0.07$). Age was negatively related with 'ever being treated for asthma' (Odds Ratio=0.93; $p<0.05$). Generally persons with the lowest socio-economic status had more respiratory symptoms than persons with a higher SES, although these differences were not always significant. The trend for SES was clearly absent for 'ever treated for asthma'.

Table 6.3. Distribution of the population over different longest held occupations (n=828)

	n	%
farmers	21	2.6
engineering and metal workers	74	9.1
wood workers	28	3.4
textile workers and tailors	16	2.0
food processing workers	34	4.2
paper and graphical workers	36	4.4
construction workers	28	3.4
painters	26	3.2
transport workers	74	9.1
warehouse workers	46	5.7
'white collar worker'	432	53.0
no information about profession	14	-

Table 6.4. Distribution of the population over the different specific exposures generated with the job exposure matrix (n=828)

exposure	low exposure n	low exposure %	high exposure n	high exposure %
1 Heavy metals	188	25.9	16	2.2
- arsenic and -compounds				
- beryllium and -compounds				
- cadmium and -compounds				
- lead and -compounds				
- mercury and -compounds				
2 Organic dusts	54	7.4	59	8.1
- cereal dust				
- textile dust				
- wood dust				
- other organic dusts				
3 Mineral dusts	79	10.9	43	5.9
- asbestos				
- coal dust				
- other mineral dusts				
4 Fumes	115	15.8	24	3.3
- welding fumes				
- soldering fumes				
- diesel fumes				
- cutting oils				
- polycyclic aromatic compounds				
5 Organic solvents	134	18.4	42	5.8
- acrylonitrile				
- benzene				
- carbon tetrachloride				
- degreasing agents				
- styrene				
- other organic solvents				
6 Adhesives	197	27.1	40	5.5
- synthetic and natural				
7 Paints	51	7.0	22	3.0
8 Cold	61	8.4	48	6.6
9 Heat	50	6.9	29	4.0
10 Working outdoors	42	5.8	72	9.9
11 Contact with animals	18	2.5	21	2.9
12 Contact with public	69	9.5	103	14.1
At least one exposure[a]	211	29.0	370	50.9[c]
Exposure to dust, fumes and/or gases[b]	247	34.0	176	24.2[c]
not enough information to estimate the occupational exposure with the matrix	101			

[a] specific exposures 1-7
[b] specific exposures 1-12
[c] at least one high exposure for the different specific exposures

Table 6.5. Relationship between respiratory symptoms, CNSLD diagnosis and treatment, and age, smoking habits and SES expressed as odds ratios (n=828)

confounder	wheezing and or asthma	shortness of breath	cough and sputum	CNSLD according physician	ever treated for: asthma	ever treated for: emphysema or chr.bronchitis
pack years of cigarettes[1]	1.018***	1.013*	1.013**	1.018***	1.005	1.001***
stopped smoking last year (y/n)	1.27	0.57*	2.46**	0.53*	0.63	0.63*
SES low[2]	2.14**	2.27*	2.18*	2.14*	1.04	1.65
SES intermediate[2]	1.43#	1.27#	1.37	1.05#	0.55	1.17
age	0.99	1.06*	1.01	0.97	0.93*	1.002

$0.05 \leq p < 0.10$
* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$
[1] odds ratio per pack year unit
[2] tested against a high SES

A logistic regression analysis with work history in industry as compared to a non-industrial work history, adjusted for age, smoking habits and SES, did not result in significantly elevated odds ratios for any of the dependent variables.

A further breakdown to specific sectors of industry revealed that only working in the construction industry was significantly related to wheezing and/or asthma (OR=3.3; $p<0.05$), cough and sputum (OR=2.6; $p<0.05$). Within the construction industry there was also a significant relationship with the number of years employed in this sector of industry.
A further analysis with longest held occupation revealed that 'blue collar workers' compared with 'white collar workers' had odds ratios significantly greater than one for the CNSLD diagnosis by the physician (Odds ratio=1.87; $p<0.05$), 'ever treated for emphysema or chronic bronchitis' (1.77; $p<0.05$), shortness of breath (1.48; $p<0.05$) and cough and sputum (1.87; $p<0.05$). These odds ratios were not reduced with more than 10% and remained significantly greater than one after adjustment for SES. Several occupations had an odds ratio significantly greater than one with some of the dependent variables, such as farmers, wood workers, construction workers, painters and paper and workers from the printing industry and warehouse workers as shown in table 6.6.

Table 6.6. Relationship between respiratory symptoms, CNSLD diagnosis and treatment and occupation adjusted for smoking habits and age expressed as odds ratios (n=811)

occupation	symptoms			CNSLD according physician	ever treated for:	
	wheezing	shortness of breath	cough and sputum		asthma	emphysema or chr.bronchitis
white collar workers	1.00	1.00	1.00	1.00	1.00	1.00
blue collar workers	1.39#	1.48*	1.87*	1.87*	0.76	1.77*
white collar workers	1.00	1.00	1.00	1.00	1.00	1.00
farmers	2.70*	1.67	1.70	3.10*	1.75	2.27#
engineering and metal workers	1.98*	1.61	1.53	1.31	0.79	1.32
wood workers	0.87	1.18	4.63*	1.86	0.47	2.18#
textile workers and tailors	0.28	2.63	-[1]	1.09	-[1]	0.49
food processing workers	1.33	0.80	2.10	1.74	-[1]	2.09#
paper and graphical workers	1.17	2.63*	1.73	2.32	0.73	0.78
construction workers	2.17*	2.20	1.92	2.26	1.68	1.99
painters	2.18*	2.25	3.59*	3.51*	0.94	1.32
transport workers	1.38	1.27	1.04	1.02	0.47	0.74
warehouse workers	1.05	2.81*	1.08	1.34	1.58	0.90

$0.05 \leq p < 0.10$
* $p<0.05$
[1] the maximum likelihood estimation procedure did not result in stable regression coefficients because the cell for exposed persons with the 'disease' was empty

The analyses with the specific exposures showed that several exposures were related to the respiratory symptoms (table 6.7). Persons with a low exposure according to the job exposure matrix had odds ratio not significantly different from one for any of the dependent variables. Therefore the low exposure was regarded as no exposure in the further analyses. The exposures to fumes, paints, adhesives, organic dust, heat and working outdoors showed positive and (borderline) significant relations with at least one of the dependent variables.

Table 6.7. Relationship between respiratory symptoms, CNSLD diagnosis and treatment and specific exposures adjusted for smoking habits and age, expressed as odds ratios (n=727)

exposure	symptoms			CNSLD according physician	ever treated for:	
	wheezing	shortness of breath	cough and sputum		asthma	emphysema or chr.bronchitis
Heavy metals	0.49	0.77	1.58	0.67	-[1]	1.23
Organic dust	0.99	0.77	2.10#	1.51	0.24	2.01*
Mineral dust	1.51	0.45	1.72	1.40	0.51	1.00
Fumes	1.93#	1.32	1.00	-[1]	-[1]	0.88
Organic solvents	1.17	1.65	2.09	1.72	0.64	0.71
Adhesives	0.55	0.56	2.46#	1.19	0.62	1.14
Paints	2.27#	1.97	3.83**	3.32**	0.62	1.64
Cold	0.88	1.97	0.69	0.58	1.67	0.71
Heat	0.82	1.30	1.52	2.27#	-[1]	0.84
Working outdoors	1.82*	2.56***	1.40	1.62	1.11	1.35
Contact animals	1.17	-[1]	0.55	1.04	-[1]	1.28
Contact public	0.82	0.16*	0.61	0.96	0.82	1.12
at least one exposure[2]	1.37#	2.33*	2.18*	1.55#	0.57#	1.31
[3]	1.25	2.23*	2.01*	1.46	0.57#	1.30
exposure to dusts fumes and/or gases[2]	1.20	1.26	2.66***	1.37	0.33*	1.34
[3]	1.07	1.23	1.78**	1.48	0.35*	1.30

$0.05 \leq p < 0.10$
* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$
[1] the maximum likelihood estimation procedure did not result in stable regression coefficients because the cell for exposed persons with the 'disease' was empty
[2] unadjusted for SES
[3] also adjusted for SES

The variable 'ever treated for asthma', formed a clear exception and generally had odds ratios smaller than one for all but two of the exposure variables. For instance the odds ratio for an 'exposure to dust, fumes and/or gases' with 'ever treated for asthma' was 0.33 ($p<0.05$), and 0.35 ($p<0.05$) after adjustment for SES. Therefore an analysis was performed in which all persons who had been 'ever treated for asthma', were excluded (table 6.8). Although persons who were treated for asthma were excluded, still a number of persons showed symptoms like wheezing. Contact with the public showed the only significant negative relationship with most of the dependent variables. A multivariate model in which all the specific exposures which contributed significantly to the models were tested at the same time did not change the overall picture. The exposure to paint and organic solvents could not be studied in the same model because the two variables were very closely related. The variable which represented the exposure to dust, fumes and/or gases contributed more clearly to the model then the variable which represented any other

occupational exposure according to the job exposure matrix. No significant interactions between occupational exposures and smoking habits were found.

Table 6.8. Relationship between respiratory symptoms, CNSLD diagnosis and treatment and specific exposures adjusted for smoking habits and age, expressed as odds ratios, after exclusion of the persons who ever have been treated for asthma (n=677)

exposure	symptoms			CNSLD according physician	ever treated for: emphysema or chr. bronchitis
	wheezing	shortness of breath	cough and sputum		
Heavy metals	0.58	0.91	1.75	1.04	1.65
Organic dust	1.24	0.89	2.36*	2.46*	2.66**
Mineral dust	1.27	1.35	2.45#	2.23	1.38
Fumes	2.05	1.65	1.82	-[1]	1.12
Organic solvents	1.38	1.62	1.90	2.72#	0.82
Adhesives	0.67	0.66	2.80*	1.93	1.55
Paint	3.06#	2.51	4.53**	6.17**	2.41#
Cold	0.76	1.32	0.82	-[1]	0.30
Heat	1.01	1.52	1.72	3.70*	1.10
Working outdoors	1.90*	2.32*	1.68	2.41*	1.55
Contact animals	1.38	0.58	1.57	1.85	2.08
Contact public	0.64	0.21*	0.57	0.64	1.12
at least one exposure[2]	1.25	1.14	2.61**	2.01*	1.57*
[3]	1.15	1.08	2.51*	1.79*	1.49#
exposure to dusts fumes and/or gases[2]	1.52#	1.27	3.13***	2.61**	1.86**
[3]	1.38	1.22	3.13***	2.41**	1.75*

0.05≤p<0.10
* p<0.05
** p<0.01
*** p<0.001
[1] the maximum likelihood estimation procedure did not result in stable regression coefficients because the cell for exposed persons with the 'disease' was empty
[2] unadjusted for SES
[3] also adjusted for SES

6.5. Discussion

The prevalence of shortness of breath, cough, sputum and wheezing was comparable or slightly higher than found in other studies (Krzyzanowski & Kauffmann, 1986, 1988; Korn et al., 1987; Lebowitz, 1982). This is probably due to the high age of the population involved, the background prevalence of symptoms attributable to other diseases, and the very high number of persons who had ever smoked during their lifetime (91%). During the year before the study, 46% of the population was still smoking cigarettes, cigars or pipe tobacco.

Age was generally not significantly related to any of the dependent

variables, because the population was too homogeneous with regard to their age or because selection, caused by a relatively high mortality due to high age had occurred. Pack years of cigarettes smoked was positively and significantly related to most of the dependent variables, except 'ever treated for asthma'. Persons who had stopped smoking in the year preceding the survey, had more CNSLD symptoms like 'shortness of breath', and 'CNSLD diagnosed by the physician'. Also more persons who had stopped smoking in the preceding year were at some time treated for bronchitis. On the contrary, of the persons who stopped smoking in the year preceding the study fewer complained about cough and sputum. It is possible that the first finding reflects the effect of CNSLD symptoms on smoking habits. Smokers with respiratory symptoms stop smoking as a result of a doctors advise based on signs pointing to the development of a chronic airway disease or as a result of their own judgment. This phenomenon was also found by other investigators (Krzyzanowski & Kauffmann, 1986, 1988). Cough and sputum may reflect more acute symptoms related to smoking which do not necessarily lead to a change in smoking habits. There was a clear trend in the odds ratios with the socio-economic status even after adjustment for smoking habits. The lower the socio-economic status the higher the odds ratio, which is in agreement with the results of the PAARC study (Krzyzanowski & Kauffmann, 1986, 1988). An important finding is the absence of a relationship between SES and the dependent variable 'ever treated for asthma'. This makes it probable that the prevalence of asthma is not related to the socio-economic status.

'Blue collar' workers had a higher prevalence for several of the respiratory symptoms and the diagnosis by the physician than 'white collar' workers. Agricultural workers, in particular seemed to have a high prevalence of CNSLD according to the diagnosis of the physician, and also a higher prevalence for wheezing and/or asthma. More agricultural workers were at sometime treated for chronic bronchitis or emphysema than controls. This is in agreement with a recent survey among a representative sample of Dutch agricultural workers (Biersteker et al., 1984). Painters had a comparable elevation of the prevalence for most of the respiratory symptoms. The information about the sector of industry and profession revealed that some of the painters were spray painters.

The specific exposures included exposure to fume, organic dust, paint, adhesives, heat and outdoor work. Most of the specific exposures were negatively, although not statistically significant, related to a previous treatment for asthma. A separate analysis for the population with the exclusion of persons who had been treated for asthma revealed that the existing trends for the exposure to organic dust, paint and working outdoors showed relatively more odds ratios larger than one then in the analysis with the whole population. The specific exposures were strongest related to cough and sputum, the CNSLD diagnosis of the physician and previous treatments for bronchitis and/or emphysema. The absence of a relationship of the occupational exposures with 'ever being treated for asthma' might therefore reflect a selection effect. Persons with some form of asthma will probably try to avoid an occupation with an occupational exposure which can enhance their symptoms. Or their general practitioner advises against an occupation in a profession with an occupational exposure or an occupation demanding a strong physical constitution.

The relationships with the exposure to paint, and to a lesser extent the relationship with organic solvents and adhesives, were not found before. The multivariate analysis showed that these relations are independent of the other occupational exposures like dust exposure. The relationship between the variable 'ever treated for chronic bronchitis or emphysema' and organic dust, seems to be a strong one. In other studies similar findings were reported. In a case-control study with emphysema patients (Kjuus et al., 1981) and a registration based mortality study among grain workers and millers relationships between organic dust en emphysema were found (Milham, 1976). Results of these studies suggest that organic dust is an important factor in the development of CNSLD.

The odds ratios for the exposure characterized as blue/white collar worker, the longest performed occupations, and existence or absence of an occupational exposure according to the matrix, were comparable to those found in other studies (Krzyzanowski & Kauffmann, 1986, 1988; Korn et al., 1987). Differences between the result of the Zutphen Study and other studies became evident after the exclusion of the persons who were previously treated for asthma. In the present study the strongest rela-

tionships were found when the analysis was based on a breakdown for the occupation. The occupational exposures generated with the job exposure matrix gave additional information about the relationship between CNSLD and specific exposures. This partially reflects earlier experiences with the use of job exposure matrices in occupational studies (Pannett et al., 1985; Hoar, 1983). Also flaws were detected in the use of the job exposure matrix. Several of the generated exposures were inappropriate for some of the occupations in the Netherlands. Researchers should therefore be careful to use matrices from other countries, especially if there are differences in industrial development. The differences in behavior for the characterisations of the exposure is probably related to differences in specificity and perhaps the presence of misclassification of the exposure. The grading as no, low and high exposure did not result in the detection of exposure-response relationships for most of the dependent variables, a problem which was already discussed by Hoar (1983) and Kromhout et al. (1987).

The population used in this study was too small to come to definite conclusions about exposure-response relationships. However, new evidence was obtained that several occupations and occupational exposures were related to respiratory symptoms, and other measures of respiratory illness like the CNSLD diagnosis by a physician and treatment for bronchitis and/or emphysema. These results are difficult to generalize in terms of population attributable risks related to occupational exposures. The study population was at high age and survivor effects have occurred. Therefore, an analysis of the longitudinal information of the Zutphen Study will also be undertaken.

6.6. Acknowledgments

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7. OCCUPATIONAL EXPOSURE AND 25-YEAR INCIDENCE RATE OF NON-SPECIFIC LUNG DISEASE - The Zutphen Study[1]

7.1. Summary

Information gathered in the 'Zutphen Study', the Dutch contribution to the Seven Countries Study that started in the sixties, was used for the present study. 878 men participated in a physical examination in 1960 and they were followed for twenty five years till July 1, 1985. During this follow-up, their morbidity status was verified regularly. With this information the occurrence of CNSLD at a specific time was coded by one physician, using strict criteria.

Occupation in 1960 was coded and used to generate specific occupational exposures with a Job Exposure Matrix. Because the exact time of diagnosis of CNSLD was known, Incidence Densities could be calculated. For 804 men a complete set of data was available. A Poisson regression analysis was used to analyse the relationships between the Incidence Density and independent variables like age, calendar period, occupation and specific occupational exposure. Blue collar workers had a significantly elevated Incidence Density Ratio (IDR) compared to white collar workers (1.82, 95% confidence limits: 1.35, 2.46). Subgroups of blue collar workers, wood and paper workers, textile workers and tailors, construction workers and transport workers had significantly elevated IDRs also. Thirty percent of the population had at least one exposure to dusts, fumes or gases in their occupation and they had a significantly elevated IDR of 1.4 compared to non-exposed workers (95% confidence limits: 1.07, 1.85). These results are in concordance with a previous cross-sectional analysis of a sample of the Zutphen population and confirm the relationship between occupational exposures and CNSLD incidence.

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[1] Submitted. D. Heederik, H. Kromhout, J. Burema, K. Biersteker & D. Kromhout. Occupational exposure and 25-year incidence rate of non-specific lung disease - The Zutphen Study

7.2. Introduction

Cross-sectional population surveys often show a positive relationship between occupational exposures to dust, fumes and gases and symptoms of Chronic Non-Specific Lung Disease (CNSLD) (Heederik et al., 1989; Krzyzanowski & Kauffmann, 1986, 1988; Krzyzanowski et al., 1988; Korn et al., 1987; Lebowitz, 1977). These studies point to an important role of occupational exposures, independent of smoking, in the development of CNSLD. Longitudinal information on the incidence of CNSLD in open populations in relation with occupational exposures has never been reported and most studies are restricted to the analyses of lung function data (Kauffmann et al., 1979; Kauffmann et al., 1982; Krzyzanowski & Kauffmann, 1986, 1988; Krzyzanowski et al., 1988). There is a need for further elucidation of the role of occupational exposures in the development of CNSLD.

The majority of longitudinal studies has so far been carried out in closed occupational populations or so-called occupational groups. For instance, the British cohort studies among miners, undertaken since the fifties are well known and have collected important evidence about the role of exposure to coal dust in the development of pneumoconiosis and chronic bronchitis (Soutar, 1986). Some researchers argue, however, that for various reasons, like the presence of a healthy worker effect, the magnitude of the relative risk for developing CNSLD due to occupational exposures cannot be estimated correctly on the basis of occupational group studies (Morgan, 1986; Parkes, 1982). For the present study, information on occupational groups, occupational exposures and the incidence of CNSLD as collected in the Zutphen Study was used, in order to test the hypothesis that occupational exposures are related to longterm CNSLD incidence and to study the magnitude of the relative risk for development of CNSLD due to occupational exposures.

7.3. Material and methods

7.3.1. Subjects

Since 1960, a longitudinal investigation of risk factors for chronic diseases has been carried out among middle-aged men from the town of Zutphen in The Netherlands (Keys et al., 1967; Kromhout et al., 1982). The Zutphen Study is the Dutch contribution to the Seven Countries Study. Zutphen is an old industrial town situated in the east of the Netherlands. In 1960 it had 25,000 inhabitants. A random sample of 1,088 men was selected; all were born between 1900 and 1919 and had lived in Zutphen for at least five years. Of the 1,088 invited men, 878 aged 40 to 59 took part in the medical examination. Risk factors like smoking were measured according to the Seven Countries Study protocol (Keys et al., 1967). The information available on current cigarette, cigar and pipe tobacco consumption was used to construct eight smoking categories. Three categories were defined for never-smokers, cigar and pipe smokers, and for ex-smokers. In addition, five categories were defined for current cigarette smokers.

7.3.2. Questionnaire

During the 1960 survey, information about occupation was asked in an open question as part of a dietary survey. The occupational data were coded in 1989 according to the British Registrar General's 1968 classification of industries and the 1966 classification of occupations by two of the authors (D. Heederik, H. Kromhout) (GRO, 1966; CSO, 1968). If the name of a specific factory or company was mentioned, additional information was gathered to confirm the classification of this industry from Occupational Health Services in the region, the Chambers of Commerce of Zutphen and Arnhem and other local authorities. By this procedure more than 90% of the factories and companies mentioned could be traced. Coding was done by both authors independently. Codes were only accepted if there was agreement, or if agreement could be reached after comparison of the codes, followed by recoding. Consistency of codes was investigated by sorting for code of industry and occupation and subse-

quently judging homogeneity of subclasses of industry and occupation. If inconsistencies were found the occupations involved were recoded again. This procedure was repeated approximately 15 times.

On the basis of the information on occupation and industry it was possible to estimate specific occupational exposures with the British Job Exposure Matrix (JEM) as developed by Pannett et al. (1985). The specific exposures generated with the JEM were graded as no exposure, low level and high level exposure. Only high exposure was used as evidence for occupational exposure in the present analysis. In the JEM a distinction was made between exposures from World War II till 1950 and from 1950 onwards. For the analysis presented in this paper the latter exposure estimates were used. The 50 exposures were grouped into twelve categories with more or less qualitatively similar exposures; e.g. exposure to fumes, organic dust, mineral dust, heavy metals, organic solvents, heat, cold, working outdoors, adhesives, paint, frequent contact with animals and frequent contact with public. The exact grouping procedures have been described elsewhere (Heederik et al., 1989, Chapter 6).

7.3.3. Medical examination

Between 1960 and 1973 all subjects were medically examined annually. Subsequently, they were reexamined in the next survey in 1977 and 1978. The last medical examination was carried out in 1985. In 1980 and 1982 a questionnaire was administered concerning their health status. Information about the mentioned morbidity status was verified by contacting the general practitioner of the participant. The vital status of the 878 men was verified after 25 years of follow-up. Each person had a complete follow-up. During the 25 years of follow-up 430 men died. Information about the cause of death was obtained from the death certificate, and from the hospital and/or the general practitioner.
One physician, using strict criteria, coded all information about morbidity and mortality during the 25 years of follow-up. The diagnosis of CNSLD was based on the following criteria:
- episodes of respiratory symptoms such as regular cough and phlegm for

longer than three months and episodes of wheezing and shortness of breath reported to the survey-physician, or:
- diagnosis of CNSLD, including asthma, chronic bronchitis or emphysema by a clinical specialist.

CNSLD incidence was defined as the first year in which the diagnosis CNSLD was established.

7.3.4. Statistical analysis

Descriptive statistics were computed using Statistical Analysis Software (SAS) program packages on a VAX computer system. Since the year in which CNSLD was diagnosed was known for each person, the approximate incidence density could be calculated as the number of persons with diagnosed CNSLD in a specific stratum divided by the total number of person years contributed by the population to that particular stratum. A person contributed person years of observation to a stratum until CNSLD was diagnosed or until death occurred. The person years of observation that each person contributed to the various subgroups were calculated on an Olivetti M28 personal computer with the algorithm developed and described by Coleman et al. (1986).

Initially a stratified analysis of the incidence density was conducted. The variables which were found to be associated with CNSLD in the classical stratified analyses were also tested in multivariate models, by using the statistical software package GLIM (Baker & Nelder, 1978), also on a personal computer. A Poisson regression analysis was conducted using maximum likelihood estimates. A full description of the Poisson regression analyses is given in the appendix of this chapter. Regression coefficients for each category of occupation or specific exposure, compared to a reference group, were calculated after correction for confounding variables. The reference group was defined as white collar workers.

The fit of the model was judged by inspection of the observed numbers of persons per cell and the predicted numbers of persons per cell. Residuals were calculated as a means to detect serious deviations between the

observed and the predicted number of cases per cell. The procedures used in GLIM to perform Poisson regression analysis have recently been described in the literature (Breslow & Day, 1987; Wacholder, 1986).

7.4. Results

Of the 878 persons who participated in the 1960 medical examination and for whom a complete follow-up record was available, 58 had experienced CNSLD according to the criteria defined earlier, before the start of the study in 1960 and were excluded from this analysis. For eight persons the information concerning their occupation was too limited to classify their occupation. For eight persons the information on their occupation was missing or unreadable. These men were also excluded from the analyses. This resulted in a population of 804 persons for whom a complete data set was available.

The characteristics of this population are given in table 7.1 with a breakdown of the population into the different occupations. This resulted in eleven occupational categories. All 'white collar workers' were grouped in one broad reference category. The reference population consisted of professional workers, technical workers and artists (code 181-121) (18.6%), administrators and manager (code 172-180) (10.2%), workers in services, sports and recreation (code 154-171) (15.6%), salesmen, including shopkeepers (code 144-153) (35.1%) and clerical workers (code 139-143) (20.5%). Several subgroups of blue collar workers were too small for separate analysis and were pooled with other groups. For instance leather workers (code 062-065) were allocated to the other production workers category.

Relatively few industries were involved. More then 70% of the metal workers were employed in one metal factory where metal products like iron and copper taps and valves were produced. Most of the engineering workers were employed in a gas producing factory, the rest was involved in small repair shops. Half of the wood, paper and paper product workers were employed in four paper and board factories, and a few were involved in handling waste paper. The other half of this subgroup worked as prin-

ters in the publishing industry. The group of transport workers consisted mainly of train drivers and truck drivers who were employed by international expedition firms. The warehouse workers worked mainly in one large metal products trading firm, the publishing industry and small transport and shipping firms. Most of the industries in which the workers were employed in the sixties still operated in 1989 except for the textile industry. Most of the companies involved in textile goods manufacture disappeared during the seventies.

Table 7.1. Characteristics of 804 men aged 40-59 at start of follow-up in 1960. Breakdown into occupational codes according to the classification of occupations*

	n	%
Smoking categories		
never smoked	24	3.0
ex-smoker	142	17.7
pipe or cigar smoker only	30	3.7
< 5 cigarettes per day	86	10.6
5-9 cigarettes per day	148	18.4
10-19 cigarettes per day	288	35.8
20-29 cigarettes per day	71	8.8
≥ 30 cigarettes per day	15	1.9
Occupation		
white collar workers (139-210*)	369	45.9
blue collar workers (1-138*):	435	54.1
farmers (001-007)	30	3.7
furnace workers (014-026)	18	2.2
engineering and metal workers(027-056)	93	11.6
wood and paper workers (057-061, 085-090)	72	9.0
textile workers and tailors (066-079)	21	2.6
food processing workers (080-084)	28	3.5
other production workers(062-065, 104-116)	14	1.7
construction workers and painters (095-103)	60	7.5
transport workers (117-136)	56	7.0
warehouse workers (137-138)	43	5.3

* GRO, 1966

Table 7.2. Number of exposed persons for the various exposure categories as generated with the job exposure matrix

Exposure	n	%
1 heavy metals	28	3.5
2 organic dust	68	8.4
3 mineral dust	57	7.1
4 fumes	50	6.2
5 organic solvents	57	7.1
6 adhesives	37	4.6
7 paint	23	2.9
8 cold	43	5.3
9 heat	30	3.7
10 working outdoors	107	13.3
11 contact animals	26	3.2
12 contact public	120	14.9
At least one exposure[a]	470	58.5
Exposure to dusts, fumes or gases[b]	239	29.7

[a] exposures 1-12
[b] exposures 1-7

Table 7.2 shows the exposure information as generated with the job exposure matrix. More than half of the population had at least one occupational exposure according to the JEM, and almost 30% had an exposure to gases, fumes or dusts. The results of the simple stratified analyses are presented in table 7.3. The incidence density (ID) was specified for categories of the confounders age (five 10 year intervals), calendar period (three 10 year intervals), smoking habits (eight categories), and occupational group (eleven occupational groups). It is clear from the table that the IDs increase with increasing age, and with increasing cigarette consumption. In the multivariate Poisson regression analyses, the smoking habits were grouped into five smoking categories on the basis of the current smoking habits (category 1: non-smokers; category 2: ex-smokers, and mild cigarette smokers (< 5 cigarettes per day) and current cigar and pipe smokers; categories 3, 4 and 5: smokers with a daily consumption of respectively 5-9 10-19 and ≥ 20 cigarettes per day respectively).

Table 7.3. Number of incident CNSLD cases, person years of observation, and incidence density by age, calendar period, smoking category and occupational group

	number of cases[1]	persons years[2]	incidence density[3]
Total	224	14325	1.56
Age			
40-49	29	2055	1.41
50-59	83	5498	1.51
60-69	82	5030	1.63
70-79	27	1663	1.62
80-89	2	74	2.69
Calendar period			
1960-1969	118	7014	1.68
1970-1979	75	5331	1.41
1980-1984	31	1977	1.57
Smoking category			
never smoked	3	554	0.54
ex-smokers	36	2441	1.52
current pipe or cigar smokers	8	527	1.42
< 5 cigarettes/day	21	1558	1.35
5-9 cigarettes/day	35	2736	1.28
10-19 cigarettes/day	86	5120	1.68
20-29 cigarettes/day	27	1178	2.29
≥ 30 cigarettes/day	8	206	3.89
Occupational group			
white collar workers	80	6957	1.15
blue collar workers	144	7367	1.95
farmers	10	497	2.01
furnace workers	6	250	2.40
engineering and metal workers	25	1694	1.48
wood and paper workers	23	1200	1.92
textile workers and tailors	9	377	2.39
food processing workers	5	518	0.96
construction workers	23	879	2.62
other production workers	4	205	1.95
transport workers	24	943	2.55
warehouse workers	15	803	1.87

[1] Number of incident CNSLD cases.
[2] Person Years of observation in stratum (PY)
[3] ID Incidence Density (10^{-2} PY^{-1}) (number of CNSLD cases/PY*100)

Adjustment of the IDRs of occupation by Poisson regression yielded similar results as the crude IDRs which can be calculated by hand from table

7.3. CNSLD incidence was positively and significantly related to age and smoking. Compared to the non-smokers the following IDRs were found for the different smoking categories: pipe, cigar smokers, ex-cigarette smokers, cigarette smokers (< 5 cigarettes per day) 2.48; cigarette smokers 5-9 cigarettes per day, 2.32; 10-19 cigarettes per day, 2.75; ≥ 20 cigarettes per day, 4.48.

Table 7.4. CNSLD incidence density ratio (IDR) for occupational groups adjusted for age, calendar period, and smoking (n=804)

Occupational group	IDR	95% confidence limits LCL[a]	UCL[b]
White collar workers	1.00	-	-
Blue collar workers	1.82	1.35	2.46
White collar workers	1.00	-	-
Farmers	1.58	0.82	3.13
Furnace workers	2.07	0.89	3.06
Engineering metal workers	1.27	0.81	2.01
Wood and paper workers	1.72	1.10	3.62
Textile workers and tailors	2.37	1.48	4.80
Food processing workers	0.85	0.34	2.14
Construction workers	2.29	1.44	3.67
Other production workers	1.58	0.59	4.30
Transport workers	2.09	1.31	3.35
Warehouse workers	1.57	0.91	2.75

[a] lower confidence limit
[b] upper confidence limit

'Blue collar workers' had a significantly elevated incidence density compared to white collar workers after adjusting for age, calendar period and smoking habits (table 7.4). This difference remained significant when members of the reference group with relatively higher educated jobs (e.g. professionals, managers, academics etc.) were removed from the analysis. The IDRs slightly increased when small tradesmen and shopkeepers were removed from the reference population. Wood and paper workers, construction workers, textile workers, and transport workers had significantly elevated IDs compared to the reference group. Especially textile and construction workers had lower confidence limits greater than 1.4. The IDRs for farmers and warehouse workers were slightly elevated without reaching statistical significance. Food pro-

cessing workers were the only group with an IDR below unity.

Table 7.5. Incidence density ratios (IDR) for occupational exposures adjusted for age, calendar period, and smoking (n=804)

Exposure	IDR	95% confidence limits LCL[a]	UCL[b]
heavy metals	2.15	1.23	3.77
organic dust	1.16	0.74	2.86
mineral dust	1.58	1.01	2.49
fumes	0.76	0.42	1.42
organic solvents	1.16	0.70	1.94
adhesives	1.86	1.10	3.15
paint	0.87	0.36	2.16
cold	1.17	0.69	1.98
heat	1.03	0.50	2.09
working outdoors	1.28	0.89	1.83
contact animals	0.91	0.43	1.92
contact public	0.70	0.47	1.10
At least one exposure	1.14	0.87	1.49
Exposure to dusts, fumes, gases	1.40	1.07	1.85

[a] lower confidence limit
[b] upper confidence limit

The results of the analyses of the relationship between CNSLD incidence and specific exposures as generated with the Job Exposure Matrix are given in table 7.5. Exposures to heavy metals, mineral dust and adhesives resulted in significantly elevated IDRs. Workers with an occupational exposure to dusts, fumes or gases had a significantly elevated IDR of 1.40.

7.5. Discussion

In this prospective study the relationship between occupation and CNSLD incidence was investigated. The method used for calculation of adjusted incidence density ratios, has to our knowledge not been applied previously in an epidemiological study of CNSLD. Relative risks for various occupations and occupational exposures were calculated after adjustment for age, calendar period and smoking habits. Incidence density ratios give a more valid assessment of the contribution of occupation and

occupational exposures to the development of CNSLD than is offered by prevalence studies of CNSLD or cross-sectional studies. This approach might be applied to several studies that have been published elsewhere (Krzyzanowski et al., 1986, 1988; Korn et al., 1987).

An example of another study in which incidence figures are analysed is the Cracow Study. In the Cracow Study, the Chronic Obstructive Pulmonary Disease (COPD) cumulative incidence after thirteen years was calculated on the basis of change in lung function over the thirteen year period (Krzyzanowski et al., 1986). Persons with a lung function above 70% of a reference value at the start of the study, but with an FEV_1 lower than 65% of a reference value at the end of the study were defined as incident COPD cases. The cumulative overall COPD incidence was 8.5%, and varied from less than one percent for young non-smokers (19-30 years) up to more than twenty percent for older smokers (51-60 years). A detailed comparison with our study is impossible because of the different nature of the incidence figures used, the difference in follow-up duration, and because of the strong differences in mean age of the populations.

The morbidity status at a certain time was based on regular medical examinations and health complaints reported to the survey physician. The presence of CNSLD was coded according to strict criteria. However, because various information sources were used, and the specificity of the information changed over the years because of changing and improving diagnostic procedures, a broad definition of CNSLD had to be used. The definition of CNSLD comprised asthma, bronchitis as well as emphysema. However, because this study started at the time that participants were forty to sixty years of age and those who had experienced CNSLD before the follow-up in 1960 were excluded, some selection bias might have occurred. It is possible that among those excluded the proportion of persons with asthma, which expresses itselves generally at an early age, is relatively higher compared to the sample studied. This would probably bias the results of our study towards more strongly age-related forms of CNSLD such as bronchitis and emphysema.

The 25 year cumulative CNSLD incidence of the Zutphen Study population appeared to be relatively high, compared to the prevalence figures.

If, for comparison we consider the answers to the British Medical Research Councils questionnaire which was administered in 1965 and 1970, to the survivors of the initial Zutphen cohort, and if we only consider the persons who had cough or sputum for at least three months each year, we get the prevalence figures for cough and for sputum which are in the 2-12% range. Such prevalence figures are comparable to the experiences in other studies (Krzyzanowski & Kauffmann, 1986, 1988; Krzyzanowski et al., 1986; Korn et al., 1987).
For every 100 person years of observation, 1.5 incident CNSLD cases were observed, during a follow-up period of 25 years. The cumulative 25-year incidence for this population was 27.9% (= 224/804). The definition of CNSLD used in this study, might explain the high incidence figures. It is possible that persons who met the criteria of CNSLD and were considered as incident cases did not actually have a chronic respiratory disease, but an exacerbation of an underlying CNSLD or a higher airway infection which lasted only a limited time. The discrepancy between prevalence and incidence figures might then be explained by the presence of only a temporary period of disease followed by remission. Other studies indicate that remission is likely to occur. High CNSLD remission figures, up to 75-100% for non-smokers and 30-90% for smokers have been found in a ten year follow-up study among 659 pulp mill workers in which the MRC questionnaire was used at the beginning and end of the study period. The prevalence rose over the ten year period because of aging, as expected (Poukkula et al., 1982). Similar observations were made in a population of 2469 foundry workers who were studied for the first time between 1967 and 1969 and between 1972 and 1975 for the second time (Verfürth & Smidt, 1980).

The relationships with the confounders were as expected on the basis of experiences reported in cross-sectional studies (Kauffmann et al., 1979; Krzyzanowski & Kauffmann, 1986, 1988; Korn et al., 1987; Lebowitz, 1977a). The incidence density increased with smoking habits and age. Although calculation of Incidence Density Ratios based on longitudinal information has considerable advantages over the use of Odds Ratios as derived in the cross-sectional analyses, the Incidence Density Ratios for smoking are comparable to Odds Ratios for smoking as derived from the earlier cross-sectional analysis of the 1985 data of the Zutphen

Study and other population studies published (Krzyzanowski & Kauffmann, 1986). The Incidence Density Ratios ranged from 1.5 to 2.8 for persons with an average cigarette consumption of 10-19 cigarettes per day, up to an Incidence Density Ratio of 4.5 for the smokers who smoked more then 20 cigarettes per day.

Occupation was analysed as the occupation held in 1960. Although a person's occupation is known to change over time, of the cohort members who were still alive in 1985 less than 17% had ever changed their occupation and worked in another type of industry. For those alive in 1965 the occupation in 1965 was known. Of the initial population of 804 persons, 27 persons became disabled or had reached the age of retirement in 1965. 88 (11%) persons had changed their occupation during those five years. Of those who changed their occupation 61 (70%) belonged to the 'blue collar' population. Of these 61 persons more than half changed to lower exposed and/or physically less demanding jobs like driver of buses and coaches, and warehouse worker. From the reference "white collar" population only four persons (15%) migrated to a job which belonged to the "blue collar" population. This migration to low exposed jobs might explain the elevated CNSLD incidence among specific subgroups like warehousemen and storekeepers, because such selective processes have probably also taken place before the start of the follow-up in 1960. A total of 15 persons changed to a job which belonged to the reference population.

This cohort differed from the population which we studied in the 1985 cross-sectional analysis presented in the previous chapter. The composition of subgroups of workers differed also. However, some of the results of this follow-up study are comparable with those of the 1985 cross-sectional survey. Occupations like farmers, wood and paper workers and construction workers which showed elevated odds ratios with respiratory symptoms or a CNSLD diagnosis by the physician in the 1985 survey had elevated IDRs in this follow-up study also. A clear elevation of the CNSLD incidence was found for textile workers and tailors in this study which was not found in the cross-sectional analysis. The small numbers in this subgroup in both studies and the disappearance of the textile industry during the 70s which resulted in a spread of the textile

workers over other occupations might explain the differences with the cross-sectional analyses at the end of follow-up of this cohort.

The relationships between the specific exposures and CNSLD incidence were less convincing. Most of the IDRs were greater than one, but only the IDRs for exposure to heavy metals, mineral dusts and adhesives differed significantly from unity. A detailed analysis in which IDRs for the different heavy metal exposures were calculated, showed that most of the persons exposed to heavy metals had a chromium exposure. In an analysis for each heavy metal separately it became clear that the significantly elevated IDR for heavy metals was attributable to occupational chromium exposure. Most of these exposed persons worked in the construction industry. The relationship found between chromium exposure and CNSLD incidence might therefore reflect a specific dust exposure in a specific sector of industry only. In general this means that great care should be given to the interpretation of results of an analysis with exposures derived from a job exposure matrix. The IDR for persons who had an exposure to dusts, fumes or gases was clearly elevated which was in line with the cross-sectional analyses of the 1985 study.

It is unlikely that the elevated Incidence Density Ratios for specific occupations are caused by a confounding effect of smoking. The elevations of the Incidence Densities for specific occupations as observed in the classical stratified analysis remained in the multivariate analysis after correction for smoking habits. This could be predicted before hand, because the smoking habits did not differ significantly between the occupational categories. The results of the study show that IDRs for specific occupations and some occupational exposures were significantly raised independently of the smoking habits. This suggests that specific occupations contribute to the development of CNSLD. The elevation of the IDR is of the same order of magnitude as the elevation for smokers in the average smoking category.

In the present study more than half of the population was a blue collar worker, 57% of the population had at least one occupational exposure and more than 25% had at least one occupational exposure to dust, fumes, gases or solvents. The population at risk in this study appears to be a

large proportion of the total male population. However, more recently occupationally exposed populations probably differ from this population, although quantitative information on occupational exposures lacks and detailed comparisons with current exposures are impossible because changes in industry have occurred. As mentioned before, the textile industry is at this moment a small proportion of the total industry in the Netherlands, while during the sixties other industries like the chemical industry developed and expanded strongly. It is noteworthy that a survey undertaken, in 1987 among 6300 Dutch males and females in three cities showed that the proportion of exposed persons of the population is still comparable to that of the older cohort in Zutphen (Kromhout, 1990).
A generalisation of these findings is impossible because of reasons discussed above, but these results emphasise the need for further epidemiological studies of the contribution of occupational exposures to the development of CNSLD.

7.6. Acknowledgements

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8.2. Introduction

The relationships between total mortality, cause specific mortality and explanatory variables such as lung function, respiratory symptoms and smoking habits have been studied during the last decade in large community based studies and occupational group studies (Higgins & Keller, 1970; Kannel et al., 1974; Todd et al., 1978; Beaty et al., 1982, 1985; Peto et al., 1983; Annesi & Kauffmann, 1986; Krzyzanowski & Wysocki, 1986; Carpenter et al., 1989; Ebi-Kryston, 1989; Ebi-Kryston et al., 1989; Sorlie et al., 1989; Vollmer et al., 1989). For most studies, the aims were to establish the predictive value of lung function measurements or respiratory symptoms for various outcomes like total mortality or cause specific mortality e.g. respiratory diseases or ischemic heart disease. Few of those studies focussed on the role of occupational exposures on total mortality or cause specific mortality, and results have been conflicting (Morgan, 1986; Kauffmann & Annesi, 1987; Bates, 1987; Franzblau, 1987). Foxman et.al. (1986) found no differences in total mortality and chronic bronchitis mortality between several populations of dust exposed workers like miners, ex-miners, foundry and chemical workers, and workers not exposed to dust after twenty years of follow-up. They found a consistent effect of smoking and lung function on total mortality and mortality from non-malignant respiratory diseases. In a population of 1061 working men an effect of dust exposure, on total mortality was found after 22 years of follow-up adjusted for age, FEV_1/H^3, phlegm and smoking habits at an initial survey (Kauffmann et al., 1987). The exposure status was established by interview. In this follow-up study the estimated risk ratio of an occupational dust exposure was 1.3. Cause specific data on mortality were not presented.

In the present study we analysed the effects of occupation, lung function and smoking habits on CNSLD incidence, CNSLD mortality, and total mortality in the Zutphen Study, in order to provide further evidence on the relationships between these variables.

8.3. Material and methods

8.3.1. Subjects

Since 1960, a longitudinal investigation of risk factors for chronic diseases has been carried out among middle aged men from the town of Zutphen in The Netherlands. The Zutphen Study is the Dutch contribution to the Seven Countries Study (Keys et al., 1967). Zutphen is an old industrial town situated in the east of the Netherlands. In 1960 it had 25,000 inhabitants. A random sample of 1,088 men was selected; all were born between 1900 and 1919 and had lived in Zutphen for at least five years. Of the 1,088 invited men, 878 aged 40 to 59 took part in the medical examination. Risk factors like smoking habits were assessed according to the Seven Countries Study protocol. The information available on current and past cigarette consumption was used to calculate the pack years of cigarettes smoked. Pack years were calculated as the product of the number of years smoked and the number of packs of cigarettes smoked per day. A package of cigarettes was assumed to contain 25 cigarettes. For the analysis presented here, follow-up data since 1965 were used, because in 1965 lung function was measured in the men still participating in the study.

8.3.2. Questionnaire

During the 1960 and 1965 surveys, information about occupation was asked in an open question as part of a dietary survey. The occupation was coded in 1989 according to the British Central Statistical Offices 1968 classification of industries (CSO, 1968) and the Registrar General's 1966 classification of occupations (GRO, 1966). If the name of a specific factory or company was mentioned, additional information was gathered from Occupational Health Services in the region, the Chamber of Commerce of Zutphen and Arnhem and other local authorities to confirm the classification of this industry. By this procedure more than 90% of the factories and companies mentioned could be traced. Coding was done by two authors independently (D.Heederik, H. Kromhout). Codes were only accepted if there was agreement, or if agreement could be reached after

comparison of the codes, followed by recoding. Detailed information about the jobs performed and types of industries involved can be found in chapter 7. For those persons who retired between 1960 and 1965 (n=26) the job in 1960 was used for the analysis.

8.3.3. Medical examination

Between 1960 and 1973 all subjects were medically examined annually. Subsequently, they were reexamined in the next survey in 1977 and 1978. The last medical examination was carried out in 1985. In 1980 and 1982 a questionnaire was administered concerning their health status. Information about the mentioned morbidity status was verified by contacting the general practitioner of the participant. The vital status of the 878 men was verified after 25 years of follow-up. Each person had a complete follow-up till July 1, 1985. During the years of follow-up 430 men died. Information about the cause of death was obtained from the death certificate, and from the hospital and/or the general practitioner. The information on the causes of death on the death certificate was compared with the morbidity history of the participant. When no differences were observed the causes of death on the death certificate were used for further analysis. When there was no agreement between the causes of death on the death certificate and the morbidity history, the case was discussed by the survey physician and the physician of the Central Bureau of Statistics (CBS) and a final decision was reached. The CBS is responsible for coding of the death certificates in The Netherlands. The causes of death were coded according to the 8th revision of the International Classification of Diseases (ICD, 1969). The cause of death was considered to be due to CNSLD if ICD Codes 490.0 to 496.0 were mentioned on the death certificate. For the analysis of CNSLD mortality data, we considered not only the primary cause of death, but also the other causes of death registered on the death certificate (secondary, and tertiary causes). One physician, using strict criteria, coded all the information about morbidity during the 25 years of follow-up. The diagnosis of CNSLD was based on the following criteria:

- episodes of respiratory symptoms such as regular cough and phlegm for longer than three months and episodes of wheezing and shortness of

breath reported to the survey-physician, or:
- diagnosis of CNSLD, including asthma, chronic bronchitis or emphysema by a clinical specialist.

In those who attended the 1965 survey, lung function was measured by spirometry. Vital Capacity (VC) and Forced Expiratory Volume in one second (FEV_1) were measured with a Godart Pulmotest by one technician. The procedures followed are described in detail by Timmers (1969). Measured values were corrected to BTPS. The Vital Capacity was measured by three maximal inhalations. The highest Vital Capacity was used for calculations presented here. The Forced Expiratory Volume in one second was established by three attempts. The two highest FEV_1 values should not differ more than 50 ml. If the difference was larger than 50 ml. one extra FEV_1 had to be produced. The mean of the two closest values was used for further calculations. The selected FEV_1 divided by the VC was calculated (FEV_1/ VC%) and used for further analysis also.

8.3.4. Statistical analysis

All analyses were performed using Statistical Analysis System Software (SAS) packages on a VAX computer system. The relationship between occupation and lung function was studied after allowing for smoking habits (pack years, and a dummy variable for cigar and/or pipe) and standing height and age in a multivariate regression analysis. Lung function of "blue collar workers" (occupational code 1-138) was compared to lung function of "white collar workers" (occupational code 139-210), and also subgroups of blue collar workers were studied.

The 20-year survival of the population was initially studied univariately by Kaplan-Meier curves, produced with Proc PHGLM. For the analysis of CNSLD mortality deaths from other causes were treated, when they occurred, as events that made a further follow-up impossible ('censoring events'). Differences between the Kaplan-Meier curves were tested for statistical significance with a log-rank test in Proc LIFETEST. For this analysis smoking habits were categorised in three subgroups of equal size for duration of smoking habits up to 1965 (duration of smoking

categories: category 1: mean=16.9 s.d.=11.7 (n=210); category 2: mean= 33.8 s.d.=1.7 (n=220); category 3: mean=42.1 s.d.=3.8 (n=238). Pack years smoked up to 1965 was also stratified into three equally sized categories (pack years smoking categories: category 1: mean= 5.2 s.d.=4.1 (n=269); category 2: mean= 8.4 s.d.=4.0 (n=242); category 3: mean=33.1 s.d.=9.1 (n=157)). For each subject an age and height specific reference value of his lung function was calculated from a regression model with age and standing height as predictors. Departures of observed values from the predicted values were calculated (residuals): lung function$_{measured}$ - lung function$_{predicted}$, and used for further analysis. Kaplan-Meier curves were produced for lung function by comparing the group with subjects who had lung function residuals >0 (above average), those with a negative residual between 0 and one standard deviation of the distribution of the residuals, those with a negative residual between one standard and two standard deviations, and those with a negative residual of a magnitude larger than two times the standard deviation of the distribution of the residuals. For the VC the cut-off points according to this definition were 0, -640 and -1280 ml. For the FEV_1 and FEV_1/VC% the cut-off points were respectively 0, -620 and -1240 ml and 0, -10% and -20%.

To analyse the relationship between survival and several independent variables simultaneously a proportional hazard analysis (Cox, 1972) was conducted also by using the PHGLM procedure in SAS. This model postulates that the ratios for any risk of death are constant over time. Assumptions of the proportional hazards model were checked by standard procedures such as visual inspection of survival and loglog curves for various combinations of independent variables. If any variable violated the proportional hazard assumption, a stratified analysis was carried out within Proc PHGLM. In such a stratified analysis the log-likelihood function is calculated separately for each group, and component likelihoods are summed over the groups to yield an overall likelihood which is maximised for parameter estimation. For this specific situation, the Proc PHGLM obtains a generalised form of Mantel-Haenszel test statistics. The ratio of a regression coefficient divided by its standard error was used for testing whether the coefficient differed statistically significant from zero. Hazard ratios were calculated from the

regression coefficients by taking the antilog of the regression coefficient. Only two-tailed probabilities were used to test statistical significance.

8.4. Results

Table 8.1 gives the characteristics of the population of the Zutphen Study in 1965. Of the 878 men who participated in the physical examination in 1960, 40 had died before January 1, 1965, for 159 no lung function data were available, and for 11 the information on their occupation was insufficient to code. Therefore a group of 668 remained for further analyses. Persons who got CNSLD before 1965 were excluded from the analysis of CNSLD incidence study. For this particular analysis a group of 587 persons remained.

The results of the regression analyses of lung function variables on smoking habits, age, standing height and occupation are given in table 8.2. Age, standing height and pack years smoked contributed significantly to most of the regression models of VC, FEV_1 and $FEV_1/VC\%$.

Table 8.1. Characteristics of 668 men of the Zutphen population in 1965. Break down to occupational codes according to the classification of occupations[1]

	mean	s.d.
Age (year)	54.8	12.6
Standing Height (cm)	173.9	6.5
VC (l)	4.25	0.77
FEV_1 (l)	2.96	0.70
Pack Years cigarettes (pack/day.years)	16.5	12.2
Number of years smoked (year)	31.4	12.6
	n	%
Smoking categories		
non cigarette smokers	51	7.6
ex cigarette smokers	214	32.0
current cigarette smoker		
< 5 cigarettes per day	49	7.3
5-9 cigarettes per day	76	11.4
10-19 cigarettes per day	173	25.9
20-29 cigarettes per day	92	13.8
≥ 30 cigarettes per day	13	2.0
current cigar or pipe smokers (0/1)	379	56.7
Occupation		
white collar workers (139-210[1])	322	48.2
blue collar workers (1-138[1])	346	51.8
farmers (001-007[1])	23	3.4
furnace workers (014-026)	15	2.2
engineering metal workers (027-056)	72	10.8
wood and paper workers (057-061, 085-090)	59	8.8
textile workers and tailors (066-079)	16	2.4
food processing workers (080-084)	21	3.1
construction workers (095-103)	43	6.7
other production workers (062-065, 104-116)	10	1.5
transport workers (117-136)	47	7.0
warehouse workers (137-138)	38	5.7

[1] GRO, 1966

Table 8.2. Regression coefficients for age, standing height, pack years of cigarettes smoked, and occupational group in regression of models for VC, FEV_1 and FEV_1/VC% in 668 men of the Zutphen Study

	VC (ml)		FEV_1(ml)		FEV_1/VC%	
Adjusted R square (%)	31		24		9	
	$\hat{\beta}$[1]	SE[2]	$\hat{\beta}$	SE	$\hat{\beta}$	SE
Constant	-3.4***	0.8	-3.9***	0.7	1.1***	0.1
Age (years)	-31.8***	4.6	-38.3***	4.4	-0.4***	0.1
Standing height (cm)	54.7***	3.9	32.5***	3.7	-0.1*	0.06
Pack years cigarettes	-5.5***	2.1	-7.5***	2.0	-0.1**	0.03
White collar workers	-		-		-	
Blue collar workers	24	50	-159***	47	-3.4***	0.7
White collar workers	-		-		-	
Farmers	-228#	138	-6	131	-4.3*	2.2
Furnace workers	-94	168	-162	160	-1.1	2.6
Engineering and metal workers	82	83	-92	80	-2.9*	1.3
Wood and paper workers	5	91	-89	88	-2.2	1.4
Textile workers and tailors	-317#	163	-385*	156	-4.5#	2.6
Food processing workers	-117	145	-96	138	0.3	2.3
Construction workers	-35	102	-200*	97	-4.8*	1.6
Other production workers	-68	230	118	220	5.2	3.6
Transport workers	-183#	99	-291*	95	-4.4*	1.6
Warehouse workers	101	109	-151	104	-4.4*	1.7

$0.10 > p \geq 0.05$
* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

[1] $\hat{\beta}$ regression coefficient

[2] SE standard error of $\hat{\beta}$

Blue collar workers had a significantly decreased FEV_1 (-159 ml, $p<0.05$) and FEV_1/VC% (-3.4%, $p<0.05$) compared to white collar workers after allowing for smoking habits, while the VC did not differ significantly between the two groups. For several subgroups of blue collar workers lung function was also statistically significantly lower. Farmers, textile workers and transport workers had a borderline significantly lowered VC. Textile workers, construction workers and transport workers had a significantly lower FEV_1. "Blue collar workers" who had changed

their occupation between 1960 and 1965 (n=78) had no significantly different lung function from "white or blue collar workers".

Table 8.3. Age, smoking habits, CNSLD mortality and total mortality of white and blue collar populations in the Zutphen Study in 1965

	White Collar Workers (n = 322)		Blue Collar Workers (n=346)	
	Mean	s.d.	Mean	s.d.
age (year)	54.2	5.4	54.8	5.4
pack years cigarettes (pack/day.year)	16.3	12.3	16.5	12.2
number of years smoked	29.9	12.3	31.4	12.6
	n	%	n	%
non cigarette smokers	25	7.8	26	7.5
ex cigarette smokers	121	37.6	93	26.9
current cigarette smoker				
< 5 cigarettes per day	19	5.9	30	8.7
5-9 cigarettes per day	30	9.3	46	13.3
10-19 cigarettes per day	70	21.7	103	29.8
20-29 cigarettes per day	48	14.9	44	12.7
≥ 30 cigarettes per day	9	2.8	4	1.2
current pipe or cigar smokers	204	63.4	175	50.6
total mortality	134	41.6	162	46.8
CNSLD mortality	12	3.7	23	6.6
CNSLD incidence	54	18.3 (n=295)*	86	29.5 (n=292)*

* total population size is smaller because those who got CNSLD between 1960 and 1965 were excluded from the analysis

Because of the relatively small size of subpopulations of blue collar workers, only a distinction between blue collar workers and white collar workers and larger subgroups of blue collar workers was made for the survival analysis. Total mortality, CNSLD incidence and mortality for both occupational categories are given in table 8.3. Of those who died from CNSLD only one died because of asthma. As can be seen from this table, blue collar workers smoked somewhat longer than white collar

workers, but this difference was not statistically significant (t-test; $p>0.50$).

Kaplan-Meier curves for total mortality with the independent variables can be found in the appendix of chapter 8. The proportional hazard analysis revealed that pack years of cigarettes smoked was a better predictor for total mortality than the number of years smoked up to 1965. Cigar and/or pipe smoking did not contribute to any of the models for total mortality ($p>0.80$). These variables were therefore omitted in further models. Age in 1965 was highly significantly related to total mortality. Therefore, all further models tested contained the variables age and pack years of cigarettes smoked.

In table 8.4 results of the proportional hazards model are presented with different combinations of variables. Age and pack years of cigarettes were always included as confounders. Those persons who had a blue collar job in 1965 showed a slightly increased total mortality, but the difference with white collar workers was not statistically significant. The addition of three dummy variables for four categories of lung function residues showed that the non-significant effect of a blue collar job diminishes further (models 2,3 and 4 compared to model 1). As can be seen, a reduced lung function is a strong predictor of total mortality. Although all lung function variables appeared to be strong predictors of total mortality, the FEV_1 seems to be the strongest predictor closely followed by the $FEV_1/VC\%$ (model 3 compared to models 2 and 4).

Table 8.4. Results of the multivariate proportional hazard analysis for total mortality for 668 men in the Zutphen population

		$\hat{\beta}$[1]	SE[2]	HR[3]	95% confidence limits LCL[4]	UCL[5]
Model 1.	Age (year)	0.094	0.011	2.56[6]	2.06	3.18
	Pack Years (pack.day^{-1}.year)	0.011	0.004	1.12[7]	1.02	1.22
	Blue vs. White collar workers	0.061	0.12	1.06	0.84	1.34
Model 2.	Age (year)	0.092	0.011	2.51[6]	2.02	3.11
	Pack Years (pack day^{-1}.year)	0.010	0.004	1.11[7]	1.02	1.20
	Blue vs. White collar workers	0.061	0.12	1.06	0.84	1.34
	$VC_{residual}$ (0 to -640 ml)	0.01	0.13	1.01	0.78	1.30
	$VC_{residual}$ (-640 to -1280 ml)	0.35	0.18	1.42	0.99	2.02
	$VC_{residual}$ (< -1280 ml)	0.55	0.26	1.73	1.04	2.89
Model 3.	Age (year)	0.095	0.011	2.59[6]	2.08	3.21
	Pack Years (pack day^{-1}.year)	0.008	0.005	1.08[7]	0.99	1.17
	Blue vs. White collar workers	0.033	0.12	1.03	0.82	1.31
	$FEV_{1,residual}$ (0 to -620 ml)	0.28	0.13	1.32	1.03	1.71
	$FEV_{1,residual}$ (-620 to -1240 ml)	0.45	0.20	1.57	1.06	2.32
	$FEV_{1,residual}$ (< -1240 ml)	1.05	0.23	2.86	1.82	4.49
Model 4.	Age (year)	0.094	0.011	2.56[6]	2.06	3.18
	Pack Years (pack day^{-1}.year)	0.010	0.003	1.11[7]	1.04	1.17
	Blue vs. White collar workers	0.002	0.12	1.00	0.79	1.27
	$FEV_1/VC_{residual}$ (0 to -10 %)	0.22	0.14	1.25	0.95	1.64
	$FEV_1/VC_{residual}$ (-10 to -20%)	0.40	0.19	1.50	1.03	2.16
	$FEV_1/VC_{residual}$ (< -20%)	0.81	0.23	2.25	1.43	3.53

[1] $\hat{\beta}$ regression coefficient
[2] SE standard error of $\hat{\beta}$
[3] HR Hazard Ratio
[4] LCL lower confidence limit
[5] UCL upper confidence limit
[6] Hazard Ratio expressed per 10 years
[7] Hazard Ratio expressed per 10 pack years

In figure 8.1. Kaplan-Meier curves for CNSLD mortality survival of blue and white collar workers are shown. The two curves were borderline significantly different, suggesting a higher CNSLD mortality among blue collar workers especially after more than ten years of follow-up (Log-rank test; $p<0.056$). The significant relationship found between CNSLD mortality and FEV_1 level in 1965 is shown in figure 8.2 (Log-rank test; $p<0.05$). Duration of smoking up to 1965 appeared to be a superior pre-

dictor of mortality compared to the number of pack years of cigarettes smoked or cigarette consumption in 1965, which is also illustrated by the Kaplan-Meier curve in figure 8.3. This last variable was further studied in a stratified analysis within the proportional hazard model as explained in the methods section, but the results were relatively poor compared to an analyses with the duration of cigarette smoking as explanatory variable in the model. Also an analyses with both duration of smoking and number of cigarettes smoked did not improve the model. Therefore age and number of years smoked were used as confounders in all other models for CNSLD mortality.

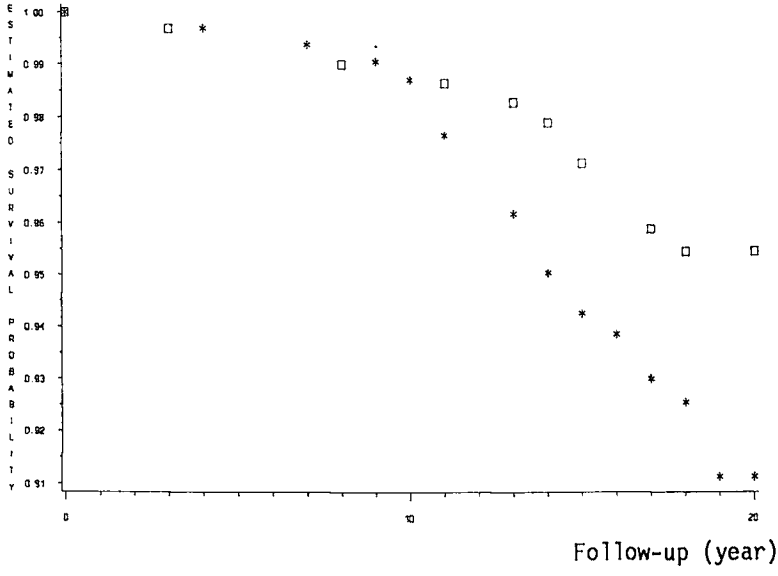
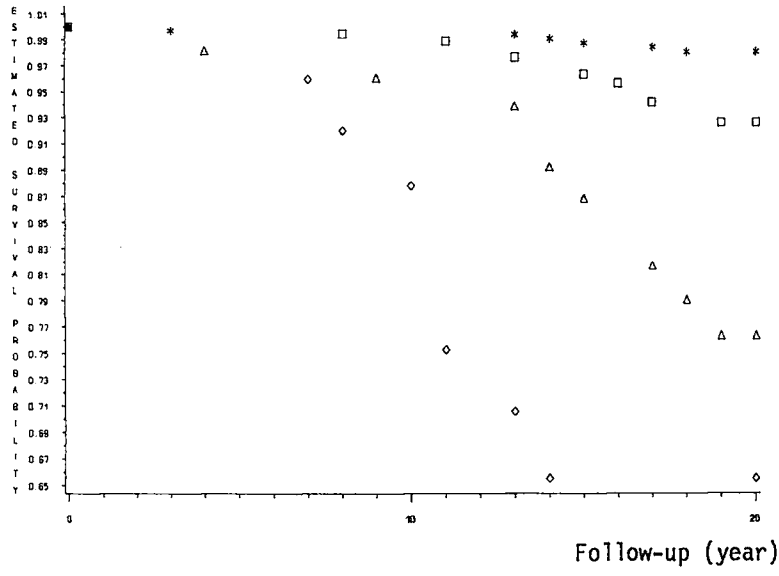


Figure 8.1. Kaplan-Meier curve for CNSLD mortality for blue and white collar workers in the Zutphen population (□ white collar workers; *: blue collar workers)



Figuur 8.2. Kaplan-Meier curve for CNSLD mortality by FEV_1 residual category in the Zutphen population (*: residual ≥ 0; □: 0 > residual ≥ -1 s.d.; △: -1 s.d. > residual ≥ -2 s.d.; ◇: residual < -2 s.d.)

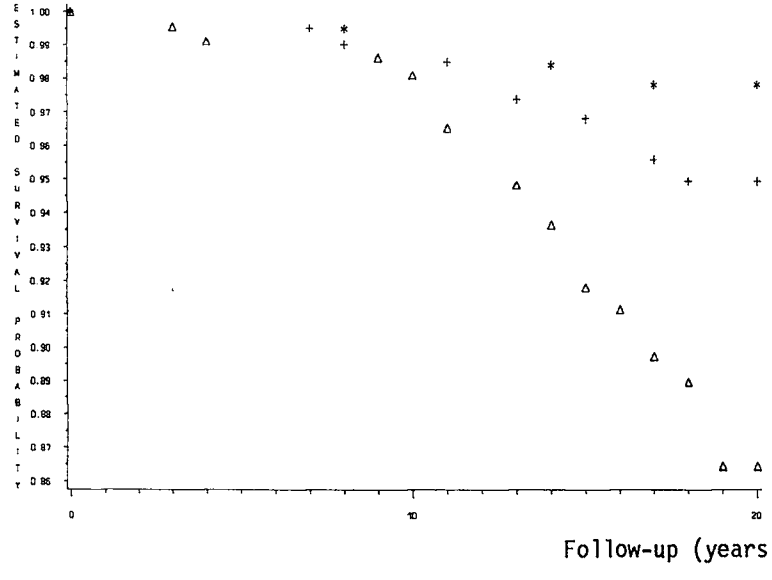


Figure 8.3. Kaplan-Meier curve for CNSLD mortality by categories of duration of smoking up to 1965 in the Zutphen population (*: category 1; +: category 2; △: category 3; see text for the definition of categories)

Table 8.5. Results of the multivariate proportional hazard analysis for CNSLD mortality for 668 men of the Zutphen Study population

	$\hat{\beta}$[1]	SE[2]	HR[3]	95% confidence limit LCL[4]	UCL[5]
Model 1. Age (year)	0.056	0.043	1.75[6]	0.75	4.07
Number of Years smoked (year)	0.067	0.029	1.95[6]	1.11	3.45
Blue vs. White collar workers	0.34	0.37	1.40	0.68	2.90
Model 2. Age (yr)	0.039	0.044	1.48[6]	0.62	3.50
Number of Years smoked (year)	0.069	0.031	1.99[6]	1.09	3.66
Blue vs. White collar workers	0.39	0.37	1.48	0.72	3.05
$VC_{residual}$ (0 to -640 ml)	0.81	0.44	2.25	0.95	5.32
$VC_{residual}$ (-640 to -1280 ml)	1.29	0.52	3.63	1.31	10.07
$VC_{residual}$ (< -1280 ml)	2.50	0.55	12.18	4.15	35.80
Model 3. Age (yr)	0.060	0.043	1.82[6]	0.78	4.23
Number of Years smoked (year)	0.068	0.032	1.97[6]	1.05	3.70
Blue vs. White collar workers	0.31	0.36	1.36	0.67	2.76
$FEV_{1,residual}$ (0 to -620 ml)	1.21	0.51	3.35	1.23	9.11
$FEV_{1,residual}$ (-620 to -1240 ml)	2.43	0.52	11.35	4.10	31.48
$FEV_{1,residual}$ (< -1240 ml)	3.24	0.55	25.53	8.69	75.04
Model 4. Age (yr)	0.057	0.043	1.77[6]	0.76	4.11
Number of Years smoked (year)	0.065	0.031	1.92[6]	1.04	3.52
Blue vs. White collar workers	0.14	0.37	1.15	0.56	2.38
$FEV_1/VC_{residual}$ (0 to -10%)	0.45	0.51	1.57	0.58	4.26
$FEV_1/VC_{residual}$ (-10 to -20%)	2.00	0.45	7.38	3.06	17.85
$FEV_1/VC_{residual}$ (< -20%)	2.48	0.49	11.94	4.57	31.20

[1] $\hat{\beta}$ regression coefficient
[2] SE standard error of $\hat{\beta}$
[3] HR Hazard Ratio
[4] LCL lower confidence limit
[5] UCL upper confidence limit
[6] Hazard Ratio expressed per 10 years

Blue collar workers had a higher CNSLD mortality than white collar workers after correcting for age and duration of smoking up to 1965 (table 8.5). However the hazard ratio for blue collar workers compared to white collar workers (HR= 1.40, model 1) was not statistically significant. This hazard ratio decreased after dummy variables for the $FEV_1/VC\%$ residuals were entered into the model. The Kaplan-Meier curve for white and blue collar workers (Figure 8.1) shows that the excess

mortality among blue collar workers appeared only after more than ten years of follow-up. Omission of these first ten years resulted in an increase of the hazard ratio for blue compared to white collar workers although it did not reach statistical significance (n=576, HR=1.72, p=0.20). An analysis in which subgroups of blue collar workers were studied did not reveal any statistically significant differences in CNSLD or total mortality compared to white collar workers. Again the FEV_1 seemed to be the strongest predictor of CNSLD mortality compared with the VC and FEV_1/VC%.

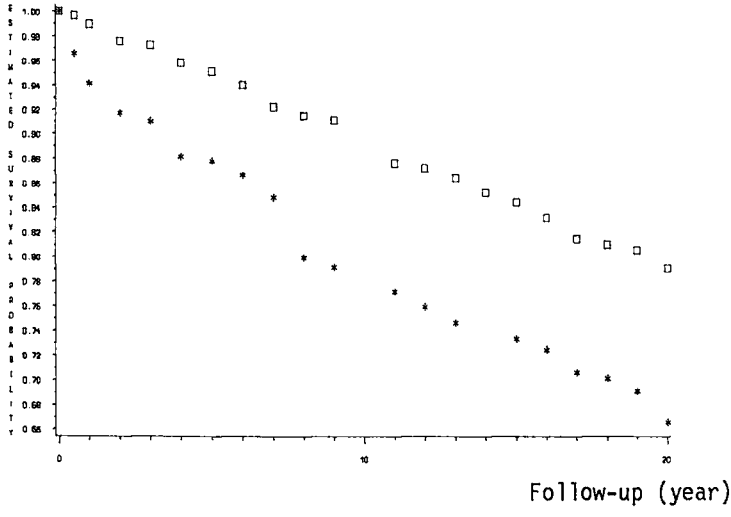


Figure 8.4. Kaplan-Meier curve for CNSLD incidence for blue and white collar workers in the Zutphen population (□: white collar-workers; *: blue collar workers)

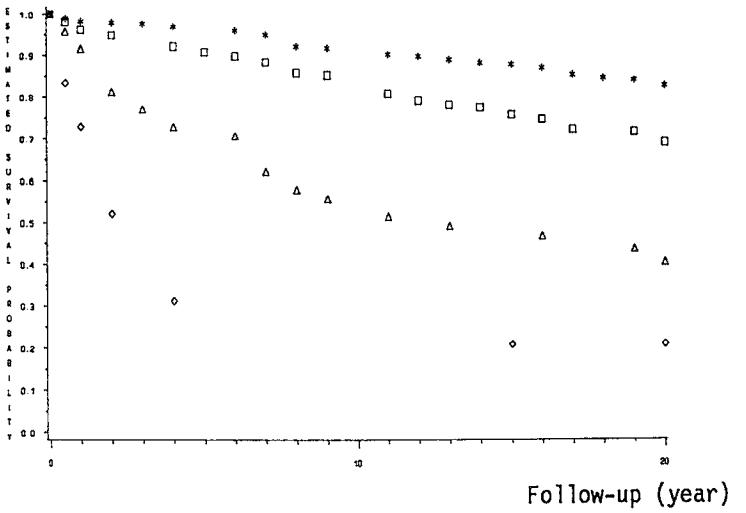


Figure 8.5. Kaplan-Meier curve for CNSLD incidence by FEV_1 residual category in the Zutphen population (*: residual ≥ 0; □: 0 > residual ≥ -1 s.d.; △: -1 s.d. > residual ≥ -2 s.d.; ◇: residual < -2 s.d.)

Table 8.6. Results of the multivariate proportional hazard analysis for CNSLD incidence for 587 men in the Zutphen population

CNSLD incidence	$\hat{\beta}$[1]	SE[2]	HR[3]	95% confidence limits LCL[4]	UCL[5]
Model 1. Age (yr)	0.037	0.016	1.45[6]	1.06	1.98
Pack Years (pack.day^{-1}.year)	0.025	0.001	1.28[7]	1.26	1.31
Blue vs. White collar workers	0.52	0.18	1.68	1.18	2.39
Model 2. Age (yr)	0.031	0.016	1.36[6]	1.00	1.87
Pack Years (pack day.year)	0.024	0.001	1.27[7]	1.25	1.30
Blue vs. White collar workers	0.54	0.18	1.71	1.21	2.44
$VC_{residual}$ (0 to -640 ml)	0.23	0.19	1.26	0.87	1.83
$VC_{residual}$ (-640 to -1280 ml)	0.93	0.24	2.53	1.58	4.06
$VC_{residual}$ (< -1280 ml)	0.95	0.47	2.59	1.03	6.50
Model 3. Age (yr)	0.036	0.015	1.43[6]	1.07	1.92
Pack Years (pack day.year)	0.023	0.001	1.26[7]	1.24	1.28
Blue vs. White collar workers	0.55	0.18	1.73	1.22	2.47
$FEV_{1,residual}$ (0 to -620 ml)	0.61	0.19	1.84	1.27	2.67
$FEV_{1,residual}$ (-620 to -1240 ml)	1.54	0.24	4.66	2.91	7.47
$FEV_{1,residual}$ (< -1240 ml)	2.55	0.39	12.81	5.96	27.51
Model 4. Age (yr)	0.042	0.016	1.52[6]	1.11	2.08
Pack Years (pack day.year)	0.025	0.001	1.28[7]	1.26	1.31
Blue vs. White collar workers	0.42	0.18	1.58	1.07	2.17
$FEV_1/VC_{residual}$ (0 to -10%)	0.51	0.19	1.67	1.15	2.42
$FEV_1/VC_{residual}$ (-10 to -20%)	1.59	0.23	4.90	3.12	7.70
$FEV_1/VC_{residual}$ (< -20%)	1.93	0.52	6.89	2.49	19.10

[1] $\hat{\beta}$ regression coefficient
[2] SE standard error of $\hat{\beta}$
[3] HR Hazard Ratio
[4] LCL lower confidence limit
[5] UCL upper confidence limit
[6] Hazard Ratio expressed per 10 years
[7] Hazard Ratio expressed per 10 pack years

Kaplan-Meier curves for CNSLD incidence were significantly different between blue and white collar workers ($p<0.05$) (figure 8.4). Similar patterns as were seen for CNSLD mortality for different categories of lung function residuals were observed for all three lung function variables. The differences between the four Kaplan-Meier curves were also statistically significant ($p<0.05$) (Kaplan-Meier curves for FEV_1-residuals are shown in figure 8.5). Numbers of pack years smoked did not violate the proportional hazards assumption for CNSLD incidence as for

CNSLD mortality. Therefore this variable was used in the multivariate proportional hazard analysis. The proportional hazard analysis showed that CNSLD incidence was higher among blue collar workers compared with white collar workers, after correcting for age and pack years smoked (table 8.6). The magnitude of the Hazard Ratio for blue versus white collar workers remained statistically significant after inclusion of the lung function residuals in the model (Model 2, 3 and 4 compared to model 1). FEV_1 residuals were the strongest predictor of CNSLD incidence compared with FEV_1/VC% and VC residuals.

8.5. Discussion

All blue collar occupational groups combined had a lowered lung function compared with white collar workers after allowing for age, standing height and pack years smoked. The lower levels of lung function were only seen for FEV_1 and FEV_1/VC% but not for Vital Capacity suggesting obstructive changes. Only textile workers and transport workers had a borderline significantly lowered Vital Capacity. Although no specific exposures were ever registered or monitored for these subgroups, previous analysis in this study with the use of the British Job Exposure Matrix (Pannett et al., 1985) showed that all the blue collar subgroups had occupational exposures to dusts, and some to gases and fumes. The decreases in lung function were in a 1-5% range, which are generally not considered as disabling reductions. Because of the variability in lung function normally found, some individuals probably have experienced larger drops in function (Soutar, 1986; Morgan, 1986).

Kaplan-Meier curves for total mortality, did not differ significantly between white and blue collar workers but were borderline significantly different when CNSLD mortality was considered. The analysis with the proportional hazards model showed that various variables were related with total and CNSLD mortality. The proportional hazard analysis for CNSLD mortality resulted in a non-significant regression coefficient for blue collar workers compared to white collar workers after correction for smoking habits and age (Hazard Ratio = 1.4). Age was, as expected,

in almost all models significantly related to mortality. Smoking habits were positively related with both total mortality and CNSLD mortality, although for CNSLD mortality the relationship was not as straightforward as might be expected. The analysis with the number of cigarettes consumed per day revealed that smokers with an intermediate cigarette consumption (8.4 pack years) had at some moment during follow-up a lower survival than moderate and non-smokers (5.2 pack years). The survival curves of these groups crossed later during the follow-up. This might reflect the effect of changing smoking habits resulting in a sort of "healthy smoker" effect. The number of years smoked did not show such an effect and was therefore used for further analysis.

The Hazard Ratio of duration of smoking and CNSLD mortality was very large. Per ten years smoking the hazard ratio was 1.95, resulting in a hazard ratio of 7.5 after 30 years of smoking cigarettes, which was approximately the mean duration of smoking in this population. After inclusion of FEV_1 residuals in the proportional hazard model, smoking remained a statistically significant predictor of subsequent total mortality, CNSLD mortality and CNSLD incidence. This probably reflects the ongoing effect of smoking on health after 1965, because exposure to tobacco smoke continued.

It is recognised that the accuracy of the death certificate in reporting cause of death is in some countries considered low, especially for CNSLD leading to an underestimation of the contribution of these diseases to total mortality (Mitchell et al., 1971). However, in a recent study in the European Community it was found that a sample of physicians had a detection rate which ranged from 60 to 92% for CNSLD (The Netherlands: 91%) if they were asked to certify a set of case histories which were further coded by the national coding offices (Mackenbach et al., 1987). Despite the reasonable accuracy of the Dutch death certificate, information bias might have influenced the findings of this study. A quantification of this bias is impossible and details from other studies are not known. Generally an internal comparison within the same study population, as conducted in the present analysis is regarded as the best approach possible to avoid such biases (Miller & Jacobsen, 1985).

A lowered lung function and especially a lowered FEV_1 was a very strong predictor of total mortality and especially of CNSLD mortality. For those with an FEV_1 residual with a magnitude below twice the standard deviation of the mean FEV_1 level, a Hazard Ratio of 25 was reached with CNSLD mortality. Persons with a less severely lower lung function showed a significantly elevated risk for total mortality and CNSLD mortality also. The relationship between a lowered FEV_1 and CNSLD mortality was reported earlier in the literature, although a detailed comparison cannot be made because of differences in the calculations done (Ebi-Kryston, 1989). Several explanations have been suggested in the literature for a relationship between lung function and especially FEV_1 reductions and total mortality or non-respiratory causes of death (Beaty et al., 1982, 1985; Kannel et al., 1974; Annesi & Kauffmann, 1986). These relationships might reflect a lowered lung function which occurs as a result of other disease processes (1). Risk factors that produce a lowered lung function might also be a risk factor for other non-respiratory causes of death (2). A third explanation might be that normal lung function is a prerequisite for well being of the whole organism (3). However, in all three explanations the FEV_1 is a strong indicator of health that should always be part of a systematic examination (Annesi & Kauffman, 1986).

In our analysis we found that if cases with CNSLD as a cause of death were excluded from the analysis, the relationships between total mortality, smoking, lung function and age diminished but remained statistically significant. This suggests that a lowered lung function is also related to other causes of death, such as cardiovascular diseases, next to CNSLD. Inferences about causal pathways concerning low lung function, smoking and occupation are difficult because the results of the Zutphen Study are strongly biased towards the mortality experience of a smoking population. More than 90% of this population had ever smoked cigarettes and a major proportion of this population was still smoking cigarettes during the follow-up period. The subgroup of non-smokers was too small to derive any definite conclusions about the effect of a lowered lung function and an occupational exposure on CNSLD incidence and mortality for this subpopulation. In other studies generally no distinction has been made in the analysis between smokers

and non-smokers. In the study of Vollmer et al. (1989) a distinction between smokers and non-smokers was made. They found that different factors were related to all-causes mortality within smoking categories. However, the absolute number of deaths in the smoking category was low and definite answers are therefore not possible.

Although no specific exposures were studied, no increased total mortality was found for those workers who were likely to have an exposure to dusts, fumes and/or gases in their job. Neither blue collar workers or subgroups of blue collar workers had an increased mortality for all causes. Although sub-groups were probably too small to derive any definite conclusions about their mortality experience, this finding is in contrast with findings of Kauffmann & Annesi (1987). The crude characterisation of occupational exposure in our study might be one explanation for this discrepancy. Qualitative differences in occupational exposure might explain the discrepancy too. The relative contribution of CNSLD mortality to total mortality is small. An elevation of the CNSLD mortality will probably not lead to an elevation of total mortality. The relationship between dust exposure and total mortality found in their study can therefore only be explained by an increase of one or several specific causes of death with a large relative contribution to total mortality. More detailed information on the composition of their cohort and its mortality is necessary to explain the differences.

Although the Hazard Ratio for CNSLD mortality with blue versus white collar workers found could be one of relevant magnitude it was statistically non-significant, probably because of the small number of CNSLD deaths, resulting in a limited statistical power. The magnitude of the effect of an occupation on CNSLD mortality encountered in the present study was small compared to the effect of smoking in this study. If the effect of a lowered lung function on CNSLD mortality is considered, the hazard ratio of occupation on CNSLD mortality is in the same order of magnitude as the hazard ratio for persons with a slightly lowered lung function.

The survival analysis with CNSLD incidence revealed that a statistically significant relationship existed between occupation, operationalised as

blue versus white collar workers, and CNSLD morbidity after correcting for age and smoking habits. This relationship was already shown in an alternative analysis in chapter 7. The relationship between occupational exposure and CNSLD incidence remained statistically significant after inclusion of the four categories for lung function residuals in the model. This is suggestive for an ongoing effect of occupation after the start of follow-up in 1960, independent of lung function level in 1960.

In conclusion, smoking habits and a lowered lung function are strong predictors of total and CNSLD mortality, while occupation appears to be weakly associated with CNSLD mortality but clearly with CNSLD incidence. To derive more precise estimates of the contribution of occupational exposure to CNSLD mortality and total mortality studies have to be undertaken in which the occupational exposure is characterised in greater detail and with greater statistical power.

8.6. Acknowledgements

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9. GENERAL DISCUSSION AND CONCLUSIONS

9.1. Evidence for a relationship between occupational exposures and CNSLD

Evidence for a relationship between occupational exposures and CNSLD comes mainly from epidemiological studies. Becklake (1985, 1988) applied Hill's criteria (Hill, 1965) for the presence of a causal relationship between occupational exposures and CNSLD. Hill's criteria comprise requirements regarding the consistency of a relationship found, the strength of a relationship, the presence of an exposure-response relationship, the specificity of the relationship, the coherence of the relationship and the biological plausibility of the relationship. Finally the question has to be asked if other factors than the one studied might explain the findings. Becklake (1985, 1988) concluded that all these criteria have been fulfilled for coal dust. As shown in the previous chapters, this evidence is based on cross-sectional, longitudinal as well as case-control studies especially among coal mine workers. The evidence for a relationship between other occupational exposures and CNSLD is generally based on less conclusive evidence comprising mostly cross-sectional and some longitudinal studies among some occupational groups as well as general population studies.

The application of Hill's criteria does leave open the possibility that occupational exposures themselves are not a sufficient cause for CNSLD in the absence of cigarette smoking. Recent evidence, however, strongly suggests that there is a relationship between occupational exposures and CNSLD independent of smoking. Two studies, one general population-based study (Korn et al., 1987), and one occupational group-based study (Marine et al., 1988), showed that relationships between occupational exposures and CNSLD were also present among life-long non-smokers. Other studies which did not allow a separate analysis among non-smokers because of small numbers, showed in multivariate analyses that effects of occupational exposures were statistically additive to those of smoking. The magnitude of the effect of an occupational exposure seemed similar among smokers, ex-smokers and non-smokers.

The severity of these effects has also been discussed by Marine et al. (1988). They showed that among non-smokers, clinically relevant changes in lung function could occur as a result of occupational coal dust exposure. The effect of exposure was comparable in magnitude to the effect of moderate smoking habits among smokers without coal dust exposure. They also concluded that current regulations for dust control in USA and British mines, based on the risk for pneumoconiosis, made it unlikely that future generations of coal miners will be put at risk by their occupation to the extent found in their study.

The evidence on the presence of a relationship between other occupational exposures and CNSLD is based on general population studies and cross-sectional occupational group studies. Especially general population studies suffer from a poor exposure characterisation. In this context it seems useful again to ask the question if an alternative explanation for the relationship found between occupational exposures and CNSLD exists. It was already argued in chapter 4 that especially information bias might be present because exposures were self-reported in most of these studies. Therefore strong emphasis was given in our analysis to a characterisation of occupational exposures by using the occupational title and by generating specific exposures with the job exposure matrix; two procedures of which it is unlikely that they are as sensitive to information bias as self-reported exposures might be. In most of the cross-sectional and longitudinal analyses of the Zutphen population it was shown that occupational groups which are known to have a dust exposure such as wood and paper workers, textile workers, tailors, and construction workers had higher prevalence of respiratory symptoms, an elevated CNSLD Incidence Density and a lower lung function. This suggests that there are other occupational exposures than coal dust capable of causing and/or aggravating CNSLD also. However, two important limitations of our data have to be considered:

- The Zutphen Study population consists of males only, who were born at the beginning of this century. Cohort effects might be present, for instance because of airway infections especially during the first part of the century because adequate treatment of infectious diseases was absent. Such cohort effects might limit the generalisability of the results. Higher occupational exposures during the first half of this

century, and changes in cigarette consumption over the years might have influenced the relationships found. Although the multivariate analyses were adjusted for smoking, the effects of occupation and occupational exposures described observed among a population consisting of mainly smokers. Direct extrapolation to other occupationally exposed populations is therefore not possible.

- The relationships found in the analyses of the Zutphen Study are limited to the occupational group level or to specific exposures generated with a Job Exposure Matrix. The specific exposures were not measured so no specific exposure-response relationships could be established. Experiences with Job Exposure Matrices are of very recent date. Validation studies of the exposures generated with these data bases have till now only been performed on a limited scale. Inferences about the specific exposures responsible for the relationships found must therefore remain tentative.

9.2. The magnitude of the contribution of occupation to the development of CNSLD

Calculations of the proportion of CNSLD due to occupation are difficult and have a limited precision (Rothman, 1986). The discussion on the proportion of cancers due to occupation illustrates the problems connected with such calculations (Higginson et al., 1980). Among the reasons for these difficulties are the multifactorial etiology of CNSLD, uncertainties about mechanisms of disease and the role of combined exposures, absence of detailed information on numbers of people exposed and level of exposure, and the absence of information on exposure-response relationships.

With these limitations in mind it is recognised that estimates of the relative contribution of a given factor to the occurrence of disease give a rough indication only of the impact of that particular factor on the population. Several researchers have made attempts to give an indication of the relative contribution of occupation to the occurrence of CNSLD in the general population or specific occupational groups (Anonymous, 1980; Elmes, 1981; Morgan, 1983; Bates, 1986; Hurley and

Soutar, 1986; Kauffmann & Annesi, 1987; Soutar, 1987). It is generally accepted by these authors that cigarette smoking forms the most important etiological factor in the development of CNSLD. The role of occupation and occupational exposure is less clear for reasons discussed above and also because many different occupational exposures exist with different relationships between exposures and CNSLD, qualitative as well as quantitative. Detailed analyses of surveys among different occupational groups showed that the contribution of occupational exposures to symptoms of bronchitis can be of the same magnitude as the magnitude of the effect of moderate smoking, although the overall contribution of occupational exposures in the general population is thought to be small (Elmes, 1981).

The cross-sectional and the longitudinal analyses of the Zutphen Study showed that approximately 50% of the male general population consisted of blue collar workers and 25-30% of the participants had a high occupational exposure to dust, fumes or gases. Approximately 50-60% of the Zutphen population had at least one high occupational exposure as estimated with a Job Exposure Matrix. In the longitudinal analysis a significantly elevated Incidence Density Ratio of 1.4 was found for an exposure to dusts, gases or fumes with a CNSLD diagnosis confirmed by a physician, adjusted for smoking habits, age and calendar period. On the basis of these figures for the IDR and the exposed fraction of the population a rough estimate of the etiological fraction of CNSLD cases attributable to the exposure to dust, fumes or gases can be made if causality is assumed (Kleinbaum et al., 1982). For an IDR of 1.4 and an exposed fraction of 0.30 in the population the etiological fraction in this study is approximately 11% for CNSLD (95% confidence limits 3 - 20%). For blue versus white collar workers a considerably higher etiological fraction of 30% can be calculated (95% confidence limits 16 - 44%). These numbers again illustrate the limited precision of such estimates.

Because of the limitations inherent to these calculations, it is impossible to generalise the estimate of the etiological fraction to other populations than the Zutphen population or to produce a precise and valid estimate of the contribution of occupation, and occupational ex-

posures to the development of CNSLD for those who are exposed nowadays. General population studies in other countries with cohorts of a lower age than the Zutphen population showed, however, similar exposed fractions and comparable odds ratios between respiratory symptoms and occupational exposures to dust, gases or fumes (Korn et al., 1987; Krzyzanowski & Kauffmann, 1988). This supports the need for new studies among occupationally exposed populations in order to produce estimates of the current contribution of occupation and occupational exposures to the development of CNSLD. Such a recommendation is also given by several national and international bodies (Whittenberger, 1983; Becklake, 1985; NHBLI, 1987). If the magnitude of the relationship between occupational exposures and CNSLD found in this study would be substantiated in studies among currently exposed cohorts, preventive strategies should not only aim at a reduction of smoking in the general population. Reduction of air pollution at the workplace has then to be considered as well.

9.3. The adversity of effects on the respiratory system

In the introduction it was shown that the existence and nature of effects of occupational exposures on the respiratory organ are heavily debated. The discussion comprises two main questions. First, whether occupational exposures to dusts, gases and fumes, are able to cause disabling respiratory effects, in the absence of other factors such as smoking. Second, whether the magnitude of a possible relationship between occupational exposures and CNSLD is of such importance that it can be regarded as a public health risk and requires specific preventive programs and strategies.

Not every measurable effect on the respiratory system is necessarily adverse. It is therefore of interest to discuss to what extent the effects of occupational exposures studied in this thesis can be called "adverse" or "disabling". The judgement whether an effect on health is acceptable or not, depends on the definition of adverse health effects. Several organisations have proposed such definitions (WHO, 1975, 1977; ATS, 1985). The American Thoracic Society (1985) defined adverse respi-

ratory health effects along the lines given by the National Academy of Sciences (1975), as (1) effects interfering with normal activity of the affected person, (2) episodic respiratory illness, (3) incapacitating illness, (4) permanent respiratory injury and/or (5) progressive respiratory dysfunction. The effects range from mortality to interference with normal activity. The health effects measured in the Zutphen Study comprise prolonged periods with respiratory symptoms, confirmed by the survey physician, and lung function changes, to a CNSLD diagnosis by a physician according to strict criteria.
For the majority of persons the effects measured can be regarded as interfering with normal activity according to the ATS criteria. For a small proportion of these a severe incapacitating airflow limitation might be involved. For instance, the (mean) reduction in lung function of blue collar workers was less than 5% lower than in white collar workers. This difference might be, however, indicative of a small increase in the number of persons with respiratory impairment. However, apart from the adverse character of respiratory symptoms or a lowered lung function itself, the prognostic value of these variables has to be considered also, when survey findings have to be interpreted.

Recent literature has shed new light on the interpretation of survey findings such as presence of respiratory symptoms and lung function reductions. In etiological studies, lung function measurements are used to determine the effects of smoking and other determinants of respiratory disease. In combination with multivariate statistical techniques lung function measurements have become a relatively sensitive technique to detect effects of the environment on the respiratory system. Small differences between populations or small changes related to a chronic exposure to dust in FVC or FEV_1 in the one hundred ml range can be detected, dependent on population size. These changes appear to have no direct clinical importance, but Soutar (1987) argues that effects of dust on lung function are often expressed as mean differences in lung function at a mean exposure level, and part of the exposed population has more extreme exposures. Secondly he mentions that the response will vary from one person to another, because of biological variability between humans. Some workers may therefore be unaffected by the dust exposure, while others experience a more than average decrease in lung

function. Thirdly, he mentions that it has been shown that estimates of an effect of dust on lung function are in most cases an underestimation of the true relationship because of the healthy worker effect. Hurley and Soutar (1986) showed that the effect of dust exposure on lung function was more than three times the average effect in miners with chronic cough complaints who left the mining industry before retiring age. For those highly exposed to coal dust (400 gh/m^3) this meant a loss in FEV_1 of at least 800 ml, which contributes significantly to disability (Hurley & Soutar, 1986).

In large scale epidemiological studies attempts have been undertaken to relate minor changes in lung function and the respiratory symptom questionnaire responses to short and long-term overall and cause specific mortality. In several studies it has been shown that lung function has an inverse relationship with total mortality (Annesi & Kauffmann, 1986; Beaty et al., 1982, 1985; Krzyzanowski & Wysocki, 1986; Sorlie et al., 1989), respiratory mortality (Ebi-Kryston, 1989; Peto et al., 1983), and mortality from cardiovascular disorders (Ebi-Kryston et al., 1989).

Respiratory symptoms show a more differentiated picture. Several studies have been published in which the predictive value of respiratory symptoms like cough, sputum and wheezing was the focus of research. Peto et al. (1983) found in a 25 year follow-up study of the "Fletcher cohort", that among men with similar initial air-flow obstruction, age-specific COPD death rates were not related to initial mucus hypersecretion, suggesting that mucus hypersecretion by itself is relatively innocent. However, Annesi and Kauffmann (1986) found in their study that initial mucus hypersecretion was related to overall mortality, after correction for initial lung function in a multivariate Cox regression analysis. Ebi-Kryston (1989) showed that chronic bronchitis, according to the MRC definition, including chronic phlegm production and breathlessness, was strongly related to bronchitis mortality (RR=13). Persistent phlegm production without a lowered FEV_1 (<65%) was, however, not significantly related to bronchitis mortality. Carpenter et al. (1989) found that those with morning cough, morning phlegm, breathlessness for walking on the level, and wheeze most days and nights had a significantly elevated total mortality and chronic bronchitis mortality, in a study of 1532

British men and women between 40 and 64 after 27 years of follow-up. Those with episodic symptoms (occasional wheeze, breathing different in summer, weather affects chest, cold usually goes to chest) had an elevated mortality too. In another study breathlessness was a strong predictor of cardiovascular disease mortality (Ebi-Kryston et al., 1989).

When faced with the literature on interpretation of respiratory epidemiological findings it is evident that a small reduction of lung function measured as FVC and FEV_1 is generally accepted as adverse. It is generally known that among those with a very low function, a high proportion is disabled, because of the incapacity associated with the function reduction. Severe reductions also have a poor prognosis with regard to mortality for the individual. Smaller reductions in lung function are associated with a statistically significant increase in mortality on a population level. A parallel with risk factors for coronary heart disease such as a high serum cholesterol level seems justified. It is generally accepted that, after intervention, small reductions in serum cholesterol level do not reduce the risk of the individual very much. However, such small reductions on a population level have important public health implications, and might lead to a considerable reduction in coronary heart disease incidence (Rose et al., 1980; Rose, 1981). Small reductions in population mean lung function levels, might therefore also be relevant from a public health standpoint. Factors leading to reductions of lung function might therefore be goals for preventive strategies in public health, and as far as occupational exposures are considered, for occupational health programs.

For respiratory symptoms there seems to be less consensus about their adverse status. In the discussion on the relationship between occupational exposures and CNSLD there is a tendency to regard severe air-flow obstructions as adverse effects only (Morgan, 1987; Anonymous, 1980). However, several studies suggest that an increased mortality risk exists among those with respiratory symptoms, although there is no general agreement that respiratory symptoms are related to increased mortality in the absence of lung function reductions. However, the American

Thoracic Society does regard respiratory symptoms as adverse because they might interfere with normal activity.

9.4. General conclusions

On the basis of a review of the literature, analysis of data of the British Pneumoconiosis Field Research among coal workers, and the Zutphen Study, it was concluded that:

- the relationship between occupational exposures and CNSLD is in most cases underestimated because of misclassification of exposure;
- occupational exposures are clearly related to lung function, CNSLD prevalence established as respiratory symptoms diagnosed by a physician, lung function, and CNSLD incidence, independent of smoking. A relationship between occupational exposures and CNSLD mortality might be present, but the statistical power of the data analysed in this study was not sufficient to detect a statistically significant relationship;
- analysis of the data available showed that the contribution of historical occupational exposures to the incidence and prevalence of CNSLD might be considerable. Extrapolation of these findings to present occupational exposures is impossible because of a lack of quantitative exposure information and industrial developments over time resulting in qualitative as well as quantitative changes in occupational exposures.
- Results of this study, of recent general population studies, and studies among more recently occupationally exposed workers legitimate further research into the presence and magnitude of the relationship between occupational exposures and CNSLD.

SUMMARY

In this thesis the relationship between occupational exposure, lung function and Chronic Non-Specific Lung Disease (CNSLD) (asthma, bronchitis, and emphysema) is studied.

Chapter 1 describes the public health aspects of CNSLD. The discussion on the relationship between occupational exposures and CNSLD is introduced briefly. It is shown that it is unclear whether occupational exposures are able to cause or aggravate CNSLD in the absence of smoking. The magnitude of a possible relationship between occupational exposures and CNSLD is also unclear.

Chapter 2 describes the historical background of CNSLD research. CNLSD was widespread in the general population at the beginning of this century and mortality was high in certain countries (e.g. Great Britain, among those living in urbanised areas), and those having a specific occupation. This high mortality was the reason for intensive research into the natural history of CNSLD and determinants of the disease. Occupational exposure was one of the determinants studied, primarily on the basis of mortality statistics. The outcome of most mortality studies was difficult to interpret although findings suggesting an adverse effect of occupation were reported. However, in the sixties the general opinion was that the contribution of occupational exposures to CNSLD mortality was low and other factors, such as airway infections, smoking, housing, and environmental air pollution were considered as more important.

In Chapter 3, some methodological issues in the establishment of exposure-response relationships in occupational epidemiological studies are discussed. Since a few years, more attention has been given to so called 'health dependent monitoring strategies'. In such strategies special emphasis is given to biological and physical processes which determine the uptake, distribution and mechanism of action of an agent. These factors determine for instance the averaging time of an exposure measurement. Characterisation of exposure to dusts from a specific particle size can be regarded as the oldest application of this principle. It is

shown that since the sixties measurement techniques have been developed to perform particle size selective sampling. This led to the demonstration of correlations between exposure indices and pneumoconiosis prevalence and incidence figures. Since then, other particle fractions that deposit in higher regions of the airways have been defined and measuring devices are being developed. However, till now these new techniques have found almost no practical application in the field of CNSLD epidemiology. It is also shown that detailed measurement strategies, in which day to day and spatial variations in the concentration of the pollutant are accounted for by sufficient exposure measurements, are seldomly applied. Generally only estimation procedures are applied, based on questionnaires, walk through surveys or Job Exposure Matrices. Limited work has been published on the precision and validity of these methods. But the studies published suggest that considerable misclassification of the exposure occurs. This probably led to underestimation of exposure-response relationships between occupational exposures and CNSLD.

Review of the recent literature in chapter 4 on the relationship between occupation, lung function, and CNSLD symptoms revealed that evidence exists that CNSLD can be independently related to occupational exposures. The evidence is based on several general population-based studies and on large epidemiological studies among occupational groups, especially coal workers and foundry workers. Different designs were used and different health endpoints measured. Most studies were cross-sectional but longitudinal lung function and morbidity studies in which respiratory symptoms were registered, were also undertaken. Case-control studies of emphysema cases whose dust-exposure has been registered in great detail provide strong evidence for the existence of a relationship between occupational dust exposure and CNSLD independent of smoking, as well as mortality studies among coal workers. Exposure-response relationships have been established for coal workers and the relationships found were reproduced in several different populations of coal workers in different countries. For other occupational groups, especially those with occupational exposures to organic dust, the evidence is less conclusive. The majority of these studies was cross-sectional. In most studies reductions of lung function and elevations of the prevalence of respiratory symptoms have been found among the exposed workers, compared

to controls. The longitudinal studies provided additional evidence that those with higher exposures have faster declines in lung function. Exposure- response relationships have till now not been established.

In chapter 5 results of the analyses of data from the British Pneumoconiosis Field Research are presented. This study of 348 British coal workers in which the exposure was known in great detail, showed that the exposure-response relationship between mixed respirable coal dust exposure and eight year change in lung function became 150-200% steeper after allowing for estimation error in the exposure. The increase in steepness was strongest if the exposure before the first lung function measurement was considered, that was the exposure for which there was evidence that the estimation error was largest. The results of the British coal worker study indicate that underestimation of exposure-response relationships, even in studies in which the exposure was characterised in great detail, can be considerable. Comparisons of contributions of different factors to some health outcome variable can be misleading if attenuated regression coefficients are considered. Although it is a misconception to believe that estimates derived after allowing for estimation error are unbiased ones, this study again illustrates that exposure estimates used for establishing exposure-response relationships lead to considerable underestimation of this relationship in a regression analysis.

In chapter 6, results are presented of an analysis of the 1985 prevalence data of the Zutphen Study. Information on respiratory symptoms, CNSLD diagnosis by a physician, occupation and occupational exposures as generated with a Job Exposure Matrix were available for 828 men aged 65-84. Results showed that for several respiratory symptoms and the CNSLD diagnosis differences in prevalence between occupational groups were found. Blue collar workers and specific subgroups such as farmers, construction workers, wood workers and painters, had a significantly elevated symptom prevalence. The differences were statistically significant in a logistic regression analysis after allowing for smoking habits and age. Statistically significant relationships were found between most of the respiratory symptoms and a confirmed CNSLD diagnosis with occupational exposures to dust, gases or fumes generated with a Job Exposure

Matrix. The prevalence of persons who have ever been treated for asthma appeared to be lower among those who had a long occupational exposure during their working life compared to those without any occupational exposure. This is suggestive of a healthy worker effect.

In chapter 7 results of the CNSLD incidence density study of the Zutphen population are given.
Presence of CNSLD at a specific time was defined as:

- episodes of respiratory symptoms such as regular cough and phlegm for longer than three months and episodes of wheezing and shortness of breath reported to the survey-physician, or:
- diagnosis of CNSLD, including asthma, chronic bronchitis or emphysema by a clinical specialist.

Occupation in 1960 was used in this analysis. Poisson regression was used to analyse the relationship between CNSLD Incidence Density and occupation and occupational exposures generated with a Job Exposure Matrix after allowing for age, smoking habits and calendar period. An Incidence Density Ratio of 1.8 was found for 'blue collar' workers compared to 'white collar' workers. Subgroups of blue collar workers such as wood and paper workers, textile workers and tailors, construction workers and transport workers also had statistically significant elevated incidence densities. Relationships with specific occupational exposures were less clear compared to the cross-sectional study. The cumulative incidence of CNSLD was high compared to prevalence figures for the Zutphen Study population, suggesting high remission rates for CNSLD.

In chapter 8, the relationship between occupation, lung function in 1965, smoking, total mortality, CNSLD mortality and CNSLD incidence were studied in a 20 year follow-up study. Lung function in 1965 was significantly related to occupation. Reductions of FEV_1 and $FEV_1/VC\%$ level in a 1 to 5% range were seen for 'blue collar' compared to 'white collar' occupations after correction for smoking habits, age and standing height, while the VC did not show statistically significant differences between these subgroups. These differences in lung function point to respiratory effects of an obstructive nature. The 20 year follow-up mortality study of the Zutphen population showed that cigarette smoking

and initial lung function levels were both strongly related to CNSLD and total mortality and CNSLD incidence. Occupation was not related to CNSLD and total mortality, but was significantly related to CNSLD incidence. Total mortality was not related to occupation while for CNSLD mortality there was an indication that a relationship appeared after more than 10 years of follow-up. It was shown that those with small reductions in lung function had a significantly elevated CNSLD incidence and mortality also. This suggested that those with small deviations in lung function from a reference level might be at higher risk for developing CNSLD and have a higher mortality risk.

These findings point to a few general conclusions:

- Because of a poor characterisation of the exposure, exposure-response relationships between occupational exposures and CNSLD are probably often underestimated.
- Occupation and occupational exposures are clearly related to respiratory symptoms and reductions in lung function.
- The relationship between smoking and CNSLD incidence appeared to be a stronger one than the relationship between occupation, occupational exposures and CNSLD incidence. However, considerable odds ratios and relative risks were found for specific exposures and some occupations. The etiological fraction for occupational exposures with CNSLD incidence is estimated to be 10-30% for the Zutphen Study. Recent studies in other countries also point to a considerable contribution of occupational exposures to the development of CNSLD. Relationships found argue for new studies among recently exposed populations.
- No evidence for a relationship between occupational exposures and total mortality was found. The relationship with CNSLD mortality after allowing for smoking habits and age is less clear. Studies with more detailed exposure information and larger statistical power are needed to elucidate the relationship between occupation and CNSLD mortality.
- Small reductions of of the lung function which are generally considered as 'normal' were related to an increased CNSLD incidence, CNSLD mortality, and total mortality. Such changes probably need more attention in occupational health surveillance.

SAMENVATTING

EPIDEMIOLOGISCH ONDERZOEK NAAR DE RELATIE TUSSEN BEROEPSMATIGE BLOOTSTELLING AAN LUCHTVERONTREINIGING EN CHRONISCHE ASPECIFIEKE RESPIRATOIRE AANDOENINGEN

In dit proefschrift wordt de relatie beschreven tussen beroepsmatige blootstelling aan stof, gassen en dampen en Chronische Aspecifieke Respiratoire Aandoeningen (CARA) (astma, bronchitis en emfyseem).

In hoofdstuk 1 wordt de omvang van CARA problematiek in de algemene bevolking beschreven. Vervolgens wordt de discussie ingeleid over de relatie tussen beroepsmatige blootstelling aan luchtverontreiniging op de werkplek en het voorkomen van CARA. Zo blijkt dat niet vaststaat of beroepsmatige blootstellingen alléén kunnen leiden tot invaliderende effecten op het ademhalingsorgaan. Daarnaast bestaat geen eenduidige kwantitatieve informatie over de relatie tussen een beroepsmatige blootstelling en het voorkomen van CARA.

In hoofdstuk 2 wordt het historisch perspectief geschetst. CARA kwam aan het begin van deze eeuw zeer veel voor en was in een aantal landen een zeer belangrijke doodsoorzaak onder de beroepsbevolking en bewoners van stedelijke gebieden. Deze hoge sterfte vormde de aanleiding voor uitgebreid onderzoek naar de oorzaken van CARA en de oorzaken in het milieu. De relatie tussen CARA en een beroepsmatige blootstelling werd toentertijd vooral onderzocht op basis van mortaliteitsregistraties. De uitkomsten van dit onderzoek waren vaak moeilijk te interpreteren, doordat andere factoren zoals rookgewoonten, voorkomen van complicerende infecties, huisvesting en buitenluchtverontreiniging ook een rol speelden, alhoewel een verhoogde mortaliteit werd geconstateerd bij mensen uit een aantal beroepen met een stofblootstelling. In de jaren zestig was de algemene opinie dat het beroep weinig bijdroeg aan het voorkomen van en de sterfte aan CARA. Overigens zijn toentertijd in veel dwarsdoorsnede onderzoeken wel verbanden gevonden tussen het hebben van een beroep waarbij men was blootgesteld aan stof, gassen of dampen en een verlaagde longfunctie of een verhoogde CARA-prevalentie. Omdat deze verschijnselen niet duidelijk correleerden met de blootstellingsduur

werd terughoudendheid betracht bij het leggen van een verband met het beroep. Als alternatieve verklaringen werden genoemd: de sinds het begin van deze eeuw sterk toegenomen rookgewoonten, de buitenluchtverontreiniging en het frequente voorkomen van luchtweginfecties.

In hoofdstuk 3 worden een aantal methodologische facetten van onderzoek naar beroepsmatige blootstelling en CARA besproken. Hieruit blijkt dat bepaalde elementen in de strategie om de beroepsmatige blootstelling aan luchtverontreiniging te karakteriseren tot nu toe relatief weinig aandacht hebben gekregen. Zo wordt pas sinds een aantal jaren aandacht besteed aan 'gezondheidseffect-relevante' meetstrategieën. Dit zijn meetstrategieën waarin biologische en fysische processen die betrekking hebben op de opname en verdeling van het agens en het werkingsmechanisme worden betrokken in de opzet van de meetstrategie. Afhankelijk van het gezondheidseffect wordt voor bijvoorbeeld een bepaalde middelingsduur van de blootstellingsmeting gekozen en worden al of niet piekconcentraties gekarakteriseerd. Specifieke methoden om een stofblootstelling te karakteriseren kan men zien als eerste uitwerking van dit principe. In de jaren zestig zijn monsternametechnieken ontwikkeld om het zogenaamde respirabel stof te meten. Dit is de stoffractie die de longen (alveoli) kan bereiken. Sinds een aantal jaren zijn andere stoffracties gedefinieerd die de depositie in de (hogere) luchtwegen benaderen. Deze fracties worden echter nog niet routinematig gemeten. Gedetailleerde blootstellingsmeetstrategieën, waarin variaties in ruimte en tijd van de blootstelling goed worden gekarakteriseerd, worden zelden toegepast. Vaak wordt gebruik gemaakt van schattingsmethoden. Deze zijn gebaseerd op gegevens afkomstig van vragenlijsten, (oriënterend) werkplekonderzoek en zogenaamde 'Job Exposure Matrices'. Over de precisie en validiteit van deze methoden is weinig gepubliceerd. De gepubliceerde onderzoeken geven aanwijzingen dat de mate van misclassificatie aanzienlijk kan zijn, wat leidt tot een onderschatting van de blootstellings-respons relatie tussen een beroepsmatige blootstelling en CARA.

In hoofdstuk 4 wordt recent onderzoek naar de relatie tussen een beroepsmatige blootstelling aan luchtverontreiniging en het voorkomen van CARA besproken. De nadruk wordt gelegd op onderzoeken die onder steekproeven van de algemene bevolking zijn uitgevoerd. In het kort worden

resultaten van onderzoek bij specifieke beroepsgroepen besproken. De nadruk wordt hierbij gelegd op mijnwerkers, waarschijnlijk de best onderzochte beroepsmatig blootgestelde populatie. Uit al deze onderzoeken blijkt dat in de algemene bevolking statistisch significante relaties tussen enerzijds beroepsmatige blootstellingen aan stof, gassen, dampen, wisselende temperaturen en anderzijds respiratoire symptomen en longfunctieverlagingen zijn gevonden. Het betrof in de meeste gevallen dwarsdoorsnede onderzoek, maar in een aantal gevallen zijn ook longitudinale onderzoeken gepubliceerd. Een groot nadeel van de meeste onderzoeken onder de algemene bevolking is dat de beroepsmatige blootstelling zelfgerapporteerd is door middel van een vragenlijst of tijdens een interview. Hoewel het niet waarschijnlijk is dat de bevindingen door informatie-bias kunnen worden verklaard, kan dit toch niet geheel worden uitgesloten. In meerdere onderzoeken onder mijnwerkers zijn blootstellings-respons relaties vastgesteld tussen een kolenstofblootstelling en de longfunctie zowel in dwarsdoorsnede- als longitudinaalonderzoek. De blootstellings-responsrelaties gevonden in de verschillende onderzoeken vertonen een grote overeenkomst, zowel voor rokers als niet-rokers. Daarnaast blijkt dat in diverse patiënt-controle onderzoeken onder emfyseempatiënten een relatie bestaat tussen een beroepsmatige stofblootstelling en emfyseem, ook bij niet-rokers. Voor andere beroepsmatige blootstellingen dan kolenstof is het bewijs voor een relatie tussen de blootstelling en het voorkomen van CARA minder omvangrijk. Dit bewijs is veelal slechts gebaseerd op dwarsdoorsnede onderzoeken en een beperkt aantal longitudinale onderzoeken. Maar ook in deze studies blijkt over het algemeen een negatief verband te bestaan tussen een beroepsmatige stofblootstelling en de longfunctie.

In hoofdstuk 5 wordt de analyse beschreven van de relatie tussen een beroepsmatige kolenstofblootstelling en longfunctieveranderingen over acht jaar bij Britse mijnwerkers. Omdat deze groep mijnwerkers deel nam aan de 'Pneumoconiosis Field Research', die over een periode van meer dan twintig jaar werd uitgevoerd, zijn zeer gedetailleerde blootstellingsgegevens voor deze groep voorhanden. De meetstrategie was in detail bekend. Op basis van de voorhanden zijnde gegevens is de fout in de per mijnwerker berekende cumulatieve stofblootstelling geschat. Met behulp van een geavanceerde statistische techniek is vervolgens de blootstel-

lings-respons relatie tussen de stofblootstelling en de longfunctieverandering over acht jaar gecorrigeerd voor deze schattingsfout. Het bleek dat de blootstellings-respons relatie na correctie ongeveer 150-200% steiler verliep dan de oorspronkelijk berekende. Het effect van de correctie was het grootst op de blootstelling lang voor de eerste longfunctiemeting. Dit was ook de blootstelling met de grootste schattingsfout. Het geconstateerde effect op de blootstellings-respons relatie komt overeen met hetgeen op grond van de theorie mocht worden verwacht. Dit betekent dat in onderzoek naar de relatie tussen een zekere blootstelling en longfunctieveranderingen de blootstellings-respons relatie wordt onderschat indien van regressie-analyse gebruik wordt gemaakt en slechts een beperkt aantal herhaalde blootstellingsmetingen is verricht.

In hoofdstuk 6 wordt verslag gedaan van het onderzoek bij 828 mannen van 65-84 jaar naar de relatie tussen enerzijds een beroepsmatige blootstelling en anderzijds respiratoire symptomen vastgesteld met een vragenlijst, de CARA-diagnose door een arts en andere indicatoren van CARA zoals het ooit behandeld zijn voor astma en chronische bronchitis of emfyseem. De beroepsmatige blootstelling aan stof, gassen en dampen werd gekaraktiseerd met een zogenaamde 'Job Exposure Matrix'. Er werden positieve verbanden gevonden tussen het beroep en beroepsmatige blootstellingen, de CARA-symptomen en de CARA-diagnose van de arts. Personen die gedurende hun leven rapporteerden dat zij ooit voor astma waren behandeld bleken juist minder vaak een beroepsmatige blootstelling gehad te hebben. Dit laatste zou op selectieve processen zoals het 'healthy worker effect' kunnen duiden.

In hoofdstuk 7 wordt verslag gedaan van longitudinaal onderzoek naar de relatie tussen beroep en beroepsmatige blootstelling en de CARA incidentie. Hiertoe zijn de morbiditeitsgegevens van de Zutphense populatie die in de periode 1960 - 1985 zijn verzameld gecodeerd door één arts. De criteria voor CARA waren:

- regelmatige episoden van hoest en slijm opgeven gedurende een periode langer dan drie maanden en piepen op de borst en kortademigheid, gemeld aan de onderzoeksarts, of
- CARA-diagnose (inclusief astma, bronchitis of emfyseem) door een klinisch specialist.

Als beroep is het beroep in 1960 genomen. Dit is door twee personen volgens het Britse systeem gecodeerd zodat op basis van beroep en industrietak met behulp van een beroepsexpositiematrix specifieke blootstellingen konden worden gegenereerd. In totaal was van 804 personen die in 1960 40-59 jaar oud waren een complete set gegevens beschikbaar. Per persoon is het aantal persoonsjaren berekend dat aan de analyse werd bijgedragen totdat CARA werd geconstateerd of de persoon overleed. Aan de hand hiervan zijn incidentiedichtheden voor CARA berekend. De gegevens werden multivariaat in een Poisson-regressie geanalyseerd. Het bleek dat personen met een zogenaamd "blauwe boorden"-beroep een hogere incidentiedichtheid voor CARA hadden dan personen met een "witte boorden"-beroep, na correctie voor leeftijd, kalenderperiode en rookgewoonten (Incidentie Dichtheids Ratio 1.8). Ook enkele beroepen vertoonden statistisch significant verhoogde incidentiedichtheden, bijvoorbeeld hout- en papierwerkers, textielwerkers en kleermakers, werkers in de bouw en werkers in het transport. De incidentiedichtheid was statistisch significant geassocieerd met een beroepsmatige blootstelling aan stof, gassen of dampen (IDR 1.4) en aan zware metalen en lijmen.

In hoofdstuk 8 wordt verslag gedaan van de analyse van de relatie tussen enerzijds beroep, rookgewoonten, longfunctie en anderzijds de CARA-incidentie, de totale mortaliteit en de CARA-mortaliteit na twintig jaar follow-up. In 1965 is middels spirometrie de Vitale Capaciteit en het geforceerde één-secondevolume (FEV_1) bepaald. De personen met een "blauwe boorden"- beroep bleken een statistisch significant lagere FEV_1 en $FEV_1/VC\%$ te hebben dan de personen met een "witte boorden"-beroep, na correctie voor lengte, leeftijd en rookgewoonten. In een verdere analyse bleken vooral textielwerkers en kleermakers, hout- en papierbewerkers en werkers in de bouw en transport een significant verlaagde longfunctie te hebben. De verlagingen zijn indicatief voor obstructieve veranderingen in de longfunctie. De twintig jaar follow-up gegevens zijn multivariaat in een zogenaamde 'overlevingsanalyse' onderzocht. De rookgewoonten en de longfunctie in 1965 bleken sterk samen te hangen met de CARA-incidentie, de mortaliteit ten gevolge van CARA en de totale mortaliteit. Het beroep was gerelateerd aan de CARA-incidentie en er werd een zwak positief verband gevonden met de CARA-mortaliteit. Het verband met de CARA mortaliteit was echter statistisch niet significant.

Op basis van het literatuuronderzoek, de analyse van de longfunctiegegevens van Britse mijnwerkers die hebben deelgenomen aan de 'Pneumoconiosis Field Research' en de analyse van de gegevens van de Zutphen Studie worden de volgende algemene conclusies getrokken:

- doordat in veel epidemiologisch onderzoek naar de relatie tussen beroepsmatige blootstelling en CARA de beroepsmatige blootstelling verre van ideaal is gekarakteriseerd wordt door misclassificatie de blootstellings-respons relatie waarschijnlijk in veel gevallen onderschat;
- beroepsmatige blootstellingen zijn gerelateerd aan het optreden van CARA, onafhankelijk van rookgewoonten;
- analyses van de gegevens van de Zutphen Studie maken duidelijk dat de bijdrage van het beroep aan het optreden van CARA aanzienlijk kan zijn. De schattingen van de etiologische fractie lopen uiteen van 10 - 30 %. Extrapolatie naar de tegenwoordige situatie is niet mogelijk door de sindsdien opgetreden industriële ontwikkeling, die waarschijnlijk heeft geleid tot aanzienlijke kwalitatieve en kwantitatieve verschuivingen in de blootstelling op de arbeidsplaats. Daarnaast speelt het feit dat de Zutphense populatie aan het begin van deze eeuw is geboren en cohorteffecten aanwezig kunnen zijn, mogelijk een verstorende rol. Echter, ook recente onderzoeken onder de algemene bevolking in het buitenland, met een lage beroepsmatige blootstelling, geven aanwijzingen dat de bijdrage van beroepsmatige blootstellingen aan het voorkomen van CARA mogelijk aanzienlijk is. Definitieve conclusies zijn niet mogelijk door beperkingen in de onderzoeksopzet van deze onderzoeken.
- de sterfte aan CARA lijkt niet verhoogd door het beroep. Het aantal aan CARA overledenen in de Zutphen Studie was echter klein en een groter onderzoek is noodzakelijk om hierover een definitieve uitspraak te kunnen doen.
- kleine longfunctieverlagingen, die weinig afwijken van de algemeen gehanteerde referentiewaarden en als 'normaal' worden beschouwd, waren gerelateerd aan een verhoogde CARA-incidentie, CARA-mortaliteit en totale mortaliteit. Overwogen moet worden om in de bedrijfsgezondheidszorg meer aandacht aan dergelijke geringe longfunctieveranderingen te besteden.

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Appendix chapter 3: Occupational exposures generated by the Job Exposure Matrix (Pannett B et al., 1985)

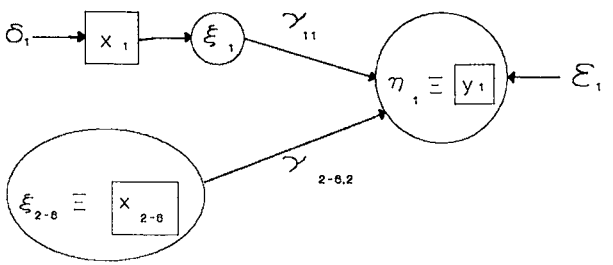
01	Acrylonitrile	26	Dust-inorganic
02	Active	27	Dust-organic
03	Adhesives-natural	28	Dust-textiles
04	Adhesives-synthc.	29	Dust-wood
05	Antiknock agents	30	Epoxy resins
06	Aromatic amines	31	Ethylene oxide
07	Arsenic & compounds	32	Formaldehyde
08	Asbestos	33	Heat
09	Benzene	34	P.A.H.'s[1] (inhaled)
10	Beryllium & compounds	35	Herbicides
11	Cadmium & compounds	36	Ionising radiation
12	Carbon tetrachlor	37	Lead & compounds
13	Chlorophenols	38	Mercury & compounds
14	Chromium/chromate	39	Nitrates
15	Cold	40	Organic solvents
16	Contact-animals	41	Outdoor occupation
17	Electro Magnetic Fields	42	Paints
18	Contact-public	43	Polychlor biphenyl
19	Cutting oils	44	Printing inks
20	Degreasing agents	45	Solder fumes
21	Detergents	46	P.A.H.'s[1] (skin contact)
22	Diesel fuel/fume	47	Styrene
23	Dyestuffs	48	Ultraviolet light
24	Dust-cereals	49	Waxes and polishes
25	Dust-coal	50	Welding fumes

[1] Polycyclic Aromatic Hydrocarbons

Appendix chapter 5:

LISREL was introduced in 1973 by Jöreskog, who also described later versions of the program (Jöreskog & Sörbom, 1986).
LISREL is a computer program for estimating coefficients in a set of linear structural equations. The variables in the equations may be directly observed or unmeasured latent variables. A LISREL model consists of two parts, the measurement model and the structural equation model. The measurement model specifies how latent variables are measured in terms of observed variables and specifies the validities and reliabilities of the observed variables. The structural model specifies causal relationships and is used to describe unexplained variance.
LISREL covers a wide range of statistical models and it has found one specific application in solving regression equations in which independent variables have been measured with error. By building in the measurement error as a stochastic variable in the LISREL framework regression coefficients are directly disattenuated for the effect of measurement error. Examples of applications of LISREL for this purpose can be found in the literature (Cuttance, 1982a+b, Jöreskog & Sörbom, 1986).

In the regression analysis of lung function changes of British coal workers six independent variables were considered.
Three dummy variables for smoking habits (one for smokers ('smo'), one for ex-smokers ('exsmo') and one for intermittent smokers ('intsmo')), weight, age and mixed coal dust exposure ('lpdust').
The first five variables were considered to be measured without error. Mixed coal dust was measured with error and in the analysis the reliability was assumed to range from 0.7 to 1.0.
The LISREL model for this analysis was:



In which η_1 is the dependent latent variable which is identical to the measured variable y_1 with measurement error ε_1. X_1 is the observed mixed coal dust exposure with measurement error δ_1. The other independent variables X_2-X_6 are measured without error and identical to ξ_2 - ξ_6. In a LISREL program run, δ_1 is given a fixed value. An example of a steering file is given below:

```
data entry          DA NI=26 NO=348 MA=CM
matrix output       CM UNIT=8 RE
format              (6D13.6)
                    LA
                    *
variables           'DFVC' 'DFEV' 'EXSMO' 'INSTSMO' 'SMO'
                    'AGE4' 'WEIGHT4' 'LPDUST'
selection of        SE
variables           'DFVC' 'AGE6' 'WEIGHT6' 'EXSMO' 'SMO' 'INTSMO'
                    'LPDUST'
model               MO NE=1 NK=6 NY=1 NX=6 LY=ID TE=ZE
                    LX=ID TD=DI PH=SY,FR
defining reliability VA 0.378 TD(6)
output request      OU SE TV VA ND=9
```

Appendix chapter 6:

Opmerking bestemd voor arts
Het is de bedoeling dat U onderstaande vragen en antwoorden in principe letterlijk voorleest. Zo nodig kunt U extra uitleg geven. Aan het eind van ieder onderwerp wordt U de ruimte gelaten om aanvullende informatie te noteren, op grond waarvan U Uw diagnose kunt stellen.
Wilt U bij elke vraag die van toepassing is, het cijfer van het juiste alternatief omcirkelen?

H. Long-aandoeningen

41. Hoest U gewoonlijk bij het opstaan? (hoesten bij de eerste sigaret, of bij het naar buiten gaan, meetellen. De keel schrapen of een enkele kuch niet meerekenen)
    1. ja
    2. nee
42. Hoest U gewoonlijk overdag of 's nachts?
    1. ja
    2. nee
43. Geeft U bij het opstaan gewoonlijk enig slijm op?
    1. ja
    2. nee
44. Geeft U gewoonlijk overdag en/of 's nachts enig slijm op?
    1. ja
    2. nee
    Zo ja, heeft U daar wel eens bloed bij gezien?
    1. ja
    2. nee
45. Heeft U regelmatig last van piepen op de borst en/of benauwdheids-aanvallen?
    1. ja
    2. nee
    Zo ja, bent U ergens overgevoelig voor?
    1. ja
    2. nee

46. Bent U onder behandeling (geweest) voor één van de volgende aandoeningen?

a) astma
   1. ja
   2. nee

b) chronische bronchitis
   1. ja
   2. nee

c) long-emfyseem
   1. ja
   2. nee

d) longontsteking
   1. ja
   2. nee

e) long-tuberculose
   1. ja
   2. nee

f) andere luchtwegaandoeningen (verkoudheid uitgezonderd)
   1. ja, namelijk _____
   _____
   2. nee

47. Hebt U last van kortademigheid als U wat sneller loopt of als U een trap oploopt?
   1. ja, na _____ trappen (etages)
   2. nee _____ *(doorgaan naar vraag 50, resp. conclusie H)*

48. Wordt U kortademig als U op straat loopt met andere mensen van Uw leeftijd?
   1. ja
   2. nee

49. Bent U kortademig als U zich wast of aankleed?
   1. ja
   2. nee

Indien één van bovenstaande vragen positief werd beantwoord

50. Bent U voor één van bovengenoemde klachten momenteel (nog) onder behandeling van een arts?
    1. ja, bij _____ (naam)
       _____ (plaats)
    2. nee

    Zo ja, wat zei hij/zij dat het was? _____
    _____

Conclusie H: CARA-anamnese

1. positief
2. dubieus
3. negatief

Doorgaan naar vraag 51

M. Rookgewoonten

72. Heeft U wel eens meer dan 1 sigaret per dag gerookt?
    1. ja
    2. nee *doorgaan met vraag 79*
73. Hoe oud was U toen U voor het eerst begon regelmatig sigaretten te roken?
    _____ jaar oud
74. Als U kijkt naar de gehele periode die U gerookt hebt, hoeveel sigaretten rookt U dan gemiddeld per dag?
    _____ sigaretten per dag
75. Inhaleert/inhaleerde U als U sigaretten rookte(e) (rookt(e) U over de longen)?
    1. ja
    2. nee
76. Rookt U nu sigaretten?
    1. ja, _____ sigaretten per dag
    2. nee, ik stopte toen ik _____ jaar oud was

77. Welk type sigaret rookt(e) U?
    a. sigaretten zonder filter
        1. ja
        2. nee
    b. sigaretten met filter
        1. ja
        2. nee
    c. shag
        1. ja
        2. nee
78. Welk merk en type sigaretten rookt(e) U meestal?

    _____

79. Hebt U ooit regelmatig sigaren gerookt?
    1. ja
    2. nee *doorgaan met vraag 85*
80. Hoe lang hebt U sigaren gerookt?
    _____ jaar
81. Hoeveel sigaren rookt(e) U gemiddeld per dag over die gehele periode?
    _____ sigaren per dag
    _____ sigaartjes per dag
    _____ sprietjes per dag
82. Rookt U nu sigaren?
    1. ja
    2. nee *doorgaan met vraag 85*
83. Hoeveel sigaren rookt U nu gemiddeld per dag?
    _____ sigaren per dag
    _____ sigaartjes per dag
    _____ sprietjes per dag
84. Welk merk en type sigaren rookt(e) U meestal?

    _____

    _____

    _____

85. Hebt U ooit regelmatig pijp gerookt?
    1. ja
    2. nee *doorgaan met vraag 91*

86. Hoe lang hebt U pijp gerookt?

_____ jaar

87. Hoeveel zakjes/blikjes pijptabak rookt U gemiddeld over die gehele periode?

_____ zakjes pijptabak per maand

_____ blikjes pijptabak per maand

88. Rookt U nu pijp?

1. ja
2. nee *doorgaan met vraag 91*

89. Hoeveel zakjes/blikjes pijptabak rookt U nu gemiddeld per maand?

_____ zakjes pijptabak per maand

_____ blikjes pijptabak per maand

90. Welk merk pijptabak gebruikt(e) U meestal?

_____

_____

_____

Leefgewoonten

7. Welk beroep hebt U het langst uitgeoefend?

_____

8. Hoe lang hebt U dit beroep uitgeoefend?

_____ jaar

9. Werkte U de langste tijd als zelfstandige of in loondienst?

O in loondienst

O als zelfstandige

10. Had U zelf personeel in loondienst óf gaf U leiding aan andere mensen?

O nee

O ja

10a. Zo ja, hoeveel mensen waren dat?

O minder dan 3 mensen

O tussen de 3 en de 25 mensen

O méér dan 25 mensen

11. Heeft U in Uw leven méér dan één beroep uitgeoefend?

O nee

O ja

11a. Zo ja, welke beroep hebt U het laatst uitgeoefend?

_____

11b. Was dit alléén een verandering van beroep of klom U hierdoor (ook) op de maatschappelijke ladder?

O het was alléén een verandering

O ik klom (ook) op de maatschappelijke ladder

O anders, namelijk _____

_____

12. Heeft U momenteel nog betaald werk?

O nee

O ja

12a. Zo ja, hoeveel uur per week?

_____ uur per week

13. Wilt U voor elk van de hieronder genoemde bedrijfstakken aangeven of U hierin minstens één jaar gewerkt heeft:

	nee	ja	zo ja aantal jaren
delfstoffenwinning	0	0	_____
voedings- en genotmiddelen-industrie	0	0	_____
textiel- en kledingindustrie	0	0	_____
schoenen- en lederwaren-industrie	0	0	_____
hout- en meubelindustrie	0	0	_____
papier- en papierwaren-industrie	0	0	_____
grafische industrie en uitgeverijen	0	0	_____

Vervolg vraag 13

	nee	ja	zo ja aantal jaren
aardolie industrie	0	0	_____
chemische industrie en kunstmatige en synthetische garen- en vezelindustrie	0	0	_____
rubber- en kunststofverwerkende industrie	0	0	_____
bouwmaterialen-, aardewerk- en glasindustrie	0	0	_____
basis metaal en metaalprodukten industrie	0	0	_____
machine industrie	0	0	_____
electrotechnische industrie	0	0	_____
transportmiddelen industrie	0	0	_____
instrumenten en optische industrie	0	0	_____

14. Bij deze vraag kunt U méér dan één hokje aankruisen als dat nodig is.
Wat zijn de inkomensbronnen van U én (indien van toepassing) de leden van Uw huishouding?
O AOW of AWW
O pensioen
O lijfrente
O inkomen uit arbeid
O inkomen uit vermogen
O anders, namelijk _____
_____

15. Met hoeveel personen moet U van dit geld rondkomen?
O alléén ikzelf
O naast mijzelf nog _____ persoon/personen

16. Wat is de laatste schoolopleiding die U vroeger volledig hebt doorlopen?
O lager school
O lager beroepsonderwijs (bijvoorbeeld ambachtschool, lager tuinbouwschool, handelsschool, praktijkdiploma)
O (M)ULO
O Middelbaar beroepsonderwijs (bijvoorbeeld M.B.A., L.O.-akten, M.T.S., kweekschool)
O H.B.S., Lyceum of Gymnasium
O hoger beroepsonderwijs (bijvoorbeeld H.T.S., M.O.-opleiding)
O universiteit of hogeschool
O anders, namelijk _____
_____

Appendix chapter 7: Poisson regression model

The incidence density as a function of two independent variables can be described as a multiplicative hazard function:

$$h(i) = b_0 \, b_1^{x_1(i)} \, b_2^{x_2(i)}$$

where: $h(i)$ = the hazard in stratum i;
b_0 = baseline incidence density; and
b_1, b_2 are coefficients associated with dummy variables x_1 and x_2

This expression for the incidence density can be reexpressed into a Poisson model by the substitution of

$$h(i) = \gamma(i)/P(i)$$

where: $\gamma(i)$ = the expected number of cases in stratum i; and
$P(i)$ = person time, the sum of the individual contributions of person time to stratum i.

$$\gamma(i) = P(i) \, b_0 \, b_1^{x_1(i)} \, b_2^{x_2(i)}$$

The number of cases with CNSLD within a specific cell is assumed to have a Poisson distribution with an expected value of $\gamma(i)$. This expression can be recalculated to

$$\ln \gamma(i) = \Gamma(i) + \beta_0 + \beta_1 x_1(i) + \beta_2 x_2(i)$$

where: $\Gamma(i)$ = $\ln P(i)$ and
β_j = $\ln b_j$ for j=0,1,2.

This model easily generalises to more than two independent variables. GLIM produces maximum likelihood estimates of the β's. By declaring $\Gamma(i)$ as an 'offset', its coefficient is set to a fixed value of 1. Incidence Density Ratios (IDR) associated with x_j (j=1,2) were calculated by taking the antilog of the regression coefficient:

$$IDR_j = \exp(\beta_j)$$

An approximate 95% confidence interval of the IDR can be calculated by:

$$\exp(\beta_j \pm 1.96\ SE_j) \text{ where } SE_j = \text{standard error of } \beta_j$$

The procedures used in GLIM to perform a Poisson regression analysis have recently been described in the literature (Breslow & Day, 1987; Wacholder, 1986).

Appendix chapter 8:

8.1. A. Regression analysis of VC (l) on standing height and age (n=668)

	df	SS	MS	F	Prob>F
model	2	11792	5896	143	0.0001
error	665	27338			
total	667	39130	41		

Adj R^2 0.30

	$\hat{\beta}$	SE	t	Prob>|t|
constant	-3.436	0.74	-0.60	0.0001
standing height (cm)	0.0545	0.0038	14.20	0.0001
age (year)	-0.0328	0.0046	-7.12	0.0001

8.1. B. Regression analysis of FEV_1 (l) on standing height and age (n=668)

	df	SS	MS	F	Prob>F
model	2	7039	3520	91.9	0.0001
error	665	25473	38,3		
total	667	32512			

Adj R^2 0.21

	$\hat{\beta}$	SE	t	Prob>|t|
constant	-0.5495	0.7212	-0.76	0.45
standing height (cm)	0.0327	0.0037	8.83	0.0001
age (year)	-0.0397	0.0044	-8.93	0.0001

8.1. C. Regression analysis of $FEV_1/VC\%$ (%) on standing height and age (n=668)

	df	SS	MS	F	Prob>F
model	2	0.3334	0.1667	16.033	0.0001
error	665	6.9134	0.0104		
total	667	7.2468			

Adj R^2 0.05

	$\hat{\beta}$	SE	t	Prob>||t||
constant	-1.1173	0.1188	9.40	0.0001
standing height (cm)	0.0012	0.0006	-1.89	0.0599
age (year)	-0.0041	0.0007	-5.55	0.0001

8.2. A. Distribution of VC residuals (l) ($VC_{measured}$ - $VC_{predicted}$)

n=668	mean	s.d.	min	max
VC residual (l)	0	0.640	-2.317	2.444

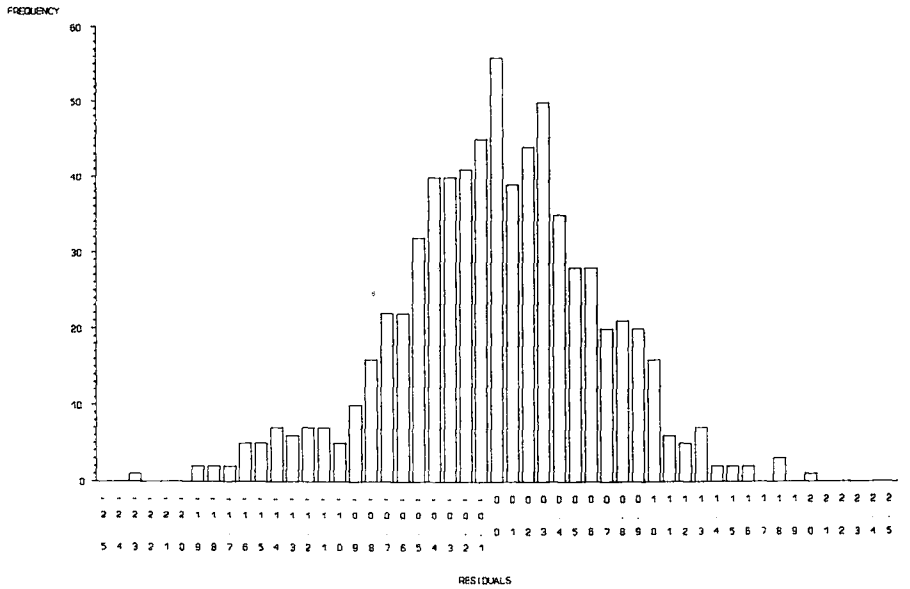
8.2. B. Distribution of FEV_1 residuals (l) ($FEV_{1,measured}$ - $FEV_{1,predicted}$)

n=668	mean	s.d.	min	max
FEV_1 residual (l)	0	0.618	-2.416	1.757

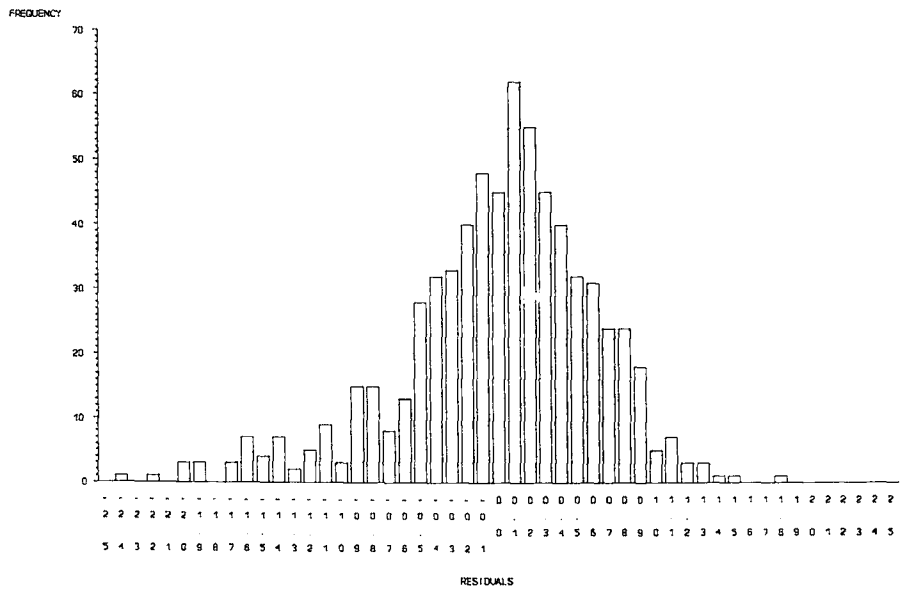
8.2. C. Distribution of $FEV_1/VC\%$ residuals (%) ($FEV_1/VC\%_{measured}$ - $FEV_1/VC\%_{predicted}$)

n=668	mean	s.d.	min	max
$FEV_1/VC\%$ residual (%)	0	10.18	-44.42	20.77

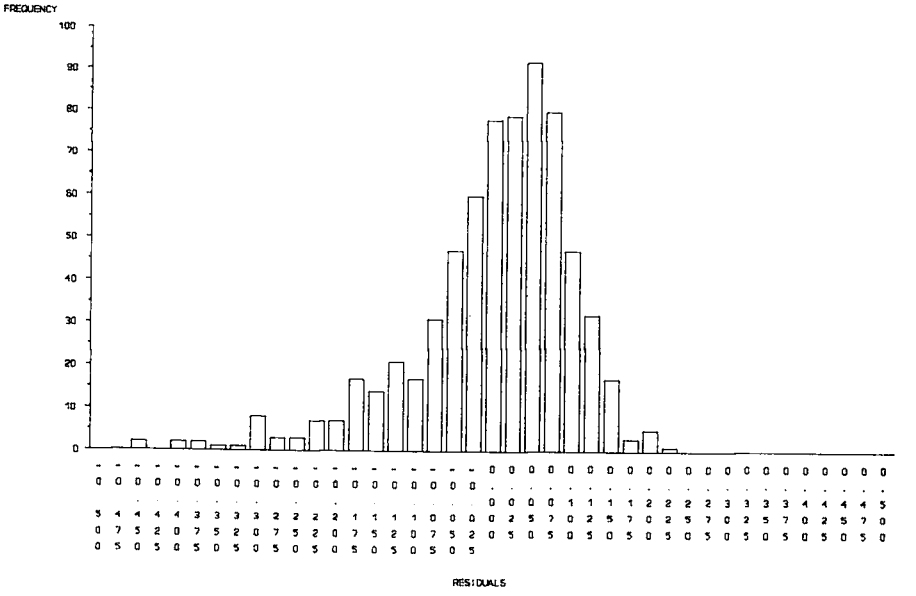
8.3a. Histogram of VC residuals (l) corrected for age (yr) and standing height (cm)



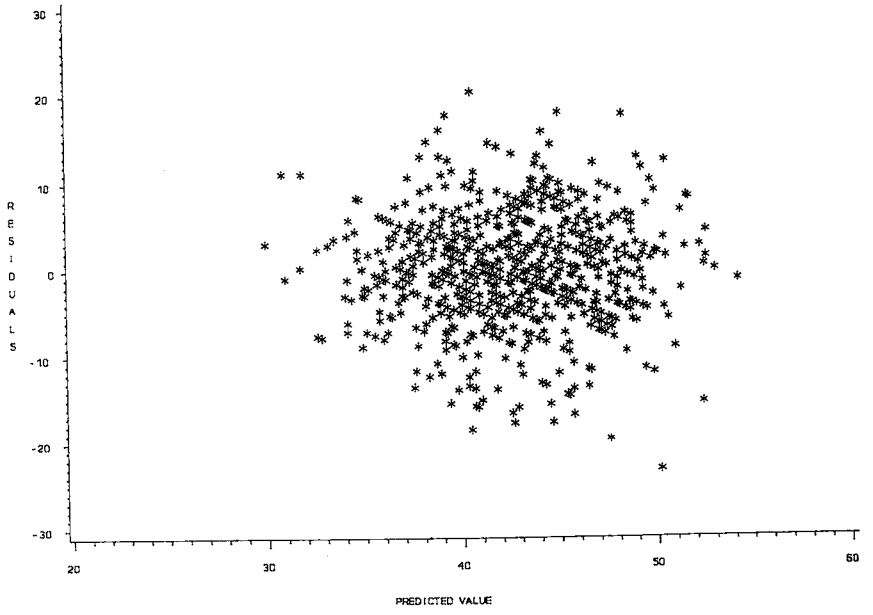
8.3b. Histogram of FEV_1 residuals (l) corrected for age (yr) and standing height (cm)



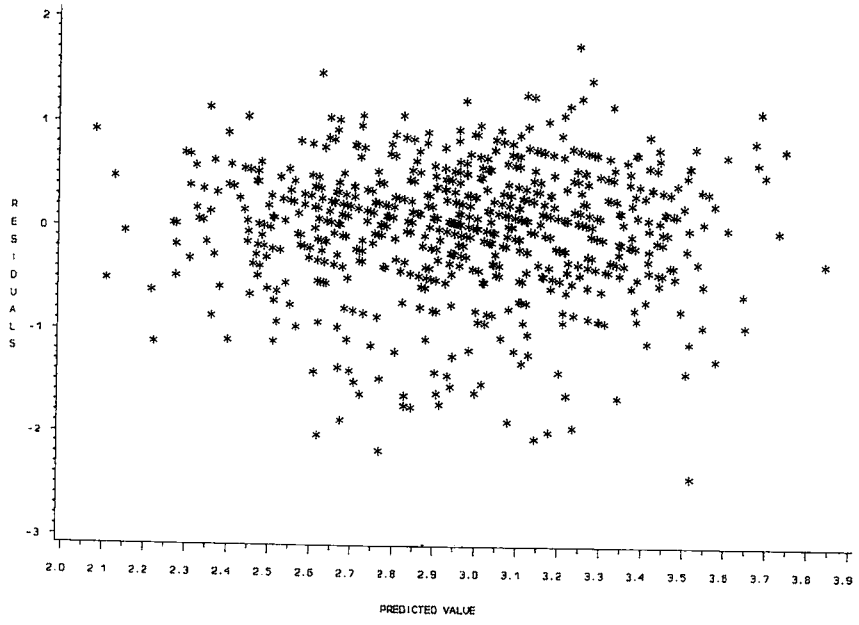
8.3c. Histogram of $FEV_1/VC\%$ residuals (%) corrected for age (yr) and standing height (cm)



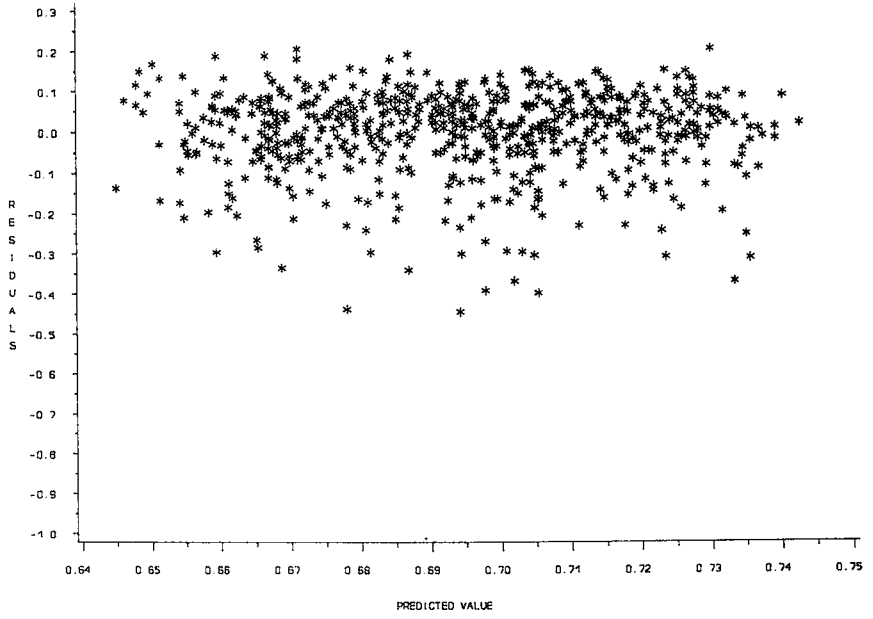
8.4a. Plot of VC residuals and predicted values with age (yr) and standing height (cm) in regression model

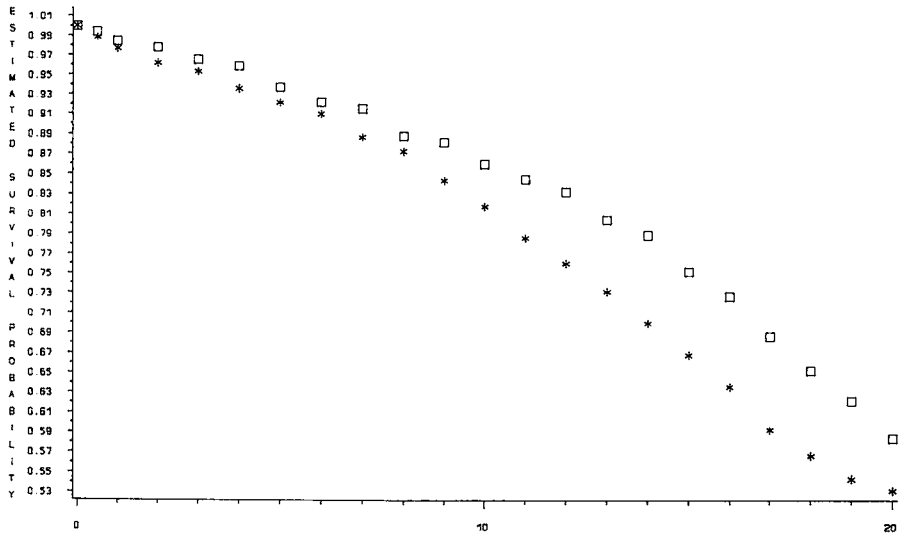


8.4b. Plot of FEV_1 residuals and predicted values with age (yr) and standing height (cm) in regression model

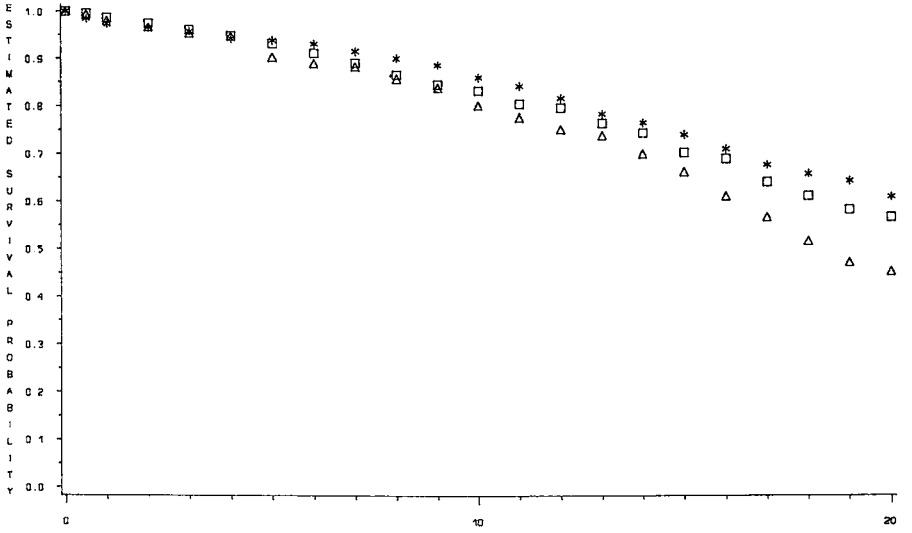


8.4c. Plot of $FEV_1/VC\%$ residuals and predicted values with age (yr) and standing height (cm) in regression model

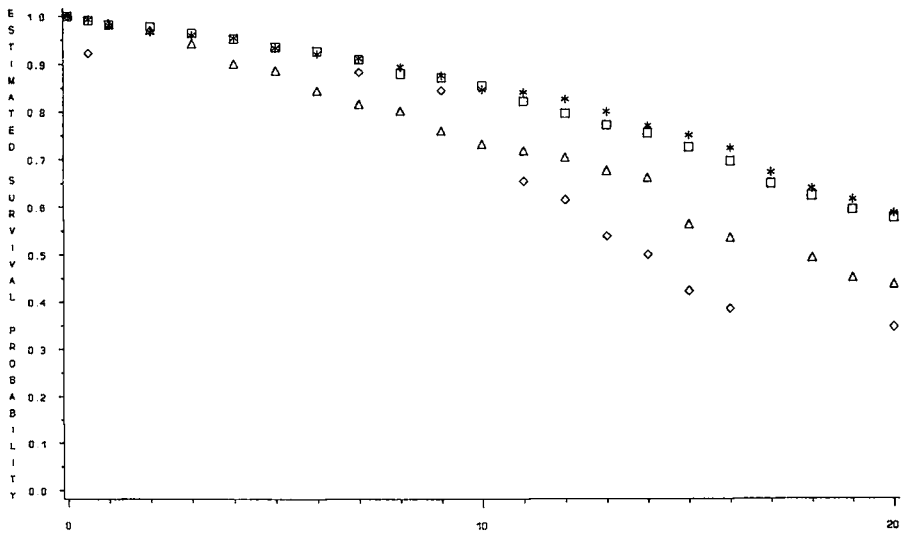




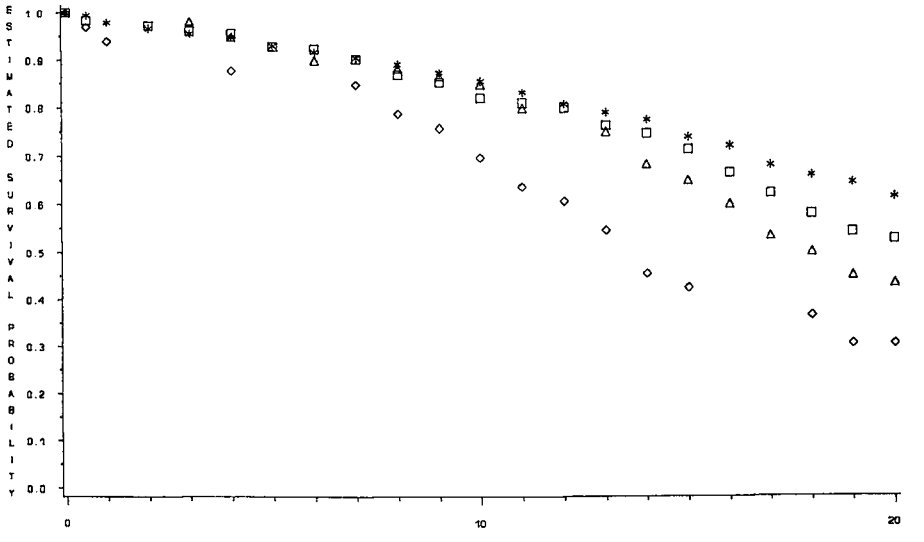
Kaplan-Meier curves for total mortality for blue and white collar workers in the Zutphen population (□ white collar workers; * blue collar workers)



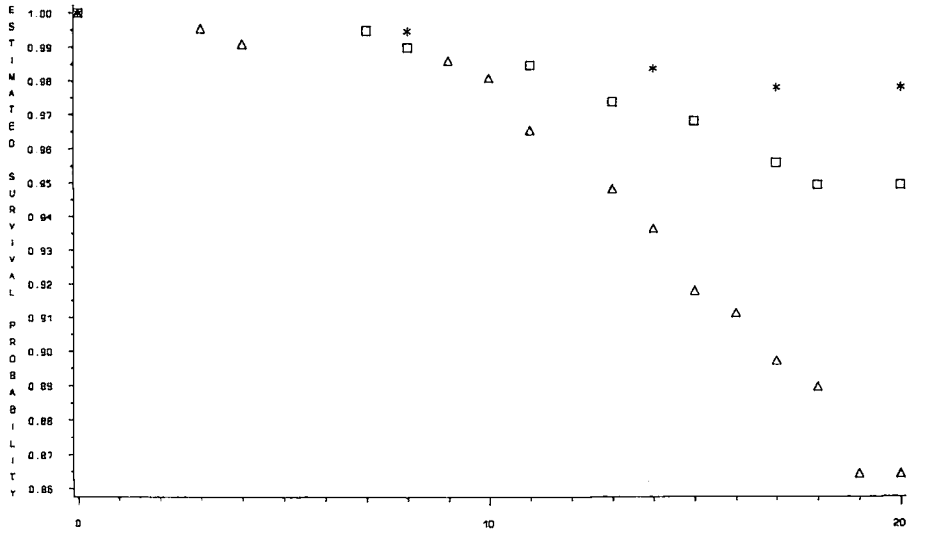
Kaplan-Meier curve for total mortality by categories of pack years of smoking up to 1965 in the Zutphen population (*: category 1; □: category 2; △: category 3; see for definitions of categories text chapter 8)



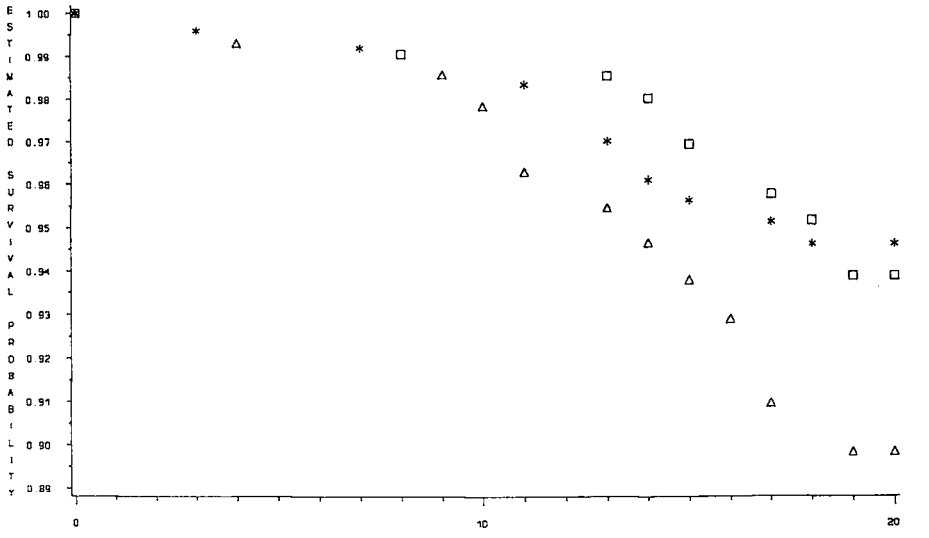
Kaplan-Meier curves for total mortality by VC residual category in the Zutphen population (*: residual ≥ 0; □: 0 > residual ≥ -1 s.d.; △: -1 s.d. > residual ≥ -2 s.d.; ◇residual < -2 s.d.)



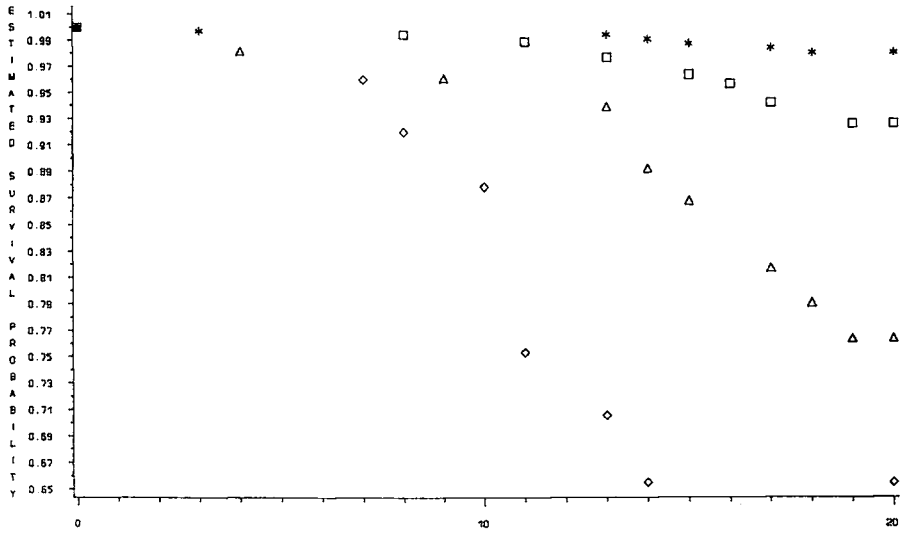
Kaplan-Meier curves for total mortality by $FEV_1/VC\%$ residual category in the Zutphen population (*: residual ≥ 0; □: 0 > residual ≥ -1 s.d.; △: -1 s.d. > residual ≥ -2 s.d.; ◇residual < -2 s.d.)



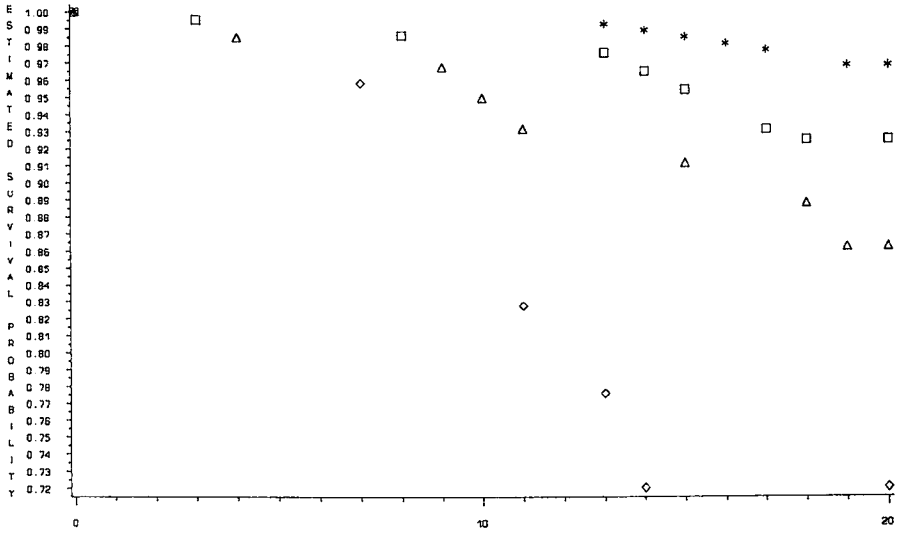
Kaplan-Meier curve for CNSLD mortality by categories of duration of smoking up to 1965 in the Zutphen population (*: category 1; □: category 2; △: category 3; see for definitions of categories text chapter 8)



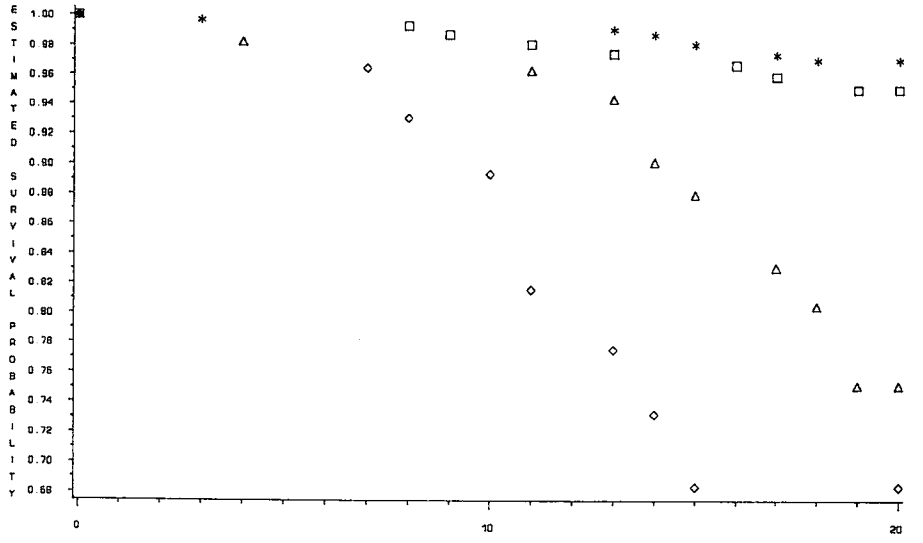
Kaplan-Meier curve for CNSLD mortality by categories of pack years of smoking up to 1965 in the Zutphen population (*: category 1; □: category 2; Δ: category 3; see for definitions of categories text chapter 8)



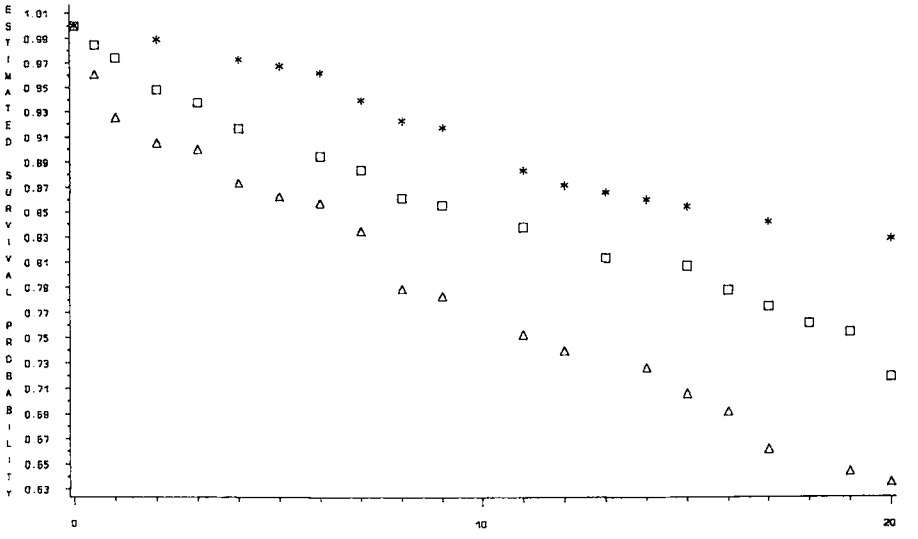
Kaplan-Meier curves for CNSLD mortality by FEV_1 residual category in the Zutphen population (*: residual ≥ 0; □: 0 > residual ≥ -1 s.d.; △: -1 s.d. > residual ≥ -2 s.d.; ◇residual < -2 s.d.)



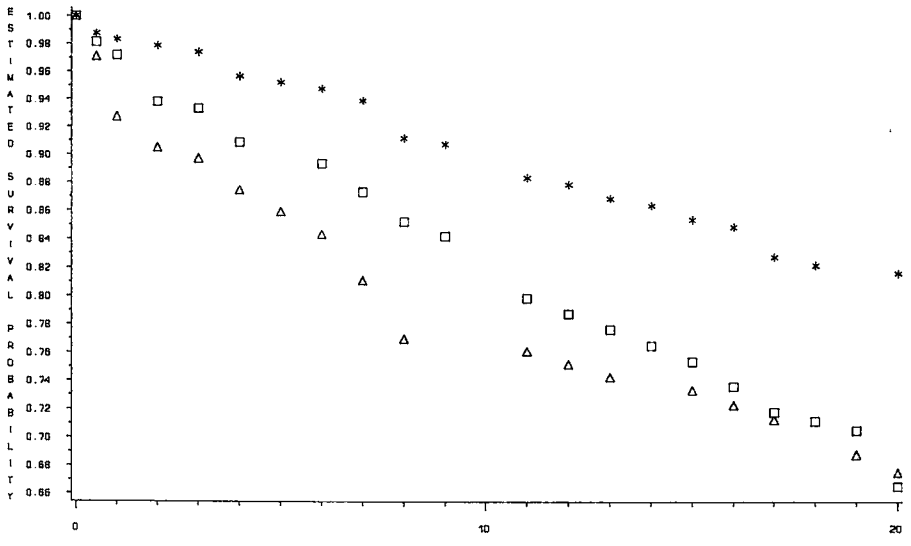
Kaplan-Meier curves for CNSLD mortality by VC residual category in the Zutphen population (*: residual ≥ 0; □: 0 > residual ≥ -1 s.d.; △: -1 s.d. > residual ≥ -2 s.d.; ◇residual < -2 s.d.)



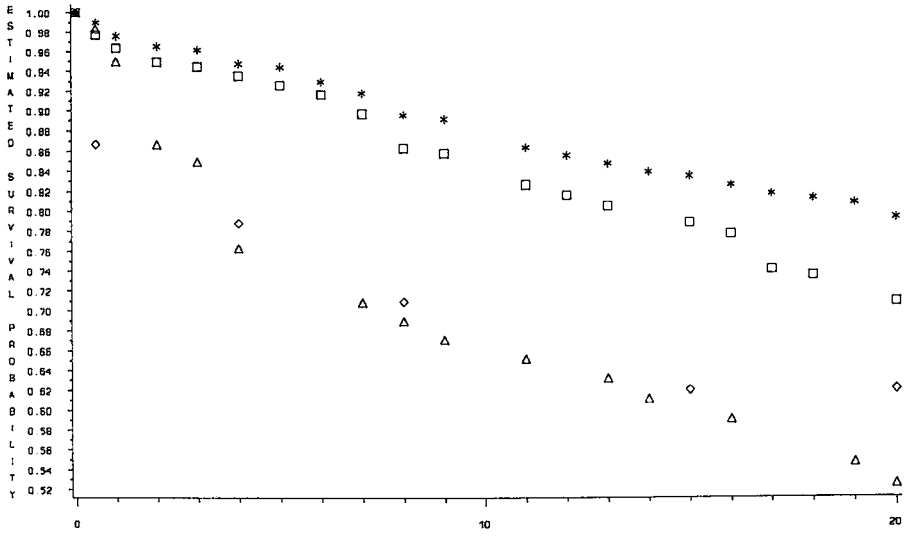
Kaplan-Meier curves for CNSLD mortality by $FEV_1/VC\%$ residual category in the Zutphen population (*: residual ≥ 0; □: 0 > residual ≥ -1 s.d.; △: -1 s.d. > residual ≥ -2 s.d.; ◇residual < -2 s.d.)



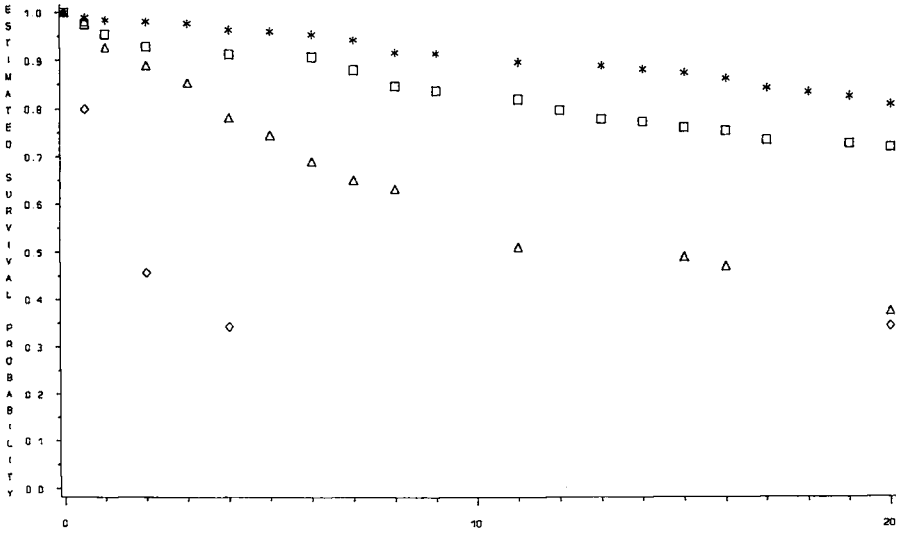
Kaplan-Meier curve for CNSLD incidence by categories of duration of smoking up to 1965 in the Zutphen population (*: category 1; □: category 2; Δ: category 3; see for definitions of categories text chapter 8)



Kaplan-Meier curves for CNSLD incidence by categories of pack years of smoking up to 1965 in the Zutphen population (*: category 1; □: category 2; △: category 3)



Kaplan-Meier curves for CNSLD incidence by VC residual category in the Zutphen population (*: residual ≥ 0; □: 0 > residual ≥ -1 s.d.; △: -1 s.d. > residual ≥ -2 s.d.; ◇residual < -2 s.d.)



Kaplan-Meier curves for CNSLD incidence by $FEV_1/VC\%$ residual category in the Zutphen population (*: residual ≥ 0; □: 0 > residual ≥ -1 s.d.; △: -1 s.d. > residual ≥ -2 s.d.; ◇residual < -2 s.d.)

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Tric's mi gabhail air Dùn-éideann
baile glas gun ghathadh grêine
's ann a lasadh e le d'bhòidhche
baile lòghmhor geal-reultach
(Sorley Maclean, Taghadh de Dhàin 1932-72, Canongate 1977).

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CURRICULUM VITAE

Dick Heederik werd geboren op 7 december 1957 te Delft. Hij volgde Ongedeeld Voorbereidend Wetenschappelijk Onderwijs-B aan het Christelijk Lyceum voor Delft en Rijswijk te Delft. In Wageningen studeerde hij vanaf 1976 milieuhygiëne. In 1984 studeerde hij af (met lof) met arbeidshygiënische gerichte afstudeervakken Gezondheidsleer en Luchthygiëne en -verontreiniging. Na zijn studie trad hij in 1984 in dienst bij de vakgroepen Gezondheidsleer en Luchthygiëne en -verontreiniging. Daar bestonden zijn voornaamste activiteiten uit het geven van onderwijs en het verrichten van onderzoek op het gebied van de bedrijfsgezondheidszorg en beroepsziekten en de arbeidshygiëne. In het bijzonder hield hij zich bezig met onderzoek op het terrein van de gezondheidseffecten ten gevolge van beroepsmatige blootstelling aan organisch stof onder werknemers in de mengvoederindustrie, de graanoverslag en de agrarische sector. In 1987 werkte hij in het kader van een gezamenlijk onderzoeksproject vier maanden bij het Institute of Occupational Medicine te Edinburgh, Schotland. Sinds medio 1988 is hij bij de vakgroep Gezondheidsleer werkzaam. Naast zijn directe onderwijs- en onderzoeksactiviteiten heeft hij deel uitgemaakt van het bestuur van de Nederlandse Vereniging voor Arbeidshygiëne en is hij lid van de TNO Commissie voor Asbest en andere minerale vezels en de Commissie Arbeidsgezondheidskundig Onderzoek (CARGO) die het Directoraat Generaal van de Arbeid van het Ministerie van Sociale Zaken en Werkgelegenheid adviseert op het gebied van arbeidsgezondheidskundig onderzoek. Sinds 1 januari 1990 is hij lid van de Universiteitsraad van de Landbouwuniversiteit Wageningen.