

**Exposure to airway irritants,
airway hyperresponsiveness and respiratory health
in an occupational population**



Anja Kremer

**Exposure to airway irritants, airway hyperresponsiveness
and respiratory health in an occupational population**

Rijksuniversiteit Groningen

**Exposure to airway irritants, airway hyperresponsiveness
and respiratory health in an occupational population**

Proefschrift

ter verkrijging van het doctoraat in de Geneeskunde
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus Dr. F. van der Woude
in het openbaar te verdedigen op
woensdag 7 juni 1995
des namiddags te 4.00 uur

door

Annette Marja Kremer
geboren op 9 december 1959
te Zevenhuizen (gem. Leek)

Promotores: Prof. Dr. G.H. Koëter
Prof. Dr. J.G.R. de Monchy

Co-promotor: Dr. B. Rijcken

To my parents

To Hans

Reading committee:

Prof. Dr. J.S.M. Boleij

Prof. Dr. D. Post

Prof. Dr. J.H.B.M. Willems

**This study was supported by grant No 88-32 from the Netherlands Asthma Fund.
SensorMedics BV provided the lung function apparatus.**

**The printing of this thesis was financially supported by the Netherlands Asthma Fund,
TNO-Prevention and Health and Akzo Nobel Fibers BV.**

Cover-photo with permission of:

Akzo Nobel Fibers BV, site Emmen



Print: Offsetdrukkerij Ridderprint B.V., Ridderkerk

Contents

1.	Introduction and research questions	1
1.1	Introduction	3
1.2	Purpose and research questions	7
1.3	References	9
2.	The company, the production process and study population	13
2.1	The company and the production process	15
2.2	Study population	15
2.3	References	18
3.	Measuring airway responsiveness	19
3.1	The use and the safety of a shortened histamine challenge test in an occupational study	21
3.1.1	Abstract	21
3.1.2	Introduction	22
3.1.3	Methods	23
3.1.4	Results	24
3.1.5	Discussion	28
3.1.6	References	30
3.2	Side-effects of histamine challenge in an occupational study	33
3.2.1	Introduction	33
3.2.2	Methods	33
3.2.3	Results	34
3.2.4	Discussion	35
3.2.5	References	36
4.	Airway hyperresponsiveness in workers exposed to low levels of irritants	37
4.1	Abstract	39
4.2	Introduction	39
4.3	Methods	40
4.4	Results	45
4.5	Discussion	50
4.6	References	54

5.	Airway hyperresponsiveness, prevalence of chronic respiratory symptoms, and lung function in workers exposed to irritants	59
5.1	Abstract	61
5.2	Introduction	62
5.3	Methods	63
5.4	Results	67
5.5	Discussion	77
5.6	References	82
6.	Airway hyperresponsiveness and work-related symptoms in workers exposed to irritants	85
6.1	Abstract	87
6.2	Introduction	87
6.3	Methods	89
6.4	Results	91
6.5	Discussion	98
6.6	References	102
7.	Sickness absence	107
7.1	Definition, registration and features of sickness absence	107
7.2	Determinants of sickness absence among workers exposed to irritants	109
7.2.1	Abstract	115
7.2.2	Introduction	116
7.2.3	Methods	117
7.2.4	Results	121
7.2.5	Discussion	130
7.2.6	References	137
8.	General discussion and conclusions	141
8.1	General discussion	143
8.2	Conclusions	157
8.3	References	158
	Summary	163
	Samenvatting	173
	Acknowledgement	185
	About the author	187

Chapter 1

Introduction and research questions

1.1 Introduction

Background

Obstructive airway diseases, including asthma, chronic bronchitis and emphysema, are called "CARA" in the Netherlands ("chronische aspecifieke respiratoire aandoeningen"), and form an important health problem in many Western countries (Weiss et al, 1993). A National Health Study in the Netherlands (VTV, 1993) revealed that CARA was in 1990 the second most prevalent chronic diseases among patients of general practitioners, 3.6% of the general population, and the fifth most prevalent causes of death (6.4% of all deaths in males, and 2.9% in females). Population studies in the Netherlands indicate a higher prevalence of CARA, about 8% of the population aged 15-65. Furthermore, respiratory disorders (CARA included) are believed to be the main reason for sick leave from work in the Netherlands, mainly short duration leaves (VTV, 1993). Respiratory disorders were the fourth common reason for a disability pension in 1992, although the proportion is low compared to the proportion of musculoskeletal disorders and mental disorders (3% *versus* 30% and 29%) (GMD, 1994).

Occupational airborne exposures play a role in the occurrence of obstructive airway diseases. Becklake (1989) reviewed studies which explored the relationship between occupational exposures and obstructive airway diseases, and concluded that airborne dust alone, or in combination with fumes and chemicals, may be causally related to chronic obstructive airway diseases. For fumes, gases and vapours without concomitant dust exposure, the causal relationship with the occurrence of these respiratory diseases was less clear. Workforce-based and general population studies showed that occupational exposures to gases and/or fumes (irritants) are associated with the presence of chronic respiratory symptoms, such as cough, phlegm and wheeze (Chan-Yeung et al, 1983; Järnholm et al, 1982; Osterman et al, 1989a; Korn et al, 1987; Kauffmann et al, 1982; Xu et al, 1992). Xu and coworkers could demonstrate an association between exposure to gases and/or fumes and a lower lung function level in a general population, whereas others could not find such an association in workforce-based populations (Oxhoj et al, 1982; Kennedy et al, 1989; Osterman et al, 1989b).

On the basis of cross sectional and longitudinal population studies performed in Europe and the United States in de years 1960-1990, Heederik and Pal (1993) estimated that the etiologic fraction of occupational exposures to the occurrence of obstructive respiratory

diseases was approximately 11% (confidence interval of 3-20%). At present time, the magnitude of this etiologic fraction might be different, because occupational exposures might have been changed quantitatively and qualitatively over time (Heederik and Pal, 1993).

Airway hyperresponsiveness

Airway hyperresponsiveness is defined as an increased tendency of the tracheobronchial tree to bronchoconstrict to a variety of stimuli in low doses that do not cause a similar reaction in normals. This phenomenon is regarded as a central feature of asthma which correlates with severity of the disease, frequency for respiratory symptoms, and need for treatment (Hargreave et al, 1981). However, airway hyperresponsiveness is also often found in subjects with obstructive respiratory diseases other than asthma (O'Connor et al, 1989). Furthermore, airway hyperresponsiveness can be present in subjects who do not report having respiratory symptoms, whereas other subjects may have asthma-like symptoms but no airway hyperresponsiveness (Rijcken et al, 1987; Enarson et al, 1987). Specific airway hyperresponsiveness is characterised by the phenomenon that bronchoconstriction occurs after airborne exposure to a specific agent, and it can exist without the presence of nonspecific airway hyperresponsiveness (Smith and Brooks, 1980).

In figure 1 a schematic presentation is presented. It shows a possible relation between airway hyperresponsiveness and allergic sensitization on the one hand, and the environmental exposures (allergic and non-allergic) on the other hand. Environmental exposures that are related with airway hyperresponsiveness can be distinguished in two groups, inciters and inducers (Dolovich and Hargreave, 1981; Cockcroft, 1987).

Inciters are those agents that provoke bronchoconstriction, but do not themselves increase airway responsiveness. In this case one can consider airway hyperresponsiveness as a risk factor, because subjects with hyperresponsive airways develop respiratory symptoms such as wheezing due to the bronchoconstriction. Cold air, exercise, cigarette smoke, dusts and low levels of airborne irritants are considered to be inciters (Cockcroft, 1987; Fish, 1982; Salvaggio, 1982).

Inducers on the other hand, provoke bronchoconstriction and increase airway responsiveness by inducing inflammatory processes in the airways. This increase can be the result of immunological responses to airborne allergens (for example house dust mite, animal dander) characterised by an IgE mediated reaction, or to immunological

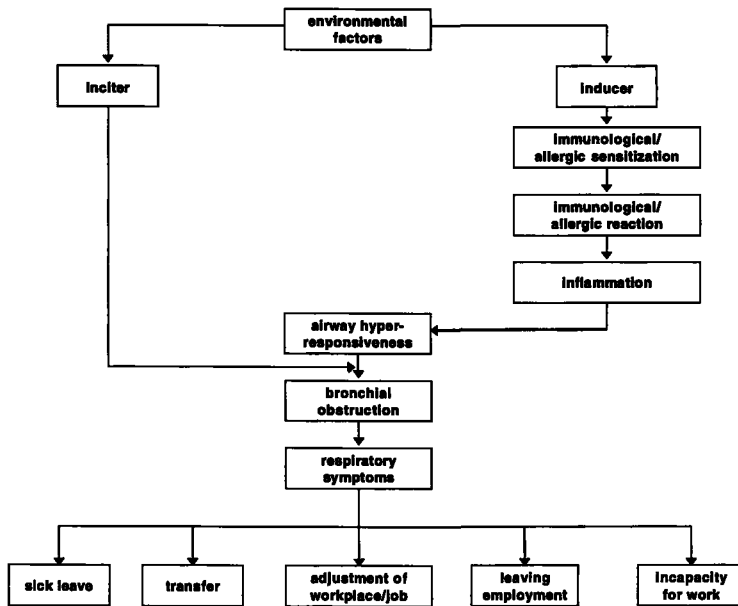


Figure 1: Scheme of the relation between environmental exposures and the development of occupational obstructive airway diseases

responses to low molecular weight chemicals (for example isocyanates and plicatic acid in red cedar) that are not always IgE-mediated (Chan-Yeung and Lam, 1986; Cockcroft, 1987; Alberts and Brooks, 1992). It is not clear whether preexisting airway hyperresponsiveness increases the susceptibility to inducing agents, whereas allergic sensitization to common airborne allergens predisposes for developing IgE-mediated sensitization to other allergens, but not to sensitization to low molecular weight chemicals (Chang-Yeung and Lam, 1986; Alberts and Brooks, 1992).

Mechanisms of occupational respiratory disorders

Occupational asthma appears to become the most prevalent occupational lung disease (Alberts and Brooks, 1992; Malo, 1993). Several definitions are used for occupational asthma. It is defined as "Variable airflow obstruction caused by a specific agent in the

workplace" and as "asthma that develops after a variable period of symptomless exposure to a sensitizing agent at work" (Chang-Yeung and Lam, 1986). Alberts and Brooks (1992) consider two types of occupational asthma:

1. Occupational allergic asthma occurs after a preceding latent period due to allergic sensitization to a substance or material present at the work site, and is characterised by work-related airflow obstruction and the presence of specific and nonspecific airway hyperresponsiveness.
2. Non-allergic occupational asthma is due to an outstanding workplace irritant exposure, develops without a preceding latent period, and is distinguished by persistent nonspecific airway hyperresponsiveness.

At present, more than 200 agents have been shown to cause allergic occupational asthma, for example isocyanates in plastic workers, nickel in metal processor workers, or wheat, rye and buckwheat in bakers (Alberts and Brook, 1992; Malo, 1993).

Other mechanisms than allergic sensitization may induce work-related airflow obstruction, such as reflex bronchoconstriction by a direct effect on the irritant receptors in the bronchial wall, broncho-obstruction due to airway inflammation caused by for example toxic gases and/or fumes or a continued allergic response, or bronchoconstriction due to agents that evoke a pharmacological response. The different underlying mechanisms lead to a spectrum of diseases ranging from quite small and symptoms-free cross-shift changes in lung function to permanent health effects, such as work-induced asthma (Fish, 1982; Chan-Yeung and Lam, 1986; Becklake, 1989; Alberts and Brook, 1992).

Although in principle one can distinguish inciters from inducers, some occupational exposures have both properties. Highly soluble gases, such as chlorine, ammonia, and sulphur dioxide (SO₂) are toxic, and exposure at high levels may induce transient airway hyperresponsiveness due to inflammatory reactions (Fish, 1982). A persistent airway hyperresponsiveness after a single exposure to high levels of toxic gases or fumes (= non-allergic occupational asthma) has also been described (Brooks et al, 1985; Alberts and Brooks, 1992). At low levels, these toxic gases have more inciter properties (Fish, 1982), but repetitive low levels of inciters may result in continued airway hyperresponsiveness (Bernstein and Bernstein, 1988).

In recent years, an important topic in respiratory research was whether airway hyperresponsiveness was a risk factor that precedes and predisposes to the development

of chronic obstructive airway disease, or conversely a manifestation of an exposure effect such as airway inflammation and airway narrowing (Chang-Yeung and Lam; 1986; Brooks and Kalica, 1987; Pride et al, 1987; O'Connor, 1989). In clinical settings, airway responsiveness is measured by means of an inhalation challenge test with a bronchoconstricting agent, such as histamine or methacholine. A disadvantage of these tests is that they are time consuming and distressing for those on whom the test is performed. To reduce the testing time, shortened standardised challenge protocols have been developed in recent years (Sterk et al, 1993). As a result, airway responsiveness is measured with increasing frequency in respiratory epidemiological studies. Despite shortened tests, applying these tests on healthy subjects in non-clinical settings, may still be reason for non-participation in occupational health surveys.

1.2 Purpose and research questions

Purpose

Sorgdrager and coworkers (1988) reviewed the literature on the relationship between occupational exposures and airway hyperresponsiveness. They concluded that certain occupational exposures are associated with an elevated prevalence of obstructive airway diseases. The role of airway hyperresponsiveness in the development of these diseases remained unclear. In continuation of the study of Sorgdrager et al (1988), the Department of Epidemiology of the University of Groningen conducted a study among workers exposed to vapours and aerosols during work. The purpose of the study was to gain more insight in the role of exposure to vapours and aerosols and airway hyperresponsiveness in the development of obstructive airway diseases, defined as respiratory symptoms or decreased lung function. The following relations may be possible:

1. Exposure causes respiratory symptoms and/or decreased lung function, which lead to an increase in airway responsiveness;
2. Exposure induces airway hyperresponsiveness, which in turn causes respiratory symptoms or a decreased lung function;
3. Exposure causes respiratory symptoms or a decreased lung function, but only or mainly in workers with hyperresponsive airways.

Insight in the relation between exposure, airway hyperresponsiveness and respiratory symptoms or decreased lung function, may give answer to the question whether the occupational physician should screen workers who are or will be exposed to vapours and mists on the presence of airway hyperresponsiveness, or on the presence of respiratory symptoms or a decreased lung function.

Research questions

A longitudinal study among workers from synthetic fibre plants who are exposed to airway irritants, was conducted between 1989 and 1992. For studying the relation between exposure and respiratory health, objective end points such as respiratory symptoms, airway hyperresponsiveness, and level of lung function (Rijcken et al, 1991) were defined. In addition, sickness absence because of respiratory problems was used as an indicator of the respiratory health of the workers.

For this thesis, the following research questions have been formulated:

1. Is in an occupational population, the use of a short histamine challenge test for assessing airway responsiveness, safe and acceptable, and what is the prevalence of the side-effects of the test? (chapter 3)
2. Have subjects exposed to airway irritants more often airway hyperresponsiveness, measured by a histamine challenge test, than non-exposed subjects, and is this associated with smoking, chronic respiratory symptoms and a history of allergy? (chapter 4)
3. Have subjects exposed to airway irritants more chronic respiratory symptoms and/or more often a low level of pulmonary function than non-exposed subjects, and is this associated with smoking, airway responsiveness and a history of allergy? (chapter 5)
4. Have subjects exposed to airway irritants more often work-related symptoms such as respiratory symptoms and nasal symptoms than non-exposed subjects, and is this associated with smoking, airway responsiveness and a history of allergy? (chapter 6)
5. Have subjects exposed to airway irritants, smokers, or subjects with chronic respiratory symptoms, airway hyperresponsiveness or a history of allergy, more and/or longer sickness absences, with special reference to absence due to respiratory symptoms? (chapter 7)

For these research questions, the data of the baseline survey and the data of the sickness absences, concerning the two year period October 1989 - October 1991, have been used. The survey was carried out at the occupational health department of the plants, from April - Juli 1989.

1.3 References

Alberts WM and Brooks SM. Advances in occupational asthma. *Clinics in Chest Medicine* 1992; 13: 281-301.

Becklake MR. Occupational exposures: Evidence for a causal association with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989; 140: S85-S91.

Bernstein D, Bernstein I: Occupational asthma. In: *Allergy Principles and Practice*. Middleton EJ, Reed C, Ellis E (eds). St Louis, CV Mosby, 1988, p 1197.

Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome. *J Occup Med* 1985; 27: 473-476.

Brooks SM and Kalica AR. Strategies for elucidating the relationship between occupational exposures and chronic air-flow obstruction. *Am Rev Respir Dis* 1987; 135: 268-273.

Chan-Yeung M, Lam S. Occupational asthma. *Am Rev Respir Dis* 1986; 133: 668-703.

Chan-Yeung M, Wong R, MacLean L, Tan F, Schulzer M, Enarson D, Martin A, Dennis R, Grzybowski S. Epidemiologic health study of workers in an aluminium smelter in British Columbia. *Am Rev Respir Dis* 1983; 127: 465-469.

Cockcroft DW. Airway hyperresponsiveness: therapeutic implications. *Ann Allergy* 1987; 59: 405-414.

Dolovich J, Hargreave F. Editorial. The asthma syndrome: inciters, inducers, and host characteristics. *Thorax* 1981; 36: 641-644.

Enarson DA, Vedal S, Schulzer M, Dybuncio A., Chan-Yeung M. Asthma, asthma-like symptoms, chronic bronchitis, and the degree of bronchial hyperresponsiveness in epidemiologic surveys. *AM Rev Respir Dis* 1987; 136: 613-617.

Fish JE. Occupational asthma: a spectrum of acute respiratory disorders. *J Occup Med* 1982; 24: 379-386.

GMD (Gemeenschappelijke Medische Dienst). Annual report 1993. Joint Medical Service, Amsterdam, 1994.

Hargreave FE, Ryan G, Thomson NC, O'Byrne PM, Latimer K, Juniper EF, Dolovich J. Bronchial responsiveness to histamine or methacholine in asthma: measurement and clinical significance. *J Allergy* 1981; 68: 347-355.

Heederik D and Pal TM. The contribution of occupational exposures to the occurrence of chronic nonspecific lung disease. In: *Prevention of respiratory diseases*. Hirsch A, Goldberg M, Martin JP, Masse G, eds. New York: Marcel Dekker, 1993, p 133-148.

Järholm B, Bake B, Lavenius B, Thiringer G, Vokmann R. Respiratory symptoms and lung function in oil mist-exposed workers. *J Occup Med* 1982; 24: 473-479.

Kauffmann F, Drouet D, Lellouch J, Brille D. Occupational exposure and 12-year spirometric changes among Paris area workers. *Br J Ind Med* 1982; 39: 221-232.

Kennedy SM, Greaves IA, Kriebel D, Eisen EA, Smith TJ, Woskie SR. Acute pulmonary responses among automobile workers exposed to aerosols of machining fluids. *Am J Ind Med* 1989; 15: 627-641.

Korn RJ, Dockery DW, Speizer FE, Ware, JH, Ferris BG. Occupational exposures and chronic respiratory symptoms: A population-based study. *Am Rev Respir Dis* 1987; 136: 298-304.

Malo J-L. Occupational asthma. In: *Prevention of respiratory diseases*. Hirsch A, Goldberg M, Martin JP, Masse G, eds. New York: Marcel Dekker, 1993, p 117-131.

O'Conner GT, Sparrow D, Weiss ST. The role of allergy and nonspecific airway hyperresponsiveness in the pathogenesis of chronic pulmonary disease. *Am Rev Respir Dis* 1989; 140: 225-252.

Osterman JW, Greaves IA, Smith TJ, Hammond SK, Robins JM, Thériault G. Respiratory symptoms associated with low level sulphur dioxide exposure in silicon carbide production workers. *Br J Ind Med* 1989a; 46: 629-635.

Osterman JW, Greaves IA, Smith TJ, Hammond SK, Robins JM, Thériault G. Work related decrement in pulmonary function in silicon carbide production workers. *Br J Ind Med* 1989b; 46: 708-716.

Oxhøj H, Andreassen H, Meyer-Henius U. Respiratory symptoms and ventilatory lung function in machine shop workers exposed to coolant-lubricants. *Eur J Res Dis* 1982; S118: 85-89.

Pride NB, Taylor RG, Lim TK, Watson JA. Bronchial hyperresponsiveness as a risk factor for progressive airflow obstruction in smokers. *Bull Eur Physiopathol Respir* 1987; 23: 369-375.

Rijcken B, Schouten JP, Weiss ST, Speizer FE, Lende R van der. The relationship of nonspecific bronchial responsiveness to respiratory symptoms in a random population sample. *Am Rev Respir Dis* 1987; 136: 62-68.

Rijcken B, Schouten JP, Rosner B, Weiss ST. Is it useful to distinguish between asthma and chronic obstructive pulmonary disease in respiratory epidemiology? *Am Rev Respir Dis* 1991; 143: 1456-1457.

Salvaggio JE. Overview of occupational immunologic lung disease. *J Allergy Clin Immunol* 1982; 70: 5-10.

Smith A, Brooks S. Absence of airway hyperreactivity to methacholine in workers sensitized to toluene diisocyanate (TDI). *J Occup Med* 1980; 22: 327-31.

Sorgdrager B, Pal TM, Lende R van der. Literatuurstudie naar beroepsmatige exposities en bronchiale hyperreactiviteit. Nederlands Astma Fonds, Leusden 1988.

Sterk PJ, Fabbri LM, Quanjer PhH, Cockcroft DW, O'Byrne PM, Anderson SD, Juniper EF, Malo J-L. Airway responsiveness. Standardized challenge testing with pharmacological physical and sensitizing stimuli in adults. *Eur Respir J*, 1993; Suppl. 16:53-83.

Weiss KB, Gergen PJ, Wagener DK. Breathing better or wheezing worse?. The changing epidemiology of asthma morbidity and mortality. *Anna Rev Publ Health* 1993; 14: 491-513.

VTG. Volksgezondheid Toekomst Verkenning. De gezondheidstoestand van de Nederlandse bevolking in de periode 1950-2010. RIVM 1993, Den Haag, Sdu Uitgeverij.

Xu X, Christiani DC, Dockery DW, Wang L. Exposure-response relationships between occupational exposures and chronic respiratory illness: A community-based study. *Am Rev Respir Dis* 1992; 146: 413-418.

Chapter 2

The company, the production process and study population

2.1 The company and the production process

The company under study manufactures synthetic fibres and polymers, which are used for example, in the carpet industry, textile industry, automotive industry (seat belts, reinforcement of car tires) or aircraft industry. At the time of the study in 1989, the company employed nearly 4000 employees of whom 3100 are working in the five production plants and 900 in the six supporting service departments, like the Engineering Department or the Personnel and Social Affairs Department. The production plants are operating continuously, seven days a week. The majority of the workers of the production plants work on the shift system.

The plants produce polyamide, polyester and para-aramide yarn and fibres. The produced polyester is a polycondensation product of terephthalic acid and ethylene glycol and polyamide is a polycondensation product of caprolactam. The production process of the yarn and fibres consists of polymerisation and polycondensation of the monomers, cutting up of the polymer, melting of the chips or granules, spinning and winding. The spun filaments can be twisted, drawn and texturised. After spinning, a synthetic oil mixture is applied to the yarn which functions as an emulsifier and lubricant.

The production process of the para-aramide fibres is quite different. The supplied polymer-powder is dissolved in a sulphuric acid solution, after which it is spun. The filaments are rinsed with water to remove the sulphuric acid, which is regenerated. The yarn is dried, wound and texturised. The polymer-powder is not produced at the para-aramide plant, but at another site. The process from dissolving the polymer up to the spinning is fully automated and takes place in separate production halls. The rest of the process takes place in one production hall.

The composition of the product (chips, granules, fibres, yarn), the colour and whether or not yarn should be twisted, drawn or texturised is determined by the specification of the individual customers.

2.2 Study population

Male employees from departments with potential exposure to airway irritants and a control group from departments presumed to be free from exposure, were invited to

participate in the survey. In May 1989 the total number of workers eligible for investigation was 909 men.

Data on exposure and exposure levels were derived from occupational hygiene studies performed by the Safety and Environmental Department of the company and by the University of Nijmegen and Agriculture University of Wageningen (de Boer, 1990; Gouders en van Til, 1991; Hartmans et al, 1990; Paardekoper, 1992). On the basis of job titles and working department at the time of the survey, the exposure status at the time of the survey of all workers was characterised. The workers were divided into seven groups.

(1) *Reference group* - This group consisted of workers of the forwarding department, the reelers of the industrial yarn plant and the texturisers of the carpet yarn plant. These workers were not subjected to exposure to airway irritants;

(2) *White collar group* - This group consisted of clerical workers and workers who were not directly involved in the production of the yarn and fibres (for example process technologists, production instructors, production floor managers), were not included in the reference group because of a different social or working background (Higgins, 1984).

(3) *The SO₂, H₂SO₄, HCl group* - This group consisted of production line workers and maintenance and instrumentation fitters who could have been exposed to sulphur dioxide (SO₂) and hydrogen chloride (HCl) vapour and sulphuric acid (H₂SO₄) and HCl aerosols, generated during the production of the para-aramide fibres. Personal sampling (seven hour time weighted average) showed maximum concentrations of SO₂ vapour of 0.30 mg/m³, of HCl aerosols of 2.1 mg/m³ and of H₂SO₄ aerosols of 0.5 mg/m³. For certain work operations peak exposures have been registered up to 40 mg/m³ HCl vapour (averaging time a few minutes) and up to 46 mg/m³ SO₂ vapour (averaging time a few seconds). During texturising of the yarn, exposure to airborne para-aramide fibres is possible. Monitoring of personal exposure to airborne para-aramide fibres over a four year period showed maximum five hour time weighted average concentrations of 0.11 respirable fibres/cm³.

(4) *Polyester vapour group* - This group consisted of workers of the polyester chip department who were involved in the polymerization and polycondensation of the monomers terephthalic acid and glycol and cutting up of the polyester polymer into chips. Some thermodegradation of the polymer can occur due the high temperature (250 to 300 °C) during polycondensation. Workers can be exposed to vapours of

these thermodegradation products like aldehyde vapours, and to diphenyl diphenyl-oxide (used as a heat transfer agent) vapour. Personal sampling showed maximum five hour time weighted average concentrations of total aldehyde vapour of 0.04 mg/m^3 , primarily consisting of acetaldehyde. No aldehyde peak exposure could be detected (averaging time 30 minutes). Personal sampling of diphenyl diphenyloxide exposure showed eight hour time weighted average concentrations up to 7.3 mg/m^3 ($n=29$; geometric mean (GM) of 2.2 mg/m^3) under normal conditions and as a result of an incident up to 48.1 mg/m^3 ($n=14$; GM 8.5 mg/m^3). For certain operations peak exposures to diphenyl diphenyloxide occur; monitoring (averaging time 30 seconds) showed peak exposures up to 60 mg/m^3 . Also, during certain operations (process temperature around 250°C) and as a result of a leak, workers can be exposed ethylene glycol vapour.

(5) *The oil mist and oil vapour group* - This group was composed of the workers who were involved in winding and stretching (spin-draw-winders) of industrial yarn (polyester and polyamide) and of the workers of the spin-draw-winding and texturising carpet yarn department. There was exposure to oil mist and oil vapour emanating from the synthetic oil mixture that is applied to the yarn, occurs. Monitoring (averaging time 20-30 seconds) near the machines revealed respirable oil aerosols up to 1.1 mg/m^3 in normal situations and up to 4.4 mg/m^3 during interruptions. Thermodegradation of some components of the oil can occur caused by the high temperature (around 180°C) of the yarn. The air in the area of one of the three production lines of the winding and stretching department is humidified with a steam humidification system. The air in the area of the other two lines and the air of the spin-draw-winding and texturising department is humidified with a cold water spray system. Exposure to airborne viable materials from the cold water spray system is possible. Results of an occupational exposure study showed low concentrations of airborne Gram negative bacteria ($n=6$; GM 47 colony forming units (cfu)/ m^3), of fungi ($n=6$; GM 7.5 cfu/m^3) and of personal exposure to endotoxine ($n=5$; GM 64 pg/m^3 (Kateman et al, 1990).

(6) *Polyamide and polyester vapour group* - This group consisted of the spinners of the industrial yarn plant who were involved in spinning of the melted polyamide and polyester chips to yarn and in exchanging spinning garnitures. Thermodegradation products of the polyamide polymer and polyester polymer can arise due the high temperature of the production process ($> 200^\circ\text{C}$). Spinners can be exposed to va-

pours of these products (for example oligomers) and to lactam vapour; measurements near the machines showed 150 minute time weighted average concentrations of lactam vapour with a GM of 15.9 mg/m^3 ($n=3$).

Personal sampling showed that both the oil mist ($n=6$) and the polyamide and polyester vapour group ($n=26$) were exposed to low concentrations of diphenyl diphenyl-oxide (eight hour time weighted average; GM 0.2 mg/m^3) and for both groups exposure to aldehyde vapour was of the same order of magnitude, independent of function tasks ($n=25$; eight hour time weighted average; GM 8.4 mg/m^3).

(7) *Multiple exposures group* - This group consisted of maintenance engineers. They were exposed to different airway irritants depending on location within the plant (for example oil mist and oil vapour, aldehyde and oligomer vapours, lactam, soldering fumes, but no acid aerosols).

2.3 References

Boer K. Blootstelling aan acetaldehyde in een polyester-produktiebedrijf. Afdeling Arbeids- en bedrijfsgeneeskunde, Instituut voor Sociale Geneeskunde, Katholieke Universiteit Nijmegen september-november 1990.

Gouders, BCM, Til H van. Karakterisering van de blootstelling aan de luchtwegen bij werknemers van de technische dienst bij AKZO-Emmen. Vakgroep Luchthygiëne en -verontreiniging. Landbouwniversiteit Wageningen 1991.

Hartmans EAM, Roest MR, Tjoe Ny EIM. Luchtwegirriterende stoffen in een aramidegaren bedrijf: Karakterisering van de blootstelling aan zwaveldioxide, zoutzuur en zwavelzuur. Vakgroep Luchthygiëne en -verontreiniging en Vakgroep Gezondheidsleer, Landbouwniversiteit Wageningen 1990-421 /V-258.

Higgins M. Epidemiology of COPD: State of the Art. Chest 1984; 85: 3S-8S.

Kateman E, Heederik D, Pal TM, Smeets M, Smid T, Spitteler M. Relationship of airborne microorganisms with the lung function and leucocyte levels of workers with a history of humidifier fever. Scand J Work Environ Health 1990; 16: 428-433.

Paardekooper, DP. Het toetsen van de semi-kwantitatieve schattingsmethode in een kunstvezelfabriek. Vakgroep Luchthygiëne en -verontreiniging, Landbouwniversiteit Wageningen 1990; V-309.

Chapter 3

Measuring airway responsiveness

3.1 The use and the safety of a shortened histamine challenge test in an occupational study¹

3.1.1 Abstract

Question: to evaluate a shortened histamine challenge test used in a study of occupational airway disease. Considered were: safety defined as the absence of a decrease in FEV₁ of greater than 40%, the occurrence of complaints, the repeatability of test results, and the average amount of time saved.

Methods: the basic method was a standard protocol of 30 s tidal breathing with sequential doubling concentrations from 1 to 32 mg/ml histamine. Subjects without indication of hyperresponsive airways were allowed to start at 4 mg/ml. If the decrease in FEV₁ was <6% a concentration was skipped. The test was terminated if the decrease in FEV₁ was at least 18%.

Results: 697 subjects performed a test. None of the subjects with a PC₂₀ value of ≤4 mg/ml (n=16) started at 4 mg/ml. Six subjects reached a ≥20% FEV₁ fall (range 21-24%) after a 4-fold increase in concentration. Five subjects had a decrease in FEV₁ of greater than 40% and these occurred after a doubling concentration. Cough, flushing, and chest tightness, were noted in 18% of the subjects. The majority of tested subjects, 56%, applied the shortest provocation scheme that was possible (phosphate solution, followed by 4, 16 and 32 mg/ml histamine), resulting in a time reduction of nearly 50% per test, reducing the total study time from 5 to 3 months.

Conclusion: the shortened histamine challenge test is time saving. Bronchoconstriction of greater than 40% did occur only in 5 subjects and was not due to skipping concentrations.

¹ Revised version of the paper: A.M. Kremer, T.M. Pal, M. Oldenziel, M. Kerkhof, J.G.R. de Monchy, B. Rijcken. The use and the safety of a shortened histamine challenge test in an occupational health study. *European Respiratory Journal* 1995, accepted for publication

3.1.2 Introduction

Measuring airway responsiveness may be important in the investigation of effects of airborne exposure. However, challenge tests are time consuming and this can be a problem in an occupational setting when healthy workers participate in a study. The full protocol of both the 2 min tidal breathing method with sequential doubling concentrations from 0.03 to 8.00 mg/ml of the agonist (total of 9 concentrations) and the dosimeter method with doubling sequential concentrations from 0.075 to 25 mg/ml of the agonist, inhaled at intervals of 5 min (Cockcroft et al, 1977; Chai et al, 1975) take at least 50 min to complete. The 30 s tidal breathing method, with doubling concentrations from 1 to 32 mg/ml (total of 7 concentrations), inhaled at intervals of 2.5 min (De Vries et al, 1962) takes about 20 min to complete.

In an occupational setting, we studied the relationship of airborne exposures, airway responsiveness and respiratory problems. Airway responsiveness was assessed by means of a histamine challenge test. To improve the acceptability of the test for both the participants and the management of the plant, we decided to apply a shorter challenge test that was less time consuming. There are various ways to achieve this, such as starting with a higher dose (or concentration) (Chatham et al, 1982; Hargreave et al, 1981; Hendrick et al, 1986), using 4-fold increases in the inhaled doses (Chatham et al, 1982; Yan et al, 1983), resuming doubling doses if a 10% FEV₁ fall occurs (Woolcock, 1985), and by decreasing the time between doses (Yan et al, 1983). We followed the recommendations of the SEPCR Working Group (Eiser et al, 1983) and of Hargreave and co-workers (1985).

Applying shortened challenge tests may imply certain risks for the participants. A high starting dose may be followed by a considerable bronchoconstriction that might not have occurred at the regular low starting dose. In general, one would not like such a sudden fall in FEV₁, say of >40%, to happen right after the initial dose. Such a degree of obstruction is likely to cause discomfort to the tested subject. Thus, subjects who are likely to have hyperresponsive airways should not be allowed to have the high starting dose. A subject might also experience such a severe obstruction if a 4-fold increased dose is applied, whereas a 2-fold increased dose would have caused a less severe obstruction. For this reason, shortened protocols resume doubling doses if a dose is followed by a decrease in FEV₁ of greater than 10%. The purpose of the current report is to evaluate whether the shortened protocol is "safe", this means whether severe

obstruction, say a fall in FEV_1 of $>40\%$, does not occur after the high initial dose or after a 4-fold increased dose. In addition, we considered the occurrence of complaints, the repeatability of test results, and the average amount of time saved.

3.1.3 Methods

Forced expirations after maximal inspiration were performed with a water-sealed spirometer. Three satisfactory manoeuvres were required of each subject, e.c. the FVC was reproducible within 5% with a maximum of 300 ml (Quanjer et al, 1994). Measurements were corrected for body temperature, atmospheric pressure, and water saturation (BTPS). Aerosols were generated by a Wiesbaden Doppelinhalator. The nebulisers were calibrated at an output of 0.13 ± 0.01 ml/min. The full 30 s tidal breathing protocol had a repeatability (Albronda, 1992) comparable to other tests (Chinn et al, 1987; Britton et al, 1986; Weeke et al, 1987). Subjects with a pre-challenge FEV_1 of less than 80% predicted (Eiser et al, 1983; Quanjer, 1983), or daily medication for a pulmonary or a cardiovascular disease were not allowed to perform a challenge test. After pre-test with phosphate solution, subjects inhaled sequential aerosols of histamine biphosphate in concentrations of 1, 2, 4, 8, 16 and 32 mg/ml at intervals of 2.5 min. The FEV_1 was measured at 30 and 90 s after each concentration. The test was terminated if there was a fall in FEV_1 of at least 20% from baseline FEV_1 or if the highest concentration had been given. Subjects were asked not to take bronchodilators within 8 hours, or antihistaminic drugs within 72 hours before the test.

The starting concentration of the short protocol was 4 mg/ml histamine. Subjects were not allowed to start at 4 mg/ml, but had to start at 1 mg/ml if they met with one or more of the following criteria: reporting dyspnoea grade III (confirming the question whether they had "shortness of breath when walking with other people of their own age on level ground"), or ever wheeze, or ever asthmatic attacks, or a "history of allergy" (confirming the question "Have you ever had hay fever?" or "Do you get eye, nose, or respiratory symptoms when you are exposed to house dust, domestic animals or fungi?"), or a fall in FEV_1 of at least 6% after phosphate solution. All subjects skipped the next concentration if the fall in FEV_1 was less than 6%. After a fall of FEV_1 of $\geq 6\%$, doubling concentrations were resumed. The test was terminated if the fall in FEV_1 was at least 18%, or if the highest histamine concentration had been given. Airway

hyperresponsiveness was defined as a PC_{20} of ≤ 32 mg/ml histamine. As PC_{15} correlates well with a PC_{20} (Eiser et al, 1983; Neijens et al, 1982), we presumed that stopping the test at an 18% FEV_1 fall would not markedly influence the PC_{20} estimation.

Complaints during or after the test, such as flushing, chest tightness, coughing, not feeling well (shivering, paleness and/or dizziness), hoarseness and throbbing headache were recorded. Only the coughing that occurred independently of the performed spirometric manoeuvres and that was distressing for the participant, was considered as a side-effect of histamine challenge.

The study was approved of the Ethics Board of the Groningen University Hospital and Medical School. Written informed consent was obtained from all participants.

3.1.4 Results

The short protocol was applied in an occupational health study in 1989 (Kremer et al, 1994). Of the 909 invited male workers, 790 subjects participated in the study. An acceptable pulmonary function test was obtained in 775 subjects. The variation coefficient of the FEV_1 was 2.5% (95% confidence interval 0.0-5.3%), thus meeting the 5% standard (Anonymus, 1987).

Table 1: Reported complaints during and after histamine challenge testing in 735 subjects.

Complaints	n (%)
Flushing	55 (7.5)
Chest tightness	48 (6.5)
Cough	20 (2.5)
Not feeling well (shivering, paleness and/or dizziness)	7 (1.0)
Hoarseness	4 (0.5)
Throbbing headache	3 (0.5)

A challenge test was performed on 735 subjects. One or more complaints were reported by 125 subjects (18%) (table 1): 7.5% had flushing (n=55), 6.5% chest tightness (n=48), 2.5% cough (n=20). Seven subjects reported not feeling well (shivering, paleness and/or dizziness, in combination with cough, headache and/or chest tightness), four subjects had

hoarseness and three subjects a throbbing headache. Coughing occurred mainly at 32 mg/ml, whereas "not feeling well" occurred also at lower concentrations of histamine (16 and 8 mg/ml).

The challenge test was not performed on 55 subjects (table 2). Daily medication for cardiovascular disease (n=15) and a FEV₁ value of less than 80% predicted (n=22) were the major reasons for exclusion. For various reasons, from 38 subjects the challenge data could not be used: the test had to be terminated because of not feeling well (n=6), coughing (n=7), or error in the procedure (n=3). Poor quality of the test caused an additional loss of data from 22 subjects.

Table 2: Reasons for excluding subjects from analysis (N=93)

I No histamine challenge test (n=55):		N
Exclusion criteria		
* daily medication for a lung disease		5
* daily medication for a cardio-vascular disease		15
* lung disease		2
* FEV ₁ <80% of the predicted value		22
Refused		2
Procedure error		1
Subjective complaints during spirometry		4
Miscellaneous reasons		4
II Data histamine challenge test rejected (n=38):		
Incomplete data		
* had to stop, not feeling well		6
* no FEV ₁ manoeuvre because of cough		7
* procedure error		3
Poor quality of the test		22

A complete test of good quality was achieved in 697 subjects (790-55-38) and 440 of these started at 4 mg/ml. There were 257 subjects with ≥ 1 positive criteria and these subjects had to start the test at 1 mg/ml histamine (table 3). If our selection criteria were right, subjects with a PC₂₀ value of ≤ 4 mg/ml should have one or more of the selection criteria (sensitivity of the criteria). This was indeed the case, so that the sensitivity of the selection criteria was 100%. However, the specificity of the selection criteria, this

Table 3: Distribution of the selection criteria, stratified by PC₂₀ values

Selection criterion	PC ₂₀ values (mg/ml)					Total (N=697) N (%)
	≤4	>4-≤8	>8-≤16	>16-≤32	>32	
	(N=16) n (%)	(N=13) n (%)	(N=38) n (%)	(N=97) n (%)	(N=533) n (%)	
Dyspnoea Grade ≥III	1 (6)	2 (15)	2 (5)	3 (3)	8 (2)	16 (2)
Ever wheeze	12 (75)	7 (54)	19 (50)	33 (34)	105 (20)	176 (25)
Ever asthmatic attack	3 (19)	2 (15)	5 (13)	6 (6)	12 (2)	28 (4)
History of allergy	7 (44)	4 (31)	9 (24)	13 (13)	57 (11)	90 (13)
≥6% FEV ₁ fall at phosphate solution	9 (56)	7 (54)	7 (18)	9 (9)	15 (3)	47 (7)
≥1 criteria positive	16 (100)	10 (77)	28 (74)	47 (48)	156 (29)	257 (37)
No criteria positive	-	3 (23)	10 (26)	50 (52)	377 (71)	440 (63)

is the proportion of subjects with a PC₂₀ value of >4 mg/ml (n=697-16) who had no positive criterion (n=440), was relatively low: 65% (440/681). This means that 35% of these 681 subjects also could have started the test at 4 mg/ml. To increase the specificity of the selection criteria, the presence of frequent wheeze (wheeze more than once a year) might have been chosen instead of ever wheeze. This would have reduced the number of subjects in whom the test had to be started at 1 mg/ml from 257 (37%) to 197 (28%), and would have increased the number of subjects with a PC₂₀ value of >4 mg/ml who could start the test at 4 mg/ml: higher specificity (73%). However, this would have implied that one subject with a PC₂₀ value of 1.53 mg/ml (31% fall in FEV₁ at 2 mg/ml), would have started at 4 mg/ml lowering the sensitivity to 94%. We did not use the presence of chronic cough, chronic phlegm and bronchitis episodes as additional criteria in the protocol to have subjects start at 1 mg/ml. This proved to be right, as including these symptoms as selection criteria would have decreased the specificity from 65% to 43%, because 308 subjects would have had to start the test at 1 mg/ml. The sensitivity could not improve by adding these criteria to the protocol because it already was 100%.

The mean fall in FEV₁ for subjects with a PC₂₀ ≤32 mg/ml was 24.2% (range 18 - 50%) with a median of 23%. Twelve (7%) of the 164 subjects with a PC₂₀ ≤32 mg/ml had a ≥18% FEV₁ fall after a 4 fold-increase in concentration. Of these 12 subjects, six had a ≥20% fall in FEV₁ (range 21 - 24%). A fall in FEV₁ of ≥30% after doubling concentration occurred in 21 subjects of whom five had a fall of ≥40% (range 40-50%).

Of these subjects, one subject had a 31% FEV₁ fall at 1 mg/ml with a previous fall at phosphate solution of 16%. In 20 subjects the challenge test was terminated because a fall of 18% or 19% in FEV₁ had occurred.

In this population, in eight subjects a 6% to 10% fall in FEV₁ at ≤ 8 mg/ml was followed by a $\geq 20\%$ fall (range 20-34%) after one doubling concentration. In another 39 subjects, a 6% to 10% fall in FEV₁ at ≤ 8 mg/ml histamine was followed by a $\geq 20\%$ fall in FEV₁ after two doubling concentrations. Thus, if we had chosen to resume doubling doses if the fall in FEV₁ was greater than 10%, 14 (6+8) to 53 (6+8+39) of the hyperresponsive subjects (9-32%) might have had a $\geq 20\%$ fall in FEV₁ after a 4-fold increase in concentration.

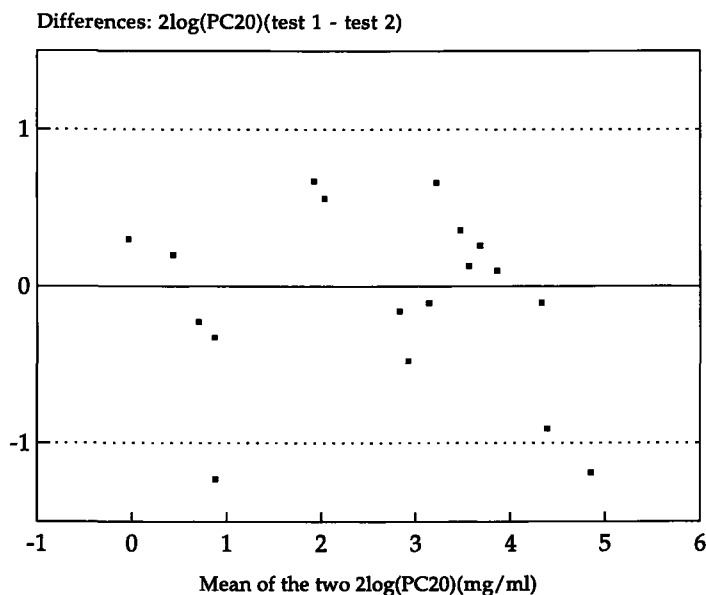


Figure 1: Repeatability of PC_{20} measurements within 5 days in 18 subjects: Differences in doubling concentration between the two PC_{20} values against the average PC_{20} value

A full protocol required approximately 20 min to complete (baseline spirometry not included). Subjects who started their test at 4 mg/ml and skipped the next concentration had to perform four provocation manoeuvres: the phosphate solution, the 4, 16 and 32

mg/ml, and this challenge test took about 11 min. The maximal time profit by skipping three concentrations could be obtained in 56% of the study population.

The repeatability of the short protocol was examined in 19 subjects with a known airway responsiveness to histamine, and who were not involved in the health survey study. The two tests were performed at the same time of the day with one to three days in between. After $^2\log$ -transformation, the differences between the two PC₂₀ estimations of 18 subjects ranged from -1.23 to +0.67 doubling concentrations with a mean of -0.08 (figure 1). The repeatability, expressed as the 95% range for a single measurement $t_{0.05}(SD)/\sqrt{2}$, was ± 0.85 doubling concentrations (Altman and Bland, 1983). For one subject, the difference could not be estimated (PC₂₀ >128 mg/ml and 37.4 mg/ml).

3.1.5 Discussion

Using the short protocol, decreases of FEV₁ of 30% or more did not occur at the 4 mg/ml starting concentration, nor after a 4-fold increase in concentration. All subjects with a PC₂₀ value of ≤ 4 mg/ml were identified by the selection criteria. A more severe bronchoconstriction was prevented in 20 subjects by stopping at 18% FEV₁ fall. The maximal reduction of time needed to complete a test was nearly 50%, and as much as 56% of the participants performed this maximally shortened test. Complaints were reported by 18% of the participants.

Although all hyperresponsive subjects were identified appropriately, the low specificity of the selection criteria of 65% resulted in a large proportion of the population that also had to start at 1 mg/ml histamine. The specificity may be higher when questions such as "Wheeze, more than once a year" (our questionnaire) or "wheeze in the last 12 months, even when one does not have a cold" (not in our questionnaire) are used instead of "ever wheeze". Chronic cough or phlegm and bronchitis periods do not provide additional information, confirming results of others (Burney et al, 1989; Lundbäck et al, 1993).

Stopping at 18% fall in FEV₁ shortened the duration of the test and resulted in a less severe bronchoconstriction in 20 of the 164 hyperresponsive subjects (12%). One purpose of this was to avoid having workers with a severe bronchoconstriction who could tell fellow workers that the challenge test is distressing. Such stories can be a reason for the nonparticipation of other subjects in the plant. The perceived safety of a

test also influences the participation in the follow-up study (Hendrick et al, 1986; Higgins et al, 1988). Falls of more than 40% in FEV_1 occurred in five of the 697 subjects. However, this happened after the normal double increase in concentration. PC_{20} values estimated by a full and a shortened protocol may be different due to a difference in the cumulative dose of the inhaled histamine. Some investigators (Yan et al, 1983; Connonly et al, 1988) found evidence to support a cumulative effect of histamine, whereas others could not demonstrate this effect (Neijens et al, 1982; Juniper et al, 1978). Tremblay and co-workers (1984) concluded that the cumulative effect of histamine might only be present once significant bronchoconstriction is reached. Anyway, differences between PC_{20} , calculated on a noncumulative scale and on a cumulative scale are within the repeatability range of the provocation test (Tremblay et al, 1984). These findings, as well as recently published safety guidelines (Sterk et al, 1993) support our decision to resume doubling concentrations when there is 6% decrease of FEV_1 . In other studies, one resumed doubling doses after a fall of FEV_1 of greater than 10%, but doses were skipped only in subjects who were not at increased risk of responding (Bakke et al, 1991; Chinn et al, 1987; Yan et al, 1983). To complete the evaluation of the short protocol, results should be compared to those from a standard full protocol, specifically with respect to subjects who started at 4 mg/ml and appeared to be hyperresponsive.

Subjects with an FEV_1 value of less than 80% predicted were not allowed to do a challenge test (Kremer et al, 1994). Other investigators used an FEV_1 value of <60% (Bakke et al, 1991; Chinn et al, 1987), or <65% (Abramson et al, 1990), or <70% (Woolcock et al, 1987), and no problems were reported. This may suggest that subjects with an FEV_1 between 70 and 80% predicted could be included, starting at 1 mg/ml histamine.

It took 3 months to complete our field work. If we had used a 2 min protocol, this would have taken 5 months. In subjects with non-responsive airways, it took 11 min to perform the challenge test, which is similar to the short protocol of Yan and co-workers [Woolcock et al, 1987; Yan et al, 1983]. This latter protocol seems to be well tolerated, but no safety data have been published.

Although we were aware that histamine may cause more side-effects, such as flushing and throbbing headache, than methacholine (Eiser et al, 1983), histamine was chosen because it was used at the health department of the plant and in our research group for epidemiological studies (Rijcken et al, 1989). Furthermore, at the time of the start of the

study, methacholine was difficult to obtain for human research purposes in this country. In a study among 342 adults, Higgins and co-workers (1988) found that histamine caused voice changes more often than methacholine, 21% versus 11%, whereas the occurrence of cough was similar with both agents, 30% and 34%. The symptoms of shivering, paleness and/or dizziness which occurred in our study in a few subjects, are most likely due to the repeated spirometric manoeuvres and not to the use of histamine. In addition to the side-effects during the test, some subjects reported that they had experienced symptoms such as hoarseness and chest tightness after they returned to work. This finding was also reported by Hendrick and co-workers (1986) who found in their study with methacholine challenge that 61 out of 222 workers had symptoms, such as cough, chest tightness or wheeze, that started within 6 hour of testing. Participants should be informed about potential side-effects in advance (Hendrick et al, 1986). We conclude that the shortened histamine challenge test is time saving and excessive bronchoconstriction did occur only in a few cases and was not due to skipping concentrations.

3.1.6 References

- Abramson MJ, Saunders NA, Hensley MJ. Analysis of bronchial reactivity in epidemiological studies. *Thorax* 1990; 45: 924-929.
- Albronda B, Wijkstra P, Gimeno F, Altena R van, Kremer AM, Monchy JGR de. Repeatability of the 30 sec histamine inhalation challenge test and comparison with the 2 min method. *Am Rev Respir Dis* 1992; 145: A732.
- Altman DG, Bland JM. Measurement in medicine: the analysis of method comparison studies. *Statistician* 1983; 32: 307-317.
- Anonymus. Standardization of spirometry - 1987 Update. *Am Rev Respir Dis* 1987; 136: 1285-1298.
- Bakke PS, Baste V, Gulsvik A. Bronchial responsiveness in a Norwegian community. *Am Rev Respir Dis* 1991; 143: 317-322.
- Britton J, Mortagy A, Tattersfield A. Histamine challenge testing: comparison of three methods. *Thorax* 1986; 41: 128-132.

Burney PGJ, Chinn S, Britton JR, Tattersfield AE, Papacosta AO. What symptoms predict the bronchial response to histamine? Evaluation in a community survey of the Bronchial Symptoms Questionnaire (1984) of the International Union Against Tuberculosis and Lung Disease. *Int J Epidemiol* 1989; 18: 165-173.

Chai H, Farr RS, Froehlich LA, Mathison DA, McLean JA, Rosenthal RR, Sheffer AL, Spector SL, Townley RG. Standardization of bronchial inhalation challenge procedures. *J Allergy Clin Immunol* 1975; 56: 323-327.

Chatham M, Bleecker ER, Norman PS, Smith PL, Mason P. A screening test for reactivity. *Chest* 1982; 82: 15-18.

Chinn S, Britton JR, Burney PGJ, Tattersfield AE, Papacosta AO. Estimation and repeatability of the response to inhaled histamine in a community survey. *Thorax* 1987; 42: 45-52.

Cockcroft DW, Killian DN, Mellon JJ, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977;7: 235-243.

Connolly MJ, Avery AJ, Walters EH, Hendrick DJ. The use of sequential doses of inhaled histamine in the measurement of bronchial responsiveness: Cumulative effect and distortion produced by shortening the test protocol. *J Allergy Clin Immunol* 1988; 82: 863-868.

De Vries K, Goei JT, Booij-Noord H, Orie NGM. Changes during 24 hours in the lung function and histamine hyperreactivity of the bronchial tree in asthmatic and bronchitic patients. *Int Arch Allergy* 1962; 20: 93-101.

Eiser NM, Kerrebijn KF, Quanjer PhH. Guideliness for standardization of bronchial challenges with (nonspecific) bronchoconstricting agents. *Bull Eur Physiop Resp* 1983; 19: 495-514.

Hargreave FE, Ryan G, Thomson NC, O'Byrne PM, Latimer K, Juniper EF, Dolovich J. Bronchial responsiveness to histamine or methacholine in asthma: measurement and clinical significance. *J Allergy Clin Immunol* 1981; 68: 347-355.

Hargreave FE, Sterk PJ, Ramsdale EH, Dolovich J, Zamel N. Inhalation challenge tests and airway responsiveness in man. *Chest* 1985; 87 (Suppl 5): 202S-206S.

Hendrick DJ, Fabbri LM, Hughes JM, Banks DE, Barkman HW, Connolly MJ, Jones RN, Weill H. Modification of the methacholine inhalation test and its epidemiological use in polyurethane workers. *Am Rev Respir Dis* 1986; 133: 600-604.

Higgins BG, Britton JR, Chinn S, Jones TD, Vathenen AS, Burney PGJ, Tattersfield AE. Comparison of histamine and methacholine for use in bronchial challenge tests in community studies. *Thorax* 1988; 43: 605-610.

Juniper EF, Frith PA, Dunnett C, Cockcroft DW, Hargreave FE. Reproducibility and comparison of responses to inhaled histamine and methacholine. *Thorax* 1978; 33: 705-710.

Kremer AM, Pal TM, Boleij JSM, Schouten J, Rijcken B. Airway hyperresponsiveness, chronic respiratory symptom prevalence and lung function in workers exposed to irritants. *Occup Environ Med* 1994; 51: 3-13.

Lundbäck B, Stjernberg N, Rosenhall L, Lindström M, Jönsson E, Andersson S. Methacholine reactivity and asthma. Report from the Northern Sweden Obstructive Lung Disease Project. *Allergy* 1993; 48: 117-124.

Neijens HJ, Hofkamp M, Degenhart HJ, Kerrebijn KF. Bronchial responsiveness as a function of inhaled histamine and the methods of measurement. *Bull Eur Physiop Resp* 1982; 18: 427-438.

Quanjer PhH. Standardized lung function testing. Report of the Working Party "Standardization of Lung Function Tests". *Bull Eur Physiop Resp* 1983; suppl 5: 1-95.

Quanjer, PhH, Tammeling GJ, Cotes E, Pederson OF, Peslin R, Yernault J-C. Standardization of lung function testing. *Eur Respir J* 6, 1993; suppl 16: 5-40.

Sterk PJ, Fabbri LM, Quanjer PhH, Cockcroft DW, O'Byrne PM, Anderson SD, Juniper EF, Malo J-L. Airway responsiveness. Standardized challenge testing with pharmacological physical and sensitizing stimuli in adults. *Eur Respir J*, 1993; Suppl. 16:53-83.

Tremblay C, Lemire I, Ghezzi H, Pineau L, Martin LL, Cartier A, Malo JL. Histamine phosphate has a cumulative effect when inhaled at five minute intervals. *Thorax* 1984; 39: 946-951.

Weeke B, Madsen F, Frolund L. Reproducibility of challenge tests at different times. *Chest* 1987; 91S: 83S-9S.

Woolcock AJ. Tests of airway responsiveness in epidemiology. In: Airway responsiveness: measurement and interpretation. Proceedings of a workshop. FE Hargreave, AJ Woolcock (eds.) Astra, Ontario, 1985: 136-140.

Woolcock AJ, Peat JK, Salome CM, Yan K, Anderson SD, Schoeffel RE, McCowage G, Killalea T. Prevalence of bronchial hyperresponsiveness and asthma in a rural adult population. *Thorax* 1987; 42: 361-368.

Yan K, Salome C, Woolcock AJ. Rapid method for measurement of bronchial responsiveness. *Thorax* 1983; 38: 760-765.

3.2 Side-effects of histamine challenge in an occupational study

A.M. Kremer, T.M. Pal, B. Rijcken, J.G.R. de Monchy

3.2.1 Introduction

Bronchial challenge tests are time consuming and this may present problems in occupational studies. In a follow-up studie we applied a time saving abbreviated 30 seconds tidal breathing protocol for assessing airway responsiveness (Kremer et al, 1994). The test was safe, but 18% of the subjects spontaneously reported complaints that might interfere with future cooperation. In the follow-up study, the side-effects were recorded systematically. In contrast to the baseline study, also subjects with values of FEV₁ between 70% and 80% were allowed to perform a test. The safety of the test for these subjects in terms of excessive decreases of FEV₁ is also evaluated.

3.2.2 Methods

After pre-test with phosphate solution, subjects inhaled for 30 seconds sequential aerosols of histamine in concentrations from 1 to 32 mg/ml. The test was terminated if, compared to the pre-challenge FEV₁, a fall in FEV₁ of $\geq 18\%$ occurred, or if the highest concentration had been given. Subjects started at 1 mg/ml histamine if they had asthma-like symptoms, or a history of allergy, or a baseline FEV₁ value between 70% and 80% predicted, or a fall in FEV₁ of at least 6% after phosphate solution. All the others started at 4 mg/ml. A histamine concentration was skipped until the FEV₁ had fallen 6% or more, then the schedule changed to doubling concentrations. After the test, significant cough reactions, chest tightness, flushing, hoarseness, throbbing headache and "not feeling well" (shivery, paleness and/or dizziness) were noted.

PC₂₀ was defined as the provocation concentration causing a 20% fall in FEV₁. The study was approved by the Ethics Board of the Groningen University Hospital and Medical School. Written informed consent was obtained from all participants. The challenge test was not performed on subjects with cardiovascular disease or lung disease requiring daily medication, or whose baseline FEV₁ was below 70% of the predicted value.

3.2.3 Results

On the basis of our exclusion criteria, 33 of the 735 participants were not allowed to do the test. Concentrations of 16 or 32 mg/ml were applied to 670 of the 702 tested subjects (95%). Side-effects were reported by 289 subjects (41%). Of 19 subjects the test was incomplete due to side-effects: in eight subjects we had to stop because of significant cough ($n=6$), or of not feeling well ($n=2$), and 11 subjects could not perform a complete FEV₁ manoeuvre at the end of the test due to coughing.

Table 1: Reported side-effects of the performed challenge test (N=702), stratified by the last administered histamine concentration.

Side-effects of the test	Last histamine concentration				Total N=702 n (%)
	≤4 mg/ml (N=17)	8 mg/ml (N=15)	16 mg/ml (N=69)	32 mg/ml (N=601)	
	n (%)	n (%)	n (%)	n (%)	
chest tightness	10 (60)	8 (53)	42 (61)	122 (20)	182 (26)
flushing	1 (6)	1 (7)	13 (19)	109 (18)	124 (18)
significant cough	-	-	11 (16)	23 (4)	34 (5)
hoarseness	-	1 (7)	8 (12)	21 (3)	30 (4)
throbbing headache	-	1 (7)	3 (4)	9 (1)	13 (1)
not feeling well ¹	-	1 (7)	1 (1)	3 (<1)	5 (1)
≥1 complaints	10 (60)	9 (60)	51 (74)	219 (36)	289 (41)

¹ in combination with significant cough, headache and/or chest tightness

Cough, flushing, hoarseness and headache occurred in most cases at 16 or 32 mg/ml histamine. 50% of the subjects with an FEV₁ fall of ≥18% ($n=175$) reported chest tightness. The mean fall in FEV₁ of those with and without chest tightness did not differ, 24.2% (range 18-44%) and 24.5% FEV₁ fall (range 18-47%), respectively. Of those with a 10%-18% ($n=161$) and with less than 10% FEV₁ fall, 40% and 6%, respectively, reported chest tightness.

Twenty three subjects had an FEV₁ predicted between ≥70%–<80%. A fall in FEV₁ of 20% or more at the lowest histamine concentration had not occurred. Seventeen of the 21 subjects with a complete test had a PC₂₀ of ≤32 mg/ml. The median fall in FEV₁ of these 17 subjects was 24% (range 18-47%).

3.2.4 Discussion

The follow-up study showed that systematical collection of data on side-effects resulted in a much higher prevalence of side-effects than was reported spontaneously during the baseline study, 41% *versus* 18%. The prevalence of cough reaction and not feeling well were comparable, whereas the prevalence of flushing, chest tightness, headache and hoarseness were much higher in the follow-up study. Flushing and throbbing headache are short-term symptoms. Chest tightness may last longer, and even can occur some time after the test, as it happened to some participants of the baseline study who experienced chest tightness after they returned to work. This was reason for us in the follow-up study to administer salbutamol to all participants whenever the FEV_1 had fallen 10% or more, even when no chest tightness was reported. The occurrence of side-effects may also have influenced the willingness to participate in the follow-up survey. The response in 1991 was lower than in 1989, 78% *versus* 87% and nine subjects refused to do the test, versus two in 1989. Possibly, the use of methacholine might have resulted in a lower prevalence of side-effects, such as significant cough, flushing and throbbing headache (Eiser et al, 1983; Higgins et al, 1988).

The exclusion criterium of an FEV_1 value of less than 80% predicted, was recommended by the SEPCR working group "Bronchial hyperreactivity" (Eiser et al, 1983). New safety guidelines, published in 1993 (Stern et al, 1993), recommend as exclusion criterium an FEV_1 of greater than or equal to the predicted value minus 3 times standard deviation ($=1.5$ l) and an FEV_1 greater than or equal to 2 l for epidemiological studies. Our criterium of $\geq 70\%$ FEV_1 predicted is more strict in case the FEV_1 predicted is less than 5.0 l.

We conclude that the abbreviated 30 s tidal breathing challenge test is safe in subjects with a baseline FEV_1 of $\geq 70\%$ predicted. Systematical registration revealed that a high proportion of the participants experienced side-effects of the histamine challenge test.

3.2.5 References

Eiser NM, Kerrebijn KF, Quanjer Ph. Guideliness for standardization of bronchial challenges with (nonspecific) bronchoconstricting agents. *Bull Eur Physiop Resp* 1983; 19: 495-514.

Hendrick DJ, Fabbri LM, Hughes JM, Banks DE, Barkman HW, Connonly MJ, Jones RN, Weill H. Modification of the methacholine inhalation test and its epidemiological use in polyurethane workers. *Am Rev Respir Dis* 1986; 133: 600-604.

Higgins BG, Britton JR, Chinn S, Jones TD, Vathenen AS, Burney PGJ, Tattersfield AE. Comparison of histamine and methacholine for use in bronchial challenge tests in community studies. *Thorax* 1988; 43: 605-610.

Kremer AM, Pal TM, Boleij JSM, Schouten J, Rijcken B. Airway hyperresponsiveness, chronic respiratory symptom prevalence and lung function in workers exposed to irritants. *Occup Environ Med* 1994; 51: 3-13.

Sterk PJ, Fabbri LM, Quanjer PhH, Cockcroft DW, O'Byrne PM, Anderson SD, Juniper EF, Malo J-L. Airway responsiveness. Standardized challenge testing with pharmacological physical and sensitizing stimuli in adults. *Eur Respir J*, 1993; Suppl. 16: 53-83.

Chapter 4

Airway hyperresponsiveness in workers exposed to low levels of irritants¹

¹ Revised version of the paper: A.M. Kremer, T.M. Pal, J.P. Schouten, B. Rijcken B. Airway hyperresponsiveness in workers exposed to low levels of irritants. *European Respiratory Journal* (1995) 8 53-61

4.1 Abstract

The purpose of this study was to assess the association between occupational exposure to low levels of airway irritants, and airway responsiveness to histamine.

In 668 male workers, the symptom prevalence was assessed according to the British Medical Research Council (BMRC) questionnaire. All subjects performed a 30 s tidal breathing challenge test. Airway hyperresponsiveness (AHR) was defined as a 20% fall in forced expiratory volume in one second (FEV_1) at ≤ 32 mg/ml histamine. On the basis of job titles and working department, the exposure status of all workers was characterised into seven groups: (1) Reference group; (2) White collars; (3) SO_2 , HCl, H_2SO_4 ; (4) Polyester vapour; (5) Oil mist and oil vapour; (6) Polyamide and polyester vapour; (7) Multiple exposures.

Using multiple logistic regression, no association was found between the exposure groups and a higher prevalence of AHR. A higher prevalence was significantly associated with a low FEV_1 , a history of allergy, and the presence of chronic respiratory symptoms. Subjects from the SO_2 group and the oil mist group with ≤ 5 exposure years had a lower prevalence of AHR, probably due to pre-employment selection procedures. There was some trend for subjects with more than 5 yrs exposure to polyester vapour and to oil mist and oil vapour to have a higher prevalence of AHR. Analyses using the dose-response slope according to O'Connor revealed similar results and provided no additional information.

4.2 Introduction

Studies of general populations and occupational populations indicate that occupational exposure to fumes and vapours in combination with dust, is a risk factor for developing chronic obstructive respiratory diseases, whereas this is less clear for exposure to fumes and vapours without concomitant exposure to dust (Becklake, 1989). It has been reported that exposure to fumes and vapours can be related to airway hyperresponsiveness. Exposure to high levels may induce persistent airway hyperresponsiveness due to mucosal inflammation of the bronchus, whereas exposure to low levels of irritants may provoke an airway narrowing due to a direct effect on the bronchial irritant receptors (Alberts and Brooks, 1992; Chan-Yeung and Lam, 1986; Cockcroft, 1987; Dolovich and

Hargreave, 1981; Fish, 1982). It has not been studied whether exposures to irritant gases or fumes at levels commonly found in occupational settings result in obstructive respiratory diseases (Becklake, 1989; Brooks and Kalica, 1987).

We carried out a cross sectional study of the relation between exposure to low levels of airway irritants without concomitant dust exposure, and the presence of airway hyperresponsiveness among workers from synthetic fibre plants. As level of responsiveness is also associated with smoking, allergy and respiratory symptoms (O'Connor et al, 1989; Rijcken et al, 1993), we wanted to determine whether the relation is different for smokers, for subjects with a history of allergy, and for subjects with chronic respiratory symptoms. Furthermore, the relation of duration of exposure to airway responsiveness was studied. During the five years prior to this study, pre-employment selection had taken place for workers who applied for jobs in a working environment with exposure to SO₂, H₂SO₄ and oil mist. This potential selection bias will be addressed in the Discussion section. In the analyses, we defined responders as subjects with a provocative concentration of histamine producing a 20% fall in forced expiratory volume in one second (PEF₂₀) at ≤32 mg/ml histamine. In addition, we used the dose-response slope as a continuous variable for airway responsiveness (O'Connor et al, 1987), because this index of responsiveness can be calculated for all subjects, and may provide additional information (Peat et al, 1992; Rijcken and Schouten, 1993).

4.3 Methods

Study design

The study was conducted among workers from synthetic fibre plants that belonged to the same industrial site, and was carried out from April to July 1989 during working days. The study was approved by the Ethics Board of the Groningen University Hospital and Medical School. Written informed consent was obtained from all participants .

Study population and exposure

The synthetic fibre plants produce polyamide, polyester and para-aramid yarn and fibres, each product being manufactured in a different department. Male employees from departments with potential exposure to airway irritants, and a control group from departments presumed to be free from exposure, were invited to participate in the

survey. In May 1989 the total number of workers eligible for investigation was 909 men.

On the basis of job titles and working department at the time of the survey, the current exposure status of all workers was characterised. The workers were divided into seven groups.

(1) Reference group; (2) White collar group; (3) SO₂, H₂SO₄, HCl group; (4) Polyester vapour group; (5) Oil mist and oil vapour group; (6) Polyamide and polyester vapour group; (7) Multiple exposures group.

A more detailed description of the study population, the production process of the synthetic fibres and yarn, and the performed exposure measurements, are described in chapter 2.

Questionnaire

Data on respiratory symptoms and smoking habits were collected by means of a self-administered Dutch version of the British Medical Research Council standardised questionnaire. Additional questions about allergy and work history were included. Subjects were considered to have chronic respiratory symptoms if they had cough or phlegm production on most days or nights for as much as three consecutive months each year during winter (chronic cough or chronic phlegm), if during the previous three years they experienced more than one period of at least three weeks with (increased) cough and phlegm (episodes of bronchitis), if they got short of breath when walking with other people of their own age on level ground (dyspnoea grade $\geq$ III), if their chest sounded wheezing or whistling more than once a year (frequent wheeze), or if they ever had attacks of shortness of breath with wheezing (asthmatic attacks). Subjects were considered to have a history of allergy if they answered yes to one of the following two questions: "Have you ever had hay fever?" and "Do you get eye, nasal or respiratory symptoms if you are exposed to house dust, domestic animals or fungi?"

Non-smokers were defined as lifelong non-smokers. Current smokers were defined as those who smoked one cigarette or more per day for at least one year. Ex-smokers were those who stopped smoking for at least one month before the examination.

Spirometry

Spirometry was performed from Monday to Friday between 8:30 and 16:00 such that for each department the measurements of the workers were equally distributed over the

day, the working week, the shifts and the survey period. Spirometry was performed with a water-sealed spirometer (2400 Pulmonary Function Laboratory; SensorMedics BV, Bilthoven, NL) with automatic data processing. A minimum of three satisfactory forced expiratory manoeuvres were required for each subject. A satisfactory test required that of two manoeuvres the forced vital capacity (FVC) was reproducible within 5%, with a maximum of 300 ml (Quanjer et al, 1993). Measurements were corrected for body temperature, atmospheric pressure, and water saturation (BTPS). In the current paper, the highest value for FVC and forced expiratory volume in one second (FEV_1) were used for analysis. FEV_1 and FVC/FEV_1 were expressed as a percentage of predicted value (FEV_1 % pred and FEV_1/FVC % pred) using the prediction equations of Quanjer co-workers (Quanjer et al, 1993).

Histamine challenge test

Airway responsiveness was measured by a histamine challenge test. Histamine was dissolved in a phosphate solution: phosphate buffer, pH 7.4 with 0.03% serum albumin and 0.5% phenol. Histamine aerosols were generated by a Wiesbaden Doppelinhalator. The nebulisers were calibrated to deliver an output of 0.13 ± 0.01 ml/min : with a driving pressure of 2.5 bar, this required an airflow of 6.5 l/min. The nebulisers contained 3 ml of solution at room temperature. The aerosols were delivered *via* an inspiratory-expiratory valve box and mouthpiece.

The challenge test was not performed on subjects with daily medication for a pulmonary or cardiovascular disease, or on subjects with a pre-challenge FEV_1 of less than 80% predicted. The basic protocol is the De Vries modification of the 30 s tidal breathing method: after pre-test with phosphate solution, subjects inhaled sequential aerosols of histamine biphosphate in concentrations of 1, 2, 4, 8, 16 and 32 mg/ml at intervals of 2.5 min (De Vries et al, 1962). The FEV_1 was measured at 30 and 90 s after each concentration. The starting concentration of the short protocol was 4 mg/ml histamine. Subjects with a history of asthma like symptoms, or allergy, or a fall in FEV_1 of at least 6% after phosphate solution, were selected to start at 1 mg/ml. All subjects skipped the next concentration if the fall in FEV_1 was less than 6%. After a fall of $FEV_1 \geq 6\%$, doubling concentrations were resumed. The test was terminated if a fall in FEV_1 of at least 18% from baseline FEV_1 (=pre-challenge FEV_1) occurred, or if the highest concentration had been given. A software programme 'Broncho-Challenge' (SensorMedics BV, Bilthoven, NL) was used for recording the results of the FEV_1 's of the challenge test.

Data analysis

Airway responsiveness was analysed both as a dichotomous and continuous variable. Subjects with a provocative concentration of histamine causing a $\geq 20\%$ fall in FEV_1 at ≤ 32 mg/ml ($PC_{20} \leq 32$ mg/ml) were considered to be responders; all the others were considered to be nonresponders. PC_{20} was calculated by log-linear interpolation of the last two data points, with extrapolation up to one doubling concentration. For the continuous variable, the dose-response slope was used (O'Connor et al, 1987). The dose-response slope is expressed as percentage fall in FEV_1 per mg/ml histamine (% FEV_1 fall per mg/ml). Distribution analysis showed that the slope variable had a highly skewed distribution. Log and reciprocal transformations of the slope variable were explored to obtain a distribution that was as close to normality as possible. Before the transformation, a constant of 0.3 was added to the slope value to eliminate zero and negative values.

Differences in mean values for the transformed dose-response slope values between groups were compared using one-way analysis of variance. Differences in prevalence of airway hyperresponsiveness were assessed using the chi-square test. The association between exposure to airway irritants and the prevalence of airway hyperresponsiveness was estimated using multiple logistic regression analysis. For the relation of exposure to the transformed value of the dose-response slope, multiple linear regression analysis was used. Both methods allow simultaneous adjustment for covariates such as age, smoking habit, allergy by history, chronic respiratory symptoms, and baseline lung function level. Normality plots of the standardized residuals estimated by linear regression analysis, showed that of the transformed slope variable the residuals of the reciprocal of the slope ($1/(\%FEV_1 \text{ fall per mg/ml} + 0.3)$), were the most normally distributed. Therefore, the results of the analysis with the reciprocal of the dose-response slope is presented.

Of the calculated odds ratio's (ORs) 95% confidence intervals (CIs) are given. An OR is significant if the CI does not include unity. Associations are considered significant at p values of <0.05 . All analyses were performed using the Superior Performing Software/PC+ (SPSS, Inc., Chicago, USA) programme (version 4.1).

Table 1: Characteristics of the study population, stratified by exposure group

	Reference (n = 180)	White collars (n = 58)	SO ₂ , HCL H ₂ SO ₄ (n = 119)	Polyester vapour (n = 94)	Oil mist and oil vapour (n = 141)	Polyamide and polyester vapour (n = 51)	Multiple exposure (n = 25)	Total (n = 668)
Response (%)	84	70	88	89	96	93	100	87
Age (yr), mean (range)	31.1 (20-56)	43.9 (27-58)	30.8 (22-57)	32.7 (22-55)	31.2 (22-58)	36.2 (22-56)	36.5 (23-53)	33.0 (20-58)
Height (cm) [§]	180.9 (6.2)	178.9 (6.6)	182.8 (6.4)	182.1 (6.9)	180.6 (5.7)	177.8 (7.1)	177.7 (6.0)	180.8 (6.5)
Tenure (yr) [§]	7.0 (7.3)	17.0 (7.9)	6.3 (5.2)	8.0 (6.5)	7.0 (6.3)	10.3 (8.0)	13.4 (10.4)	8.4 (7.5)
Years in current exp.group								
≤ 5 [n (%)]	130 (72)	38 (66)	116 (97)	57 (61)	106 (75)	29 (57)	12 (48)	488 (73)
>5	50 (28)	20 (34)	3 (3)	37 (39)	35 (25)	22 (43)	6 (24)	117 (27)
Smoking habit [n (%)]								
non-smokers	54 (30)	3 (5)	35 (29)	19 (20)	24 (17)	6 (12)	6 (24)	147 (22)
ex-smokers	26 (14)	21 (36)	32 (27)	28 (30)	32 (23)	14 (28)	8 (32)	161 (24)
smokers	100 (56)	34 (59)	52 (44)	47 (50)	85 (60)	31 (61)	11 (44)	360 (54)
Allergy [n (%)]	22 (12)	7 (12)	17 (14)	12 (13)	18 (13)	4 (8)	7 (28)	87 (13)
One or more chronic resp. symptoms [n (%)]	43 (24)	14 (24)	17 (14)	27 (29)	45 (32)	20 (39)	10 (40)	176 (26)
FEV ₁ % pred [§]	104.6 (11.7)	105.3 (12.6)	106.1 (10.6)	103.8 (11.7)	104.5 (11.8)	103.9 (11.3)	106.3 (12.0)	104.8 (11.6)
FEV ₁ /FVC % pred [§]	97.2 (6.8)	97.2 (8.1)	97.4 (6.6)	96.9 (6.7)	97.0 (6.9)	96.7 (6.9)	98.0 (5.5)	97.1 (6.8)

[§] mean, with (standard deviation)

4.4 Results

Of the 909 workers who were invited, 790 (87%) participated in the survey. The response was 70% for the white collar group, 84% for the reference group, and ranged from 88% for the SO₂ group to 100% for the multiple exposure group. Of these 790 men, 28 were excluded from the analyses because of different cultural, lingual or racial background, which could influence questionnaire response or the results of the lung function test. Furthermore, 51 subjects were excluded from the histamine challenge test: one refused, five subjects had daily medication for a lung disease and 15 for a cardiovascular disease, 22 had a baseline FEV₁ <80% predicted and eight had no test for miscellaneous reasons. Eleven subjects had an incomplete challenge test, and for 20 subjects the quality of the test was poor. Of the remaining 680 men, 12 could not be included because of incomplete data on smoking or lung function (no FVC). Thus, data from 668 subjects were available for the analyses.

The study population was young, with 50% of the subjects younger than 31 years (range 20-58 yrs) (table 1). The prevalence of current smoking ranged from 44% in the SO₂ and the multiple exposure group to 61% in the polyamide and polyester vapour group. A history of allergy was present in 14% of the non-smokers, 15% of the ex-smokers and 12% of the smokers.

The 119 subjects who did not attend the survey were on average older (37.8 ± 11.1 yrs) and had a longer tenure (11.9 ± 9.0 yrs). The 94 subjects who were excluded from analyses were also on average older (37.3 ± 12.1 yrs), had a higher prevalence of lifelong non-smoking (27%) and ex-smoking (28%), a lower prevalence of a history of allergy (7%), and a higher prevalence of chronic respiratory symptoms (29%). To the extent that pulmonary function data were available (n=74), the FEV₁ % pred ($93.1\% \pm 14.7\%$) and FEV₁/FVC % pred ($93.0\% \pm 10.3\%$) were lower in excluded subjects.

Airway hyperresponsiveness

Airway hyperresponsiveness, defined as a PC₂₀ of ≤ 32 mg/ml, was present in 23% of the subjects. The reference group had a prevalence of airway hyperresponsiveness of 26%. The other exposure groups had a lower prevalence with the exception of the polyester vapour group (28%). Differences were not statistically significant (table 2). Airway hyperresponsiveness was found significantly more often in smokers (26%), subjects with a history of allergy (34%) and subjects with chronic respiratory symptoms

Table 2: The prevalence, the unadjusted odds ratio's (OR) and the adjusted odds ratio's[§] with 95% confidence interval (95% CI) for the prevalence of airway hyperresponsiveness ($PC_{20} \leq 32$ mg/ml) (N=668).

Exposure group	Total		Unadjusted		Adjusted	
	N	n (%)	OR	95% CI	OR	95% CI
Reference	180	47 (26)	1.0	-	1.0	-
White collars	58	15 (24)	1.0	0.5-1.9	1.1	0.5-2.6
SO ₂ , H ₂ SO ₄ , HCl	119	21 (18)	0.6	0.3-1.1	0.7	0.3-1.2
Polyester vapour	94	26 (28)	1.1	0.6-1.9	1.1	0.6-2.1
Oil mist and oil vapour	141	25 (18)	0.6	0.4-1.1	0.5	0.3-1.0*
Polyamide vapour and polyester vapour	51	12 (24)	0.8	0.4-1.8	0.9	0.4-2.0
Multiple exposures	25	5 (20)	0.7	0.6-1.9	0.8	0.3-2.1

[§] ORs are adjusted for age, age², smoking habit, a history by allergy, FEV₁ % pred and FEV₁/FVC % pred

* $p < 0.05$

(35%). Airway hyperresponsiveness was found more often among older subjects aged 50-59 years (32%) than among younger subjects aged 20-29 years (23%), but this difference did not reach statistical significance. The prevalence of airway hyperresponsiveness increased significantly with decreasing value of FEV₁ % pred and FEV₁/FVC % pred.

Multiple logistic regression analyses revealed that the magnitude of the associations between exposure groups and the prevalence of airway hyperresponsiveness did not change after adjustment for age, smoking habit, history of allergy, and baseline lung function (table 2). The exposure groups were associated with a lower prevalence of airway hyperresponsiveness (ORs < 1.0) with the exception of polyester vapour group (OR 1.1). The association with a lower prevalence was statistically significant for the oil mist group (OR 0.5). An additional regression analysis, which included chronic respiratory symptoms as an independent variable, showed similar ORs for the exposure groups as presented in table 2.

Smoking habit and age were not significantly associated with a higher prevalence of airway hyperresponsiveness, with respective ORs for ex-smoking and smoking of 0.8 (95% CI 0.4-1.6) and 1.3 (95% CI 0.8-2.1) and for age and age² of 0.90 (95% CI 0.75-1.07), and 1.001 (95% CI 0.999-1.004). An additional regression analysis without

adjustment for lung function level, showed no association between a higher prevalence and older age. Subjects with a history of allergy were responders significantly more often, with an OR 2.2 (95% CI 1.3-3.8). Baseline lung function level was significantly associated with airway hyperresponsiveness. The prevalence of airway hyperresponsiveness was 1.5 (95% CI 1.3-1.9) and 2.5 times higher (95% CI 1.9-3.4) when the FEV₁ and the FEV₁/FVC ratio were, respectively, 10% lower than the predicted values.

Stratified logistic regression analyses were performed to investigate whether the association between exposure groups and the prevalence of airway hyperresponsiveness was different for smokers and non-smokers, for subjects with and without a history of allergy, and for subjects with and without chronic respiratory symptoms. These analyses did not show marked differences in magnitude of the ORs for the exposure groups between the strata. This indicates that the association between exposure group and the presence of airway hyperresponsiveness is not different for smokers, for subjects with chronic respiratory symptoms or for subjects with a history of allergy.

Table 3: Prevalence and odds ratios (OR)[§] with 95% confidence interval (95% CI) for the prevalence of airway hyperresponsiveness (PC₂₀ ≤32 mg/ml), stratified by exposure years (N=668).

Exposure group	Exposure years (yr)					
	≤5 (N=488)			>5 (N=180)		
	n (%)	OR	95% CI	n (%)	OR	95% CI
Reference	38 (29)	1.0	-	9 (18)	1.0	-
White collars	11 (29)	1.1	0.4-3.3	4 (20)	1.4	0.3-7.0
SO ₂ , H ₂ SO ₄ , HCl	21 (18)	0.6	0.3-1.1	0 -	<0.1 [†]	-
Polyester vapour	16 (28)	1.0	0.5-2.1	10 (27)	2.3	0.7-7.5
Oil mist and oil vapour	13 (12)	0.3	0.1-0.6**	12 (34)	2.1	0.6-7.0
Polyamide vapour and polyester vapour	7 (24)	1.0	0.4-2.8	5 (23)	1.2	0.3-4.8
Multiple exposures	4 (33)	1.2	0.3-4.8	1 (8)	0.4	<0.1-4.2

[§] the ORs are adjusted for age, age², smoking habit, allergy by history, FEV₁ % pred and FEV₁/FVC % pred.

[†] no reliable estimation of the OR could be obtained (only 3 subjects in this stratum)

** p < 0.01

The possible association of the duration of the current exposure with the presence of airway hyperresponsiveness was examined. Logistic regression analyses were carried out,

stratified by two duration categories: ≤ 5 and > 5 exposure years (table 3). For subjects with ≤ 5 exposure years, the exposure groups were not associated with a higher prevalence of airway hyperresponsiveness. The oil mist group was significantly associated with a lower prevalence (OR 0.3). For subjects with more than 5 exposure years, the polyester vapour group (OR 2.3) and the oil mist group (OR 2.1) were associated with a higher prevalence of airway hyperresponsiveness, but these associations were not statistically significant.

Associations between exposure groups and prevalence of airway hyperresponsiveness might have been compromised by the presence of subjects who had recently changed jobs or were employed. Restricting the analysis of table 2 to subjects with at least 6 months of exposure, and an analysis with subjects with at least one year of exposure, did not change the results. ORs for the exposure groups remained essentially the same.

Exclusion of subjects from analyses might have biased the results of table 3. Of the 94 subjects who were excluded (subjects with different racial or cultural background not included), 32 subjects had > 5 exposure years, and a relatively large proportion belonged to the reference group: 15 subjects. Taking the relation of lung function level to airway responsiveness (57% of the subjects with an FEV_1 of 80-89% pred were responders) and the lower mean FEV_1 % pred of the excluded subjects into account, one can postulate that exclusion of subjects with > 5 exposure years might have resulted in a lower prevalence of airway hyperresponsiveness in the reference group, explaining at least in part the stronger association between the prevalence of airway hyperresponsiveness and the polyester vapour and oil mist group.

Dose-response slope

Analyses were also performed with the continuous variable dose-response slope. The geometric mean (GM) value of the dose-response slope was 0.31 % FEV_1 fall per mg/ml. This corresponds with an average fall in FEV_1 of 10% at 32 mg/ml histamine. The GM dose-response values of the exposure groups compared with the reference group, correspond with the prevalence of airway hyperresponsiveness data (tables 2 and 4). The results of the linear regression analyses confirmed the results of the logistic regression analyses, with the exception of the significance level of the difference between the reference group and the SO_2 group and the oil mist group. The value of the intercept of 1.432 corresponds with 0.36% FEV_1 fall per mg/ml histamine for a 20 year

Table 4: Geometric mean, the unadjusted and adjusted linear regression coefficients (β) for the dose-response slope $1/(\%FEV_1 \text{ fall per mg/ml} + 0.3)$ (N=668).

Exposure group	GM %FEV ₁ fall per mg/ml	GMD ¹	Unadjusted		Adjusted	
			β	SE ²	β	SE
Reference	0.33	1.03	-		-	
White collars	0.28	0.98	0.151	0.115	0.037	0.114
SO ₂ , H ₂ SO ₄ , HCl	0.25	0.91	0.233	0.090**	0.202	0.082*
Polyester vapour	0.37	1.19	-0.094	0.097	-0.120	0.089
Oil mist, oil vapour	0.30	1.08	0.082	0.086	0.096	0.078
Polyamide vapour and polyester vapour	0.33	0.84	0.003	0.121	-0.037	0.111
Multiple exposures	0.31	0.88	0.052	0.162	-0.044	0.150
Intercept			1.588	0.057	1.432	0.094

[§] adjustment for age-20, (age-20)², smoking habit, a history by allergy, FEV₁ (%-100%) pred and FEV₁/FVC (%-100%) pred.

¹ geometric standard deviation.

² standard error.

* p<0.05; ** p<0.01

old subject from the reference group with normal lung function. The explanatory variables in the regression analysis (table 4) explained 20% of the variation of the dose-response slope.

Stratified analysis revealed no additional information. In the analysis stratified by duration of exposure, the association between ≤ 5 years of exposure and lower dose-response slope value was significant for the SO₂ group and for the oil mist group (table 5). Subjects from the polyester vapour group and the oil mist vapour with >5 exposure years had higher mean dose-response values than those from the reference group. The difference was of borderline significance for the polyester vapour group. These results are in agreement with the logistic regression analysis presented in table 3.

Table 5: Linear regression coefficients (β)[§] for 1/(%FEV₁ fall/mg/ml+0.3), stratified by exposure years (N=668).

Exposure group	Exposure years			
	≤ 5 (n = 488)		> 5 (n = 180)	
	β	SE ¹	β	SE
White collars	0.076	0.144	0.009	0.221
SO ₂ , H ₂ SO ₄ , HCl	0.227	0.084**	1.499 ²	0.490**
Polyester vapour	-0.028	0.104	-0.354	0.176*
Oil mist, oil vapour	0.190	0.085*	-0.153	0.176
Polyamide vapour and polyester vapour	-0.086	0.136	-0.039	0.205
Multiple exposures	-0.019	0.198	-0.135	0.251

[§] the coefficients are adjusted for age-20, (age-20)², smoking habit, a history by allergy, FEV₁ (%-100%) pred and FEV₁/FVC (%-100%) pred.

¹ standard error.

² three subjects in this stratum

* p<0.1; * p<0.05; ** p<0.01

4.4 Discussion

In this analysis, no association could be demonstrated between exposure to airway irritants encountered in this study and a higher prevalence of airway hyperresponsiveness. On the contrary, there was a tendency for a lower prevalence among workers exposed to irritants. Adjustment for smoking, allergy by history, and baseline lung function level did not alter the associations between exposure groups and airway responsiveness. Stratified analyses did not indicate that the association was different for smokers, for subjects with a history of allergy or chronic respiratory symptoms. Subjects with more than 5 years of exposure to polyester vapour and to oil mist and oil vapour had a higher prevalence of airway hyperresponsiveness than the reference group, but these differences did not reach a significant level. Analyses using a dose-response slope as the parameter for airway responsiveness showed similar results and provided no additional information.

It has been described that single high exposure peaks of gases or fumes induced transient airway hyperresponsiveness or a persistent hyperresponsiveness (Brooks and Kalica, 1987; Fish, 1982). There has been no extensive study whether exposures to gases, vapours or fumes at levels commonly found in occupational settings result in respiratory diseases (Becklake, 1989; Brooks and Kalica, 1987). Søyseth and Kongerud (1992) could not demonstrate a relation between airway hyperresponsiveness and airborne exposure to fluoride and dust in 339 aluminium potroom workers. Kennedy et al. (1990) found that workers from a metal foundry (n=45) and two cedar sawmills (n=413) had a higher prevalence of airway hyperresponsiveness than office workers (n=196), but that this difference was not present after adjustment for baseline lung function. In a general population aged 18-73 years, Bakke et al. (1991) found no association between occupational airborne exposure to fumes, mists, gases or dusts and a higher prevalence of airway hyperresponsiveness. The last two studies did not distinguish between exposure to gases, vapours or fumes and airborne dust. Occupational and general population studies do indicate that occupational exposure to irritants is associated with chronic respiratory symptoms (Chan-Yeung et al, 1983; Järholm et al, 1982; Osterman et al, 1989a; Kauffmann et al, 1982; Korn et al, 1987; Xu et al, 1992), whereas an association with a lower lung function level could not be demonstrated (Oxhoj et al, 1982; Kennedy et al, 1989; Osterman et al, 1989b), with the exception of the study by Xu et al. (1992). In the latter study, a general population study in Beijing in China, a significant lower lung function level was found among subjects with occupational exposure to gases/fumes classified as high intensity (=very frequent or daily exposure to high concentrations) compared to subjects with little exposure to gases/fumes.

We, also, could not demonstrate an association between low level exposure to airway irritants and a higher prevalence of airway hyperresponsiveness, although the workers are potentially exposed to acid aerosols and acid vapour, oil mist and oil vapour, aldehydes/acetaldehydes vapour, glycol and/or lactam vapour, that are known to produce an irritating effect on the respiratory tract or to induce respiratory symptoms (Brabec, 1982; Ferguson and Wheeler, 1973; Hackney et al, 1989; Järholm et al, 1982; Parkes, 1982; Rowe and Wolf, 1982). Irritation of the eyes and the mucous membranes have been reported for diphenyl-diphenyloxide exposures (Hefner et al, 1975; Sandmeyer, 1982). In a previous report, we confirmed the reported association between exposure to irritants and a higher prevalence of chronic respiratory symptoms and the absence of an

association with a lower lung function level (Kremer et al, 1994a).

A limitation of this study was the power. Power analyses showed that differences in prevalence of airway hyperresponsiveness between groups should have been at least 15% to be statistically significant. However, the main finding of this study is not that we could not demonstrate a significant higher prevalence of airway hyperresponsiveness among exposed workers, but that we were faced with a lower prevalence in the SO₂ group and the oil mist group for workers with ≤5 exposure years. The known susceptibility of asthmatics for exposure to SO₂ (Koenig et al, 1982; Sheppard et al, 1980), was the reason for the company to have the policy not to employ subjects with a suspected history of asthma like symptoms in the para-aramide plant, because of the possible exposure to SO₂ and SO₄²⁻. This was done ever since the para-aramide fibre came into production in 1984. Pre-employment selection also took place for workers from the oil mist and oil vapour group. In the years 1984-1989, the medical department of the plant had a tendency not to pass subjects with a history of asthma like symptoms for employment in a workplace environment with exposure to oil mist and oil vapour. This was necessary because respiratory problems that resembled the syndrome of endotoxine fever had been reported, resulting in transfer of a few workers (Kateman et al, 1990), although the reported respiratory problems were not accompanied by an increased airway responsiveness. The other exposure groups were not subjected to pre-employment selections. Our findings may also have been biased by the fact that some workers from the current reference group have an occupational work history at other departments. Moreover, the level of exposure within each exposure group may differ.

The finding that the exposure groups were not associated with a higher prevalence of airway hyperresponsiveness, might also be because the level of exposure is too low, despite peak exposures during certain task performances, or the exposure time is too short. In the 10 - 15 years prior to the study, the company adjusted machines and improved the active ventilation to reduce airborne exposures. If the exposure had the same potency to induce airway hyperresponsiveness as for example red cedar, isocyanates, or some high molecular weights agents (for example flour and cereals), some subjects would have developed asthmatic symptoms within a few years (Malo et al, 1992). This would have been noticed by the occupational health department. It is more likely that the airway irritants at exposure levels encountered in this study incite respiratory symptoms, preferentially in subjects with hyperresponsive airways (Fish,

1992), which would also explain the presence of work-related respiratory symptoms as described in a previous report (Kremer et al, 1994b).

In addition to pre-employment selection, exclusion of subjects from analyses might have affected the results. In particular, it might have contributed to the relatively low prevalence of airway hyperresponsiveness in workers from the reference group with more than 5 exposure years. Thus, the question remains open whether exposure of more than 5 years to low levels of irritants as encountered by the workers of the polyester vapour group and the oil mist group is associated with a higher prevalence of airway hyperresponsiveness (table 4), or that it is partly an artifact caused by exclusion of subjects from analyses.

On average, the response was high. The lowest response was among the white collar workers, in whom no exposure related airway hyperresponsiveness was to be expected. The major reason for these workers not attending was lack of time. Of the other exposure groups, reasons for not attending varied from no interest, no time (production had higher priority), absence from work due to illness and vacation. The low non-response in combination with the variation of reasons not to come, will probably not have caused a strong bias towards no effect.

In this study, the associations between airway hyperresponsiveness on the one hand and current smoking, a history of allergy, and chronic respiratory symptoms on the other hand are in agreement with other studies (Rijcken et al, 1993). Also, the lack of a significant association between a higher prevalence of airway hyperresponsiveness and current smoking after adjustment for lung function level, is described by others (Bakke et al, 1991; Kennedy et al, 1990; Rijcken et al, 1988).

In contrast to the PC_{20} , the dose-response slope can be calculated of each subject and, therefore, the dose-response slope may have a greater statistical power than PC_{20} (Peat et al, 1992). But, the explanatory variables explained only 20% of the variation of the dose-response slope. Peat et al. (1992) found a similar result in their study of a general population sample. Our hypothesis was that analyses with the continuous parameter dose-response slope would show the same associations between airway responsiveness and risk factors as the analyses with the dichotomous variable responder *versus* non-responder (Rijcken and Schouten, 1993). The results of the analyses were indeed similar.

In summary, the current analyses could not demonstrate a significant association between exposure to irritants and increased airway responsiveness. The good health surveillance and the achievement of reduced exposure levels might have contributed to this result. However, long term respiratory health effects may still occur as suggested by the finding that subjects from the polyester vapour group and the oil mist and oil vapour group with more than 5 exposure years had higher prevalence of airway hyperresponsiveness. No additional information was obtained by using the continuous dose-response slope variable compared to the analyses with the dichotomous airway hyperresponsiveness variable. Further research is needed to elucidate the relation between exposure to airway irritants and airway responsiveness.

4.6 References

Alberts WM and Brooks SM. Advances in occupational asthma. *Clinics in Chest Medicine* 1992; 13: 281-301.

Bakke PS, Baste V, Gulsvik A. Bronchial responsiveness in a Norwegian community. *Am Rev Respir Dis* 1991; 143: 317-322.

Becklake MR. Occupational exposures: Evidence for a causal association with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989; 140: S85-S91.

Brabec MJ. Aldehydes and Acetals. In Clayton GD, Clayton FE (eds): "Patty's Industrial Hygiene and Toxicology." 3rd ed. John Wiley & Sons, Inc. New York, 1982; p 2629-2669.

Brooks SM, Kalica AR. Strategies for elucidating the relationship between occupational exposures and chronic air-flow obstruction. *Am Rev Respir Dis* 1987; 13: 268-273.

Chan-Yeung M, Lam S. Occupational asthma. *Am Rev Respir Dis* 1986; 133: 686-703.

Chan-Yeung M, Wong R, MacLean L, Tan F, Schulzer M, Enarson D, Martin A, Dennis R, Grzybowski S. Epidemiologic health study of workers in an aluminium smelter in British Columbia. *Am Rev Respir Dis* 1983; 127: 465-469.

Cockcroft DW. Airway hyperresponsiveness: therapeutic implications. *Ann Allergy* 1987; 59: 405-414.

De Vries K, Goei JT, Booy-Noord H, Orie NGM. Changes during 24 hours in the lung function and histamine hyperreactivity of the bronchial tree in asthmatic and bronchitic patients. *Int Arch Allergy* 1962; 20: 93-101.

Dolovich J, Hargreave F. Editorial. The asthma syndrome: inciters, inducers, and host characteristics. *Thorax* 1981; 36: 641-644.

Ferguson WS, Wheeler DD. Caprolactam vapour exposures. *Am Ind Hyg Ass J* 1973; 34: 384-389.

Fish JE. Occupational asthma: a spectrum of acute respiratory disorders. *J Occup Med* 1982; 24: 379-386.

Hackney JD, Linn WS, Avol EL. Acid fog: Effects on respiratory function and symptoms in healthy and asthmatic volunteers. *Environ Health Perspect* 1989; 79: 159-162.

Hefner RE, Leong BKJ, Kociba RJ, Gehring PJ. Repeated inhalation toxicity of diphenyl oxide in experimental animals. *Toxicol Appl Pharmacol* 1975; 33: 78-86.

Järholm B, Bake B, Lavenius B, Thiringer G, Vokmann R. Respiratory symptoms and lung function in oil mist-exposed workers. *J Occup Med* 1982; 24: 473-479.

Kateman E, Heederik D, Pal TM, Smeets M, Smid T, Spitteler M. Relationship of airborne microorganisms with the lung function and leucocyte levels of workers with a history of humidifier fever. *Scand J Work Environ Health* 1990; 16: 428-433.

Kauffmann F, Drouet D, Lellouch J, Brille D. Occupational exposure and 12-year spirometric changes among Paris area workers. *Br J Ind Med* 1982; 39: 221-232.

Kennedy SM, Greaves IA, Kriebel D, Eisen EA, Smith TJ, Woskie SR. Acute pulmonary responses among automobile workers exposed to aerosols of machining fluids. *Am J Ind Med* 1989; 15: 627-641.

Koenig JQ, Pierson WE, Horike M, Frank R. Effects of inhaled sulfur dioxide (SO₂) on pulmonary function in healthy adolescents: Exposure to SO₂ or SO₂ + sodium chloride droplets aerosol during rest and exercise. *Arch Environ Health* 1982; 37: 5-9.

Kennedy SM, Burrows B, Vedal S, Enarson DA, Chan-Yeung M. Methacholine responsiveness among working populations. *Am Rev Respir Dis* 1990; 142: 1377-1383.

Korn RJ, Dockery DW, Speizer FE, Ware, JH, Ferris BG. Occupational exposures and chronic respiratory symptoms: A population-based study. *Am Rev Respir Dis* 1987; 136: 298-304.

Kremer AM, Pal TM, Boleij JSM, Schouten J, Rijcken B. Airway hyperresponsiveness, chronic respiratory symptom prevalence and lung function in workers exposed to irritants. *Occup Environ Med* 1994a; 51: 3-13.

Kremer AM, Pal TM, Boleij JSM, Schouten J, Rijcken B. Airway hyperresponsiveness, and work-related symptoms in workers exposed to irritants. *Am J Indus Med* 1994b; 26: 655-669.

Malo J-J, Ghezzo H, D'Aquino C, L'Archevêque J, Cartier A, Chang-Yeung M. Natural history of occupational asthma: Relevance of type of agent and other factors in the rate of development of symptoms in affected subjects. *J Allergy Clin Immunol* 1992; 90: 937-944.

O'Connor G, Sparrow D, Taylor D, Segal M, Weiss ST. Analysis of dose-response curves to methacholine. *Am Rev Respir Dis* 1987; 136: 1412-1417.

O'Conner GT, Sparrow D, Weiss ST. The role of allergy and nonspecific airway hyperresponsiveness in the pathogenesis of chronic pulmonary disease. *Am Rev Respir Dis* 1989; 140: 225-252.

Osterman JW, Greaves IA, Smith TJ, Hammond SK, Robins JM, Thériault G. Respiratory symptoms associated with low level sulphur dioxide exposure in silicon carbide production workers. *Br J Ind Med* 1989a; 46: 629-635.

Osterman JW, Greaves IA, Smith TJ, Hammond SK, Robins JM, Thériault G. Work related decrement in pulmonary function in silicon carbide production workers. *Br J Ind Med* 1989b; 46: 708-716.

Oxhoj H, Andreassen H, Meyer-Henius U. Respiratory symptoms and ventilatory lung function in machine shop workers exposed to coolant-lubricants. *Eur J Res Dis* 1982; S118: 85-89.

Parkes WR . "Occupational Lung Diseases". 2nd ed. London: Butterworth, 1982; p 472-482.

Peat, JK, Salome CM, Berry G, Woolcock AJ. Relation of dose-response slope to respiratory symptoms and lung function in a population study of adults living in Busselton, western Australia. *Am Rev Respir dis* 1992; 146: 860-865.

Quanjer, PhH, Tammeling GJ, Cotes E, Pederson OF, Peslin R, Yernault J-C. Standardization of lung function testing. *Eur Respir J* 6, 1993; suppl 16: 5-40.

Rowe VK, Wolf MA . Glycols. In Clayton GD, Clayton FE (eds). "Patty's Industrial Hygiene and Toxicology". 3rd ed. John Wiley & Sons, Inc. New York, 1982; p 3817-3832.

Rijcken B, Schouten JP. Measuring bronchial responsiveness in epidemiology. *Eur Respir J* 1993; 6: 617-618.

Rijcken B, Schouten JP, Weiss ST, Speizer FE, Lende R van der. The relationship between airways responsiveness to histamine and pulmonary function level in a random population sample. *Am Rev Respir Dis* 1988; 137: 826-832.

Rijcken B, Schouten JP, Mensinga TT, Weiss ST, Vries K de, Lende R van der. Factors associated with airways responsiveness to histamine in a population sample of adult. *Am Rev Respir Dis* 1993; 147: 1447-1453.

Sandmeyer EE. Aromatic hydrocarbons. In Clayton GD, Clayton FE (eds). "Patty's Industrial Hygiene and Toxicology". 3rd ed. John Wiley & Sons, Inc. New York, 1982; p 3325-3331.

Sheppard D, Wong WS, Uehara CF, Nadel JA, Boushey HA. Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. *Am Rev Res Dis* 1980; 122: 873-878.

Søyseth V, Kongerud J. Prevalence of respiratory disorders among aluminium potroom workers in relation to exposure to fluoride. *Br J Indus Med* 1992; 49: 125-130.

Xu X, Christiani DC, Dockery DW, Wang L. Exposure-response relationships between occupational exposures and chronic respiratory illness: A community-based study. *Am Rev Respir Dis* 1992; 146: 413-418.

Chapter 5

Airway hyperresponsiveness, prevalence of chronic respiratory symptoms and lung function in workers exposed to irritants¹

¹ Revised version of the paper: A.M. Kremer, T.M. Pal, J.S.M. Boleij, J.P. Schouten, B. Rijcken. *Occupational and Environmental Medicine* **51** (1994) 3-13

5.1 Abstract

The association between occupational exposure to airway irritants and the prevalence of chronic respiratory symptoms and level of lung function, and whether these associations were modified by airway hyperresponsiveness, smoking, and a history of allergy were studied in 668 workers from synthetic fibre plants. Respiratory symptoms were recorded with a self administered Dutch version of the British Medical Research Council questionnaire, with additional questions on allergy. Airway responsiveness was measured by a 30 second tidal breathing histamine challenge test. On the basis of job titles and working department, the current exposure status of all workers was characterised as (1) no exposure, reference group; (2) white collar workers; (3) SO₂, HCl, H₂SO₄; (4) polyester vapour; (5) oil mist and vapour; (5) polyamide and polyester vapour; (6) multiple exposure. Workers exposed to airway irritants were not simultaneously exposed to airborne dust. Airway hyperresponsiveness (AHR), defined as a 20% fall in forced expiratory volume in one second (FEV₁) at ≤32 mg/ml histamine, was present in 23% of the subjects. The association between exposure groups and prevalence of symptoms was estimated by means of multiple logistic regression; the association with level of lung function (forced vital capacity (FVC), FEV₁, maximum mid-expiratory flow rate (MMEF) was estimated by means of multiple linear regression. Both methods allow simultaneous adjustment for potential confounding factors. The exposure groups were associated with a higher prevalence of chronic respiratory symptoms. Lower prevalence of symptoms was found for workers exposed to SO₂, HCl, H₂SO₄ exposure, most likely due to pre-employment selection procedures. Current smoking, AHR and a history of allergy were significantly associated with a higher prevalence of chronic respiratory symptoms, independent of each other, and independent of irritant exposure. The association between exposure and prevalence of symptoms was greater in smokers than in ex-smokers and non-smokers. This difference was most clearly seen in the polyester vapour and polyamide and polyester vapour group. No modification of the association between exposure groups and prevalence of symptoms by airway hyperresponsiveness could be shown. The exposure groups were not significantly associated with a lower level of lung function. Adjustment for chronic respiratory symptoms did not change the results. There were no indications of a possible interaction between exposure and AHR, current smoking, or a history of allergy on lung function. Workers from the polyester vapour and the oil mist and vapour group with >10 years of exposure, had a lower FEV₁

($\beta = -295$ and -358 ml) and a significantly lower MMEF ($\beta = -1080$ and -1247 ml/s; $p < 0.05$) than the reference group. The number of workers of both groups were, however, small ($n = 10$ and $n = 13$ respectively).

5.2 Introduction

Exposure to gases, vapours and fumes can cause respiratory symptoms and bronchoconstriction by different pathophysiological mechanisms: direct effect on the irritant receptors in the wall or mucosal inflammation of the bronchus (Chang-Yeung and Lam, 1986). Accidental exposure to high concentrations of irritant gases and fumes more commonly results in acute chemical pneumonitis (Vedal and Chan-Yeung, 1989). A reactive airways dysfunction syndrome in which the respiratory symptoms persisted for years after the exposure, has been described after exposure to a single high concentration of an irritant (Brooks et al, 1985). Of current interest is whether low level exposure to these gases, vapours and fumes causes respiratory health effects. It has been postulated that pre-existing airway hyperreactivity may enhance the onset of respiratory symptoms and airway obstruction in subjects exposed to occupational irritants (Cockcroft, 1987; Sluiter et al, 1991). Also, allergy and cigarette smoking may also be related to increased risk of respiratory problems.

Whether exposures to irritant gases or fumes at levels commonly found in occupational settings result in respiratory diseases has not been studied extensively (Becklake, 1989; Brooks and Kalica, 1987; Korn et al, 1987). A study among Paris area workers showed that exposures to gases caused accelerated decline of FEV_1 only in the presence of simultaneous exposure to heat or dust (Kauffmann et al, 1982). Korn and coworkers found in a general population study that exposures to gas or fumes, after controlling for exposure to dust, was significantly associated with increased prevalence of respiratory symptoms. They also reported that exposure to gases or fumes was associated with an increased prevalence of a decreased FEV_1/FVC ratio (< 0.6), but this association was not significant (Korn et al, 1987).

To get more insight into the relation between occupational exposures to irritants and obstructive airway disease, we conducted a longitudinal study at synthetic fibre plants among workers having known low level exposure to airway irritants. We also wanted

to study the role of bronchial hyperreactivity, smoking and a history of allergy. The purpose of the current report is to present the cross sectional findings of the prevalence of chronic respiratory symptoms and level of pulmonary function in workers exposed to occupational airway irritants. We also studied whether an association between exposure to irritants, respiratory symptoms, and level of lung function was different for subjects with increased airway reactivity, for smokers, and for subjects with a history of allergy. For these analyses, data from the base line study were used.

5.3 Methods

Study design

The study was designed prospectively and was conducted among workers from synthetic fibre plants that belonged to the same industrial location. The base line survey was performed from April to July 1989, during working days. The study has been approved by the Ethical Board of the Groningen University Hospital and Medical School. Written informed consent was obtained from all participants.

Study population and exposure

The synthetic fibre plants produce polyamide, polyester and para-aramid yarn and fibres, each product being manufactured in a different department. Male employees from departments with potential exposure to airway irritants and a control group from departments presumed to be free from exposure were invited to participate in the survey. In May 1989 the total number of workers eligible for investigation was 909 men. On the basis of job titles and working department at the time of the survey, the current exposure status of all workers was characterised. The workers were divided into seven groups.

(1) Reference group; (2) White collar group; (3) SO₂, H₂SO₄, HCl group; (4) Polyester vapour group; (5) Oil mist and oil vapour group; (6) Polyamide and polyester vapour group; (7) Multiple exposures group. A more detailed description of the study population, the production process of the synthetic fibres and yarn and the performed exposure measurements, are described in chapter 2.

Questionnaire

Data on smoking habits and respiratory symptoms were collected by means of a self administered Dutch version of the British Medical Research Council standardised questionnaire. Additional questions about work related respiratory symptoms, allergy and work history were included. Subjects were considered to have chronic respiratory symptoms if they had cough or phlegm production on most days or nights for as much as three consecutive months each year during winter (chronic cough or chronic phlegm), if during the previous three years they experienced more than one period of at least three weeks with (increased) cough and phlegm (episodes of bronchitis), if they become short of breath when walking with other people of their own age on level ground (dyspnoea $\geq$ grade III), if their chest sounded wheezing or whistling more than once a year (frequent wheeze), or if they ever had attacks of shortness of breath with wheezing (asthmatic attacks). Nasal catarrh is defined as being troubled with a clogged or runny nose or sneezing for as much as three consecutive months each year. Subjects were considered allergic if they answered yes to one of the following two questions: "Have you ever had hay fever?" and "Do you get eye, nasal or respiratory symptoms if you are exposed to house dust, domestic animals or fungi?"

Non-smokers are defined as lifelong non-smokers. Ex-smokers are those who stopped at least one month before the examination. Current smokers are defined as those who smoked one cigarette or more per day for at least one year. Smoking habit as a continuous variable is expressed as pack-years. This is the product of the number of years a person has smoked and the packs of cigarettes (25 cigarettes) smoked per day. The cigar consumption was recalculated to pack-years. It was assumed that a small cigar is equal to two cigarettes and a big cigar is equal to five cigarettes.

Spirometry

Spirometry was performed from Monday to Friday between 8:30 and 16.00 such that for each department the measurements of the workers were equally distributed over the time of the day, the working week, the shifts and the survey period. Spirometry was performed with a water sealed spirometer (2400 Pulmonary Function Laboratory; SensorMedics BV, Bilthoven, NL) with automatic data processing (IBM-AT computer). A minimum of three satisfactory forced expiratory manoeuvres were required of each subject. A satisfactory test required that of two manoeuvres the forced vital capacity (FVC) was reproducible within 5% with a maximum of 300 ml (Quanjer, 1983).

Measurements were corrected for body temperature, atmospheric pressure, and water saturation (BTPS). Analyses were performed on the largest FVC, forced expiratory flow in one second (FEV_1) and the forced expiratory flow between 25 and 75% points of the FVC curve (MMEF). The FEV_1 was also expressed as a percentage of predicted value ($\%FEV_1$) with the prediction equations of Quanjer and colleagues (Quanjer, 1983).

Histamine challenge test

Airway responsiveness was measured by a histamine challenge test. Initial FEV_1 was the highest prechallenge FEV_1 . Subjects with cardiovascular disease or lung disease requiring daily medication were not permitted to perform the test. Subjects with a prechallenge FEV_1 below 80% of the predicted value were also excluded. The basic protocol is the De Vries modification of the 30 s tidal breathing method: after pretest with phosphate solution, subjects inhaled sequential aerosols of histamine biphosphate in concentrations of 1, 2, 4, 8, 16 and 32 mg/ml (De Vries, 1962). At 30 and 90 s after each concentration subjects performed an FEV_1 manoeuvre. The test was ended if there was a decrease in FEV_1 of at least 18%, or if the highest concentration had been given. Subjects with a history of asthma like symptoms, or allergy, or with a fall in FEV_1 after phosphate solution of 6% or more started with 1 mg/ml. All other subjects started with 4 mg/ml. Quadrupling histamine concentrations were given until the FEV_1 had fallen at least 6%, then the schedule was changed to doubling concentrations. A software programme, Broncho-Challenge (SensorMedics BV), was used for recording the results of the FEV_1 values of the histamine challenge test.

The provocation concentration causing a 20% fall in FEV_1 (the PC_{20}) was calculated by log linear interpolation of the last two data points, with extrapolation up to one doubling concentration (maximum 64 mg/ml). The threshold value was defined as the concentration by which the subject would have experienced a fall in FEV_1 of 20% or more. Airway hyperresponsiveness was defined as a 20% fall in FEV_1 at 32 mg/ml histamine or less. In the analyses airway responsiveness is considered as a dichotomous variable with threshold values ≤ 32 mg/ml and ≥ 64 mg/ml of histamine.

Data analysis

Statistical significance of the unadjusted differences in symptom prevalence between groups in contingency tables was assessed by X^2 -analysis. A p value of <0.05 was considered significant. The association between exposure to airway irritants and respira

Table 1: Characteristics of the study population stratified by exposure group

	Reference (n = 180)	White collar (n = 58)	SO ₂ , HCL H ₂ SO ₄ (n = 119)	Polyester vapour (n = 94)	Oil mist and vapour (n = 141)	Polyamide and polyester vapour (n = 51)	Multiple exposure (n = 25)	Total (n = 668)
Age (y, mean (range))	31.1 (20-56)	43.9 (27-58)	30.8 (22-57)	32.7 (22-55)	31.2 (22-58)	36.2 (22-56)	36.5 (23-53)	33.0 (20-58)
Height (cm (SD))	180.9 (6.2)	178.9 (6.6)	182.8 (6.4)	182.1 (6.9)	180.6 (5.7)	177.8 (7.1)	177.7 (6.0)	180.8 (6.5)
Duration of total employment (y (SD))	7.0 (7.3)	17.0 (7.9)	6.3 (5.2)	8.0 (6.5)	7.0 (6.3)	10.3 (8.0)	13.4 (0.4)	8.4 (7.5)
Years in current exposure group								
≤2 (n (%))	68 (38)	12 (21)	39 (33)	13 (14)	58 (41)	11 (22)	-	201 (30)
>2 - ≤5	62 (34)	26 (45)	77 (65)	44 (47)	48 (34)	18 (35)	12 (48)	287 (43)
>5 - ≤10	35 (19)	11 (19)	3 (3)	27 (29)	22 (16)	13 (25)	6 (24)	117 (18)
>10	15 (8)	9 (16)	-	10 (11)	13 (9)	9 (18)	7 (28)	63 (9)
Smoking habit (n (%))								
non-smoker	54 (30)	3 (5)	35 (29)	19 (20)	24 (17)	6 (12)	6 (24)	147 (22)
ex-smoker	26 (14)	21 (36)	32 (27)	28 (30)	32 (23)	14 (28)	8 (32)	161 (24)
smoker	100 (56)	34 (59)	52 (44)	47 (50)	85 (60)	31 (61)	11 (44)	360 (54)
pack-years (mean (SD))	6.8 (8.2)	21.2 (11.7)	8.4 (7.7)	6.4 (6.3)	10.8 (8.5)	15.0 (10.2)	13.3 (9.7)	11.2 (9.5)
Allergy (n (%))	22 (12)	7 (12)	17 (14)	12 (13)	18 (13)	4 (8)	7 (28)	87 (13)
Airway hyperrespon- siveness (n (%))	47 (26)	15 (26)	21 (18)	26 (28)	25 (18)	12 (24)	5 (20)	151 (23)
%FEV ₁ , predicted (SD)	104.6 (11.7)	105.3 (12.6)	106.1 (10.6)	103.8 (11.7)	104.5 (11.8)	103.9 (11.3)	106.3 (12.0)	104.8 (11.6)
FVC (l) (SD)	5.655 (0.718)	5.233 (0.848)	5.878 (0.793)	5.688 (0.795)	5.636 (0.715)	5.334 (0.826)	5.348 (0.742)	5.620 (0.783)
FEV ₁ (l) (SD)	4.575 (0.643)	4.144 (0.719)	4.750 (0.633)	4.552 (0.665)	4.557 (0.664)	4.270 (0.710)	4.338 (0.622)	4.530 (0.679)
MMEF (l/s) (SD)	4.620 (1.310)	4.123 (1.327)	4.747 (1.232)	4.434 (1.292)	4.522 (1.230)	4.221 (1.188)	4.442 (1.149)	4.530 (1.286)

tory symptoms was measured by multiple logistic regression. This method allows simultaneous adjustment for potential confounders such as age, smoking habit, airway responsiveness, and history of allergy. The odds ratio (OR) of a category relative to the reference category was estimated by taking the antilog of the coefficient of that category. The additional effect of the combination of two variables was assessed by including interaction terms in the model. For a continuous variable, the OR is an estimate of change in log odds per unit of measurement. The 95% confidence intervals (95% CIs) were given for ORs. An OR was significant if the 95% CI did not include unity.

The differences in means for %FVC, %FEV₁ and %MMEF predicted were tested by a two tailed *t* test, and *p* values <0.05 were considered significant. The association between exposure to airway irritants and level of lung function was analysed with multiple linear regression. This method allows also simultaneous adjustment for covariates such as age, smoking habit, airway responsiveness, and a history of allergy. To adjust for the effect of smoking and age on lung function, several indices of smoking habit and age were examined. We examined smoking as a categorical, an ordinal, and as a continuous variable. Of these, the continuous variables pack-years and smoking duration explained the largest amount of variance of the regression model (largest adjusted R^2). Pack-years were used in the analyses. We examined age, age² and (age + age²). Age² and (age + age²) explained more of the variance than age. We choose (age + age²) because the decrease of lung function with age may be larger in older than in younger subjects (Buist, 1982). Also (age + age²) may provide a better modelling of the turnover from lung function growth to decline (Sparrow and Weiss, 1989). The described relations are considered significant at *p* values <0.05.

The analyses were performed with the Superior Performing Software System/PC+ (SPSS, Inc., Chicago) programme (version 4.0).

5.4 Results

Of the 909 men who were invited, 790 (87%) took part in the study. Of these, 28 were excluded because of different cultural or racial backgrounds. Of the remaining 762, 680 gave an acceptable histamine challenge test. Forty three had no test because they did not meet the inclusion criteria and eight had no test for miscellaneous reasons, 11 had incomplete data and for 20 the quality of the test was poor. Of the remaining 680 men

Table 2: Prevalence of respiratory symptoms stratified by exposure group, smoking habit, allergy history, and airway hyperresponsiveness.

Exposure group	Chronic cough n (100%)	Chronic phlegm n (%)	Bronchitis episodes n (%)	Dyspnoea ≥grade III n (%)	Frequent wheeze n (%)	Asthmatic attacks n (%)	Any symptom* n (%)	Nasal catarrh n (%)	n (%)
Reference	180	4 (2)	14 (8)	22 (12)	4 (2)	18 (10)	9 (5)	43 (24)	56 (20)
White collars, SO ₂ , H ₂ SO ₄ , HCl	58	1 (2)	-	7 (13)	1 (2)	8 (14)	2 (3)	14 (24)	9 (16)
Polyester vapour	119	2 (2)	2 (2)	10 (8)	1 (1)	7 (6)	1 (1)	17 (14)	13 (11)
Oil mist and vapour	94	3 (3)	6 (6)	15 (16)	-	12 (13)	2 (2)	27 (29)	21 (22)
Polyamide and polyester vapour	141	8 (6)	10 (7)	22 (16)	2 (1)	22 (16)	12 (9)	45 (32)	29 (21)
Multiple exposures	51	6 (12)	8 (16)	9 (18)	6 (12)	12 (24)	1 (2)	20 (39)	10 (20)
Smoking habit	25	1 (4)	2 (8)	8 (32)	-	3 (12)	1 (4)	10 (40)	5 (20)
non-smoker	147	1 (1)	5 (3)	17 (12)	3 (2)	6 (4)	6 (4)	23 (16)	17 (12)
ex-smoker	161	1 (1)	5 (3)	11 (7)	2 (1)	9 (6)	5 (3)	18 (11)	18 (11)
smoker	360	23 (6)	32 (9)	65 (18)	9 (3)	67 (17)	17 (5)	109 (30)	87 (24)
History of allergy	581	19 (3)	33 (6)	70 (12)	12 (2)	62 (11)	18 (3)	142 (24)	86 (15)
no	87	6 (7)	9 (10)	23 (27)	2 (2)	20 (23)	10 (12)	34 (39)	36 (42)
yes	517	18 (4)	32 (6)	68 (13)	6 (1)	46 (9)	13 (3)	103 (20)	89 (17)
Airway hyperresponsiveness	151	7 (5)	10 (7)	25 (17)	8 (5)	36 (24)	15 (10)	47 (31)	33 (22)
no	668	25 (4)	42 (6)	93 (14)	14 (2)	82 (12)	28 (4)	176 (26)	122 (18)
yes									
Total									

One or more respiratory symptoms present but nasal catarrh was not taken into account

12 could not be included because of incomplete data on smoking or lung function. Thus, data of 668 men were used for the analysis.

The study population was young, with 50% of the subjects younger than 31 years (range 20-58); (table 1). Current smoking ranged from 44% in the SO₂ and multiple exposure group to 61% in the polyamide and polyester vapour group. The amount of pack-years was on average higher among the older exposure groups. Airway hyperresponsiveness was present in 23% of the subjects. The prevalence was low in the SO₂ (18%) and the oil mist group (18%). The prevalence of a history of allergy was 14% for the nonsmokers, 15% for the ex-smokers, and 12% for the smokers. Thirty four percent of the subjects with a history of allergy also had airway hyperresponsiveness. On average, the subjects who were excluded from further analyses were older (37.3 (12.1), had a higher prevalence of never smoking (27%) and ex-smoking (28%), a lower prevalence of a history of allergy (7%) and a lower %FEV₁ predicted (93.1% (14.7) than those of the study population.

Respiratory symptoms

Compared with the reference group, the prevalence rate of any symptom was higher in the polyester vapour, the oil mist and vapour, the polyamide and polyester vapour, and the multiple exposure groups and lower in the SO₂ group (table 2). In general, a higher prevalence of symptoms was significantly associated with current smoking, airway hyperresponsiveness, and a history of allergy.

To estimate the association of the various exposure groups with the presence of respiratory symptoms, multiple logistic regression with simultaneous adjustment for potential confounding factors was used (table 3). No differences in prevalence of respiratory symptoms were found between the white collar group and the reference group (OR for any symptom 1.0). Compared with the reference group, workers exposed to SO₂, HCL and H₂SO₄ had a lower prevalence (OR for any symptoms 0.6), and workers exposed to polyester vapour had a higher prevalence of chronic symptoms (OR 1.5). Workers exposed to oil mist and vapour had a higher prevalence of chronic cough (OR 2.4), wheeze (OR 1.8), and ever asthmatic attacks (OR 2.2), workers exposed to polyamide and polyester vapour had a significantly higher prevalence of cough (OR 5.4), dyspnoea (OR 6.1) and wheeze (OR 3.0) and the engineers with multiple exposures had significantly more episodes of bronchitis (OR 3.5). The prevalence of nasal catarrh did not differ between the exposure groups.

Table 3: Estimated odds ratios (with 95% confidence interval) for the prevalence of respiratory symptoms by exposure group, smoking habit, airway responsiveness and a history of allergy. With as reference categories the reference group, the non-smokers, the subjects with normal airway responsiveness and the non-allergic.

	Chronic cough (n = 25)	Chronic phlegm (n = 42)	Bronchitis episodes (n = 93)	Dyspnoea ≥grade III (n = 14)	Frequent wheeze (n = 82)	Asthmatic attacks (n = 28)	Any symptom ^a (n = 176)	Nasal catarrh (n=122)
Exposure group								
White collar	0.4 (0.0-4.0)	-	1.2 (0.4-3.3)	0.5 (0.0-6.0)	1.0 (0.4-2.8)	0.8 (0.1-4.4)	1.0 (0.5-2.3)	0.9 (0.4-2.2)
SO ₂ , H ₂ SO ₄ , HCl	1.0 (0.2-5.5)	0.2 (0.1-1.0)*	0.7 (0.3-1.5)	0.5 (0.1-4.6)	0.7 (0.3-1.8)	0.2 (0.0-1.3)	0.6 (0.3-1.2)	0.5 (0.2-1.0)
Polyester vapour	1.6 (0.3-7.7)	0.8 (0.3-2.3)	1.5 (0.7-3.1)	-	1.5 (0.6-3.3)	0.4 (0.1-2.1)	1.5 (0.8-2.7)	1.3 (0.7-2.5)
Oil mist and vapour	2.4 (0.7-8.5)	0.8 (0.4-2.0)	1.3 (0.7-2.5)	0.7 (0.1-4.1)	1.8 (0.9-3.7)	2.2 (0.9-5.7)	1.6 (1.0-2.8)	1.1 (0.6-1.9)
Polyamide and polyester vapour	5.4 (1.4-22.0)*	2.2 (0.8-5.7)	1.8 (0.7-4.2)	6.1 (1.5-24.0)*	3.0 (1.2-7.2)*	0.5 (0.1-3.9)	2.3 (1.2-4.7)*	1.1 (0.5-2.6)
Multiple exposures	1.7 (0.2-17.0)	1.0 (0.2-4.8)	3.5 (1.3-9.7)*	-	1.4 (0.6-3.3)	0.6 (0.1-6.0)	2.6 (1.0-6.5)*	1.0 (0.3-3.0)
Age (y)	1.06 (1.01-1.12)*	1.01 (0.97-1.06)	1.00 (0.97-1.03)	1.04 (0.97-1.11)	1.03 (1.00-1.06)*	0.99 (0.95-1.05)	1.00 (0.98-1.03)	0.99 (0.96-1.02)
Smoking habit								
ex-smoker	0.5 (0.0-8.7)	0.9 (0.2-3.3)	0.5 (0.2-1.2)	0.5 (0.1-3.8)	1.0 (0.3-3.0)	0.8 (0.2-3.1)	0.6 (0.3-1.1)	1.0 (0.5-2.1)
smoker	8.5 (1.1-65)*	2.7 (1.0-7.3)*	1.7 (0.9-3.1)	0.9 (0.2-3.5)	4.9 (2.0-11.9)**	1.0 (0.4-2.8)	2.4 (1.5-4.0)**	2.6 (1.5-4.7)**
Airway hyperresponsiveness	1.1 (0.4-2.7)	0.9 (0.4-1.9)	1.2 (0.7-2.0)	4.6 (1.5-14.5)**	2.9 (1.7-4.8)**	4.3 (1.9-9.7)**	2.1 (1.4-3.2)**	1.1 (0.7-1.7)
Allergy	3.6 (1.3-10.2)*	2.3 (1.0-5.1)*	2.9 (1.6-5.1)**	1.3 (0.3-6.8)	3.2 (1.7-6.0)**	3.8 (1.6-8.8)**	2.1 (1.3-3.6)**	4.8 (2.8-8.0)**

* p<0.05; ** p<0.01

* one or more of the respiratory symptoms present, but nasal catarrh excluded. * p < 0.05; ** p < 0.01

We also examined whether the associations between the exposure groups and a higher prevalence of respiratory symptoms were influenced by the level of lung function. The logistic regression analysis of table 3 was repeated with additional adjustment for %FEV₁ predicted. Low %FEV₁ was significantly associated with a higher prevalence of any symptom (OR 0.96; 95% CI 0.95-0.98). Compared with the results of table 3, the ORs for the exposure groups remained essentially the same.

Age (table 3) was associated with a higher prevalence of chronic cough (OR 1.06), dyspnoea (OR 1.04) and wheeze (OR 1.03), but not with any symptom (OR 1.00). Smokers, subjects with airway hyperresponsiveness and subjects with a history of allergy reported significantly more respiratory symptoms with respective ORs for any symptom of 2.4, 2.1 and 2.1.

The associations of airway hyperresponsiveness and a history of allergy with a higher prevalence of symptoms were independent of one another. The OR for airway hyperresponsiveness remained essentially the same after excluding a history of allergy from the logistic regression analysis.

To assess whether the associations between the exposure groups and a higher prevalence of symptoms was different for current smokers and non-smokers, or for hyperresponsive v normally responsive subjects (effect modification), stratified analyses were performed. Subjects were defined as symptomatic if one or more respiratory symptoms (any symptom) was present. In the analysis stratified by smoking (table 4), the ORs for any symptom for smokers of the polyester vapour group was 2.2, of the oil mist and vapour group 1.9, and of the polyamide and polyester vapour group 4.0. In the unstratified analysis (table 3), these ORs were 1.5, 1.6 and 2.3. The ORs were smaller for non-smokers, suggesting that the difference from the reference group in prevalence of symptoms was greater for smokers than for non-smokers. In the analysis stratified by hyperresponsiveness (table 4), the ORs for any symptom for hyperresponsive subjects of the polyester vapour group was 0.8, of the oil mist and vapour group 1.4, and of the polyamide and polyester vapour group 1.9. The corresponding ORs for the normal responsive subjects were 2.0, 1.8 and 2.5. Thus the difference in prevalence of symptoms compared with the reference group was smaller for subjects with airway hyperresponsiveness than for subjects with normal airway responsiveness. These results might be explained because one or more respiratory symptoms was used as the definition of any symptom. Thus, an additional analysis was performed using two or more respiratory symptoms to define prevalence of symptoms. The exposure ORs for the hyperresponsive subjects

Table 4 Estimated ORs (95% CI) for the prevalence of any symptom (n=176) by exposure group stratified by smoking habit and by airway hyperresponsiveness.

Exposure group	Smoking habit			Airway hyperresponsiveness	
	non-smoker (n = 147)	ex-smoker (n = 161)	current smoker (n = 360)	no (n = 517)	yes (n = 151)
White collar	-	1.1 (0.2- 7.1)	1.2 (0.5- 3.0)	1.3 (0.5- 3.5)	0.6 (0.2- 2.5)
SO ₂ , H ₂ SO ₄ , HCl	0.4 (0.1- 1.5)	0.2 (0.0- 2.5)	0.8 (0.4- 1.8)	0.7 (0.3- 1.5)	0.6 (0.2- 1.9)
Polyester vapour	0.2 (0.0- 1.7)	1.6 (0.3- 7.8)	2.2 (1.0- 4.5)*	2.0 (1.0- 4.1)	0.8 (0.3- 2.4)
Oil mist and vapour	1.2 (0.4- 3.9)	1.3 (0.2- 6.6)	1.9 (1.0- 3.6)*	1.8 (1.0- 3.4)	1.4 (0.5- 3.7)
Polyamide and polyester vapour	-	1.3 (0.2- 9.7)	4.0 (1.7- 9.4)**	2.5 (1.1- 5.9)*	1.9 (0.5- 7.3)
Multiple exposures	2.6 (0.4-17.4)	1.9 (0.2-16.1)	2.7 (0.7- 9.4)	3.2 (1.1- 9.2)*	1.7 (0.2-13.1)

* $p < 0.05$; ** $p < 0.01$

ORs are also adjusted for age and a history of allergy.

were similar to or slightly larger than the ORs for the normally responsive subjects. For the hyperresponsive subjects the ORs of the polyester vapour group was 1.8 (95% CI 0.4-8.7), of the oil mist and vapour group 2.1 (95% CI 0.5-8.6) and of the polyamide and polyester vapour group 2.9 (95% CI 0.5-15.8). For the normally responsive subjects these ORs were 1.0 (95% CI 0.3-3.1), 1.5 (95% CI 0.6-3.7) and 3.0 (95% CI 1.0-9.0). Thus the use of a more restrictive definition of presence of symptoms, resulted in a stronger association between exposure and prevalence of symptoms for the hyperresponsive subjects.

The small numbers of subjects with a history of allergy in the various exposure groups did not allow a similar stratified analysis for subjects with or without a history of allergy.

The stratified analyses were also performed with adjustment for level of lung function, including %FEV₁ predicted as an independent variable. The associations between the exposure groups and the prevalence of symptoms remained the same.

To test whether the difference of the ORs for the exposure groups between smokers and non-smokers and hyperresponsive and normally responsive subjects were significant, the logistic regression analyses of any symptom (one or more symptoms) were repeated including interaction terms. The analyses confirmed the stratified analyses. The ORs for

the exposure group - smoking terms ranged from 1.5 to 8.3 - indicating that the association between exposure group and a higher prevalence of symptoms was stronger for smokers than for non-smokers. The polyester vapour-smoking term was of borderline significance with an OR of 3.3 (95% CI 0.9-12.1). The polyamide and polyester vapour-smoking term was significant with an OR of 8.3 (95% CI 1.3-51.4). Including the exposure-airway hyperresponsiveness interaction terms caused a small increase in the exposure ORs. The ORs for the interaction terms did not reach significance and were, as was to be expected, less than 1.0, ranging from 0.4 to 0.8.

Exclusion of subjects from analyses might have affected the study results. We repeated the logistic regression analysis with age, smoking habit, allergy history, and exposure group as independent variables, including and excluding 94 subjects of whom we did not have complete lung function data or histamine challenge data (28 subjects with different cultural or racial background not included). The magnitude of the ORs for the exposure groups in these two analyses were similar.

Lung function

A first examination of the relation of level of lung function with smoking habit, airway responsiveness, history of allergy, respiratory symptoms, work related symptoms, and exposure group, was assessed by calculating the mean %FVC, %FEV₁, and %MMEF of the predicted value for each subgroup. Smokers had significantly lower mean %FEV₁ and mean %MMEF values than the non-smokers. Subjects with hyperresponsive airways and subjects with chronic respiratory symptoms had significantly lower mean %FVC, %FEV₁ and %MMEF than subjects with normal responsive airways and no chronic respiratory symptoms. The mean %predicted lung function of subjects with and without a history of allergy and of subjects with and without work related symptoms, did not differ significantly. Compared with the reference group, the polyester vapour, the oil mist and vapour, and the polyamide and polyester vapour group had lower mean %FEV₁ and mean %MMEF values. The SO₂, the white collars and the multiple exposure group had higher mean %lung function values.

Multiple linear regression analyses were performed to estimate the association between the exposure groups and the level of lung function with simultaneous adjustment for potential confounders. With adjustment for age, length, and smoking habit, the exposure groups were not significantly associated with a lower level of lung function (table 5, regression model 1). Adjustment for airway responsiveness and a history of allergy did

Table 5: Regression coefficients (β) and standard errors (SEs) for FEV₁ and MMEF: the coefficients are adjusted for age, age² and height

	FEV ₁ (ml)					
	model 1		model 2		model 3	
	β	SE	β	SE	β	SE
Exposure group						
White collars	34	94	33	78	30	77
SO ₂ , H ₂ SO ₄ , HCl	53	68	34	57	21	56
Polyester vapour	-67	73	-55	61	-45	60
Oil mist and vapour	9	64	-18	54	-4	53
Polyamide and polyester vapour	-3	93	-15	77	9	76
Multiple exposures	38	124	26	103	55	102
Pack-years	-8	3**	-7	3**	-5	3*
Airway hyperresponsiveness			-298	45**	-271	45**
Allergy			-25	57	1	55
Any symptom [§]					-173	43**

* $p < 0.1$; * $p < 0.05$; ** $p < 0.01$

[§] One or more respiratory symptoms present but nasal catarrh was not taken into account

not change these results (regression model 2). The results also did not change with adjustment for chronic respiratory symptoms (regression model 3). The MMEF was lower for the SO₂ (-73 ml/s), the polyester vapour (-61 ml/s), the oil mist and vapour (-117 ml/s), and the polyamide and polyester vapour group (-47 ml/s), but these differences were not significant.

Smoking, expressed as pack-years was significantly associated with lower FVC (-8 ml/y), FEV₁ (-8 ml/y) and MMEF (-12 ml/s y; $p = 0.054$) values. The levels of significance decreased after adjustment for airway hyperresponsiveness and respiratory symptoms (table 5). Airway hyperresponsiveness was significantly associated with lower FEV₁ and MMEF, but not significantly with FVC (-49 ml; $p = 0.37$). A history of allergy was not significantly associated with a decreased lung function (regression model 2; all p values > 0.2).

To determine whether there was a difference in the association between exposure groups and level of lung function for smokers as compared with non-smokers, for hyperres

Table 5 continued

	MMEF (ml/s)					
	model 1		model 2		model 3	
	β	SE	β	SE	β	SE
Exposure group						
White collars	143	196	134	187	128	186
SO ₂ , H ₂ SO ₄ , HCl	11	142	- 48	135	- 73	135
Polyester vapour	-115	153	- 81	146	- 61	145
Oil mist and vapour	- 65	134	-145	128	-117	128
Polyamide and polyester vapour	- 62	192	- 95	183	- 47	183
Multiple exposures	106	257	46	246	103	245
Pack-years	- 12	6 [§]	- 9	6	- 5	6
Airway hyperresponsiveness			-876	107**	-825	108**
Allergy			72	133	121	133
Any symptom [§]					-336	104**

ponsive v normally responsive subjects and for subjects with and without a history of allergy, we performed linear regression analyses stratified by each of these characteristics. These analyses showed no indication for a possible interaction between exposure to irritants and current smoking, airway hyperresponsiveness, and the presence of a history of allergy.

To investigate whether the duration of employment in the current exposure group was associated with a lower level of lung function, the multiple regression analyses were stratified by four duration categories: ≤ 2 , $>2\text{--}\leq 5$, $>5\text{--}\leq 10$ and >10 years of exposure. In the first three categories, the exposure groups were not significantly associated with a lower level of lung function. In the category with >10 exposure years, however, all exposure groups had lower FVC (ranging from -110 ml to -197 ml), FEV₁ (ranging from -121 ml to -358 ml), and MMEF values (ranging from -354 ml/s to -1247 ml/s). The oil mist and vapour group had a significantly lower mean FEV₁ (-358 ml) and MMEF (-1247 ml/s). For the polyester vapour group the FEV₁ was not significantly lower (-295 ml, $p = 0.14$) but the MMEF was significantly lower (-1080 ml/s).

Table 6: Regression analyses of the population with more 10 years of exposure

Exposure group	FEV ₁ : subjects with no histamine challenge data				MMEF: subjects with no histamine challenge data			
	included		excluded		included		excluded	
	(n = 81)		(n = 63)		(n = 81)		(n = 63)	
	β	SE	β	SE	β	SE	β	SE
	(ml)		(ml)		(ml/s)		(ml/s)	
White collar	129	212	- 1	217	168	526	49	578
SO ₂ , H ₂ SO ₄ , HCl	-		-		-			
Polyester vapour	-175	206	-361	206 [#]	-898	511 [#]	-1235	550 [*]
Oil mist and vapour	-159	185	-465	189 [*]	-906	459 [#]	-1495	504 ^{**}
Polyamide and polyester vapour	156	205	- 71	216	58	509	- 185	575
Multiple exposures	192	232	- 60	228	140	577	- 408	608

[#] p<0.1; ^{*} p<0.05; ^{**} p<0.01

The regression coefficients (β) and standard errors (SEs) for FEV₁ and MMEF, are adjusted for age, age², length, pack-years, a history of allergy, and chronic respiratory symptoms.

Exclusion of subjects from the analysis might have had an effect on the results. We therefore repeated the overall analyses, including 66 subjects of whom we had a complete data set but no histamine challenge data. No obvious differences were noted in the associations between the exposure groups and the level of lung function, compared with the analyses that excluded these 66 subjects. For the analysis stratified by the duration of exposure, including the 66 subjects changed the associations between exposure groups and level of lung function in the category with >10 years of exposure, but not in the other exposure categories. In the category with >10 years of exposure, the polyester vapour and the oil mist and vapour group were still associated with a lower level of lung function, but these associations were no longer statistically significant (table 6). Of the 66 excluded subjects 18 (27%) had >10 years of exposure and 10 of these 18 subjects belonged to the reference group. Excluding these 18 subjects resulted in an increase of the mean level of lung function (for example, %FEV₁ increased from 102% to 106%), and this increase was greatest in the reference group (for example, %FEV₁ increased from 103% to 112%). Thus by excluding these subjects, the differences between the workers with >10 years of exposure of the reference group and the exposed groups increased.

5.5 Discussion

Exposure to irritants, as encountered in this study, was associated with a higher prevalence of respiratory symptoms but not with a lower mean FVC, FEV₁, and MMEF. The workers from the polyester vapour and the oil mist and vapour group with more than 10 years of exposure had lower lung function values than the reference group. Stratified analyses showed that the association between the polyester vapour and polyamide and polyester vapour group and the prevalence of respiratory symptoms was greater for smokers than for non-smokers. The association between exposure to irritants and respiratory symptoms was smaller for subjects with airway hyperresponsiveness than for subjects with normal airway responsiveness.

In the synthetic fibre plants under study, workers are exposed to a mixture of airway irritants. In addition to the multiple exposure, workers are exposed to high environmental temperatures near the machines at some places, which may interact with exposure to irritants (Kauffmann et al, 1982). Most of the measured (and known) vapour concentrations are lower than the Dutch threshold limit values (TLVs) with the exception of diphenyl diphenyloxide and possibly lactam. For the polyester vapour group, personal exposure to diphenyl diphenyloxide seems to be occasionally high compared with the Dutch TLV of 7 mg/m³. The Dutch TLV is mainly based on unpleasant odour perception. Irritation of the eyes and the mucous membranes have been reported for exposures of 19 to 25 mg/m³ (Hefner et al, 1975; Sandmeyer, 1982). For the polyamide and polyester vapour group personal exposure to lactam vapour could reach the Dutch TLV level of 20 mg/m³. Lactam vapour can cause throat irritation and cough (Ferguson and Wheeler, 1973). One of the most suspected thermodegradation products of polyester is acetaldehyde. Acetaldehyde can cause hypersecretion of the upper respiratory tract and bronchial mucus (Parkes, 1982). Personal exposure measurements showed low concentrations of acetaldehyde compared with the Dutch TLV of 180 mg/m³. We also found that the level of exposure was independent of function tasks: the acetaldehyde exposure of production floor managers and production line workers from the oil mist group and vapour and the polyamide and polyester vapour group were similar. This means that acetaldehyde was measured, irrespective of polyester vapour exposure. Thus exposure to aldehyde was not a marker for exposure to polyester vapour. A possible explanation for the low homogeneous acetaldehyde

exposure is that the measured acetaldehyde emanated from tobacco smoke (IARC, 1985). On average, the workers from the oil mist and vapour group and the polyamide and polyester vapour group, smoke a considerable amount when they are not working at the machines.

The engineers who are responsible for the maintenance and cleaning of the machines are more likely to have short term high exposures than production line workers. Moreover, interviews showed that they are also exposed to varying environmental temperatures. Engineers reported significantly more episodes of bronchitis but not more of the other symptoms. It is possible that as well as irritant exposure, the varying environmental temperatures could contribute to high prevalence of episodes of bronchitis.

Low level exposure to airway irritant is associated with a higher prevalence of respiratory symptoms. Chan-Yeung and coworkers reported more cough, phlegm and wheeze in 797 aluminium smelter workers exposed to low concentrations of hydrogen fluoride (0.48 mg/m^3 , eight hour time weighted average) and SO_2 (2.0 mg/m^3 , eight hour time weighted average) (Chang-Yeung et al, 1983). Osterman and coworkers showed in a health study among 145 silicon carbide production workers that the prevalence of symptoms such as phlegm, wheeze and dyspnoea were significantly and dose-dependently related to SO_2 measured cumulatively, or by average SO_2 exposure while employed. They reported mean current exposure to SO_2 of 0.69 mg/m^3 (eight hour time weighted average), which is low, but 20% of the workers had daily exposure to SO_2 of 2.7-4.0 mg/m^3 (Osterman et al, 1989a). Experimental studies with volunteers showed that exposure to 2.66 mg/m^3 SO_2 (= 1 ppm) can cause acute falls in FEV_1 , $\text{FEF}_{50\%}$, and $\text{FEF}_{75\%}$ (Koenig et al, 1982) and that asthmatic, non-allergic subjects are much more sensitive to the effect of inhaled SO_2 than non-asthmatic, non-allergic subjects (Koenig et al, 1982; Sheppard et al, 1980). This susceptibility of asthmatic persons to exposure to SO_2 , was the reason why the company did not employ subjects with a suspected history of asthma like symptoms in the para-aramide plant, because of the possible exposure to SO_2 and H_2SO_4 . This was done ever since the para-aramide fibre came into production in 1984. The low prevalence of chronic respiratory symptoms and of the airway hyperresponsiveness in the SO_2 group are probably due to this pre-employment selection. As well as selection, the maximum exposure duration of only four and a half years at the time of the survey may contribute to the low prevalence of respiratory symptoms and to the fact that the mean level of lung function did not differ from the reference group.

A higher symptom prevalence in workers exposed to oil mist has also been reported by others. Robertson and coworkers reported current asthmatic symptoms in 25 patients due to various oil mists (Robertson et al, 1988). Järholm and coworkers found a higher prevalence of cough and phlegm in 164 metal workers exposed to mineral and emulsified oil mist (Järholm et al, 1982). It remains unclear whether in our study the association between exposure to oil and respiratory symptoms is due only to oil exposure. The spindraw winders were also exposed to airborne microorganisms and endotoxin, although the measured concentrations were low (Katemman et al, 1990). Although Järholm and coworkers found respiratory symptoms, they did not find differences in FVC and FEV_1 between the exposed metal workers and non-exposed office workers. The minimum duration of exposure was three years (Järholm et al, 1982). Also in other cross sectional studies, no association was found between exposure to oil mist and a lower levels of lung function (Ely et al, 1970; Oxhoj et al, 1982). Kennedy and coworkers found acute FEV_1 falls during the working days among 89 automobile workers exposed to oil mist, but no falls in FEV_1 occurred over the course of the working week. At the beginning of the working week, no differences were found in FEV_1 between exposed machinists ($n = 89$) and the controls (assemblers; $n = 42$). All workers had worked for at least five years for the company and all workers performed the same job in the same area for at least six months. These authors concluded that the results of the cross sectional lung function data may have been biased because non-participants had lower lung function than the participants, and workers who had respiratory symptoms might have left the company within five years of employment (Kennedy et al, 1989). Thus in a cross sectional study of a working force, selection bias, such as self selection and pre-employment selection (SO_2 group in this study) may explain a finding of no association between exposure and a lower lung function (Gamble et al, 1976; Kennedy et al, 1989), and may underestimate the association between exposure and prevalence of symptoms. As well as selection, our findings may also have been biased by the fact that some workers from the current reference group have an occupational work history at other departments. Moreover, the exposure level within each exposure group may differ. Within the polyester vapour, the oil mist and vapour and the polyamide and polyester vapour group, workers can have different main function tasks, resulting in personal exposure differences. For the SO_2 group the personal exposure may differ from time to time because certain function tasks were rotated. In our study, current smoking modified the association between the polyester vapour and

polyamide and polyester vapour group and respiratory symptoms. Osterman and coworkers also found that the association between exposure to SO₂ and respiratory symptoms was greater in smokers than in current non-smokers (Osterman et al, 1989a). Studies in general populations did not show significant interactions between current smoking and either dust or fume exposure on prevalence of symptoms (Korn et al, 1987; Viegi et al, 1991). In our study, it remains unclear whether there was really an interaction between smoking and exposure to irritant or that the numbers of the never and ex-smokers are just too small. Anyhow, the stratified analyses showed for the smokers a more accurate estimation of the association between exposure group and the prevalence of symptoms than the unstratified analyses.

An explanation for smaller ORs for the exposure group of the hyperresponsive subjects compared with the ORs of the normally responsive subjects (table 4), may be that subjects with airway hyperresponsiveness and symptoms have not been employed at all or have left their jobs. In occupational health surveillance, the presence of airway hyperresponsiveness in workers can be an exclusion criterium for employment. In our study population it was, as mentioned before, an exclusion criterium for the SO₂ group, and to a lesser degree also for employment in the industrial yarn plant (oil mist and vapour group). In the years 1984-9 the medical department of the synthetic fibre plant had a tendency not to employ subjects with a history of asthma like symptoms as spin-draw-winders. This was done because respiratory problems had been reported by some workers, which were suspected to be work related. For employment in the production departments of the other exposure groups, no such respiratory health criteria were applied.

In general, allergy may be associated with increased risk of developing chronic airway obstruction and chronic symptoms (Weiss et al, 1989). A history of allergy was an important predictor of prevalence of respiratory symptoms, but not of a lower level of lung function, although 34% of the allergic subjects had airway hyperresponsiveness. Also Fletcher and coworkers did not find an association in a male working population between a history of allergy and the FEV₁ (Fletcher et al, 1976). Population based data indicate a decreasing prevalence of allergy after age 40 (Burrows, 1989). Thus because of the relatively young age of our population (76% younger than 40 years) the role of allergy in the prevalence of symptoms may be greater than in older populations. In the current study, a history of allergy is assessed on the basis of the self reported estimate of being allergic and this estimate may be less reliable than positive skin tests to

common airborne allergens. Thus the association between allergy and symptoms may differ from studies in which allergy is defined on the basis of positive skin tests to common airborne allergens.

Although our study results may have been biased by factors as mentioned in this discussion, it is also possible that exposure to irritants at levels commonly found in industrial settings, does not lead to an increased loss of pulmonary function or only to a lesser degree. A study in a general population and in an occupational population, showed that exposure to gas or fumes was associated with a lower lung function only in the presence of simultaneous exposure to heat or dust (Kauffmann et al, 1982; Korn et al, 1987). Osterman and coworkers studied silicon carbide production workers, and found that respiratory symptoms were associated with low exposure to level SO₂, but that a lower level of lung function was not associated with SO₂ but with exposure to dust (Osterman et al, 1989a; Osterman et al, 1989b). In our study, workers who are exposed to irritants are not simultaneously exposed to airborne dust. Although the evidence of an association between occupational exposures to gases, vapours, fumes and a lower lung function, is not consistent (Becklake, 1989), occupational studies do report that there is an association between these agents and a higher prevalence of chronic respiratory symptoms (Korn et al, 1987; Järholm et al, 1982; Osterman et al, 1989a; Osterman et al, 1989b). Our study is in agreement with these findings.

In conclusion, our findings show that exposure to multiple airway irritants encountered in these synthetic fibre plants is, compared with a reference group, associated with a higher prevalence of chronic respiratory symptoms. This association was seen most clearly in the workers who smoke. Our study could not show an overall association between the irritant exposure and a lower level of lung function. The results indicate that workers with more than 10 years of exposure to polyester vapour and to oil mist and vapour have a decreased lung function. Furthermore, we found no indication of a possible interaction between exposure to airway irritants, airway hyperresponsiveness, current smoking or a history of allergy on level of lung function. We agree with Becklake (1989) that further investigation is needed to clarify the relation between occupational exposure to low concentrations of irritants and respiratory health problems in the absence of exposure to airborne dust.

5.6 References

Becklake MR. Occupational exposures: Evidence for a causal association with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989; 140: S85-S91.

Brooks SM, Kalica AR. Strategies for elucidating the relationship between occupational exposures and chronic air-flow obstruction. *Am Rev Respir Dis* 1987; 135: 268-273.

Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome. *J Occup Med* 1985; 27: 473-476.

Buist SA. Evaluation of lung function: concepts of normality. In: Simmons DH, ed. *Current pulmonology*. New York: Wiley and Sons, 1982; 141-65.

Burrows B. Distribution of allergy in the general population. In: Sluiter HJ, van der Lende R, eds. *Bronchitis IV*. Assen: Van Gorcum, 1989; 3-10.

Chan-Yeung M, Lam S. Occupational asthma. *Am Rev Respir Dis* 1986; 133: 668-703.

Chan-Yeung M, Wong R, MacLean L, Tan F, Schulzer M, Enarson D, Martin A, Dennis R, Grzybowski S. Epidemiologic health study of workers in an aluminium smelter in British Columbia. *Am Rev Respir Dis* 1983; 127: 465-469.

Cockcroft DW. Airway hyperresponsiveness: therapeutic implications. *Ann Allergy* 1987; 59: 405-414.

De Vries K, Goei JT, Booy-Noord H, Orie NGM. Changes during 24 hours in the lung function and histamine hyperreactivity of the bronchial tree in asthmatic and bronchitic patients. *Int Arch Allergy* 1962; 20: 93-101.

Ely TS, Pedley SF, Hearne FT, Stille WT. A study of mortality, symptoms and respiratory function in humans exposed to oil mist. *J Occup Med* 1970; 12: 253-261.

Ferguson WS, Wheeler DD. Caprolactam vapour exposures. *Am Ind Hyg Ass J* 1973; 34: 384-389.

Fletcher C, Peto R, Tinker C, Speizer FE. *The natural history of bronchitis and emphysema*. Oxford: Oxford University Press, 1976.

Gamble JF, McMichael AJ, Williams T, Battigelli M. Respiratory function and symptoms: an environmental-epidemiological study of rubber workers exposed to a phenol-formaldehyde type resin. *Am Ind Hyg Ass J* 1976; 37: 499-513.

Hefner RE, Leong BKJ, Kociba RJ, Gehring PJ. Repeated inhalation toxicity of diphenyl oxide in experimental animals. *Toxicol Appl Pharmacol* 1975; 33: 78-86.

Higgins M. Epidemiology of COPD: State of the Art. *Chest* 1984; 85: 3S-8S.

IARC. Monographs on the evaluation of the carcinogenic risk of chemicals to humans: Alkyl compounds, aldehydes, epoxides and peroxides. International Agency for Research on Cancer. Lyon, 1985;vol.36.

Järholm B, Bake B, Lavenius B, Thiringer G, Vokmann R. Respiratory symptoms and lung function in oil mist-exposed workers. *J Occup Med* 1982; 24: 473-479.

Kateman E, Heederik D, Pal TM, Smeets M, Smid T, Spitteler M. Relationship of airborne microorganisms with the lung function and leucocyte levels of workers with a history of humidifier fever. *Scand J Work Environ Health* 1990; 16: 428-433.

Kauffmann F, Drouet D, Lellouch J, Brille D. Occupational exposure and 12-year spirometric changes among Paris area workers. *Br J Ind Med* 1982; 39: 221-232.

Kennedy SM, Greaves IA, Kriebel D, Eisen EA, Smith TJ, Woskie SR. Acute pulmonary responses among automobile workers exposed to aerosols of machining fluids. *Am J Ind Med* 1989; 15: 627-641.

Koenig JQ, Pierson WE, Horike M, Frank R. Effects of inhaled sulfur dioxide (SO₂) on pulmonary function in healthy adolescents: Exposure to SO₂ or SO₂ + sodium chloride droplets aerosol during rest and exercise. *Arch Environ Health* 1982; 37: 5-9.

Korn RJ, Dockery DW, Speizer FE, Ware JH, Ferris BG. Occupational exposures and chronic respiratory symptoms. *Am Rev Respir Dis* 1987; 136: 298-304.

Parkes WR. *Occupational Lung Diseases*. 2nd ed. London: Butterworth, 1982;472.

Quanjer, PhH. Standardized lung function testing. Report of the Working Party "Standardization of Lung Function Tests". *Bull Eur Physiop Resp* 1983; suppl 5: 1-95.

Robertson AS, Weir DC, Burge PS. Occupational asthma due to oil mist. *Thorax* 1988; 43: 200-205.

Osterman JW, Greaves IA, Smith TJ, Hammond SK, Robins JM, Thériault G. Respiratory symptoms associated with low level sulphur dioxide exposure in silicon carbide production workers. *Br J Ind Med* 1989a; 46: 629-635.

Osterman JW, Greaves IA, Smith TJ, Hammond SK, Robins JM, Thériault G. Work related decrement in pulmonary function in silicon carbide production workers. *Br J Ind Med* 1989b; 46: 708-716.

Oxhoj H, Andreassen H, Meyer-Henius U. Respiratory symptoms and ventilatory lung function in machine shop workers exposed to coolant-lubricants. *Eur J Res Dis* 1982; S118: 85-89.

Sandmeyer EE. Aromatic hydrocarbons. In: Clayton GD, Clayton FE, eds. *Patty's Industrial Hygiene and Toxicology*, third edition. John Wiley & Sons, Inc. New York, 1982; 3325-3331.

Sheppard D, Wong WS, Uehara CF, Nadel JA, Boushey HA. Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. *Am Rev Res Dis* 1980; 122: 873-878.

Sluiter HJ, Koëter GH, Monchy JGR de, Postma DS, Vries K de, Orie NGM. The Dutch hypothesis (chronic non-specific lung disease) revisited. *Eur Respir J* 1991; 4: 479-489.

Sparrow D, Weiss ST. Background. In: Weiss ST, Sparrow D, eds. *Airway responsiveness and atopy in the development of chronic lung diseases*. New York: Raven Press, 1989; 1-21.

Vedal S, Chan-Yeung M. Airway responsiveness and atopy in occupational airways disease. In: Weiss ST, Sparrow D, eds. *Airway responsiveness and atopy in the development of chronic lung disease*. New York: Raven Press, 1989; 271-292.

Viegi G, Prediletto R, Paoletti P, Carrozzi L, Di Pede F, et al. Respiratory effects of occupational exposure in a general population sample in North Italy. *Am Rev Respir Dis* 1991; 143: 510-515.

Weiss ST, O'Connor GT, Sparrow D. The role of allergy and airway responsiveness in the natural history of chronic airflow obstruction (CAO). In: Weiss ST, Sparrow D, eds. *Airway responsiveness and atopy in the development of chronic lung disease*. New York: Raven Press, 1989; 181-240.

Chapter 6

Airway hyperresponsiveness and the prevalence of work-related symptoms in workers exposed to irritants¹

¹ Revised version of the paper: A.M. Kremer, T.M. Pal, J.S.M. Boleij, J.P. Schouten, B. Rijcken. *American Journal Industrial Medicine* (1994) **26** 655-669

6.1 Abstract

The association between exposure to airway irritants and the presence of work-related symptoms and whether this association was modified by airway hyperresponsiveness, smoking, and allergy by history, was studied in 668 workers of synthetic fiber plants. A Dutch version of the BMRC questionnaire with additional questions on allergy and work-related symptoms was used to assess symptoms and a standardised histamine challenge test of airway hyperresponsiveness (AHR) was employed. Work-related symptoms were defined as having more than usual eye and respiratory symptoms during work. On the basis of job titles and working department, the exposure status of all workers was characterized into seven groups: (1) reference group; (2) white collars; (3) SO₂, HCl, H₂SO₄; (4) polyester vapour; (5) oil mist and vapour; (6) polyamide and polyester vapour; (7) multiple exposure. The association between exposure groups and work-related symptom prevalence was estimated by means of multiple logistic regression.

The overall prevalence of the work-related symptoms were: cough 9%, phlegm 6%; dyspnoea 7%, wheeze 2%; eye symptoms 16%; nasal symptoms 15%. Exposure to airway irritants was significantly associated with work-related symptoms, independent of AHR, smoking, allergy by history and chronic respiratory symptoms. The association of exposure group with work-related symptoms was stronger for subjects with AHR than for subjects with no AHR. The association with dyspnoea and/or wheeze was also stronger for smokers than for non-smokers and ex-smokers. In contrast, the association between exposure and a higher prevalence of work-related symptoms was stronger in subjects with no history of allergy than in subjects with history of allergy. This is most likely due to the relatively high prevalence of background symptoms in (non-exposed) allergic subjects. It is concluded that exposure to irritants in the working environment might lead to respiratory symptoms, even if exposure levels are relatively low.

6.2 Introduction

The role of airway hyperresponsiveness in the relation between occupational airborne exposures and chronic obstructive airway disease, is of interest. A large number of occupational agents such as isocyanates and red cedar have known or suspected allergic

properties (Brooks and Kalica, 1987; Chang-Yeung and Lam, 1986). These agents can be regarded as inducers of airway hyperresponsiveness (Cockcroft, 1987; Dolovich and Hargreave, 1981). Occupational exposures to irritants such as gases, vapours and fumes can cause respiratory symptoms and bronchoconstriction by different mechanisms: exposure to low levels may have a direct effect on the irritant receptors in the bronchial wall, and exposure to high levels may lead to mucosal inflammation of the bronchus (Chang-Yeung and Lam, 1986; Cockcroft, 1987). Agents that trigger bronchospasm in subjects with pre-existing airway hyperresponsiveness, such as exposure to low levels of irritants, can be considered as inciters (Cockcroft, 1987; Dolovich and Hargreave, 1981). The number of studies describing respiratory health effects caused by recurrent low level occupational exposures to irritants is limited. Little is known about the importance of (pre-) existing airway hyperresponsiveness, the role of an allergic constitution, and cigarette smoking (Brooks and Kalica, 1987) as factors that may enhance the identification of susceptible workers.

We conducted a longitudinal study at synthetic fiber plants among workers with known low levels of exposure to airway irritants. The overall goal of the study was to investigate the relation of occupational exposure to airway irritants and obstructive airway disease, with emphasis on the possible role of airway hyperresponsiveness. In a previous cross sectional analysis, it was demonstrated that exposure to airway irritants as encountered in this study was associated with a higher prevalence of chronic respiratory symptoms (Kremer et al, 1994). Acute responses to irritant exposure may precede chronic respiratory responses (Becklake, 1989). We recorded whether workers had more than usual eye, nasal or respiratory symptoms during work. The purpose of the current analyses is to study, cross sectionally, the association of occupational exposure to airway irritants with these work-related symptoms, and to assess whether this association was different for subjects with airway hyperresponsiveness, for smokers, and for subjects with a history of allergy. For these analyses, data of the baseline survey, performed in 1989, were used.

6.3 Methods

Study design

The study was designed as a prospective study and conducted among workers from synthetic fiber plants that belonged to the same industrial location. The baseline survey was carried out from April to July 1989 during working days. The study was approved by the Ethics Board of the Groningen University Hospital and Medical School. Written informed consent was obtained from all participants.

Study population and exposure

The synthetic fibre plants produce polyamide, polyester and para-aramid yarn and fibres, each product being manufactured in a different department. Male employees from departments with potential exposure to airway irritants and a control group from departments presumed to be free from exposure were invited to participate in the survey. In May 1989 the total number of workers eligible for the study was 909 men.

On the basis of job titles and working department at the time of the survey, the current exposure status of all workers was characterised. The workers were divided into seven groups.

(1) Reference group; (2) White collar group; (3) SO₂, H₂SO₄, HCl group; (4) Polyester vapour group; (5) Oil mist and oil vapour group; (6) Polyamide and polyester vapour group; (7) Multiple exposures group.

A more detailed description of the study population, the production process of the synthetic fibres and yarn and the performed exposure measurements, are described in chapter 2.

Questionnaire

Data on respiratory symptoms and smoking habits were collected by means of a self administered Dutch version of the BMRC standardised questionnaire. Additional questions concerning work-related symptoms, allergy and work history were included. Subjects were considered to have work-related symptoms if during their work they experienced more than usual cough, phlegm production, shortness of breath (dyspnoea), wheeze, itching or watering eyes, tickling or watering nose and sneezing.

Subjects were considered to have chronic respiratory symptoms if they had cough or phlegm production on most days or nights for as much as three consecutive months each

year during winter (chronic cough or chronic phlegm), if during the previous three years they experienced more than one period of at least three weeks with (increased) cough and phlegm (episodes of bronchitis), if they become short of breath when walking with other people of their own age on level ground (dyspnoea grade $\geq$ III), if their chest sounded wheezing or whistling more than once a year (frequent wheeze), or if they ever had attacks of shortness of breath with wheezing (asthmatic attacks). Nose catarrh is defined as being troubled with a clogged or runny nose and/or sneezing as much as three consecutive months each year. Subjects were considered to have a history of allergy if they answered yes to one of the following two questions: "Have you ever had hay fever?" and "Do you get eye, nasal or respiratory symptoms if you are exposed to house dust, domestic animals or fungi?" Non-smokers were defined as lifelong non-smokers. Current smokers were defined as those who smoked one cigarette or more per day for at least one year. Ex-smokers were those who stopped smoking for at least one month before the examination.

Histamine challenge test

Airway responsiveness was measured by a histamine challenge test. Baseline FEV₁ was the highest pre-challenge value of three technically satisfactory forced expiratory manoeuvres. The challenge test was not performed in subjects with cardiovascular disease or lung disease requiring daily medication. Subjects whose baseline FEV₁ was below 80% of the predicted value (Quanjer, 1983) were also excluded. The basic protocol is the De Vries modification of the 30 s tidal breathing method: after pre-test with phosphate solution, subjects inhaled sequential aerosols of histamine biphosphate in concentrations of 1, 2, 4, 8, 16 and 32 mg/ml (De Vries, 1962). At 30 and 90 s after each concentration subjects performed an FEV₁ manoeuvre. The test was ended if a fall in FEV₁ of at least 18% from baseline FEV₁ occurred, or if the highest concentration of histamine had been given. Subjects with a history of asthma-like symptoms, or allergy, or a fall in FEV₁ fall of 6% or more after phosphate solution, started with 1 mg/ml histamine. All the others started with 4 mg/ml. Quadrupling histamine concentrations were given until the FEV₁ had fallen at least 6%, then the schedule changed to doubling concentrations. Forced expirations after maximal inspiration were recorded with a water-sealed spirometer (2400 Pulmonary Function Laboratory; SensorMedics BV, Bilthoven, NL) with automatic data processing (IBM-AT computer). A software programme "Broncho-Challenge" (SensorMedics BV), was used for recording the results

of the FEV₁s of the challenge test.

The provocation concentration causing a 20% fall in FEV₁ (the PC₂₀) was calculated by log-linear interpolation of the last two data points, with extrapolation up to one doubling concentration (maximum 64 mg/ml). In the analyses, airway responsiveness is considered as a dichotomous variable, considering subjects with PC₂₀ values ≤32 mg/ml as hyperresponsive and subjects with PC₂₀ values >32 mg/ml histamine as nonresponsive.

Data analysis

The association between exposure to airway irritants and the prevalence of work-related symptoms was studied with multiple logistic regression. This method allows simultaneous adjustment for covariates such as age, smoking habits, airway responsiveness, and a history of allergy. The odds ratio (OR) of an explanatory variable, relative to the reference category, was estimated by taking the antilog of the coefficient of that variable. For a continuous variable, the OR is an estimate of change in log odds per unit of measurement. Stratified analyses were performed to determine whether the estimated ORs were different for smokers, for subjects with airway hyperresponsiveness, and for subjects with a history of allergy. The additional effect of the combination of two variables was assessed by including interaction terms in the regression model.

Of the calculated ORs 95% confidence intervals (CIs) are given. An OR is significant if the CI does not include unity. All analyses were performed using the the Superior Performing Software/PC+ (SPSS, Inc., Chicago) programme (version 4.1).

6.4 Results

Of the 909 workers who were invited, 790 (87%) took part in the survey. Of the participating men, 28 were excluded from analysis because of different cultural or racial backgrounds. In addition, one refused the histamine challenge test, and 50 subjects did not meet the inclusion criteria for the challenge test: five had daily medication for a lung disease and 15 for a cardiovascular disease, 22 had a baseline FEV₁ <80% predicted, and eight subjects were excluded for miscellaneous reasons. Furthermore, for 20 subjects the quality of the challenge test was poor and 23 had incomplete data on smoking, lung function, or challenge test, leaving 668 subjects for analysis.

Table 1: Characteristics of the synthetic fiber plant workers, stratified by exposure group; The Netherlands, 1989

	Reference (n = 180)	White collars (n = 58)	SO ₂ , HCL H ₂ SO ₄ (n = 119)	Polyester vapour (n = 94)	Oil mist and vapour (n = 141)	Polyamide and polyester vapour (n = 51)	Multiple exposures (n = 25)	Total (n = 668)
Age (y (SD))	31.1 (7.8)	43.9 (8.1)	30.8 (6.8)	32.7 (7.5)	31.2 (8.2)	36.2 (9.4)	36.5 (8.4)	33.0 (8.7)
Duration of (y (SD))								
total employment	7.0 (7.3)	17.0 (7.9)	6.3 (5.2)	8.0 (6.5)	7.0 (6.3)	10.3 (8.0)	13.4 (10.4)	8.4 (7.5)
current exposure group	4.5 (5.2)	6.4 (6.3)	3.1 (1.5)	5.8 (4.3)	4.2 (4.0)	6.2 (5.4)	8.4 (6.2)	4.8 (4.7)
Smoking habit (n (%))								
non-smokers	54 (30)	3 (5)	35 (29)	19 (20)	24 (17)	6 (12)	6 (24)	147 (22)
ex-smokers	26 (14)	21 (36)	32 (27)	28 (30)	32 (23)	14 (28)	8 (32)	161 (24)
smokers	100 (56)	34 (59)	52 (44)	47 (50)	85 (60)	31 (61)	11 (44)	360 (54)
Allergy (n (%))	22 (12)	7 (12)	17 (14)	12 (13)	18 (13)	4 (8)	7 (28)	87 (13)
Airway hyperreson- siveness (n (%))	47 (26)	15 (26)	21 (18)	26 (28)	25 (18)	12 (24)	5 (20)	151 (23)
One or more chronic respi- ratory symptoms (n (%))	43 (24)	14 (24)	17 (14)	27 (29)	45 (32)	20 (39)	10 (40)	176 (26)
Nasal catarrh (n (%))	56 (20)	9 (16)	13 (11)	21 (22)	29 (21)	10 (20)	5 (20)	112 (18)

The study population (table 1) was relatively young, with 50% of the subjects younger than 31 years (range 20-58 years). The prevalence of current smoking ranged from 44% in the SO₂ group and the multiple exposed group to 61% in the polyamide and polyester vapour group. Airway hyperresponsiveness was present in 23% of the subjects: the prevalence was low in the SO₂ group (18%) and the oil mist group (18%). The prevalence of a history of allergy was 14% for the non-smokers, 15% for the ex-smokers, and 12% for the smokers; 34% of the subjects with a history of allergy also had hyperresponsive airways.

Compared with the reference group, all groups with occupational exposures reported more work-related symptoms such as cough, phlegm, dyspnoea, wheeze, eye, and nasal symptoms (table 2). The overall prevalence ranged from 2% (wheeze) to 31% (nasal symptoms). The low prevalence of the eye symptoms in the SO₂ group (5%) is due to the fact that the workers of the SO₂ group are obligated to utilize protective eyewear. Multiple logistic regression with simultaneous adjustment for potential confounding factors was used to estimate the association of the various occupational exposures with the presence of work-related symptoms (table 3). The prevalence of the work-related symptoms in the white collar group did not differ from the reference group, except for the eye symptoms (OR 3.8). Workers exposed to SO₂, HCl and H₂SO₄ reported dyspnoea more often (OR 2.7) and significantly more cough (OR 12.7) and nasal symptoms (OR 3.1). Workers exposed to polyester vapour reported significantly more cough (OR 3.7) and eye symptoms (OR 3.6). They reported more dyspnoea (OR 2.3) and nasal symptoms (OR 2.1), but these differences were not statistically significant. Exposure to oil mist and oil vapour, polyamide and polyester vapour, and multiple exposures were also significantly associated with a higher prevalence of work-related symptoms.

In this young group, age was not significantly associated with work-related symptoms. Smokers and ex-smokers reported more phlegm and wheeze and significantly more dyspnoea than non-smokers, with respective ORs for dyspnoea of 3.6 and 3.2. Subjects with airway hyperresponsiveness had more wheeze (OR 1.9), but this association did not reach statistical significance. A history of allergy was associated with a higher prevalence of all work-related symptoms. These associations were significant with the exception of phlegm.

Stratified logistic regression analyses were performed to assess whether the association between exposure group and the presence of work-related symptoms was different for

Table 2: Self reports of work related symptoms among synthetic fiber plant workers, stratified by exposure group

	n (100%)	Cough n (%)	Phlegm n (%)	Dyspnoea n (%)	Wheeze n (%)	Itching or watering eyes n (%)	Watery nose or sneezing n (%)	One or more symptoms n (%)
Total	688	60 (9)	37 (6)	47 (7)	13 (2)	104 (16)	103 (15)	205 (31)
Exposure group								
Reference	180	4 (2)	4 (2)	4 (2)	2 (1)	8 (4)	16 (9)	23 (13)
White collars	58	1 (2)	1 (2)	2 (3)	-	7 (12)	4 (7)	9 (16)
SO ₂ , H ₂ SO ₄ , HCl	119	27 (23)	5 (4)	7 (6)	-	6 (5)#	26 (22)	44 (37)
Polyester vapour	94	7 (7)	4 (4)	5 (5)	-	13 (14)	15 (16)	24 (26)
Oil mist and vapour	141	14 (10)	17 (12)	20 (14)	6 (4)	49 (35)	23 (16)	67 (48)
Polyamide and poly- ester vapour	51	3 (6)	4 (8)	4 (8)	4 (8)	16 (31)	12 (24)	26 (51)
Multiple exposures	25	4 (16)	2 (8)	5 (20)	1 (4)	5 (20)	7 (28)	12 (48)

protective eyewear obligatory

Table 3: Estimated ORs (95% CI) for the prevalence of work related symptoms by exposure group, with simultaneous adjustment for age, smoking habit, airway responsiveness, and a history of allergy (668 synthetic fiber plant workers).

Exposure group [§]	Cough (n = 60)		Phlegm (n = 37)		Dyspnoea (n = 47)		Wheeze (n = 13)		Eye symptoms (n = 104)		Nasal symptoms (n = 103)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
White collars	1.0	0.1- 9.2	0.8	0.1- 7.7	1.5	0.2- 9.3	<0.1	<0.1->100	3.8	1.2-11.8*	0.9	0.3- 3.1
SO ₂ , H ₂ SO ₄ , HCl	12.7	4.3-37.6**	1.9	0.5- 7.2	2.7	0.8- 9.7	<0.1	<0.1->100	1.1	0.4- 3.3	3.1	1.5- 6.1**
Polyester vapor	3.7	1.1-13.0*	1.9	0.5- 7.7	2.3	0.6- 8.8	<0.1	<0.1->100	3.6	1.4- 9.2**	2.1	1.0- 4.6*
Oil mist and vapour	4.9	1.6-15.5**	5.5	1.8-16.9**	7.1	2.3-21.6**	4.1	0.7-22.0	11.6	5.2-25.9**	2.1	1.0- 4.1*
Polyamide and polyester vapour	3.2	0.7-14.9	3.6	0.9-15.5*	3.8	0.9-16.1*	8.2	1.3-53.3*	11.7	4.5-30.3**	3.7	1.6- 8.6**
Multiple exposures	7.8	1.8-34.6**	3.7	0.6-22.0	10.7	2.5-45.5**	2.2	0.1-33.1	5.1	1.5-17.6*	4.0	1.4-11.4**
Age (y)	0.99	0.95-1.03	0.99	0.94-1.03	0.99	0.95-1.03	1.06	0.99-1.13	0.98	0.95-1.01	0.99	0.96-1.02
Smoking habit												
ex-smoker	0.8	0.4- 1.9	2.4	0.7- 8.0	3.6	1.1-11.8*	>100	<0.1->100	0.9	0.4- 1.9	0.6	0.3- 1.2
smoker	0.8	0.4- 1.5	2.3	0.8- 6.9	3.2	1.1- 9.5*	>100	<0.1->100	1.0	0.5- 1.8	1.1	0.6- 1.9
Airway hyperresponsiveness												
veness	0.9	0.4- 1.8	0.8	0.4- 2.0	1.4	0.7- 2.9	1.9	0.5- 6.8	0.6	0.3- 1.1	1.0	0.6- 1.7
Allergy	2.1	1.1- 4.3*	1.7	0.7- 4.0	2.3	1.1- 4.9*	11.5	3.0-43.6**	2.5	1.4- 4.6**	2.4	1.4- 4.2**

* p < 0.1; * p < 0.05; ** p < 0.01

§ odds ratios relative to the reference group.

Table 4: Estimated ORs (95% CI) for the prevalence of work related symptoms for synthetic fiber plant workers with exposure compared to subjects without exposure, stratified by smoking habit, or by airway responsiveness, or by a history of allergy. (N=668)

		Cough and/or phlegm			Dyspnoea and/or wheeze			Eye symptoms			Nasal symptoms		
		n (%)	OR	95% CI	n (%)	OR	95% CI	n (%) [§]	OR	95% CI	n (%)	OR	95% CI
Nons stratified	(n = 668)	80 (12)	4.8	2.4- 9.9**	52 (8)	3.8	1.7- 8.8**	98 (18%)	5.3	2.9- 9.5**	103 (15)	2.7	1.6- 4.5**
Stratified by:													
Smoking habit													
non-smoker	(n = 147)	20 (14)	3.9	1.1-14.5*	4 (3)	0.6	<0.1-4.4	18 (16)	4.3	1.3-14.2*	24 (17)	2.7	0.9- 7.8 [§]
ex-smoker	(n = 161)	18 (11)	>100	<0.1->100 ^{§§}	14 (9)	1.7	0.4- 6.5	24 (19)	3.8	1.2-12.2*	18 (11)	3.5	0.8-14.7*
smoker	(n = 360)	42 (12)	3.9	1.6- 9.7**	34 (9)	10.7	2.5-45.7**	56 (18)	6.7	2.9-15.6**	61 (17)	2.6	1.3- 5.2**
Airway hypersensitivity													
no	(n = 517)	64 (12)	3.2	1.4- 7.1**	38 (7)	3.1	1.2- 7.8**	81 (19)	4.3	2.3- 7.9**	79 (15)	2.1	1.1- 3.9*
yes	(n = 151)	16 (11)	13.7	1.7- >100*	14 (9)	14.7	1.8->100*	17 (13)	20.5	2.5->100**	24 (16)	4.4	1.4-13.9*
History of allergy													
no	(n = 581)	63 (11)	4.2	1.9- 8.9**	38 (7)	6.7	2.0-22.3**	78 (16)	5.8	3.0-11.4**	79 (14)	3.4	1.8- 6.4**
yes	(n = 87)	17 (20)	11.5	1.4-95.4*	14 (16)	1.6	0.4- 6.3	20 (29)	3.7	1.1-13.1*	24 (28)	1.4	0.5- 4.1

ORs are adjusted for age, smoking habit, airway responsiveness, and a history of allergy.

[§] SO₂ group excluded.

^{§§} no reliable estimation of the magnitude of the OR.

smokers, for subjects with airway hyperresponsiveness, and for subjects with a history of allergy. In these analyses, the groups with exposure to airway irritants were combined to one "current exposed" group because of the small numbers of subjects with symptoms in some of the exposure groups. The reference group and the white collar group were combined to one "non-exposed" group. The workers exposed to SO₂, HCl and H₂SO₄ wore protective eye wear and were therefore excluded in the analysis with the eye symptoms as the dependent variable. To obtain a larger number of subjects with work-related symptoms in each stratum, the symptoms cough, phlegm, dyspnoea, and wheeze were combined to two symptom groups: cough and/or phlegm and dyspnoea and/or wheeze.

Stratified analysis with dyspnoea and/or wheeze as the dependent variable (table 4), showed that the association with exposure was stronger for smokers (OR 10.7) than for non-smokers (OR 0.6) and ex-smokers (OR 1.7). The association between exposure and eye symptoms was stronger for smokers (OR 6.7) than for non-smokers (OR 4.3) and ex-smokers (OR 3.8). No marked differences in the ORs were present for cough and/or phlegm and nasal symptoms. For all work-related symptoms, subjects with hyperresponsive airways had higher ORs for exposure than those with nonresponsive airways. Exposure to irritants was associated with a higher prevalence of work-related symptoms in subjects both with and without a history of allergy (ORs > 1.0). The finding that these associations for dyspnoea and/or wheeze, eye symptoms, and nasal symptoms were stronger in subjects without a history of allergy, is addressed in the Discussion.

To evaluate whether the differences in the associations between exposure and the work-related symptoms as shown in the stratified analyses of table 4 were statistically significant, the nonstratified multiple logistic regression analysis of table 4 was repeated including four interaction terms: "current exposed-smoking", "current exposed-ex-smoking", "current exposed-airway hyperresponsiveness", and "current exposed-allergy". The analysis with the interaction terms confirmed the stratified analysis.

The analysis of table 3 was also performed with adjustment for the presence of chronic respiratory symptoms and chronic nasal catarrh (Appendix, table 1). The associations between work-related symptoms and exposure groups remained essentially the same, with the exception of increased ORs for cough and for dyspnoea of the SO₂, H₂SO₄, HCl group. These increases might be due to the low prevalence of chronic respiratory symptoms in this group (table 1). Subjects with chronic respiratory symptoms had

significantly more work-related symptoms compared with subjects with no chronic respiratory symptoms, and this relation was independent of the exposure status.

6.5 Discussion

In this study, exposure to airway irritants was significantly associated with a higher prevalence of the work-related symptoms cough, phlegm, dyspnoea, wheeze, itching or watering eyes and tickling or watering nose and/or sneezing. The association between exposure and dyspnoea and/or wheeze and eye symptoms was stronger in smokers than non-smokers. In subjects with airway hyperresponsiveness, exposure was more strongly associated with a higher prevalence of all work-related symptoms than in subjects with normal responsive airways. The association between exposure and a higher prevalence of work-related symptoms was stronger in subjects with no history of allergy than in subjects with a history of allergy, except for cough and/or phlegm.

In the synthetic fiber plants under study, the airways are potentially exposed to acid aerosols and vapour, oil mist and vapour, aldehydes/acetaldehydes vapour, and lactam vapour. These exposures are known to produce an irritating effect on the respiratory tract or to cause respiratory symptoms (Hackney et al, 1989; Parkes, 1982; Brabec, 1982; Järholm et al, 1982; Ferguson and Wheeler, 1973). Glycol may be a respiratory hazard in circumstances where glycol is used at elevated temperatures (Rowe and Wolf, 1982), as is the case during the production of polyester yarn (up to 250 °C). Irritation of the eyes and the mucous membranes has been reported for diphenyl diphenyloxide exposures of 19 to 25 mg/m³ (Sandmeyer, 1982; Hefner et al, 1975). Personal sampling (eight hour time weighted average) among the workers from the polyester vapour group revealed that these exposure levels do occur as a result of an interruption in the production process (Kremer et al, 1994).

In the current study, workers exposed to SO₂ vapour, HCl and H₂SO₄ aerosols reported more cough and nasal symptoms than dyspnoea or wheeze (table II), suggesting that the upper airways are more affected than the lower airways. It is quite possible that the upper airways are more exposed than the lower airways. SO₂ is a soluble gas and, when inhaled, most of it is absorbed in the upper airways (Ericsson and Camner, 1983). The acidic aerosols (HCl and H₂SO₄) may be neutralized by normal excretion of endogenous

ammonia into the airways, which prevents deposition in the lower airways (Lippmann et al, 1987). Spinning of the sulphuric acid solution causes visible airborne sulphuric acid (H_2SO_4) aerosols. Measurements revealed only low levels of H_2SO_4 aerosols (Kremer et al, 1994). The airborne H_2SO_4 particles probably have larger mass median aerodynamic diameters (MMAD) than absorbed by the indicator silica tubes and the solid sorbent tubes used for exposure measurements; and thus, only a fraction of the total inspirable aerosols exposure is measured. Industrial aerosols can have an MMAD up to 14 μm , whereas acidic ambient aerosols typically have MMADs of 0.3 to 0.6 μm (Lippmann et al, 1987). This means that, although, in an industrial setting the total airborne exposures may be high compared with ambient exposures, only a fraction of the industrial exposures reaches the lower airways.

The workers from the polyester vapour group, the oil mist group and the polyamide and polyester vapour group are all exposed to vapours that are generated during common machining operations. The maintenance engineers have multiple exposures because they operate at different locations. All these exposure groups reported significantly more work-related symptoms than the reference group. Physical effort, temperature changes, and exposure to tobacco smoke (passive smoking) may contribute to the occurrence of work-related symptoms in this study. These exposures are also present in the reference group, and thus may explain the occurrence of the work-related symptoms reported by this group. The white collar group is composed of workers who do not work (anymore) at the production lines. This group may have work-related symptoms because occasionally some of them spend some time close to the machines, performing managerial functions, and therefore may be exposed.

Increased workload might induce more work-related symptoms because of a higher minute ventilation, and thereby a higher irritant exposure. While no information about the workload was collected in this study, and thus no adjustment for personal workload could be performed, the average workload of the workers in this study is light to moderate and similar for the reference group and the exposed groups. For this reason, it seems unlikely that large differences in prevalence of symptoms would occur due to predominantly nasal breathing in the exposed groups.

Work-related symptoms such as shortness of breath, wheeze, throat, nose, and eye irritation in relation to airway irritants were reported in occupational health studies of workers exposed to colophony fumes (Burge et al, 1981) and formaldehyde in combination with solvents (Alexandersson and Hedenstierna, 1988), but no information was

available of a possible association with smoking habits. Gamble and coworkers (1976) found significantly more work-related symptoms such as ease of breathing away from work, cough, chest tightness, and burning eyes, in 52 workers exposed to a phenol-formaldehyde type resin. Active smoking was not significantly associated with work-related symptoms (Gamble et al, 1976).

Airway irritants can cause a cough reflex and preferentially induce bronchoconstriction in subjects with airway hyperresponsiveness by stimulating the irritant receptor (Alberts and Brooks, 1992; Cockcroft, 1987; Dolovich and Hargreave, 1981; Salvaggio, 1982). Smoking, airway hyperresponsiveness, and allergy are all associated with mucosal inflammation of the bronchi (Monchy et al, 1989; O'Connor et al, 1989; O'Byrne et al, 1989; Pride, 1989), and in the case of allergy mucosal inflammation also of the nose and the eyes is possible. Inflammation of the mucosa may damage the epithelium, increasing vulnerability to further damage by airway irritants (Alberts and Brooks, 1992). In the current study, exposure to irritants was significantly associated with work-related cough, dyspnoea, wheeze, eye, and nasal symptoms independent of airway responsiveness, smoking, or allergy. This indicates an irritating effect of the airborne exposure encountered in this study. Table 4 shows that the association between exposure and dyspnoea and/or wheeze was higher in subjects who smoked, or who had hyperresponsive airways. This finding suggests that existing airway inflammation, or functional alterations in the mucosa (Persson et al, 1992) may play an important role in the occurrence of the work-related symptom dyspnoea and/or wheeze. In subjects with airway hyperresponsiveness, exposure was also more strongly associated with a higher prevalence of cough and/or phlegm, eye and nasal symptoms. This could be an indication of an increased responsiveness of the sensory nerves in the mucosa of the upper airways (Persson et al, 1992) and the eyes.

In the current study, a history of allergy is assessed on the basis of self reported estimate of being allergic. This estimate may be less reliable than positive skin tests to common airborne allergens or measurement of specific serum IgE, but often it is the only information occupational health physicians may be able to obtain. Surprisingly, the association between exposure and dyspnoea and/or wheeze, eye symptoms, and nasal symptoms was stronger in subjects without a history of allergy than in those with a history of allergy. Prevalence data showed that subjects with a history of allergy had a higher prevalence of work-related symptoms than subjects with no history of allergy, both in the "current exposed" group and the "non-exposed group"; yet, the differences

in prevalence of symptoms between subjects with and without a history of allergy was greater in the "non-exposed" group than in the "current exposed" group. For example, of the "non-exposed" group 14% of the subjects with a history of allergy ($n = 4$) and 1% of the subjects with no history of allergy ($n = 3$) reported dyspnoea and/or wheeze. For the "current exposed" group these prevalences were 17% ($n = 10$) and 9% ($n = 35$), respectively. As a result, the statistical association between irritant exposure and symptoms was smaller for subjects with a history of allergy (table 4). A possible explanation for the high prevalence of work-related symptoms in the non-exposed allergic subjects may be that the exposure levels encountered by subjects of the "non-exposed" group may still be sufficient to cause a biological response in allergic subjects (Becklake, 1989). It is also possible that, whether exposed at work or not, subjects with a history of allergy may more frequently report work-related symptoms such as dyspnoea and/or wheeze, eye and nasal symptoms because they are familiar with these symptoms. If this reporting bias is present, we do not know whether it is different for subjects of the reference group as compared with the other exposure groups.

In the questionnaire, no data were collected on the frequency of the occurrence of work-related symptoms. Thus, it is possible that if the frequency of the occurrence of work-related symptoms could have been taken into account, the magnitude of the association between exposure and symptoms for subjects with a history of allergy (table 4) would increase.

Selection bias (for example, workers who had work-related symptoms left the company), misclassification of the exposure status of the participants of this study, and exclusion of subjects from analyses might have had an effect on the results. Yet, all these factors would have biased the association of exposure and work-related symptoms towards no effect, resulting in underestimation of the association.

Work-related symptoms may precede the development of chronic respiratory symptoms (Alberts and Brooks, 1992; Becklake, 1989). In the current analysis, estimation of the association between exposure groups and work-related symptoms with adjustment for chronic respiratory symptoms also showed that subjects who did not have chronic respiratory symptoms reported work-related symptoms. This indicates a direct exposure effect. Becklake (1989) stated that there is increasing evidence that acute respiratory responses to airborne agents appear to be risk factors for chronic airflow limitation. Longitudinal follow-up of the current study population may provide data to answer the question whether there is a link between acute and chronic respiratory responses.

In conclusion, our study shows that in workers exposed to low levels of irritants, exposure to these irritants is significantly associated with a higher prevalence of work-related symptoms, and this is true for subjects with and without airway hyperresponsiveness, cigarette smoking, a history of allergy, or chronic respiratory symptoms. The association of exposure group with work-related symptoms was stronger for hyper-responsive subjects than for nonresponsive subjects. The association with dyspnoea and/or wheeze was also stronger for smokers than for non-smokers and ex-smokers. Except for cough and/or phlegm, the association between exposure and a higher prevalence of work-related symptoms was stronger in subjects with no history of allergy than in subjects with history of allergy. This latter finding was most likely due to the relatively high prevalence of work-related symptoms in non-exposed allergic subjects.

6.6 References

Alberts WM and Brooks SM. Advances in occupational asthma. *Clinics in Chest Medicine* 1992; 13:281-301.

Alexandersson R, Hedenstierna G. Respiratory hazards associated with exposure to formaldehyde and solvents in acid-curing paints. *Arch Environ Health* 1988; 43: 222-227.

Becklake MR. Occupational exposures: Evidence for a causal association with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989; 140: S85-S91.

Brabec MJ. Aldehydes and Acetals. In Clayton GD, Clayton FE (eds): "Patty's Industrial Hygiene and Toxicology." 3rd ed. John Wiley & Sons, Inc. New York, 1982; pp 2629-2669.

Brooks SM, Kalica AR. Strategies for elucidating the relationship between occupational exposures and chronic air-flow obstruction. *Am Rev Respir Dis* 1987; 135: 268-273.

Burge PS, Edge G, Hawkins R, White V, Taylor AJN. Occupational asthma in a factory making flux-cored solder containing colophony. *Thorax* 1981; 36: 828-834.

Chan-Yeung M, Lam S. Occupational asthma. *Am Rev Respir Dis* 1986; 133: 686-703.

Cockcroft DW. Airway hyperresponsiveness: therapeutic implications. *Ann Allergy* 1987; 59: 405-414.

De Vries K de, Goei JT, Booy-Noord H, Orie NGM. Changes during 24 hours in the lung function and histamine hyperreactivity of the bronchial tree in asthmatic and bronchitic patients. *Int Arch Allergy* 1962; 20: 93-101.

Dolovich J, Hargreave F. Editorial: The asthma syndrome: inciters, inducers, and host characteristics. *Thorax* 1981; 36: 641-644.

Ericsson G, Camner P. Health effects of sulfur oxides and particulate matter in ambient air. *Scand J Work Environ Health* 1983; S3: 1-52.

Ferguson WS, Wheeler DD. Caprolactam vapour exposures. *Am Ind Hyg Assoc J* 1973; 34: 384-389.

Gamble JF, McMichael AJ, Williams T, Battigelli M. Respiratory function and symptoms: an environmental-epidemiological study of rubber workers exposed to a phenol-formaldehyde type resin. *Am Ind Hyg Assoc J* 1976; 37: 499-513.

Hackney JD, Linn WS, Avol EL. Acid fog. Effects on respiratory function and symptoms in healthy and asthmatic volunteers. *Environ Health Perspect* 1989; 79: 159-162.

Hefner RE, Leong BKJ, Kociba RJ, Gehring PJ. Repeated inhalation toxicity of diphenyl oxide in experimental animals. *Toxicol Appl Pharmacol* 1975; 33: 78-86.

Järnholm B, Bake B, Lavenius B, Thiringer G, Vokmann R. Respiratory symptoms and lung function in oil mist-exposed workers. *J Occup Med* 1982; 24: 473-479.

Kateman E, Heederik D, Pal TM, Smeets M, Smid T, Spitteler M. Relationship of airborne microorganisms with the lung function and leucocyte levels of workers with a history of humidifier fever. *Scand J Work Environ Health* 1990; 16: 428-433.

Kremer AM, Pal TM, Boleij JSM, Schouten JP, Rijcken B. Airway hyperresponsiveness, chronic respiratory symptom prevalence and lung function in workers exposed to irritants. *Occup Environ Med* 1994; 4: 3-13.

Lippmann M, Gearhart JM, Schlesinger RB. Basis for a particle size-selective TLV for sulfuric acid aerosols. *Appl Ind Hyg* 1987; 2: 188-199.

Monchy JGR de, Postma DS, Kauffman HF, Vries K de. In Sluiter HJ, van der Lende R (eds): "Bronchitis IV". Assen: Van Gorcum, 1989; pp 198-207.

O'Byrne PM, Jones GL, Manning PJ. Inflammatory processes in the pathogenesis of asthma. In Sluiter HJ, van der Lende R (eds): "Bronchitis IV". Assen: Van Gorcum, 1989; pp 187-195.

O'Conner GT, Sparrow D, Weiss ST. The role of allergy and nonspecific airway hyperresponsiveness in the pathogenesis of chronic pulmonary disease. *Am Rev Respir Dis* 1989; 140: 225-252.

Parkes WR. "Occupational Lung Diseases". 2nd ed. London: Butterworth, 1982; pp 472-482.

Persson CGA, Svensson C, Greiff L, Andersson M, Wollmer P, Alkner U, Erjefält I. The use of the nose to study the inflammatory response of the respiratory tract. *Thorax* 1992; 47: 993-1000.

Pride NB. Smoking and bronchial responsiveness. In Sluiter HJ, van der Lende R (eds). "-Bronchitis IV". Assen: Van Gorcum, 1989; pp 71-79.

Quanjer, PhH. Standardized lung function testing. Report of the Working Party "Standardization of Lung Function Tests". *Bull Eur Physiop Resp* 1983; suppl 5: 1-95.

Rowe VK, Wolf MA. Glycols. In Clayton GD, Clayton FE (eds). "Patty's Industrial Hygiene and Toxicology". 3rd ed. John Wiley & Sons, Inc. New York, 1982; pp 3817-3832.

Salvaggio JE. Overview of occupational immunologic lung disease. *J Allergy Clin Immunol* 1982; 70: 5-10.

Sandmeyer EE. Aromatic hydrocarbons. In Clayton GD, Clayton FE (eds). "Patty's Industrial Hygiene and Toxicology". 3rd ed. John Wiley & Sons, Inc. New York, 1982; pp 3325-3331.

Appendix

Table 1: Estimated ORs (95% CI) for the prevalence of work related symptoms by exposure group, with simultaneous adjustment for chronic respiratory symptoms and nasal catarrh (668 synthetic fiber plant workers).

Exposure group [§]	Cough (n = 60)		Phlegm (n = 37)		Dyspnoea (n = 47)		Wheeze (n = 13)		Eye symptoms (n = 104)		Nasal symptoms (n = 103)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
White collars	1.0	0.1- 9.6	0.7	0.1- 7.3	1.5	0.2- 9.5	<0.1	<0.1->100	4.0	1.3-12.8*	1.0	0.3- 3.3
SO ₂ , H ₂ SO ₄ , HCl	20.3	6.4-64.5**	2.3	0.6- 9.5	3.5	0.9-12.9	<0.1	<0.1->100	1.2	0.4- 3.7	3.7	1.8- 7.5**
Polyester vapour	3.5	1.0-12.9 [§]	1.3	0.3- 5.8	1.8	0.5- 7.4	<0.1	<0.1->100	3.5	1.4- 9.0**	2.1	1.0- 4.5 [§]
Oil mist and vapour	4.4	1.3-14.3*	4.8	1.5-15.5**	6.9	2.2-21.9**	6.3	0.8-47.6 [§]	11.9	5.3-26.7**	2.1	1.0- 4.3*
Polyamide and polyester vapour	2.7	0.5-13.2	2.5	0.6-11.6	2.9	0.7-12.9	10.2	1.2-89.2*	11.4	4.4-30.3**	3.7	1.5- 8.9**
Multiple exposures	6.1	1.3-19.1*	2.2	0.3-14.5	8.7	1.9-39.8**	1.7	0.1-41.4	4.9	1.4-17.3*	4.1	1.4-12.2**
One or more chronic respir. symptoms	7.8	3.8-16.0**	13.7	5.6-33.4**	7.0	3.4-14.7**	28.9	2.9->100**	1.8	1.1- 2.9*	1.4	0.8- 2.3
Nasal catarrh	1.2	0.6- 2.6	0.8	0.3- 1.9	1.1	0.5- 2.3	2.6	0.6-11.3	2.1	1.2- 3.6*	3.2	1.9- 5.3**

ORs are adjusted for age, smoking habit, airway responsiveness, and a history of allergy.

^{*} $p < 0.1$; ^{*} $p < 0.05$; ^{**} $p < 0.01$

[§] odds ratios relative to the reference group.

chapter 7

Sickness absence

7.1 Definition, registration and features of sickness absence

Definition

In the Netherlands, the Sickness Benefit Act guarantees the employee 70% of his wage in case of absence up to one year, provided he works more than 12 hours per week. Sickness absence, therefore, includes all spells of work incapacity due to illness, accidents or maternity leave, with a maximum duration of 365 calendar days. Additional collective labour agreements grant most employees payment of their full wages. In contrast to most of the other countries in Europe, no distinction is made between occupational diseases ("risque professionnel") and other diseases ("risque social") (Veerman, 1990).

Registration

The company, which was investigated in the present study, paid the sickness benefits. The company employs lay inspectors and occupational physicians whose duties are registering sickness absence, verifying spells and guiding sick employees during their absence period. Information on incapacity to work is obtained by the lay inspector who visits sick employees at home or from the medical examination by the occupational physician. In cases where a sick employee is not visited by a lay inspector during the first days of absence, data on reasons for sickness absence, whether a general practitioner is consulted or not, and expected date of recovery, are obtained by means of a mailed form. The lay inspectors code the reported reason for sickness absence (chapter headings) in accordance with the coding list of the National List of Diagnosis for Sickness Absenteeism, which is based on the International Classification of Diseases and Accidents. The absence registration includes: date of onset, date of recovery (= first working day), reason for absence (=absence diagnosis), type of shift, department and, if applicable, a code for reduction of work capacity. The absence record can have two codes for the absence diagnosis. A second diagnosis is added in cases in which the diagnosis coded by the occupational physician differs from the diagnosis coded by the lay inspector (= first diagnosis). If there is a change of illness during the absence period, this is coded and recorded as a second diagnosis. The code for respiratory symptoms includes: acute infections of the upper airways, common cold, lower respiratory complaints, diseases of the tonsils, chronic bronchitis and asthmatic bronchitis.

Measures of sickness absence

There are two basic aspects of sickness absence: the number of spells of sickness absence per person in a certain period of time (frequency) and the mean duration of these spells. Another measure is the product of frequency and duration, the total number of absence days per person in a certain period of time (percentage of days lost). In this study, absence frequency is based on the number of spells that ended in a certain period of time. The duration and percentage of days lost, are based on calendar days. This means that days off after recovery (i.e. weekend), but preceding the first day back at work are included in the sickness absence.

The total number of days lost is more influenced by the duration than the frequency of absences. Figure 1 shows that 70% of the total number of spells per year are spells with a duration of less than 10 days, and these spells count for less than 30% of the total number of days lost per year. The importance of the distinction between frequency and duration is obvious (Smulders, 1980).

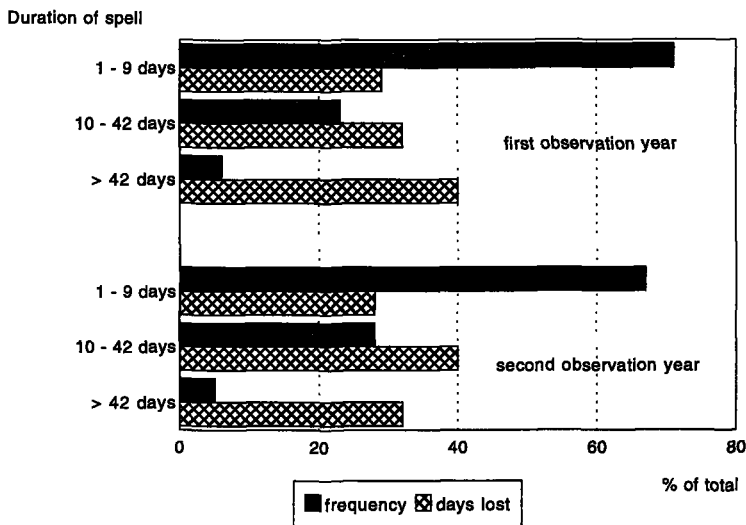


Figure 1: Contribution of short (1- 9 days), medium (10-42 days) and long (>42 days) spells to the total frequency of spells per year and to the total annual number days lost. Data of subjects who worked the whole year October 1989 - October 1990 (N=864) and October 1990 - October 1991 (N=843) at the departments under study.

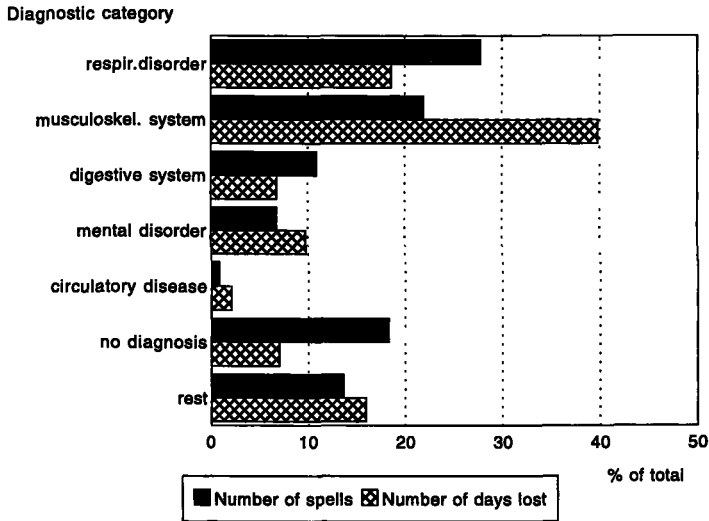


Figure 2: Contribution of the diagnostic categories to the total number of spells ($n=1719$) and the total number of annual days lost. Data of subjects who worked a whole year at the departments under study ($N=864$), October 1989 - October 1990.

Commonly, short spells are defined as absences of less than eight days. In our study about 80% of the study population worked in a five-shift system. This system is composed of five days of work and three days off after a day- or afternoon-shift, or four days off after a night-shift. This means that if a five-shift worker is ill for one working week of five days, the total duration of his absence is eight or nine days. Inspection of the sickness absence data shows that among the five-shift workers 14.5% and 12% of the spells had a duration of eight and nine days respectively, whereas 1.9% had a duration of ten days. Among the day workers the cut off point was eight days: 17.3% of the spells lasted seven days, whereas 2.6% lasted eight days. For this reason, short spells are defined as absences of less than ten days.

Reasons for sickness absence

In our study population, data on sickness absences were collected over a period of two years, October 1989 till October 1991. Among the 864 subjects 1719 spells of sickness absence were registered during the first observation year. About 18% of these spells

were not classified. Absence due to respiratory symptoms¹ is the most prevalent reason for being absent from work, with 28% of the total number of spells. The second most prevalent reason are disorders of the musculoskeletal system, with 22%. Less than 1% of all spells of sickness absence is caused by cardiovascular diseases (figure 2). Looking at the number of days lost, absence due to disorders of the musculoskeletal system count for 40% of the total number of days lost, whereas absence with respiratory causes count for 19%. The distribution of absence spells over diagnostic categories during second observation year, is similar.

The distribution of spells with a duration of 1-9, 10-42 and more than 42 days reveals that absence due to respiratory symptoms of less than ten days account for 60% of all days lost due respiratory symptoms, whereas only 15% of the days lost are due to absence spells lasting more than 42 days. Figure 1 shows that the overall contributions of short and long spells to the total number of days lost, are 29% and 40% respectively, in the first observation year. This means that absence from work due to respiratory symptoms are, on average, relatively short.

National registration of sickness absence

In the Netherlands, several institutions publish yearly data on sickness absence among them the Central Bureau of Statistics (CBS), the Social Security Council ("Sociale Verzekeringsraad", SVr), the Netherlands Institute for Working Conditions (NIA), and the Organization for Applied Scientific Research - Prevention and Health² (TNO-PG) (Veerman et al, 1992).

The CBS and SVr obtain data from industrial associations and it comprises the sickness absence data on that part of the labour force in the Netherlands that is compulsory insured according to the Sickness Benefit Act (67% of the total Dutch labour force), the absence data of civil servants who are insured according the General Civil Pension Fund Act, and data of employees who are facultatively insured. CBS and SVr give

¹ Diseases of the respiratory system include acute infections of the upper airways, sinusitis, common cold (also gastroenteritis), chronic bronchitis, asthmatic bronchitis (National List of Diagnosis for Sickness Absenteeism)

² Before January 1994, TNO-Prevention and Health was called TNO-National Institute for Preventive Health (TNO-NIPG)

information on absence in different types of industry, including frequency and duration of absence spells, and percentage of days lost. The TNO-PG system contains in 1994 data on around 100 companies that participate voluntarily. This survey mainly covers large companies, and not all industries are equally well represented. In addition to the absence data, the TNO-NIPG system gives information on type of industry, type of work (white collar versus blue collar) and gender.

The NIA registration system comprises data on around 170 companies with 50 employees or more. A relatively large number of the companies belong to the service category. Most companies are medium-sized (100-499 employees). Their participation is also voluntary. The system includes detailed information on sickness absence in different branches of industry, age groups, tenure, shift work, type of work and education level. In 1992, NIA had to stop with their registration survey of sickness absence data (Nieuwland, 1992).

Both NIA and TNO-PG can't provide information on the reason for sickness absence (Reuling, 1989; Klein Hesselink and Reuling, 1990; Veerman et al, 1992). CBS can provide data on the reason for sick absence, but only on 30% of all absences. This is because 70% of the absences are not diagnosed (CBS, 1986).

Since 1986, NIA and TNO-PG publish sickness absence data derived from different registration systems. These data are considered to be representative for Dutch companies with 50 employees or more. This system comprises data of about 500 companies, but it can only provide absence data on the level of industry (branch and size). Analysis at the individual level is not possible (Veerman et al, 1992).

Recently, some changes have occurred with respect to the social security of sick employees. Due to the implementation of the Reduction of Illness Absenteeism Act in 1994, all employers in the Netherlands have to pay the sickness benefits of their employees during the first few weeks of sick leave¹. By law, the employer has to inform the industrial associations about all sick leaves of their employees. However, in practice some employers 'tend to forget' to give notice of sick leaves of only a few days. This would mean an under-registration of sickness absence. In the future, the CBS and SVr will probably also use another source for their information on sickness absence. Data could be derived from a questionnaire survey conducted every year by the CBS

¹ Generally, the first two weeks for employers with less than 15 workers and the first six weeks for employers with 15 workers or more.

among Dutch citizens aged 15-64 years, the Labour Force Survey ("Enquête Beroepsbevolking") (SVr, 1994).

As part of the occupational health survey among workers exposed to airway irritants, we studied prospectively the sickness absence of the workers with respect to their respiratory health. Results of the analyses are presented in the following part of this chapter.

7.2 Determinants of sickness absence among workers exposed to irritants

A.M. Kremer, T.M. Pal, V. Fidler, B. Rijcken, G.H. Koëter

7.2.1 Abstract

The purpose of this study was to examine prospectively the sickness absence among 653 workers exposed to airway irritants, in relation to their respiratory health. A Dutch version of the BMRC questionnaire with additional questions concerning allergy and work-related symptoms, was used to assess respiratory symptoms. Airway hyperresponsiveness was measured by a standardised histamine challenge test. Exposure was dichotomised as exposed and non-exposed. Sickness absence data were collected during a period of two years. Multivariate regression analyses were used to examine the relation of exposure, respiratory health and smoking habit to sickness absence. Both absence due to any illness and absence due to respiratory symptoms (RS), were evaluated.

On average, a worker was absent two times a year due to illness. Altogether 6.7% of the calendar days per year were lost in these spells of absence. Respiratory symptoms were the most prevalent reason for sick leave (28%). We could not demonstrate an overall association between exposure and more sickness absence (frequency and days lost), both for all absences as for absence due to RS. Results suggested that exposed smokers have an increased risk for being absent from work because of RS as opposed to exposed non-smokers. Whereas for non-exposed subjects, smokers had an decreased risk for being absent. Subjects with a history of allergy, with airway hyperresponsiveness (AHR) or with work-related symptoms were more often absent because of RS, although for subjects with AHR the difference was not significant. A lower level of lung function was not a significant predictor of being absent, because of its relation with AHR. The presence of chronic respiratory symptoms was a predictor of more absence among older subjects, but not among younger subjects. As for the frequency of absence due to any illness, generally the same associations, although smaller in magnitude, were found with these respiratory health variables. This indicates that respiratory health parameters are associated with health in general. In contrast to absence due to RS, smokers were more often absent due to any illness than non-smokers. Older subjects were significantly less often absent than younger subjects. But, it applied only for those

who did not report chronic respiratory symptoms. Age was the only significant predictor for the duration of sickness absence: the older the subject, the longer the duration.

7.2.2 Introduction

A considerable proportion of the reason for sick leave from work are respiratory diseases, according to some studies as much as 28% to 50% (Athanasou, 1975; Ferguson, 1972; Chevalier et al, 1987; Dimberg et al, 1989). Information on whether the presence of chronic respiratory symptoms or a decreased lung function is associated with more absence from work due to respiratory diseases is, however, limited. In 1975, Athanasou published a review of the literature on the association between sickness absence, respiratory impairment and smoking, and concluded that individuals with chronic respiratory disease have an increased sickness absence risk. So these individuals are a potential economic loss. Since that review, only a limited number of studies describing respiratory health in relation to sickness absence due to respiratory symptoms, have been published (Jedrychowski, 1976; Comstock et al, 1981; Smith et al, 1981). These studies show that subjects with chronic respiratory symptoms and a lower than average lung function level tend to be longer and more often absent from work due to respiratory diseases.

Occupational exposure to gases, vapours and fumes can induce respiratory symptoms and bronchial obstruction (Brooks and Kalica, 1987; Chan-Yeung and Lam, 1986). Therefore, occupational exposures might be responsible for an increased risk for absence from work due to respiratory symptoms. As part of an occupational health survey among workers exposed to airway irritants, we studied prospectively the sickness absence of the workers with respect to their respiratory health. The purpose of the current analyses is to assess which determinants are associated with sickness absence. More specifically, the importance of exposure to irritants and the interrelation of this factor with other factors such as job function, age, smoking habit, airway responsiveness, allergy and respiratory symptoms with regard to sickness absence. Both absence due to any illness and due to respiratory symptoms will be evaluated.

7.2.3 Methods

Study design

The study was designed as a prospective study and carried out among workers from synthetic fibre plants that belonged to the same industrial site. Data on respiratory characteristics were collected during the baseline survey that was carried out from April to July 1989 during working days. Data on sickness absence were collected over a two year observation period from October 1989 till October 1991. The study was approved by the Ethics Board of the Groningen University Hospital and Medical School. Written informed consent was obtained from all participants.

Study population

At the time of the study in 1989, nearly 4000 employees worked at the plants. For this survey, a total number of 909 male employees were invited for the medical examination in Spring 1989. They worked at departments with potential exposure to airway irritants, or at departments presumed to be free from exposure. Of the 790 workers who took part in the survey (response 87%), 786 subjects were available at the beginning of the current study in October 1989. Of these 786 subjects, 26 were excluded from analysis because of different cultural, racial or lingual background. In addition, 105 subjects left the study during the two years of observation as a result of resignation (mainly as a consequence of reorganization; $n=53$), transfer and leaving the study population ($n=34$), voluntary retirement ($n=16$) and death ($n=2$). Of the remaining 655 subjects, two were excluded because no lung function data were available. Thus, data from 653 subjects were available for analysis.

The subjects who left the study population during the follow-up were on average younger, had a lower prevalence of respiratory symptoms, a lower mean %FEV₁ predicted and more often hyperresponsive airways. They were more often absent from work due to illness, and had a higher percentage days lost from illness (for definition see the statistical analysis) during the first observation year (table 1). The largest differences were seen in the percentage days lost as a result of musculoskeletal disorders and mental disorders, 4.4% and 2.3%, respectively, for those who left as opposed to 2.3% and 1.0% for the study population.

Table 1 : Comparison of the study population with the subjects who left the study in the period 1 October 1989 - 1 October 1991.

	Follow-up between 01/10/1989 and 01/10/91	
	complete (n = 653)	incomplete (n = 105)
Age (y (SD))	34 (8.9)	33 (11.0)
Tenure (y (SD))	10 (7.8)	7 (9.4)
%FEV ₁ predicted (SD)	104 (12.5)	102 (12.0)
Smoking habit (n (%))		
non-smoker	129 (22)	25 (24)
ex-smoker	146 (25)	25 (24)
smoker	318 (54)	55 (52)
≥1 Chron.resp.symptoms (n (%))	181 (28)	11 (10)
≥1 Work-related symptoms (n (%))	216 (33)	17 (16)
History of allergy (n (%))	78 (12)	16 (15)
Airway hyperresponsiveness (n (%))		
yes	130 (20)	24 (23)
not known	60 (9)	19 (18)
Absence in 1st year		
frequency of spells: all/RS ¹	2.0 / 0.56	2.4 / 0.54
average %lost days: all/RS	6.8 / 1.3	10.9 / 1.8

¹ respiratory symptoms

Exposure and job category

The synthetic fibre plants produce polyamide, polyester and para-aramide yarn and fibres, each product being manufactured in different departments. The production process of the yarn and fibres consists of polymerization and polycondensation of the monomers, cutting up of the polymer, melting of the chips (temperature of the process over 200 °C), spinning and winding. The spun filaments can be twisted, drawn and texturised. After spinning a synthetic oil mixture is applied to the yarn which functions as an emulsifier and lubricant.

Exposure measurements were carried out and have been reported (chapter 2; Kateman et al, 1990). The overall exposures were relatively low: on average the eight hour Time Weighted Averages of the measured components were well below the Dutch Threshold Limit Values.

On the basis of job titles and working department at the time of the survey, seven groups were defined (chapter 2):

(1) No exposure group; (2) White-collar group; (3) SO₂, H₂SO₄, HCl group; (4) Polyester vapour group; (5) Oil mist and oil vapour group; (6) Polyamide and polyester vapour group; (7) Multiple exposures group. Since job category is associated with the level of sickness absence (Prins and Graaf, 1986; Chevalier et al, 1987; Dimberg et al, 1989), all job titles were subdivided into skilled and unskilled jobs. Process technologists, maintenance engineers, blue collar workers with an industrial training, production floor managers, production instructors and clerical workers were considered as having skilled jobs. For the current analysis, exposure was characterised as exposed and non-exposed to airway irritants. As a result, four exposure-function groups were defined: (1) non-exposed - unskilled; (2) exposed - unskilled; (3) exposed - skilled and (4) non-exposed - skilled. The data of the workers whose job changed in the periode between the medical examination in 1989 and the end of the study in October 1991, were analysed separately. As can be seen in table 2, workers who were exposed had primarily skilled jobs, whereas the workers of the previously defined non-exposure group had mainly unskilled jobs.

Table 2 : Distribution of the workers among the exposure groups as defined in Spring 1989, stratified by exposure-function category

	Total (n = 653)	Non-exposed unskilled (n = 128)	Exposed- unskilled (n = 65)	Exposed- skilled (n = 359)	Non-exposed- skilled (n = 65)	Transferred (n = 36)
Exposure group (n (%))						
No exposure	155 (24)	128 (63)	-	-	12 (18)	15 (42)
White collars	62 (9)	-	8 (12)	-	53 (82)	1 (3)
SO ₂ , H ₂ SO ₄ , HCl	137 (21)	-	4 (6)	130 (36)	-	3 (8)
Polyester vapour	90 (14)	-	5 (8)	85 (24)	-	-
Oil mist and vapour	134 (21)	-	-	123 (34)	-	11 (30)
Polyamide vapour and polyester vapour	52 (8)	-	48 (74)	-	-	4 (11)
Multiple exposures	23 (4)	-	-	21 (6)	-	2 (6)

Medical examination Spring 1989 and sickness absence data

Data on respiratory symptoms and smoking habits were collected by means of a self-administered Dutch version of the BMRC standardised questionnaire. Definitions of chronic respiratory symptoms, work-related symptoms, history of allergy and smoking habits, are given in the chapters five and six. Pulmonary function measurements were performed with a water-sealed spirometer and are described in chapter five. In the current analysis the highest value for FEV₁ is used and expressed as a percentage of predicted value (%FEV₁) using the prediction equations of Quanjer and colleagues (Quanjer et al, 1983). Airway responsiveness was measured by a 30 s tidal breathing challenge test. This test is described in chapter four. In the current analysis subjects with PC₂₀ values of 32 mg/ml histamine or less are considered as responders and subjects with PC₂₀ values of more than 32 mg/ml as non-responders.

The collection of sickness absence data is described in paragraph 7.1. For the current analysis, only the first diagnosis was used. If the first absence diagnosis was coded as 'unknown', the second diagnosis, if any, was used. A temporary reduction of work for medical reasons was not considered as sickness absence. For the calculation of age and tenure, the date of 1 October 1989 was used.

Statistical analysis

Regression analyses were used to study the relation between sickness absence and the explanatory variables exposure-function category, age, smoking habit, chronic respiratory symptoms, work-related symptoms, a history of allergy, airway hyperresponsiveness and lung function level. The following features of sickness absence were taken as dependent variables:

Frequency of spells: number of ended absence spells per person during the two year observation period. The distribution of these numbers was reasonably described by a Poisson distribution. Poisson regression was used for the analysis.

Duration per spell: number of calendar days per spell of absence. The frequency distribution of the duration of multiple spells within a person was well described by the log-normal distribution. The mean log(duration) per person was also nearly normally distributed, so that linear regression could be applied to mean log(duration).

Percentage days lost: the percentage of calendar days lost due to illness per person during the observation period. Linear regression analysis was applied to logit of these percentages, i.e. log(percentage days lost/percentage days at work).

Annual number of days lost: this is categorised as 0-2, 3-9, 10-28, ≥ 29 days for all absences and as 0-2, 3-6, 7-9, ≥ 10 days for absence due to respiratory symptoms. For these data, the multinomial logistic regression was used.

Although these features of absence are closely related, they do not necessarily carry the same information. For example, a certain explanatory variable could result in a large increase of the frequency of short spells, but in only a small increase in the total number of days lost.

The regression analyses allow simultaneous evaluation of effects of covariates such as age, smoking habit and symptoms. In the regression analysis, age was centred at 20 years by subtracting 20 from each observed age. This means that the intercept of the regression analysis is an estimate of the mean value of the dependent variable for a 20 years old subject in the reference category. Tenure is not included in the regression analysis, because of its dependence on age. The analyses were carried out for all spells and spells due to respiratory symptoms only.

Results of regression analyses are presented in terms of rate ratio's (RRs, Poisson regression), odds ratio's (ORs, logistic regression) and regression coefficients (beta's, linear regression) and the corresponding 95% confidence intervals (95% CI). Statistical tests with p-values less or equal to 0.05 are considered as significant. The computations were carried out in SPSS/PC (SPSS, 1992), EGRET (EGRET, 1991) and SYSTAT (SYSTAT, 1992).

7.2.4 Results

Of the 653 subjects of whom data were available for this study, 50% were younger than 32 years (range 21-59 years). At the time of the medical examination, 54% of the subjects were current smokers, 28% reported one or more chronic respiratory symptoms, and 12% had a history of allergy (tables 1 and 3). Work-related symptoms were reported by 33% of the subjects. From 60 subjects no histamine challenge test data were available, because the test was not performed ($n=38$), incomplete ($n=5$) or of poor quality ($n=17$). Of the 593 subjects with a complete test, 130 were responder (22%). During the two years of observation, 2466 ended spells of absence were recorded with a geometric mean duration per spell of 7.7 days (table 4). Altogether 6.7% of the

Table 3 : Characteristics of the study population

	Non-exposed- unskilled (n = 128)	Exposed- unskilled (n = 65)	Exposed- skilled (n = 359)	Non-exposed- skilled (n = 65)	Transferred (n = 36)
Age (y (SD))	34 (8.8)	39 (10.6)	33 (7.5)	44 (8.5)	31 (5.7)
Tenure (y (SD))	9 (7.8)	12 (8.8)	7 (6.1)	19 (8.6)	8 (6.5)
%FEV ₁ predicted (SD)	102 (12)	104 (11)	104 (12)	103 (15)	107 (13)
Smoking habit (n (%))					
non-smoker	36 (28)	8 (12)	85 (24)	7 (11)	11 (31)
ex-smoker	16 (12)	17 (26)	94 (26)	27 (42)	6 (17)
smoker	76 (59)	40 (62)	180 (50)	31 (48)	19 (53)
≥1 Chron.resp.symptoms (n (%))	32 (25)	22 (34)	93 (26)	32 (21)	36 (13)
≥1 Work-related symptoms (n (%))	20 (16)	29 (45)	145 (40)	10 (15)	12 (33)
History of allergy (n (%))	9 (7)	3 (5)	50 (14)	12 (19)	4 (11)
Airway hyperresponsiveness (n (%))					
yes	35 (27)	15 (23)	70 (20)	10 (15)	5 (14)
not known	10 (8)	4 (6)	14 (4)	9 (14)	1 (3)

Table 4 : Absence characteristics by diagnostic category. Observation period of 2 years.

Diagnostic category	Number of spells n (%)	Duration of spell in days GM (GSD) ¹	Percentage days lost % (% of total)	Frequency of spell/person N
All diagnosis	2466 (100)	7.7 (2.5)	6.7 (100%)	3.9
Respiratory tract system (common cold included)	700 (28)	6.8 (1.8)	1.2 (18)	1.1
Musculoskeletal system	543 (22)	13.2 (2.7)	2.5 (38)	0.8
Digestive system	234 (10)	5.2 (2.4)	0.4 (6)	0.4
Mental disorders	185 (8)	11.7 (3.0)	0.9 (14)	0.3
Circulatory diseases	8 (<1)	9.3 (3.0)	<0.1 (<1)	<0.1
No diagnosis	444 (18)	3.9 (2.1)	0.5 (7)	0.7
Rest	352 (14)	10.0 (2.5)	1.1 (17)	0.5

¹ geometric mean and geometric standard deviation

calendar days per year (24.5 days) were lost in these spells. Respiratory symptoms were the most prevalent reason for absence (28%), whereas the largest proportion of the percentage days lost was attributed by spells due to disorders of the musculoskeletal system (38%). Of 444 spells (18%) the reason for absence was not known. A total of 608 subjects (93%) were at least absent once, and 378 subjects (58%) were at least one time absent because of respiratory symptoms.

Skilled workers were less often absent from work and had a lower percentage days lost than unskilled workers, both for absence due to any illness and due to respiratory symptoms. These differences were greatest for the non-exposed skilled workers (table 5). As compared with the non-exposed unskilled workers, the exposed unskilled workers had a higher percentage days lost due to respiratory symptoms (1.7% *versus* 1.3%).

On average, the frequency of all spells was higher among younger subjects, smokers, subjects with work-related symptoms, subjects with chronic respiratory symptoms, subjects with a history of allergy and subjects with hyperresponsive airways (table 5). The same associations were present for the frequency of absence spells due to respiratory symptoms with the exception of smoking habit. Smokers and ex-smokers were less often absent because of respiratory symptoms than non-smokers. In general, the differences in frequencies between subgroups were in accordance with differences in percentages days lost, with the exception of age. Older subjects were less often absent from work than younger subjects, but lost more days due to illness given the fact that absences among older subjects last on average longer than among younger subjects. In addition to older age, the mean duration per spell of absence was relatively high among exposed unskilled workers.

Frequency

Multivariate analysis of the frequency of all spells and spells due to respiratory symptoms (table 6) showed that exposed- and non-exposed skilled workers were significantly less often absent than non-exposed unskilled workers. This was independent of age, smoking habits and the other health parameters.

With regard to age, smoking habit and the respiratory health variables, the multivariate analysis (table 6) was generally in accordance with the results of the univariate analysis (table 5). Some differences were present. Age was a significant predictor of being absent: the older the age, the less often absent. But, it applied only for subjects who did not report chronic respiratory symptoms. For symptomatic subjects, the frequency of

Table 5 : Absence characteristics, stratified by various subgroups. Observation period of 2 years (N=653).

	number	All sickness absences			
		frequency		duration of	percentage
		of spells		spells in	days lost
	N	N	(SD) ¹	GM ² (GSD)	% (SD)
Exposure-function category					
non-exposed - unskilled	128	4.3	(2.4)	8.0 (2.5)	7.6 (6.9)
exposed - unskilled	65	4.2	(2.5)	9.4 (2.3)	7.6 (5.8)
exposed - skilled	359	3.8	(2.5)	7.4 (2.6)	6.3 (7.8)
non-exposed - skilled	65	2.8	(2.8)	7.4 (2.8)	5.5 (8.4)
transferred	36	4.4	(2.8)	7.3 (2.8)	8.4 (10.7)
Age					
20 - 29	252	4.2	(2.5)	7.2 (2.6)	6.9 (8.0)
30 - 39	218	4.1	(2.5)	7.6 (2.5)	6.8 (7.7)
40 - 49	127	3.2	(2.5)	8.4 (2.5)	5.7 (6.6)
50 - 49	56	3.2	(2.7)	10.0 (2.6)	7.7 (9.0)
Smoking habit					
non-smoker	147	3.6	(2.5)	7.2 (2.4)	5.5 (6.3)
ex-smoker	160	3.5	(2.6)	8.0 (2.7)	6.7 (8.5)
smoker	346	4.1	(2.6)	7.8 (2.6)	7.2 (7.9)
≥1 Chronic respiratory symptoms					
no	472	3.7	(2.6)	7.5 (2.5)	6.3 (7.5)
yes	181	4.2	(2.6)	8.1 (2.6)	7.8 (8.4)
≥1 Work-related symptoms					
no	437	3.6	(2.5)	7.8 (2.6)	6.4 (7.2)
yes	216	4.4	(2.7)	7.6 (2.5)	7.3 (8.4)
History of allergy					
no	575	3.8	(2.6)	7.8 (2.6)	6.6 (7.6)
yes	78	4.3	(2.7)	7.4 (2.5)	7.6 (9.0)
Airway hyperresponsiveness					
no	463	3.7	(2.6)	7.5 (2.5)	6.1 (7.2)
yes	130	4.2	(2.6)	8.4 (2.7)	8.4 (9.0)
not known	60	4.0	(2.5)	7.8 (2.6)	7.7 (8.4)
Total	653	3.9	(2.6)	7.7 (2.5)	6.7 (7.8)

¹ standard deviation;² geometric mean and geometric standard deviation

Table 5 : Continued

	<u>Sickness absence due to respiratory symptoms</u>			
	number	frequency	duration of	percentage
	N	of spells N (SD) ¹	spells in days GM ² (GSD)	days lost % (SD)
Exposure-function category				
non-exposed - unskilled	128	1.3 (1.5)	6.6 (1.8)	1.4 (2.0)
exposed - unskilled	65	1.3 (1.3)	8.3 (1.8)	1.7 (2.2)
exposed - skilled	359	1.0 (1.2)	6.8 (1.8)	1.1 (1.5)
non-exposed - skilled	65	0.8 (1.5)	7.1 (1.7)	0.9 (1.9)
transferred	36	1.3 (1.6)	6.2 (1.7)	1.3 (1.6)
Age				
20 - 29	252	1.2 (1.3)	6.4 (1.8)	1.2 (1.8)
30 - 39	218	1.2 (1.4)	6.8 (1.7)	1.3 (1.6)
40 - 49	127	0.8 (1.0)	7.6 (1.8)	1.0 (1.5)
50 - 49	56	0.9 (1.5)	9.2 (1.8)	1.4 (2.5)
Smoking habit				
non-smoker	147	1.2 (1.3)	7.1 (1.8)	1.4 (1.9)
ex-smoker	160	0.9 (1.2)	6.9 (1.8)	1.0 (1.7)
smoker	346	1.1 (1.3)	6.8 (1.8)	1.2 (1.7)
≥1 Chronic respiratory symptoms				
no	472	1.0 (1.2)	6.8 (1.8)	1.1 (1.6)
yes	181	1.3 (1.4)	7.1 (1.9)	1.5 (2.0)
≥1 Work-related symptoms				
no	437	1.0 (1.2)	6.9 (1.8)	1.1 (1.6)
yes	216	1.3 (1.5)	6.8 (1.8)	1.5 (2.0)
History of allergy				
no	575	1.1 (1.3)	6.8 (1.8)	1.2 (1.7)
yes	78	1.4 (1.3)	7.0 (1.8)	1.6 (1.8)
Airway hyperresponsivenss				
no	463	1.0 (1.3)	6.7 (1.8)	1.1 (1.7)
yes	130	1.3 (1.3)	7.3 (1.9)	1.6 (2.1)
not known	60	1.3 (1.2)	6.9 (1.8)	1.4 (1.6)
Total	653	1.1 (1.3)	6.9 (1.8)	1.2 (1.8)

¹ standard deviation;² geometric mean and geometric standard deviation

Table 6 : Rate ratio's (RR) with 95% confidence interval (95% CI) for the frequency of sickness absence: all absences and absence due to respiratory symptoms (n = 653).

	All		Respiratory symptoms	
	RR	95% CI	RR	95% CI
Exposure-function category ¹				
exposed - unskilled	0.95	0.82 - 1.11	0.96	0.73 - 1.27
exposed - skilled	0.82	0.74 - 0.91 **	0.73	0.61 - 0.89 **
non-exposed - skilled	0.71	0.59 - 0.84 **	0.71	0.51 - 0.98 *
transferred	1.02	0.85 - 1.22	1.02	0.74 - 1.42
Age-20				
no chron.resp.symptoms	0.985	0.979- 0.981**	0.980	0.968-0.991 **
≥1 chron.resp.symptoms	0.996	0.987- 1.004	1.003	0.988-1.019
Smoking				
ex-smoker	1.13	1.00 - 1.28 #	0.93	0.74 - 1.17
smoker	1.18	1.06 - 1.30 **	0.95	0.79 - 1.14
History of allergy	1.11	0.98 - 1.25 #	1.31	1.05 - 1.62 *
≥1 Chron.respir. symptoms	0.91	0.77 - 1.07	0.76	0.56 - 1.03 #
≥1 Work-related symptoms	1.20	1.10 - 1.31 **	1.36	1.16 - 1.60 **
% FEV ₁ predicted	0.998	0.994- 1.001	0.996	0.990- 1.003
Airway hyperresponsiveness				
yes	1.11	1.00 - 1.23 #	1.18	0.98 - 1.43 #
not known	1.13	0.98 - 1.31 #	1.28	0.99 - 1.67 #

p<0.1; * p<0.05; ** p<0.01

¹ relative to the non-exposed - unskilled workers

being absent did not decrease or increase with age. In contrast to table 5, ex-smokers were more often absent due to any illness (RR=1.13). The association between the presence of chronic respiratory symptoms and frequency of spells was age dependent. For subjects aged 20 years the RR for chronic respiratory symptoms was 0.76, whereas for example for subjects aged 50 years the RR was 1.62.

Subjects with a low %FEV₁ predicted were not significantly more often absent. The known association between level of lung function and airway hyperresponsiveness (subjects with a low level of lung function have more often hyperresponsive airways, than those with a normal level of lung function), might have affected the significance level of this association. Additional analysis without adjustment for airway hyperresponsiveness, confirmed this hypothesis. In these cases, subjects with a low %FEV₁ predicted were significantly more often absent, both for all spells (RR 0.996, 95% CI 0.993-1.000)

Table 7 : Linear regression coefficients (β) with standard errors (SE) for the mean log(duration) of sickness absence: all absences and absence due to respiratory symptoms (n = 653).

	All ¹		Respiratory symptoms ¹	
	β	SE	β	SE
Exposure-function category ²				
exposed - unskilled	0.11	0.10	0.15	0.10
exposed - skilled	-0.08	0.07	0.02	0.07
non-exposed - skilled	-0.15	0.11	-0.07	0.12
transferred	0.01	0.12	-0.06	0.12
Age-20				
no chron.resp.symptoms	0.008	0.004*	0.009	0.004*
≥ 1 chron.resp.symptoms	0.019	0.006**	0.024	0.006**
Smoking				
ex-smoker	-0.02	0.08	-0.13	0.08
smoker	0.01	0.07	-0.07	0.07
History of allergy	<-0.01	0.08	0.08	0.08
≥ 1 Chron.respir. symptoms	-0.04	0.06	-0.18	0.11
≥ 1 Work-related symptoms	-0.11	0.11	-0.02	0.06
%FEV ₁ predicted	0.001	0.002	<-0.001	0.002
Airway hyperresponsiveness				
yes	0.07	0.07	0.03	0.07
not known	0.09	0.10	-0.07	0.09

p<0.1; * p<0.05; ** p<0.01

¹ subjects with no spells excluded² relative to the non-exposed - unskilled workers

as for spells of absence due to respiratory symptoms (RR 0.993; 95% CI 0.987-0.999). Exposed workers reported clearly more work-related symptoms than non-exposed subjects (table 3). Therefore, including work-related symptoms in the regression analyses might have influenced the association between exposure-function category and the frequency of spells. Exclusion of work-related symptoms resulted in similar RRs for this variable.

Smoking, airway hyperresponsiveness and a history of allergy may affect the association between exposure-function category and the frequency of absence from work due to respiratory symptoms. Additional analyses with interaction terms, revealed that a history of allergy and airway hyperresponsiveness did not significantly modify these associations. Current smoking had an effect on the association between the exposed

function categories and the frequency of spells due to respiratory symptoms. The RRs of the interaction terms for smoking with exposed-unskilled and with exposed- skilled were 2.20 (95% CI 0.96-5.08) and 1.67 (95% CI 1.09-2.56), respectively. The RR for smoking decreased from 0.95 to 0.67 (95% CI 0.49-0.96).

Duration

The linear regression analysis of the data of subjects with ≥ 1 spells of absence (table 7) shows that age was the only significant predictor for longer spells of absence. The duration increased significantly with age, both for all spells as for spells of absence due to respiratory symptoms. This increase was greater for subjects with chronic respiratory symptoms than for subjects without these symptoms. The differences in duration of spells between exposed- and non-exposed unskilled workers as shown in table 5, did not reach a significant level.

Days lost

The results of the linear regression analysis of the percentage days lost (table 8), reflect the differences between frequency and duration. Within the group of subjects who were absent at least once, higher frequencies of spells (RRs greater than 1.0) are in most cases reflected in a higher percentage days lost (B 's greater than 0.0). Although some explanatory variables were significantly associated with a higher frequency of absence spells, their association with percentage days lost did not reach a significant level. Skilled workers, exposed- and non-exposed, had significantly fewer days lost than the non-exposed unskilled workers. Subjects with airway hyperresponsiveness had significantly more days lost than those with normal airway responsiveness. As for absence due to respiratory symptoms, older age among subjects with symptoms, was significantly associated with more days lost.

The results of the linear regression analysis of table 8 reveal whether explanatory variables are associated with more or fewer days lost among subjects with one or more spells. In this analysis, information on subjects who had not been absent is not used. Therefore, multinomial regression was used to study the associations between explanatory variables and the annual number of days lost (tables 9 and 10). In these analyses, subjects with 0-2 days lost per year were used as the reference category. Generally, lower frequencies of spells correspond in the multinomial regression with values of ORs smaller than unity. An increase in the magnitude of the ORs of a variable

Table 8 : Linear regression coefficients (β) with standard errors (SE) for the logit of percentage days¹ lost due illness: all absences and absence due to respiratory symptoms (n = 653).

	All ²		Respiratory symptoms ²	
	β	SE	β	SE
Exposure-function category ³				
exposed - unskilled	-0.03	0.18	0.04	0.15
exposed - skilled	-0.34	0.13 **	-0.18	0.11
non-exposed - skilled	-0.56	0.20 **	-0.20	0.19
transferred	-0.05	0.22	-0.07	0.19
Age-20 no chron.resp.symptoms	-0.011	0.007 #	0.005	0.006
Age-20 ≥ 1 chron.resp.symptoms	0.006	0.010	0.029	0.009 **
Smoking				
ex-smoker	0.13	0.14	-0.20	0.13
smoker	0.19	0.12	-0.14	0.10
History of allergy	0.13	0.15	0.15	0.12
≥ 1 Chron.respir. symptoms	-0.16	0.20	-0.33	0.18 #
≥ 1 Work-related symptoms	0.09	0.10	0.17	0.09 #
%FEV ₁ predicted	-0.002	0.004	-0.001	0.004
Airway hyperresponsiveness				
yes	0.26	0.12 *	0.20	0.11 #
not known	0.24	0.17	0.02	0.14

p<0.1; * p<0.05; ** p<0.01

¹ logit = $\log(\% \text{ days lost} / (\% \text{ days at work}))$ ² subjects with no spells excluded³ relative to the non-exposed- unskilled workers

across the three categories, indicates that among subjects with one or more spells of absence, the variable is associated with a higher number of days lost. ORs of similar magnitudes indicate that no association exists between the variable and a higher or lower number of days lost among subjects with at least one spell. ORs greater than unity and of similar magnitudes indicate that an explanatory variable is associated with more days lost as compared with the reference category.

The results of the multinomial analysis (tables 9 and 10) were different from the results of the regression analysis (table 8). Although most ORs did not reach a significant level, table 9 shows that the exposed-unskilled and the transferred categories are associated with more days lost due to illness. Airway hyperresponsiveness was

Table 9 : Sickness absence due to any illness: odds ratio's (ORs) with 95% confidence interval (95% CI) for the annual number of days lost (N=653).

	<u>3 - 9 days (N=129)</u>		<u>10 - 28 days (N=252)</u>		<u>≥29 days (N=195)</u>	
	OR ¹	95% CI	OR ¹	95% CI	OR ¹	95% CI
Exposure-function category ²						
exposed - unskilled	1.89	0.50 - 7.17	1.47	0.45 - 4.76	1.63	0.50 - 5.30
exposed - skilled	1.71	0.74 - 3.93	0.99	0.49 - 2.02	0.66	0.32 - 1.37
non-exposed - skilled	0.93	0.31 - 2.74	0.57	0.22 - 1.47	0.23	0.08 - 0.68 **
transferred	4.71	0.50 - 45.6	4.26	0.51 - 35.6	4.24	0.50 - 35.9
Age-20, no chron.resp.symptoms	0.97	0.93 - 1.01	0.97	0.93 - 1.00 *	0.95	0.92 - 0.99 *
Age-20, ≥1 chron.resp.symptoms	0.96	0.90 - 1.03	0.95	0.95 - 1.09	0.99	0.93 - 1.05
Smoking habit						
ex-smoker	1.76	0.76 - 4.08	1.19	0.55 - 2.57	2.37	1.05 - 5.37 *
smoker	1.74	0.83 - 3.67	1.90	0.98 - 3.67 *	2.56	1.26 - 5.20 *
History of allergy	1.31	0.51 - 3.40	1.03	0.42 - 2.51	1.51	0.62 - 3.70
≥1 Chron.resp.symptoms	1.56	0.37 - 6.68	1.31	0.34 - 4.97	1.02	0.26 - 3.97
≥1 Work-related symptoms	1.04	0.52 - 2.07	1.28	0.69 - 2.39	1.50	0.79 - 2.87
%FEV ₁ predicted	1.00	0.98 - 1.02	0.99	0.97 - 1.02	0.99	0.97 - 1.02
Airway hyperresponsiveness						
yes	0.45	0.20 - 1.05 *	0.88	0.44 - 1.75	1.15	0.56 - 2.34
not known	3.04	0.76 - 12.2	3.85	1.04 - 14.2 *	3.01	0.77 - 11.7

¹ relative to those subjects with annual days lost of 0-2 days (n = 77).

² relative to the non-exposed - unskilled workers

p < 0.1; * p < 0.05; ** p < 0.01

associated with more days lost among those with one or more spells (table 8). But, compared with subjects with normal airway responsiveness, no association was present between airway hyperresponsiveness and more days lost (table 9).

As for days lost due to respiratory symptoms, the results of the multinomial analysis were generally in agreement with the linear regression analysis. Difference was present for subjects of whom the airway responsiveness was not known. These subjects had more days lost as compared with subjects with normal airway responsiveness (RRs greater than 1.0). Whereas, within the group of subjects with one or more spells, no association was found with a higher percentage days lost (table 8).

Table 10 : Sickness absence due to respiratory symptoms: odds ratio's (ORs) with 95% confidence interval (95% CI) for the annual number of days lost (N=653).

	<u>3 - 6 days (N=163)</u>		<u>7 - 9 days (N=75)</u>		<u>≥10 days (N=95)</u>	
	OR ¹	95% CI	OR ¹	95% CI	OR ¹	95% CI
Exposure-function category ²						
exposed - unskilled	1.18	0.54 - 2.57	1.04	0.38 - 2.85	1.69	0.71 - 4.06
exposed - skilled	0.88	0.53 - 1.48	0.62	0.32 - 1.21	0.65	0.34 - 1.24
non-exposed - skilled	0.45	0.19 - 1.07 *	0.58	0.20 - 1.73	0.47	0.17 - 1.34
transferred	0.45	0.15 - 1.35	0.62	0.18 - 2.13	1.21	0.44 - 3.34
Age-20, no chron.resp.symptoms	0.98	0.94 - 1.02 *	0.98	0.94 - 1.02	0.98	0.94 - 1.02
Age-20, ≥1 chron.resp.symptoms	1.01	0.97 - 1.06	0.99	0.93 - 1.05	1.03	0.98 - 1.08
Smoking habit						
ex-smoker	1.27	0.68 - 2.35	0.62	0.29 - 1.33	0.62	0.29 - 1.33
smoker	1.46	0.87 - 2.47	0.59	0.32 - 1.09 *	0.89	0.49 - 1.61
History of allergy	1.41	0.74 - 2.66	1.33	0.58 - 3.05	2.66	1.36 - 5.17 **
≥1 Chron.resp.symptoms	0.62	0.27 - 1.45	0.93	0.31 - 2.78	0.56	0.20 - 1.51
≥1 Work-related symptoms	0.97	0.63 - 1.51	1.62	0.92 - 2.85 *	1.39	0.82 - 2.34
% FEV ₁ predicted	0.98	0.97 - 1.00 *	0.99	0.97 - 1.02	1.00	0.98 - 1.02
Airway hyperresponsiveness						
yes	0.80	0.47 - 1.37	1.45	0.74 - 2.83	1.82	1.00 - 3.29 *
not known	1.32	0.64 - 2.75	2.13	0.88 - 5.14 *	1.81	0.75 - 4.38

¹ relative to those subjects with annual days lost of 0-2 days (n = 320).² relative to the non-exposed - unskilled workers

p < 0.1; * p < 0.05; ** p < 0.01

7.2.5 Discussion

Exposed skilled and unskilled workers were not more often absent because of respiratory symptoms than non-exposed unskilled workers, suggesting that exposure is not a predictor for sickness absence. Further analysis showed that exposed smokers had an increased risk for being absent due to respiratory symptoms as opposed to exposed non-smokers. Subjects with a history of allergy, airway hyperresponsiveness or work-related symptoms were absent more often and had higher percentages days lost due to respiratory symptoms, and this was independent of the exposure-function category. Subjects with chronic respiratory symptoms were less often absent from work due to respiratory symptoms and had a lower percentage days lost than asymptomatic subjects,

but the differences with asymptomatic subjects decreased significantly with age. Subjects with a lower level of lung function were not more often absent. With respect to all absences, in general the same associations were found, although the magnitude of most associations was smaller. In contrast to absence due to respiratory symptoms, smokers and ex-smokers were significantly more often absent, and had higher percentages days lost than non-smokers. The duration of spells, both for any illness as for respiratory symptoms, increased significantly with increasing age.

At the start of the survey, exposure groups were defined in order to explore the relation between exposure to airway irritants and health parameters, such as the prevalence of respiratory symptoms and airway hyperresponsiveness (Kremer et al, 1994a; Kremer et al, 1995). Job function was only of importance if it meant that one was not directly involved in the production of yarn and fibres, or that one was little or not exposed, for example foreman and production instructor. For that reason they were placed in the white collar group. As a result, the white collar group is composed of workers with different social or working backgrounds as compared with the other exposure groups. In the current study, one could suggest to use the non-exposed skilled workers as a reference group for the exposed-skilled workers. However, the non-exposed skilled workers were mainly derived from the former defined white collar group, and because of their different social or working background they were not used as reference for the exposed skilled workers.

Function category is associated with the level of sickness absence. In general, managers are less frequent absent from work and have a lower number of days lost due to illness than manual workers (Prins and Graaf, 1986; Chevalier et al, 1987; Dimberg et al, 1989). Our results are in agreement with this observation.

We did not find an overall association between exposure and a higher level of sickness absence (frequency or days lost). Exposed skilled workers had even a lower level of sickness absence, indicating that also for blue collar workers industrial training is a predictor for a decreased risk of sickness absence.

A high proportion of the number of absence spells was due to respiratory symptoms (28%). This is also found in other studies (Athanasou, 1975; Ferguson, 1972; Chevalier et al, 1987; Dimberg et al, 1989). Dimberg and coworkers (1989) found among 2814 employees from a Swedish engineering plant, that respiratory symptoms counted for even 50% off all spells of which only 2% had no diagnosis. In the current study, the

proportion of 28% might have been even higher, had all reasons for sick leave been known. Many of these spells undoubtedly have been due to respiratory symptoms. Although respiratory symptoms is the most frequent reason for being absent from work, it is not the main factor in the number of days lost. Absence due to musculoskeletal disorders plays a more important role in the number of days lost, because of the longer duration of these absences. These findings are in agreement with data of other studies (Chevalier et al, 1987; Dimberg et al, 1989).

It is known from population studies that smokers have on average more chronic respiratory symptoms and a lower level of lung function (Janzon et al, 1981; O'Connor et al, 1989). Because of this one would expect that smokers are more often absent because of respiratory symptoms than non-smokers. In our study, this was not the case. Our results are in agreement with the studies of Jedrychowski (1976) and Post and coworkers (1994). However, others found an association between smoking and more days lost because of respiratory symptoms (Athanasou, 1975; Smith et al, 1981; Dimberg et al 1989). Our study confirms the common finding that smokers have an increased risk for being absent from work and for having more days lost because of illness (Athanasou, 1975; Janzon et al, 1981; Leigh, 1986; Deursen et al, 1988; Dimberg et al, 1989; Post et al, 1994).

Sickness absence is a complex behavioral phenomenon in which a multiplicity of health, socioeconomic, psychological and work-related factors are involved (Athanasou, 1975; Smulders, 1980; Leigh, 1986; Leigh, 1989). Smoking habit is also a behaviour, influenced by environment, society and culture. Subjects may stop smoking or decide not to smoke for different reasons (Slama and Karsenty, 1993). Smokers may differ from non-smokers in other factors than the smoking habit, such as lifestyle factors (Athanasou, 1975; Gabel et al, 1990; Parkes, 1983). Thus, both biological and behavioral factors may be responsible for differences between smokers and non-smokers with respect to sickness absence.

It is biologically plausible that smoking, airway hyperresponsiveness and a history of allergy all interact with the exposure effect of irritants on the occurrence of respiratory symptoms. The three factors mentioned are associated with inflammation of the bronchi (Monchy et al, 1989; O'Connor et al, 1989; O'Byrne et al, 1989; Pride, 1989), and with respiratory symptoms (O'Connor et al, 1989; Mensinga et al, 1990). An additional factor, such as occupational exposure to irritants, may provoke or enhance chronic respiratory symptoms or enhance acute respiratory symptoms in case of a respiratory

infection. Eventually this may lead to absence from work or to an increased duration of an absence. Airway hyperresponsiveness and a history of allergy were associated with higher frequencies of absence spells due to respiratory symptoms and with more days lost, but these associations were independent of exposure(-function category). Both smoking and exposure were not associated with more spells of absence due to respiratory symptoms. Therefore, the statistical interaction between current smoking and the exposed-unskilled and -skilled category is surprising. Whether this is a biological effect or whether other mechanisms are involved (for example behaviour factors) is unclear.

In the current study, a history of allergy is based on the self-reported "being allergic". This information is less reliable than positive skin tests to common airborne allergens or measurement of specific serum IgE. Still, subjects reporting a history of allergy were significantly more often absent because of respiratory symptoms, and more days were lost due to these spells. Comstock and coworkers (1981) found in a prospective study performed in the years 1962-1972, that among 1386 employees from a telephone company a history of hay fever at any time in the past was associated with decreased risk of sickness absence due to respiratory symptoms lasting at least eight days. The different results between their study and ours might be explained by the following factors. For one, the older age range (45-60 years), and by that a lower prevalence of current allergies (Burrows, 1989). As well as their definition of "history of allergy" (defined by the question: "Have you ever had hay fever"), and possibly a different perception of allergies at that time as compared with nowadays.

Comstock and coworkers (1981) studied whether low lung function level was associated with an increased risk for days lost because respiratory symptoms. They found that after adjustment for age and smoking, low FEV₁ values were a significant predictor of more days lost, whereas in our study this association was only weak (table 8). The difference in magnitude of the associations might partly be explained by the fact that Comstock et al only analysed sickness absences lasting at least eight days (the more serious respiratory illnesses) and by the older age range of their population. It is also possible that the respiratory health of the working population has improved in the last 20 years as a result of changed smoking habits and improved medical care (a cohort effect). Generally, improved medical care shortens the duration of respiratory illnesses, resulting in a decrease of magnitude of the association between level of lung function and more days lost due to these illnesses.

Age is an important predictor of the frequency of sickness absence. In this study, the frequency decreased with age, a finding that is also found in other studies (Klein Hesselink and Reuling, 1990; Dimberg et al, 1989; Prins and de Graaf, 1986; Sexton and Schuman, 1985). However, some studies showed an increase with age (Pines et al, 1985; Comstock et al, 1981). Our finding that the decrease of frequency with increasing age was only true for subjects who report no chronic respiratory symptoms, has not been described before. So, our results indicate a change in the role of respiratory symptoms with increasing age.

In this study the number of subjects with chronic respiratory symptoms and airway hyperresponsiveness might have been affected by pre-employment selection. This selection took place in the years 1984-1989 for workers from the SO₂, H₂SO₄, HCL group and the oil mist and oil vapour group (Kremer et al, 1994a; Kremer et al, 1995). For both groups, subjects with a history of asthma-like symptoms were less likely passed for a function in a workplace environment with exposure to SO₂ and H₂SO₄ or oil mist and oil vapour. Lower prevalence of respiratory symptoms and airway hyperresponsiveness will not compromise associations between these measures of respiratory health and sickness absence. But, because of the smaller number of subjects with respiratory symptoms or airway hyperresponsiveness, the significance levels of these associations will be lower (the confidence intervals will be wider). This effect might have influenced the significant level of the association between airway hyperresponsiveness and the frequency of spells (table 6). Loss to follow-up may imply a healthy worker effect as well (Pearce et al, 1986). Respiratory health problems seemed not to be a main reason for leaving the company or study population (table 1). This is in accordance with the observation of the health department of the company. In the ten years prior to this study, respiratory disorders were seldom a reason for permanent disability from work, in contrast to earlier years.

Work-related symptoms were a significant predictor of more sickness absence, independently of the other respiratory health variables. The proportion of subjects that reported work-related symptoms was, as previously reported, significantly higher among exposed than among non-exposed workers (Kremer et al, 1994b). But, these symptoms did not have an effect on the association between exposure-function category and the frequency of spells. The finding that the prevalence of work-related symptoms was lower among those who left the study, might suggest that these symptoms are not associated with health problems that play a role in the turnover of this population.

Subjective respiratory health measures, such as reported allergy symptoms, chronic respiratory symptoms or work-related symptoms were stronger predictors of absence spells due to respiratory symptoms than objective health parameters, such as level of lung function and airway hyperresponsiveness. However, it is conceivable that more permanent health problems resulting in changing or quitting jobs, result in different associations. For purposes of health surveillance, and programmes for reducing the level of sickness absence (frequency and duration), subjective health data may be better indicators for sickness absence and easier to obtain than objective health data. Taking the large proportion of smokers in the population into account, quitting smoking may have a greater impact on the level of sickness absence.

Respiratory health is associated with absence due to any illness. This may be the result of its association with absence due to respiratory symptoms. But, table 5 shows that differences in mean frequency of spells, and percentage days lost between subgroups, are smaller in case of absence due to respiratory symptoms than in case of all illness. This means that respiratory health problems are not only predictors for more absence due to respiratory symptoms, but also for (some) other illnesses. This is not a surprise, because respiratory health problems occur also as a result of other diseases, for example cardiovascular disease. Respiratory health problems may even reflect a general decreased resistance to illness.

In the current study we could not demonstrate an overall association between exposure to airway irritants and more sickness absence (frequency and days lost) due to respiratory symptoms. Exposed smokers had an increased risk for being absent as opposed to exposed non-smokers. Whereas, for non-exposed subjects, smokers were not more often absent than non-smokers. Subjects with a history of allergy, airway hyperresponsiveness or work-related symptoms were absent more often because of respiratory symptoms, although for subjects with airway hyperresponsiveness the difference did not reach a significant level. A lower level of lung function was not a significant predictor of absence, because of its relation with airway hyperresponsiveness. The presence of chronic respiratory symptoms was a predictor of more sickness absence among older subjects, but not among younger subjects. The frequency of absence spells decreased with age, though not in subjects with respiratory symptoms. As for all absences, generally the same associations, although smaller in magnitude, were found with the respiratory health variables. This indicates that respiratory health parameters

are associated with health in general. Furthermore, smokers were absent more often and lost more days per year than non-smokers. This is in contrast to absence due to respiratory symptoms.

7.2.6 References

Athanasou JA. Sickness absence and smoking behaviour and its consequences. *J Occup Med* 1975; 17: 441-445.

Brooks SM, and Kalica AR. Strategies for elucidating the relationship between occupational exposures and chronic air-flow obstruction. *Am Rev Respir Dis* 1987; 135: 268-273.

Burrows B. Distribution of allergy in the general population. In: Sluiter HJ, van der Lende R, eds. *Bronchitis IV*. Assen: Van Gorcum, 1989; 3-10.

CBS. Compendium of health statistics of the Netherlands 1986. Central Bureau of Statistics, Ministry of Welfare, Health and Cultural Affairs. 's-Gravenhage: Staatsuitgeverij/ CBS-publicaties.

Chan-Yeung M, and Lam S. Occupational asthma. *Am Rev Respir Dis* 1986; 133: 668-703.

Chevalier A, Luce D, Blanc C, Goldberg M. Sickness absence at the French national electric and gas company. *Br J Indus Med* 1987; 44: 101-110.

Cockcroft DW. Airway hyperresponsiveness: therapeutic implications. *Ann Allergy* 1987; 59: 405-414.

Comstock GW, Stone RW, Tonascia JA, Johnson DH. Respiratory survey findings as predictors of disability from respiratory diseases. *Am Rev Respir Dis* 1981; 124: 367-371.

Dimberg L, Olafsson A, Stefansson E, Aagaard H, Odén A, Andersson GJ, Hagert C-G, Hansson T. Sickness Absenteeism in an engineering industry - an analysis with special reference to absence for neck and upper extremity symptoms. *Scand J Soc Med* 1989; 17: 77-84.

Deursen CGL van, Raat H, Garretsen HFL. Alcohol, smoking and diagnoses of absenteeism in Rotterdam civil servants (Dutch, with English summary). *T Alc Drugs* 1988; 15: 25-33.

De Vries K, Goei JT, Booy-Noord H, Orie NGM. Changes during 24 hours in the lung function and histamine hyperreactivity of the bronchial tree in asthmatic and bronchitic patients. *Int Arch Allergy* 1962; 20: 93-101.

EGRET. Statistics and epidemiology research corporation, Seattle, 1991.

Fish JE. Occupational asthma: a spectrum of acute respiratory disorders. *J Occup Med* 1982; 24: 379-386.

Ferguson D. Some characteristics of repeated sickness absence. *Br J Indus Med* 1972; 29: 420-431.

Gabel HD, Colley-Niemeyer BC. Smoking in a public health agency: its relationship to sick leave and other lifestyle behaviour. *Southern Med J* 1990; 83: 13-17.

Janzon L, Lindell S-E, Trell E. Smoking and disease. *Scan J Soc Med* 1981; 9: 127-133.

Kateman E, Heederik D, Pal TM, Smeets M, Smid T, Spitteler M (1990): Relationship of airborne microorganisms with the lung function and leucocyte levels of workers with a history of humidifier fever. *Scand J Work Environ Health* 16:428-433.

Klein Hesseling DJ, Reuling AMH. Verzuim door ziekte en ongevallen 1988-1989, The Netherlands Institute for Working Conditions (NIA), 1989, Amsterdam.

Kremer AM, Pal TM, Boleij JSM, Schouten JP, Rijcken B. Airway hyperresponsiveness, chronic respiratory symptom prevalence and lung function in workers exposed to irritants. *Occup Environ Med* 1994a; 51: 3-13.

Kremer AM, Pal TM, Boleij JSM, Schouten JP, Rijcken B. Airway hyperresponsiveness and the prevalence of work-related symptoms in workers exposed to irritants. *Am J Indus Med* 1994b; 26: 655-669.

Kremer AM, Pal TM, Schouten JP, Rijcken B. Airway hyperresponsiveness, function in workers exposed to low level of irritants. *Eur Resp J* 1995; in press.

Jedrychowski W. Sickness absence caused by chest diseases in relation to smoking and chronic bronchitis symptoms. *Br J Indus Med* 1976; 33: 243-248.

Leigh JP. Correlates of absence from work due to illness. *Human Relations* 1986; 39: 81-100.

Leigh JP. Specific illnesses, injuries, and job hazards associated with absenteeism. *J Occup Med* 1989; 31: 792-797.

Mensinga TT, Schouten JP, Rijcken B, Weiss ST, Speizer FE, Lende R van der. The relationship of eosinophilia and positive skin test reactivity to respiratory symptoms prevalence in a community-based population study. *J Allergy Clin Immunol* 1990; 86: 99-107.

Monchy JGR de, Postma DS, Kauffman HF, Vries K de. Eosinophil infiltration following early and late phase allergic reactions. In Sluiter HJ, van der Lende R (eds): "Bronchitis IV". Assen: Van Gorcum, 1989; 198-207.

Nieuwland JJ van. Verzuim door ziekte en ongevallen 1990-1991, The Netherlands Institute for Working Conditions (NIA), 1992, Amsterdam.

O'Byrne PM, Jones GL, Manning PJ. Inflammatory processes in the pathogenesis of asthma. In Sluiter HJ, van der Lende R (eds): "Bronchitis IV". Assen: Van Gorcum, 1989; 187-195.

O'Conner GT, Sparrow D, Weiss ST. The role of allergy and nonspecific airway hyperresponsiveness in the pathogenesis of chronic pulmonary disease. *Am Rev Respir Dis* 1989; 140: 225-252.

Parkes KR. Smoking as a moderator of the relationship between affective state and absence from work. *J Appl Psych* 1983; 68: 698-708.

Pearce N, Checkoway H, Shy C. Time-related factors as potential confounders and effect modifiers in studies based on an occupational cohort. *Scand J Work Environ Health* 1986; 12: 97-107.

Pines A, Skulkeo K, Pollak E, Peritz E, Steif J. Rates of sickness absenteeism among employees of a modern hospital: the role of demographic and occupational factors. *Br J Indus Med* 1985; 42: 326-335.

Post WK, Burdorf A, Bruggeling TG. Relations between respiratory symptoms and sickness absence among workers in the animal feed industry. *Occup Environ Med* 1994; 51: 440-446.

Pride NB. Smoking and bronchial responsiveness. In Sluiter HJ, van der Lende R (eds). "Bronchitis IV". Assen: Van Gorcum, 1989; 71-79.

Prins R, Graaf A de. Comparison of sickness absence in Belgian, German and Dutch firms. *Br J Indus Med* 1986; 43: 529-536.

Quanjer, PhH. Standardized lung function testing. Report of the Working Party "Standardization of Lung Function Tests". *Bull Eur Physiop Resp* 1983; suppl 5:1-95.

Reuling AMH. Ziekteverzuim 1987-1988, The Netherlands Institute for Working Conditions (NIA), 1989, Amsterdam.

Sexton M, Schumann BC. Sex, race, age, and hypertension as determinants of employee absenteeism. *Am J Epidemiol* 1985; 122: 302-310.

Slama K, Karsenty S. Understanding smoking behaviour and change: A key to prevention. In: Prevention of respiratory diseases. Hirsch A, Goldberg M, Martin JP, Masse G, eds. New York: Marcel Dekker, 1993; 559-574.

Smith GC, Athanasou JA, Reid CC, Ferguson DA. Sickness absence, respiratory impairment and smoking in industry. *Med J Aust* 1981; 1:235-237.

Smulders PGW. Comments on employee absence/attendance as a dependent variable in organizational research. *J Appl Psychol* 1989; 65: 368-371.

SPSS. SPSS Inc., Chicago, 1992.

SVr. Ontwikkeling ziekteverzuim en arbeidsongeschiktheid. 1e kwartaal 1994. Juli 1994, The Social Security Council, Zoetermeer.

SYSTAT. Systat, Inc., Evanston, 1992.

Veerman TJ. Ziekteverzuim: definities, termen, wetten. In: Handboek ziekteverzuim. PGW Smulders, TJ Veerman, eds. 's Gravenhage: Delwet.-Grav., 1990; 19-31.

Veerman TJ, Smulders PGW, Gründemann RWM. Statistische informatie over arbeidsongeschiktheid. Labour Inspection, Ministry of Welfare, Health and Cultural Affairs, 1992, 's-Gravenhage. ISSN 0921-9218; S130.

Chapter 8

General discussion and conclusions

8.1 General discussion

The purpose of this thesis was to gain more insight in the role of airway hyperresponsiveness in the development of obstructive airway diseases due to exposure to airway irritants. The following relations between airway disease and exposure may be possible:

1. Exposure causes respiratory symptoms and/or a decreased lung function, which leads to an increase in airway hyperresponsiveness. This would mean that airway hyperresponsiveness is not a risk factor for the development of respiratory symptoms or decreased lung function.
2. Exposure induces airway hyperresponsiveness, which in turn causes respiratory symptoms or a decreased lung function.
3. Exposure causes respiratory symptoms or a decreased lung function, but only or mainly in subjects with preexisting airway hyperresponsiveness. In this case, airway hyperresponsiveness is a risk factor.

In the present studies we found that exposure to irritants was associated with a higher prevalence of respiratory symptoms. This association was independent of the presence of airway hyperresponsiveness. The exposed workers had on average not a lower level of lung function. Although exposed workers had more often chronic respiratory symptoms, they had not more frequently a certain degree of hyperresponsiveness. Further analysis showed that exposure of more than 10 years might be associated with a lower level of lung function and a higher prevalence of airway hyperresponsiveness. Stratified analyses did not indicate that among subjects with airway hyperresponsiveness the associations between exposure and respiratory symptoms, and exposure and a lower level of lung function were stronger than among subjects with no airway hyperresponsiveness. Other possible risk factors for the development of obstructive airway disease, such as smoking and allergy, defined as a history of allergy, were also studied. We found that among smokers the association of exposure with a higher prevalence of respiratory symptoms was stronger than among ex-smokers and non-smokers, suggesting that smokers are more susceptible for developing respiratory symptoms in case of exposure to irritants than ex-smokers and non-smokers. No indication was found that exposed subjects with a history of allergy had an increased risk for having chronic respiratory symptoms, lower level of lung function or airway hyperresponsiveness as compared with exposed subjects who did not report a history of allergy. The

investigation of the interrelations between chronic respiratory symptoms, airway hyperresponsiveness, level of lung function, a history of allergy, smoking and age was not a research question, but the associations found were in agreement with other studies.

Thus, the cross sectional analyses described in the chapters 4 and 5 could only demonstrate an association between exposure to airway irritants and a higher prevalence of chronic respiratory symptoms. No indication was found that subjects with hyperresponsive airway are more at risk when exposed than exposed subjects with normal responsive airways, nor that exposure induces airway hyperresponsiveness. However, our data do suggest that exposed smokers are at greater risk for developing respiratory symptoms than exposed subjects who do not smoke. So, taking into account the type and level of the exposure, our data favour non of the three hypotheses mentioned.

The analysis of work-related eye, nasal and respiratory symptoms showed that the exposure was high enough to cause acute work-related symptoms. Chapter 6 revealed that for these symptoms subjects with airway hyperresponsiveness were more susceptible for exposure than subjects with normal responsive airways. As for the acute lower respiratory tract symptoms wheeze and dyspnoea, smokers were also more susceptible for the exposure. These analyses suggest that the exposure as encountered in this study acts as an inciter, and that subjects with hyperresponsive airways and smokers are more at risk for having work-related symptoms. The association between exposure and a higher prevalence of work-related symptoms was statistically stronger for subjects who did not have a history of allergy than for subjects with a history of allergy. This is most likely due to the relatively high prevalence of (reported) background work-related symptoms in exposed and non-exposed allergic subjects.

Sickness absence data were also analysed to study whether exposure to airway irritants was associated with more or longer sickness absence due to respiratory symptoms. No overall association was found between exposure and more sickness absence (frequency and duration) due to respiratory symptoms. What we did find was that, though initial analysis indicated that smokers did not have an increased risk for being absent due to respiratory symptoms, exposed smokers had an increased risk for being absent as opposed to exposed non-smokers. So, exposure may have an effect on the frequency of

being absent from work due to respiratory symptoms, but only in smokers. Furthermore, we could demonstrate that measures of respiratory health were associated with a higher frequency of being absent from work due to respiratory symptoms. Subjective respiratory health measures, such as reported allergic symptoms, chronic respiratory symptoms or work-related symptoms were more strongly associated with a higher frequency of being absent due to respiratory symptoms, than the objective health parameters, such as airway hyperresponsiveness and lower level of lung function. This suggests that absence from work is more an indicator of illness behaviour and perception, than of functional abnormalities of the respiratory tract. The finding that the older the age, the more the respiratory symptoms contribute to sickness absence, indicates a change in the role of respiratory symptoms with increasing age. This study showed that measures of respiratory health are also associated with a higher level of absence due to any illness.

Occupational obstructive respiratory diseases

The majority of occupational respiratory studies of obstructive airway diseases, such as occupational asthma, refers to its relation with exposure to sensitising agents and (organic) dust. Occupational asthma is now considered the most common occupational respiratory condition (Malo, 1993). It was estimated in 1979 that 2% of all asthmatics in the U.S had occupational asthma. In Japan 15% of all asthma in men is due to an occupational exposure (Alberts and Brooks, 1992). More recent data revealed that among subjects aged 18-64 years with a working history in the US, 15% of the doctor's diagnosed asthma was attributed to the workplace (Malo, 1993). Results of a general population survey in Norway in 1985, showed that attributable risk of occupational dust or gas exposure for respiratory symptoms ranged from 11-19%, being lowest for cough in the morning and highest for asthma (Bakke et al, 1991). But, there is no information on the relative frequency of different types of asthma that are related to irritant exposures. These types, induced or exacerbated, may be the most frequently occurring types in some industries (Venables, 1994).

Our study results are in agreement with the limited amount of research on respiratory health and occupational exposures to gases, vapours and fumes. Occupational and general population studies indicate that these exposures are associated with chronic respiratory symptoms (Chang-Yeung et al, 1983; Järholm et al, 1982; Osterman et al, 1989a; Korn et al, 1987; Kauffmann et al, 1982, Xu et al, 1992), whereas an association

with a lower level of lung function could not be demonstrated (Oxhoj et al, 1982; Kennedy et al, 1989; Osterman et al, 1989b), with the exception of the study by Xu and coworkers (1992). In the study of Xu and coworkers, a significant lower level of lung function was found among subjects with occupational exposure to high levels of gases and fumes as compared with those with low levels of exposure to gases and fumes. Kauffmann and coworkers (1982) found in a study among Paris area workers an association between a greater decrease in lung function, defined as annual loss of forced expiratory volume in one second (ml/yr), and a high level of exposure to gases, but only with simultaneous exposure to noticeable dust. As for airway hyperresponsiveness, other studies also could not find indications for an increased prevalence among subjects exposed to gases, vapours or fumes at levels commonly found in occupational settings (Soyseth and Kongerud, 1992; Kennedy et al, 1991; Bakke et al, 1991). Exposure to low levels of irritants probably leads in many exposed subjects and especially in smokers, to a low level of inflammation of the bronchi which leads to symptoms. The degree of inflammation is probably too low to induce airflow limitation.

Limitations of the study

Several factors may have influenced the results of our study. Exposure characterisation, statistical power of the analyses, healthy worker effect and selection due to the study itself, are the most relevant factors, and will be discussed.

Exposure was characterised qualitatively on group level. The exposure measurements that were available (environmental and personal measurements) allowed the conclusion that on average the exposure level was low, although peak exposures did occur (chapter 2). We did not have personal exposure measurements of all functions or function tasks. This means that dose-response relations between exposure level and respiratory health could not be studied and only an average association between exposure and respiratory health could be estimated. Also, some workers might have been classified as exposed, while they had in fact a negligible exposure. As for the subjects who were classified as non-exposed, some have a working history with exposure to vapours and mists. Both effects, misclassification and exposure in the past, will bias effects of current exposure on respiratory health towards no effect (Rothman, 1986).

Several groups were distinguished on the basis of the job function of the workers and the type of exposure. A disadvantage of splitting up the study population in several groups was that the number of workers per group decreased, and by that loss of

statistical power in testing differences between exposed and non-exposed workers. The initial reason for not combining the exposure groups to one exposed group, was that the exposure as encountered by the different groups may act differently on the airways. Combining them could compromise an association between exposure and the respiratory health parameter under study. The study showed indeed that differences were present in the magnitude of the association between an exposure group and respiratory health. In addition to different types of exposure, differences were present between exposure groups with respect to pre-employment selection of workers. This selection did not only compromise an association between exposure and respiratory health problems (if present), but even reversed the association suggesting that exposure prevents respiratory health problems. Merging exposure groups would now mean that the selection effects of one group (pre-employment selection) would have been masked by the association of exposure with more respiratory health problems of another group. This was reason for us not to use one exposed group in the analysis of the prevalence of chronic respiratory symptoms and airway hyperresponsiveness (chapters 4 and 5), and level of lung function (chapter 5). As for the work-related symptoms and sickness absence, the associations with the exposure groups with pre-employment selection, were similar in magnitude as compared with the associations with the exposure groups where no pre-employment selection had occurred. In these analyses, exposed workers were assigned to one exposure group. The gain of having more statistical power was more important than losing the information of the separate exposure groups with respect to work-related symptoms and sickness absence.

The previous mentioned pre-employment selection is one of the factors that contribute to the healthy worker effect. The healthy worker effect is a major problem of cross sectional studies in occupational epidemiology. It can be defined as the observation that workers in some occupations or industries have a lower morbidity and lower mortality than the general population. Thus, workers are on average healthier. Factors that are involved in this effect are: selection by the employer based on health or risk factors, self selection by the worker based on health, and a tendency of workers who develop diseases to change jobs or to leave employment (Choi, 1992; Howe et al, 1988). In an occupational health study, effects of pre-employment selection can be reduced when the comparison group or reference group, is derived from the same population as the exposed group, and also subjected to pre-employment selection. In practice, this will

often be difficult to achieve. The working environment of an internal comparison group (no exposure), will frequently be used to place workers who are rejected for another job because of health or risk factors, or to transfer workers to because of health problems. During the five years prior to our study, pre-employment screening was applied for workers from the SO₂ group and from the oil mist group. An effect of this screening procedure was the lower prevalence of airway hyperresponsiveness in these groups as compared with the other exposure groups (chapter 4). An additional effect of excluding workers with risk factors (for example, marked airway hyperresponsiveness) in pre-employment screening, can be a reduced probability of an exposure effect on respiratory health. A lower prevalence of respiratory health problems may also affect the significance level of an exposure effect. This means that findings of an association between exposure and respiratory health parameters may be underestimated in workers from the SO₂ group and from the oil mist group who were employed less than five years.

Another healthy worker effect was also present in this study. Reorganization of the company and the possibility for workers to go with early retirement in the years prior to the study and during the follow-up period. The result was that the number of workers older than 55 years was relatively low, and that the number of subjects with a long exposure history was small. The sickness absence data give reason to believe that workers who left employment (and also those who were transferred) were on average less healthy. Most likely, this will also be true for the older subjects who left the company in the years prior to our study. So, the finding that the associations between exposure of more than 10 years and a lower level of lung function and possibly a higher prevalence of airway hyperresponsiveness, were not significant, may be due to the loss of the older workers who left employment before the normal age of retirement. Effects of reorganizations, leaving or changing jobs because of poor health are less in community-based studies. In these studies, subjects are selected regardless of their current occupational status. But, in these studies, a healthy worker effect can still be present. In some industries only subjects with good health are selected into the workforce by means of a pre-employment screening (Korn et al, 1987; Xu et al, 1992). Nevertheless, such studies proved to be surprisingly effective in identifying health consequences of occupational exposures, despite the fact that information on occupational exposures was self-reported (Becklake, 1989).

In addition to the selections mentioned, non-response may have an effect on the study results as well. The non-response in our study was low (13%), with the highest non-response among the white collar workers (chapter 4), in whom no exposure related respiratory health problems were to be expected. The major reason for these workers not attending was lack of time. Of the other exposure groups, reasons for not attending varied from no interest, no time (production had higher priority), absence from work due to illness and vacation. The low non-response in combination with the variation of reasons not to come, will probably not have caused a strong bias towards no effect. Another factor relevant to the study results, is the exclusion of subjects from analysis who were not allowed to perform a histamine challenge test, or of whom the data of the challenge test could not be used. Reason for excluding were various (chapter 3), but the older the age the larger the proportion of subjects that was excluded because of health criteria, such as a low level of lung function, use of medication for a cardiovascular disease or pulmonary disease. For the workers with more than 10 years of exposure, this exclusion probably caused an increase of the difference of the mean level of lung function and prevalence of airway hyperresponsiveness between the reference group and the exposure groups.

So, the lack of associations between exposure and the level of lung function and airway hyperresponsiveness, for the group of workers with less than 10 years of exposure, may reflect a healthy worker effect, a lack of power to detect small exposure effects, or it indicates that at low concentrations no permanent health effects occur (Becklake, 1989). In addition to the low level of exposure, the maximal duration of exposure to SO_2 , H_2SO_4 , HCl at the time of the study was five years. Together with the pre-employment screening, these five years may have been too short to detect chronic respiratory health effects in workers exposed to SO_2 , H_2SO_4 , HCl . As for the subjects with more than 10 years of exposure, the lower level of lung function and the higher prevalence of airway hyperresponsiveness, may be the result of higher past exposures. In the 10 to 15 years prior to the study, the company adjusted machines and improved active ventilation in order to reduce airborne exposures. This means that the findings of the workers with less than 10 years of exposure with respect to level of lung function and airway responsiveness, may indicate a successful intervention programme in reducing airborne exposures. Still, acute effects of exposure on the airways (work-related symptoms) remained (chapter 6).

Smoking

An important interfering factor in studies concerning effects of occupational exposure on health is smoking, because of its relation with the occurrence of respiratory symptoms, a decreased lung function and the presence of airway hyperresponsiveness (Rijcken et al, 1987; O'Connor et al, 1989; Kauffmann et al, 1993). In those cases where exposed workers are more likely to be smokers or heavier smokers than non-exposed workers, smoking is not only an interfering factor, but also a confounder (Rothman, 1986). If one does not adjust for smoking in the analysis, exposure may appear to be associated with a respiratory disease, while in fact smoking is the real factor that caused the association. In our study, smoking was not a confounder, because the proportion of workers that smoked among the exposed and non-exposed workers did not differ significantly. To a certain extent, the smoking habits of our population is influenced by the type of work. The workers have to watch to the production process carefully, which means that they monitor properly running machines most of the time. At the time of the study it was allowed for the workers from the oil mist and oil vapour group and the workers from the polyamide and polyester vapour group to smoke in certain areas of the working place. Many workers of these groups did so during their shifts.

The question whether smoking interacts with occupational exposures is of importance (Becklake, 1989). Fifty five percent of our study population smoked. This is high, even for an occupational population. In the Netherlands, 49% of the working population in 1986 smoked, whereas of the non working population 36% smoked (Lourijssen and Wortel, 1994). This study showed that smokers are more susceptible to exposure to vapours and mists as encountered. The associations between exposure and a higher prevalence of chronic respiratory symptoms (chapter 5), exposure and a higher prevalence of work-related dyspnoea and wheeze (chapter 6), were stronger for smokers than for non-smokers. Also, the analysis of the sickness absence due to respiratory symptoms suggests that some interaction was present between exposure and smoking. Only a few other studies could demonstrate an interaction between smoking and occupational exposures. Korn et al (1987) found in a community-based study an interaction between years of smoking and occupational exposure to gases or fumes for the prevalence of dyspnoea Grade III (higher prevalence with increasing years of smoking), but not for the symptoms wheeze, chronic cough and chronic phlegm. Osterman and coworkers (1989a) found in an occupational study that the association

between exposure to SO₂ and respiratory symptoms was stronger for smokers than for current non-smokers. Musk and coworkers (1982) found in a study among fire fighters that current smokers reported more wheezing on exposure to smoke, and that this was unrelated to objective changes in lung function. Others could not find a significant interaction between current smoking and either dust or fume exposure on the prevalence of symptoms (Bakke et al, 1991; Viegi et al, 1991; Xu et al, 1992; Heederik et al, 1989).

The impact of smoking on respiratory health was present in this population, despite the fact that the population was relatively young. Smokers had more often symptoms such as chronic cough, chronic phlegm and wheeze, and a lower level of lung function (chapter 5). Elmes (1981) concluded after reviewing the literature on the importance of occupational airborne dust exposure as compared with cigarette smoking, that, on general population level, controlling tobacco smoking would make a far greater improvement on respiratory health than control of occupational exposure. For our population, this may be true also. The occupational airborne exposure might have reached a level that quitting smoking may, on the long term, have a greater impact on the respiratory health of the exposed workers than reducing the airborne exposure. Employers could introduce a smoking cessation programme, as part of a health promotion programme.

History of allergy

The significant associations of a history of allergy with several respiratory health parameters and sickness absence due to respiratory symptoms were surprising, because in this study allergy is based on self-reported "being allergic". This information is less reliable than the positive skin test or measurements of specific serum IgE to common airborne allergens, such as house dust mite, dog, cat or grass mix. Therefore, some misclassification will have occurred. For example, subjects may have been classified allergic, while they had only a non-allergic rhinitis. The finding that a history of allergy was associated with airway hyperresponsiveness independent of the presence of chronic respiratory symptoms (chapter 4), such as wheeze and chronic cough, indicates that information on a history of allergy identifies a distinct group from the group with chronic respiratory symptoms.

Allergy is associated with inflammation of the bronchial mucosa, even if one has only an allergic rhinitis or allergic conjunctivitis (Monchy et al, 1989; Djukanovic et al,

1992). Damage to the airway epithelium due to an inflammatory process, may result in exposure of irritant receptors. Stimulation of these receptors by irritants produces cough as well as bronchoconstriction (Fish, 1982; Alberts and Brooks, 1992). Therefore, we hypothesized that being allergic could be a risk factor for developing obstructive airway diseases for workers who are exposed to airway irritants. In our study, we did not find an indication that being allergic modified the association between exposure and respiratory health, suggesting allergy is not a risk factor for chronic health effects. This finding can be an effect of pre-employment screening. Though a history of allergy was not used as a selection criterium at the pre-employment health examination, some pre-selection of allergic subjects might have occurred, as a results of its association with airway hyperresponsiveness and chronic respiratory symptoms. But, the finding that the proportion of the subjects from the SO₂ group with a history of allergy, did not differ from the reference group suggests that this bias, if present, is small. It is also quite possible that allergic subjects have an increased susceptibility for irritant exposure only when they are troubled by allergic symptoms, for example during the hay fever season. Some workers at the medical examination of this study mentioned that they experienced only work-related symptoms during their allergy-season. The analysis of work-related symptoms showed that subjects with a history of allergy experienced respiratory symptoms at work more often than non-allergic subjects, both exposed as well as non-exposed subjects. This indicates that allergy is a risk factor for acute respiratory health effects. As discussed in chapter 6, the higher prevalence of work-related symptoms for allergic subjects as compared with non-allergic subjects within the non-exposed group, might be due to a low (unknown) background exposure in the workplace of the non-exposed subjects, or a reporting bias.

Skin tests and tests for measuring specific serum IgE identify also subjects who have no allergic symptoms, but who do have the ability to respond with the production of specific IgE antibodies¹ after an allergen exposure. This aspect is of importance for occupations where exposures can be responsible for IgE-mediated responses in the airways (Chang-Yeung and Lam, 1986; Alberts and Brooks, 1992). As for exposure to irritants, the distinction between subjects with a tendency to allergic sensitization

¹ This ability to produce specific IgE antibodies toward environmental allergens is called atopy (Sparrow and Weiss, 1989).

(=ability to produce specific IgE) who have allergic symptoms and those who do not have allergic symptoms, may be relevant.

Work-related symptoms

A question of interest is whether acute respiratory health effects of exposure identifies a worker at risk for an increased annual decline of lung function due to that exposure (Becklake, 1989). Some studies showed that work-related lung function changes due to isocyanate exposures, predicted excess annual decline of lung function. As for fire fighters who are exposed to smoke, some found associations between acute responses and chronic responses on exposure to smoke (Becklake, 1989), while others did not (Musk et al, 1982). In our study subjects with chronic respiratory symptoms had more often work-related symptoms than those who had no chronic respiratory symptoms (chapter 6). But subjects with work-related symptoms did not have a lower level of lung function (chapter 5). Subjects with work-related symptoms were also more frequently absent from work due to illness, especially due to respiratory symptoms. Yet, the prevalence of work-related symptoms was lower among the workers who left the study population in the years 1989-1991 as compared with those who remained in the study, whereas those who left had a higher level of sickness absence. Thus, this study could not find indications that acute responses are associated with chronic health effects other than the chronic respiratory symptoms.

A limitation in this study was that no information was obtained whether the symptoms related to work, occurred frequently. It is possible that subjects who often experience respiratory health problems at work are those who are at risk for developing an impaired respiratory health.

Sickness absence from work

Subjects with chronic airway diseases have an increased risk for being absent from work, and therefore a potential economic loss. This concluded Athanasou in 1975 after reviewing the literature. No recent data are available on what proportion of sickness absence from work is attributed to obstructive airway diseases of workers. As mentioned in chapter 7, the number of studies investigating the relation between respiratory health and absence from work due to illness is limited, but confirm in general the conclusion of Athanasou (1975). Van der Lende (1989) calculated from data of the Vlaardingen-Vlagentwedde study and national sickness absence data, that in the Netherlands 15%

of all sickness absence is due to obstructive airway diseases. But not clear is whether frequency or the annual number of days lost is meant, and whether the presence of obstructive airway disease has an attributable risk for sickness absence of 15%. The Vlaardingen-Vlagentwedde study did show that the more respiratory symptoms, the more often subjects reported they had been absent from work due to respiratory symptoms at least once in the three years prior to the study (Rijcken et al, 1992). This association was stronger for subjects who reported occupational exposure to gases, vapours and fumes, indicating an association between these exposures and more absence due to respiratory symptoms. However, in this analysis no adjustment was made for job function which is a potential interfering factor in sickness absence statistics (chapter 7). Associations between measures of respiratory health and sickness absence may have been changed in the last 20 years, as a result of improved national health care (improved respiratory health), improved working conditions with respect to airborne exposures, and changed smoking habits, but also due to changing perceptions of health (Winter, 1993). If for example subjects with minor health problems have a tendency to take sick leave more easily than subjects with more pronounced health problems, the statistical associations between measures of health and sickness absence will be compromised. Levels of sickness absence between countries may differ as a result of differences in the legitimization of sick leave, the level of sickness benefits, employment policy and absence control, and social-cultural differences (Prins en Graaf, 1986). These factors can be responsible for differences seen in the strength of the associations between health indicators and level of sickness absence, but most likely the direction of the associations will be the same. Furthermore, the strength of a statistical association (significance level) will be affected by interrelation of explanatory variables. For example, in our study a lower level of lung function was significantly associated with a higher frequency of absence due to respiratory symptoms, but only when airway hyperresponsiveness was not taken into account.

Most studies of sickness absence examined the influence of socioeconomic factors, such as marital state, education and work-related factors (for example, job satisfaction and earnings), on the level of sickness absence (Steers and Rhodes, 1978; Leigh, 1986). Although significant associations are found between these factors and the level of sickness absence, they explain statistically only a small part of the variation in sickness absence between groups (Leigh, 1986). Health variables and hazardous conditions at the job appear to be most important, yet least researched predictors of sickness absence

(Leigh, 1991). North and coworkers (1993) found among nonindustrial civil workers, that after adjustment for health related behaviours, ethnic group, work characteristics and social circumstances, large differences in the sickness absence rate persisted between grade of employment. This illustrates the complexity of sickness absence. For example, Hendrix and Taylor (1987) concluded that although smoking is associated with more sick leave from work, prohibiting smoking at the job or simply refusing to employ smokers will reduce the level of sickness absence. However, this reduction will be less than many believe, because of the interrelation of smoking with other interfering factors for the level of sickness absence, such as life style and stress.

Relevance for the occupational medicine

The limited amount of information on the respiratory health effects of irritant exposures at levels commonly found in industries, and whether for example smoking, increased airway responsiveness, or allergy, are risk factors, interfere with the decision making in setting priorities for preventive activities and health surveillance. Furthermore, these type of exposures are often multiple, and, therefore, hard to quantify and qualify. In case of multiple exposures, it is also difficult to attribute respiratory health problems of exposed workers to a specific airborne agent.

With respect to the type of exposures under study, it is of interest to know whether the occupational physician should focus on the presence of airway hyperresponsiveness: is airway hyperresponsiveness a risk factor which has to be screened for at the pre-employment examination, or is it a health effect that has to be looked at in health surveillance. Our study demonstrated that airway hyperresponsiveness is a risk factor for work-related eye, nasal and respiratory symptoms. But, with the information available on work-related symptoms, we could not find an indication that work-related symptoms are associated with impaired respiratory health. However, it is possible that pre-employment screening introduced a certain bias.

Pre-employment screening, but also health surveillance screening on airway hyperresponsiveness has certain risks. Apart from the definition of what should be considered as significant hyperresponsive, airway responsiveness can vary in time. In a general population study, the airway hyperresponsiveness, measured with a challenge test, changed with two or more histamine concentrations steps in 21% of the subjects within a three-year interval. Variability was present in subjects both with and without chronic respiratory symptoms (Rijcken et al, 1993). Of our study population 470 subjects were

tested for the second time, two years after the baseline study. Of them, 13% had changed their responder status, whereas the prevalence of airway hyperresponsiveness had not changed (Kremer et al, 1993). Reports in patients (Juniper et al, 1982; Lowhagen and Lindholm, 1983; Madsen et al, 1985) suggest that less variability in the degree of airway hyperresponsiveness can be seen in subjects with stable asthma, as compared with subjects with mild asthma, subjects with less stable asthma, or subjects with no chronic respiratory symptoms. This aspect of airway hyperresponsiveness will compromise its predicted value as a risk factor for developing respiratory problems. Nowadays, employers have a tendency to screen employees on objective health parameters, because of increasing demands on the working capacities of employees, and reducing the costs of sickness absence. In case of airway responsiveness which is an objective health parameter, results of one inhalation provocation test of an individual should be interpreted with caution, especially if the subject is not known to have asthma like symptoms. On the other hand, the predictive value of airway hyperresponsiveness as a risk factor, or as an indicator of impaired respiratory health, increases when other obstructive airway disease related factors are present.

Whether the presence of respiratory symptoms in the absence of a lower level of lung function or airway hyperresponsiveness, should be considered as an adverse health effect of the exposure, is difficult to say. In general, there is increasing evidence that respiratory symptoms, especially mucus hypersecretion (chronic phlegm) and breathlessness when walking on level ground (dyspnoea grade III), are independent predictors of total mortality (Bakke, 1991). Our finding that the irritant exposure was associated with more chronic respiratory symptoms, but not with a lower level of lung function is also found by others (Becklake, 1989). In our study, the prevalence of one or more chronic respiratory symptoms did not increase with age, whereas among older subjects the prevalence of chronic cough and frequent wheeze were significantly higher than among younger subjects. The interaction of age on the effect of chronic respiratory symptoms on the level of sickness absence, indicate a change in the role of respiratory symptoms with increasing age. Still, other than respiratory health problems are much more associated with impaired health (chapter 1). In the Netherlands, only 3% of the subjects with a disability pension is disabled because of respiratory disorders (and thus chronic respiratory symptoms). Our result that absence due to respiratory symptoms is mainly composed of short spells (chapter 7.1) and not with long spells, is in agreement with this.

8.2 Conclusions

1. The applied short histamine challenge test for assessing airway responsiveness is safe and acceptable in an occupational population, although the prevalence of side-effects was high.
- 2a*. The airborne exposures as encountered in this study were associated with a higher prevalence of chronic respiratory symptoms among exposed workers, but no overall associations were found with a lower level of lung function or a higher prevalence of airway hyperresponsiveness.
- 2b*. Airborne exposure as encountered by the polyester vapour group and the oil mist and oil vapour group, may result in a lower level of lung function and a higher prevalence of airway hyperresponsiveness among the exposed workers, provided the exposure lasted more than 10 years.
- 3*. No indication was present that airway hyperresponsiveness is a risk factor for permanent respiratory health effects of exposure.
4. Exposed smokers are more at risk for developing chronic respiratory symptoms than exposed non-smokers.
5. The airborne exposures as encountered in this study incite acute work-related cough, phlegm, dyspnoea, wheeze, nasal symptoms and eye symptoms. With respect to these symptoms, subjects with a history of allergy and subjects with airway hyperresponsiveness are more at risk. Smoking appears to be a risk factor too, but only for the occurrence of dyspnoea and wheeze.
- 6a. The exposure is not associated with temporary health problems defined as more sickness absence due to any illness and absence due to respiratory symptoms or longer spells of absence,
- 6b. with the exception for smokers. Exposed smokers seemed to have an increased risk for being absent due to respiratory symptoms as opposed to exposed non-smokers.
- 7a. Chronic respiratory symptoms, work-related symptoms, a history of allergy and airway hyperresponsiveness are associated with a higher frequency of sickness absence, both due to any illness and due to respiratory symptoms.
- 7b. Subjective respiratory health measures, such as reported allergic symptoms, chronic respiratory symptoms or work-related symptoms were more strongly associated with more absence due to respiratory symptoms, than the objective health parameters airway hyperresponsiveness and a lower level of lung function.

- 7c. Generally, smokers are more often, but not longer, absent than non-smokers. In the absence of exposure to irritants, smoking is not associated with a higher frequency of absence due to respiratory symptoms.
- 7d. The interaction of the association between age and chronic respiratory symptoms on the level of sickness absence, indicates a change in the role of these symptoms with increasing age.

* These conclusions may, to some extent, be limited by:

- the low level of the current airborne exposures;
- the higher level of airborne exposure in the past (workers with more than 10 exposure years);
- the short maximal duration of exposure (SO₂, H₂SO₄, HCl group; the relatively young age of the study population);
- pre-employment selection of workers with no asthma like symptoms in the five years prior to this study (SO₂, H₂SO₄, HCl group; oil mist and oil vapour group);
- the relatively small proportion of workers with a long duration of current exposure due to (1) reorganizations and early retirement, and (2) exclusion of older subjects with incomplete data from analysis;
- the impossibility to correct for past exposures, especially in the reference group.

8.3 References

Alberts WM and Brooks SM. Advances in occupational asthma. *Clinics in Chest Medicine* 1992; 13: 281-301.

Bakke P. Obstructive airway diseases and occupational airborne exposure. Thesis, 1991. University of Bergen, Bergen, Norway. ISBN 82-91166-00-5.

Bakke P, Eide GE, Hanoa R, Gulsvik A. Occupational dust or gas exposure and prevalences of respiratory symptoms and asthma in a general population. *Eur Resp J* 1991; 4: 273-278.

Becklake MR. Occupational exposures: Evidence for a causal association with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989; 140:S85-S91.

Chan-Yeung M, Lam S. Occupational asthma. *Am Rev Respir Dis* 1986; 133: 686-703.

Chan-Yeung M, Wong R, MacLean L, Tan F, Schulzer M, Enarson D, Martin A, Dennis R,

Grzybowski S. Epidemiologic health study of workers in an aluminium smelter in British Columbia. *Am Rev Respir Dis* 1983; 127: 465-469.

Choi BKC. Definitions, sources, magnitude, effect modifiers, and strategies of reduction of healthy worker effect. *J Occup Med* 1992;34:979-988.

Djukanovic R, Lai CKW, Wilson JW, Britten KM, Wilson SJ, Roche WR, Howarth PH, Holgate ST. Bronchial mucosal manifestations of atopy: a comparison of markers of inflammation between atopic asthmatics, atopic nonasthmatics and healthy controls. *Eur Resp J* 1992; 5: 538-544.

Elmes PC. Relative importance of cigarette smoking in occupational lung disease. *Br J Indus Med* 1981; 38: 1-13

Fish JE. Occupational asthma: a spectrum of acute respiratory disorders. *J Occup Med* 1982; 24: 379-386.

Hendrix WH, Taylor GS. A multivariate analysis of the relationship between cigarette smoking and absence from work. *Am J Health Promotion* 1987; 2: 5-11.

Howe GR, Chiarelli AM, Lindsay JP. Components and modifiers of the healthy worker effect: evidence from three occupational cohorts and implications for industrial compensation. *Am J Epidemiol* 1988; 128: 1364-1375.

Järholm B, Bake B, Lavenius B, Thiringer G, Vokmann R. Respiratory symptoms and lung function in oil mist-exposed workers. *J Occup Med* 1982; 24: 473-479.

Juniper EF, Frith PA, Hargreave FE. Long-term stability of bronchial responsiveness to histamine. *Thorax* 1982; 37: 288-291.

Kauffmann F, Drouet D, Lellouch J, Brille D. Occupational exposure and 12-year spirometric changes among Paris area workers. *Br J Ind Med* 1982; 39: 221-232.

Kauffmann F, Annesi I, Enarson DA. Tobacco smoke and bronchial responsiveness. In: *Prevention of respiratory diseases*. Hirsch A, Goldberg M, Martin JP, Masse G, eds. New York: Marcel Dekker, 1993, p.463-496.

Kennedy SM, Greaves IA, Kriebel D, Eisen EA, Smith TJ, Woskie SR. Acute pulmonary responses among automobile workers exposed to aerosols of machining fluids. *Am J Ind Med* 1989; 15: 627-641.

Kennedy SM, Burrows B, Vedal S, Enarson DA, Chang-Yeung M. Methacholine responsiveness among working populations. *Am Rev Respir Dis* 1990; 142: 1377-1383.

Korn RJ, Dockery DW, Speizer FE, Ware, JH, Ferris BG. Occupational exposures and chronic respiratory symptoms: A population-based study. *Am Rev Respir Dis* 1987; 136: 298-304.

Kremer AM, Rijcken B, Pal TM. The role of bronchial responsiveness in the development (or occurrence) of chronic nonspecific lung diseases in case of exposure to irritants (In Dutch). Report 93-PA-24, 1993, University of Groningen, the Netherlands.

Leigh JP. Correlates of absence from work due to illness. *Human Relations* 1986; 39: 81-100.

Leigh JP. Specific illnesses, injuries, and job hazards associated with absenteeism. *J Occup Med* 1989; 31: 792-797.

Leigh JP. Employee and job attributes as predictors of absenteeism in a national sample of workers: the importance of health and dangerous working conditions. *Soc Sci Med* 1991; 33: 127-137.

Lowhagen O, Lindholm NB. Short-term and long-term variation in bronchial response to histamine in asthmatic patients. *Eur J Respir Dis* 1983; 64: 466-472.

Madsen F, Rathlou NHH, Frolund L, Svendsen UG, Weeke B. Short and long term reproducibility of responsiveness to inhaled histamine: Rt compared to FEV₁ as measurement of response to challenge. *Eur J Respir Dis* 1985; 76: 193-203.

Malo J-L. Occupational asthma. In: Prevention of respiratory diseases. Hirsch A, Goldberg M, Martin JP, Masse G, eds. New York: Marcel Dekker, 1993, p.117-131.

Monchy JGR de, Postma DS, Kauffman HF, Vries K de. In: Sluiter HJ, van der Lende R (eds): "Bronchitis IV". Assen: Van Gorcum, 1989; p 198-207.

Musk AW, Peters JM, Bernstein L, Rubin C, Monroe CB. Pulmonary function in firefighters: A six-year follow-up in the Boston fire department. *Am J Indus Med* 1982; 3: 3-9.

North F, Syme SL, Feeny A, Head J, Shipley MJ, Marmot MG. Explaining socioeconomic differences in sickness absence: the Whitehall II study. *Br Med J* 1993; 306: 361-366.

O'Conner GT, Sparrow D, Weiss ST. The role of allergy and nonspecific airway hyperresponsiveness in the pathogenesis of chronic pulmonary disease. *Am Rev Respir Dis* 1989; 140: 225-252.

Osterman JW, Greaves IA, Smith TJ, Hammond SK, Robins JM, Thériault G. Respiratory symptoms associated with low level sulphur dioxide exposure in silicon carbide production workers. *Br J Ind Med* 1989a; 46: 629-635.

Osterman JW, Greaves IA, Smith TJ, Hammond SK, Robins JM, Thériault G. Work-related decrement in pulmonary function in silicon carbide production workers. *Br J Ind Med* 1989b; 46: 708-716.

Oxhoj H, Andreassen H, Meyer-Henius U. Respiratory symptoms and ventilatory lung function in machine shop workers exposed to coolant-lubricants. *Eur J Res Dis* 1982; S118: 85-89.

Prins R, Graaf A de. Comparison of sickness absence in Belgian, German and Dutch firms. *Br J Indus Med* 1986; 43: 529-536.

Rijcken B, Schouten JP, Weiss ST, Speizer FE, Lende R van der. The relationship of nonspecific bronchial responsiveness to respiratory symptoms in a random population sample. *Am Rev Respir Dis* 1987;136:62-8

Rijcken B, Schouten JP, Lucht F van der, Groothoff JW. School- en werkverzuim bij CARA. *Caravisie* 1992; 3: 14-15.

Rijcken B, Schouten JP, Weiss ST, Rosner B, Vries K de, Lende R van der. Long-term variability of bronchial responsiveness to histamine in a random population sample of adults. *Am Rev Resp Dis* 1993; 148: 944-9.

Rothman KJ. *Modern Epidemiology*. Little, Brown and Company, Boston/Toronto, 1986.

Soyseth V, Kongerud J. Prevalence of respiratory disorders among aluminium potroom workers in relation to exposure to fluoride. *Br J Indus Med* 1992; 49: 125-130.

Sparrow D, Weiss ST. Background. In: *Airway responsiveness and atopy in the development of chronic lung diseases*. Weiss ST, Sparrow D, eds. New York:Raven Press, 1989;1-21.

Steers RM, Rhodes SR. Major influences on employee attendance: a process model. *J Appl Psychol* 1978; 63: 391-407.

Venables KM. Prevention of occupational asthma. *Eur Respir J* 1994; 7: 768-778.

Winter CR de. Using work, health and sick leave to predict work disability. *Internat Soc Sec Rev* 1993; 46: 41-50.

Xu X, Christiani DC, Dockery DW, Wang L. Exposure-response relationships between occupational exposures and chronic respiratory illness: A community-based study. *Am Rev Respir Dis* 1992; 146: 413-418.

Summary

Chapter 1 describes the background of the study. Occupational airborne exposures play a role in the occurrence of obstructive airway diseases. It is generally accepted that exposure to dust or to sensitising vapours, are causally related to these diseases. For fumes, gases and vapours with an irritating effect, this relation is less clear. In recent years, an important topic in respiratory research was whether airway hyperresponsiveness was a risk factor that precedes and predisposes to the development of obstructive airway diseases, or conversely a manifestation of an exposure effect, such as airway inflammation and airway narrowing. In case of exposure to airway irritants this means, in the first case, that preferentially subjects with airway hyperresponsiveness develop respiratory health problems. Whereas, in the second case, airway hyperresponsiveness develops at the same time as, or after the occurrence of respiratory health problems. A longitudinal study among workers airway irritants, was conducted between 1989 and 1992. For this thesis, the following research questions have been formulated:

1. Is in an occupational population, the use of a short histamine challenge test for assessing airway responsiveness, safe and acceptable, and what is the prevalence of the side-effects of the test?
2. Have subjects exposed to airway irritants more often airway hyperresponsiveness than non-exposed subjects, measured by a histamine challenge test, and is this associated with smoking, chronic respiratory symptoms, or a history of allergy?
3. Have subjects exposed to airway irritants more chronic respiratory symptoms and/or more often a low level of pulmonary function than non-exposed subjects, and is this associated with smoking, airway responsiveness or a history of allergy?
4. Have subjects exposed to airway irritants more often work-related symptoms such as respiratory symptoms and nasal symptoms than non-exposed subjects, and is this associated with smoking, airway responsiveness or a history of allergy?
5. Have subjects exposed to airway irritants, smokers, or subjects with chronic respiratory symptoms, airway hyperresponsiveness or a history of allergy, more and/or longer sickness absences, with special reference to absence due to respiratory symptoms?

For these research questions, the data of the baseline survey performed in the period April-Juli 1989, and the data of the sickness absences, concerning the two year period October 1989 - October 1991, have been used.

Chapter 2 describes briefly the company, the work environment and the study population. The company is composed of five production plants, and it produces synthetic fibres and yarn. A total of 909 male workers were invited to participate in the health survey. On the basis of job titles and working department, the exposure status of all workers was characterised. The workers were divided into seven groups.

1. *Reference group*: Workers who are not subjected to exposure to airway irritants;
2. *White collar group*: Clerical workers and workers who are not directly involved in the production of the yarn and fibres;
3. *SO₂, H₂SO₄, HCl group*: Workers who can be SO₂ and HCl vapour and H₂SO₄ and HCl aerosols;
4. *Polyester vapour group*: Workers who can be vapours of thermodegradation products of the produced polyester polymer like aldehyde vapours, to diphenyl--diphenyloxide vapour and to ethylene glycol vapour;
5. *Oil mist and oil vapour group*: Workers who can be (synthetic) oil mist and oil vapour;
6. *Polyamide and polyester vapour group*: Workers who can be vapours of thermodegradation products of the polyamide- and polyester polymer and to lactam vapour;
7. *Multiple exposure group*: Maintenance engineers who have multiple exposures depending on location within the plant and the type of work.

The overall measured exposures to the airway irritants were relatively low, and on average well below the Dutch Threshold Limit Values.

Chapter 3 evaluates the use of an inhalation test for measuring the airway responsiveness in this occupational population. A standard tidal breathing method was abbreviated, for the purpose of having a test that was faster and less tiring than the full test with doubling concentrations from 1 to 32 mg/ml histamine. This was achieved by (1) starting with a higher concentration for subjects with no indication of increased airway responsiveness; (2) by skipping a concentration if the decrease in forced expiratory volume in one second (FEV₁) was less than 6%, and (3) by stopping the test when the fall in FEV₁ was at least 18% instead of the common used 20%. A PC₂₀ was defined as the provoking concentration of histamine producing a 20% fall in FEV₁. Data from 697 subjects of the baseline study could be used.

We evaluated the occurrence of excessive decreases in FEV₁ after challenge (= a fall in

FEV₁ of more than 30%), and the time needed to complete the test. All subjects with a PC₂₀ value of 4 mg/ml histamine or less (n=16) were identified by the selection criteria. They had to start at 1 mg/ml. No large falls in FEV₁ occurred after a 4-fold increase in concentration. In 20 subjects the test was stopped at 18 or 19% FEV₁ fall. This prevented a more severe bronchoconstriction. Five subjects did have an excessive bronchoconstriction (fall in FEV₁ of $\geq 40\%$ - 50%), but this occurred after a doubling concentration. The time saving aspect was maximal in 56% of the subjects who had a provocation scheme of phosphate solution 4, 16 and 32 mg/ml histamine.

Data of the follow-up survey were used to describe the occurrence of side-effects of the challenge test. During that survey, side-effects were systematically registered. The proportion of the 702 tested subjects that reported one or more side-effects was high, 41%. Chest tightness was most prevalent (26%), followed by flushing (18%), significant cough reaction (5%), hoarseness (4%), throbbing headache (1%) and not feeling well (1%). Chest tightness, due to airway narrowing, and not feeling well, caused by repeated spirometric manoeuvres can be considered as complaints that occurred independent of histamine. Whereas the other complaints might have occurred less often when methacholine was used.

Chapter 4 discusses whether subjects exposed to low levels of irritants had more often hyperresponsive airways than non-exposed subjects. A total of 790 subjects participated in the survey (response 87%). Data from 668 subjects were used for the analysis. Airway hyperresponsiveness, defined as a 20% fall in FEV₁ at ≤ 32 mg/ml histamine, was present in 23% of the subjects. Workers who were exposed did not have more frequently hyperresponsive airways than non-exposed workers. Subjects with a low FEV₁, or a history of allergy, or chronic respiratory symptoms, did have significantly more often hyperresponsive airways. Subjects from the SO₂ group and the oil mist group with five years of exposure or less, had a lower prevalence of airway hyperresponsiveness (respective ORs of 0.6 and 0.3). This was most likely due to pre-employment procedures in the five years prior to this study. There was some trend for subjects with more than 5 years of exposure to polyester vapour and to oil mist and oil vapour to have a higher prevalence of airway hyperresponsiveness (respective ORs 2.3 and 2.1). This may partly be caused by exclusion of subjects from analysis. No additional information was obtained by using the continuous dose-response slope variable (=

%FEV₁ fall per mg/ml histamine) as compared with the analysis with the dichotomous airway hyperresponsiveness variable (yes/no).

Chapter 5 deals with the question whether workers who were exposed, had more often chronic respiratory symptoms (defined as chronic cough, chronic phlegm, bronchitis periods, dyspnoea, wheeze, and/or ever asthmatic attack) and/or a lower level of lung function than the workers who were not exposed. The following lung function parameters were evaluated: FVC (forced volume capacity), FEV₁ (forced expiratory volume in one second) and MMEF (maximum mid expiratory flow).

One or more chronic respiratory symptoms were reported by 26% of the subjects. Workers from the SO₂, HCl, H₂SO₄ group had a lower prevalence of one or more symptoms as compared with the reference group (OR=0.6), most likely due to pre-employment procedures. The other exposure groups were associated with a higher prevalence of symptoms (range ORs 1.5-2.6). The association between exposure and a higher prevalence of symptoms was greater in smokers than in ex-smokers and non-smokers. This difference was most clearly seen in the polyester vapour group and the polyamide and polyester vapour group: with respective ORs of 2.2 and 4.0 for smokers as opposed to 0.2 and <0.1 for never smokers. No such modification of the association between exposure groups and the prevalence of symptoms by airway hyperresponsiveness, or by a history of allergy could be demonstrated. Current smoking, airway hyperresponsiveness, and a history of allergy were significantly associated with a higher prevalence of chronic respiratory symptoms, independent of each other, and independent of irritant exposure.

The exposure groups were not significantly associated with a lower level of lung function. Adjustment for chronic respiratory symptoms did not change the results. We found no indication of a possible interaction between exposure and current smoking, airway hyperresponsiveness, or a history of allergy on level of lung function. Workers from the polyester vapour group and the oil mist group with more than 10 years of exposure, had a lower FEV₁ and a significantly lower MMEF than the reference group. However, the number of workers of both groups were small (n=10 and n=13, respectively).

In **chapter 6** an analysis is presented of whether workers exposed to irritants reported having more than usual eye, nasal or respiratory symptoms during work, than non-exposed workers. The overall prevalence of these work-related symptoms were: cough 9%, phlegm 6%; dyspnoea 7%, wheeze 2%; eye symptoms 16%; nasal symptoms 15%. Exposure to airway irritants was significantly associated with the presence of these symptoms, independent of airway hyperresponsiveness, smoking, allergy by history and chronic respiratory symptoms. We investigated whether smokers, subjects with airway hyperresponsiveness, or subjects with a history of allergy reported more work-related symptoms than those without these characteristics. For this purpose, exposure status was dichotomized into exposed and non-exposed. The ORs for exposed were 4.8 for cough and/or phlegm, 3.8 for dyspnoea and/or wheeze, 5.3 for eye symptoms, and 2.7 for nasal symptoms. Stratified analysis showed that these associations of exposure with work-related symptoms were stronger for subjects with hyperresponsive airways than for subjects with no hyperresponsive airways. The association with dyspnoea and/or wheeze was also stronger for smokers than for ex-smokers and non-smokers. In contrast, the association between exposure and a higher prevalence of symptoms was stronger for subjects who did not report a history of allergy than for subjects with a history of allergy. This is most likely due to the relatively high prevalence of background work-related symptoms in (non-exposed) allergic subjects.

In **chapter 7** we studied prospectively the sickness absence of the workers with respect to their respiratory health. Exposure was characterised as exposed and non-exposed. Data from 653 subjects were available for analysis. On average, a worker was absent two times a year due to illness. Respiratory symptoms were the most prevalent reason for sickness absence (28%). Altogether 6.7% of the calendar days per year were lost. Exposed workers were not more often absent than non-exposed workers, both for all absences as for absence due respiratory symptoms. Results suggested that exposed smokers have an increased risk for being absent from work because of respiratory symptoms as opposed to exposed non-smokers. For non-exposed subjects, smokers were less often absent because of respiratory symptoms than non-smokers. Subjects with a history of allergy, with airway hyperresponsiveness, or with work-related symptoms were more often absent because of respiratory symptoms. Lower level of lung function was associated with more absence. This association was not significant, because of its relation with airway hyperresponsiveness. As for the frequency of being absent due to

any illness, generally the same associations, though smaller in magnitude, were found with these respiratory health variables. This indicates that respiratory health parameters are associated with health in general. Age was a significant predictor of being absent. The known finding that the older the age, the less often absent, was also true for this population. But, it applied only for subjects who did not report chronic respiratory symptoms. For symptomatic subjects, the frequency of being absent did not decrease or increase with age. With regard to all sickness absence, smokers were absent more often than non-smokers, and this was independent of the exposure. Age was the only significant predictor for the duration of sickness absence. The older the subject, the longer the duration.

In **chapter 8** a general discussion is presented. Several factors that might have had an effect on the results of this study, are discussed, such as exposure characterisation, the power of the analyses, healthy workers effect and selection due to the study itself. The study resulted in the following conclusions:

1. The applied short histamine challenge test for assessing airway responsiveness is safe and acceptable in an occupational population, although the prevalence of side-effects was high.
- 2a*. The airborne exposures as encountered in this study were associated with a higher prevalence of chronic respiratory symptoms among exposed workers, but no overall associations were found with a lower level of lung function or a higher prevalence of airway hyperresponsiveness.
- 2b*. Airborne exposure as encountered by the polyester vapour group and the oil mist and oil vapour group, may result in a lower level of lung function and a higher prevalence of airway hyperresponsiveness among the exposed workers, provided the exposure lasted more than 10 years.
- 3*. No indication was present that airway hyperresponsiveness is a risk factor for permanent respiratory health effects of exposure.
4. Exposed smokers are more at risk for developing chronic respiratory symptoms than exposed non-smokers.
5. The airborne exposures as encountered in this study incite acute work-related cough, phlegm, dyspnoea, wheeze, nasal symptoms and eye symptoms. With respect to these symptoms, subjects with a history of allergy and subjects with airway hyperresponsiveness are more at risk. Smoking appears to be a risk factor too, but only for the occurrence of dyspnoea and wheeze.

- 6a. The exposure is not associated with temporary health problems defined as more sickness absence due to any illness and absence due to respiratory symptoms or longer spells of absence,
- 6b. with the exception for smokers. Exposed smokers seemed to have an increased risk for being absent due to respiratory symptoms as opposed to exposed non-smokers.
- 7a. Chronic respiratory symptoms, work-related symptoms, a history of allergy and airway hyperresponsiveness are associated with a higher frequency of sickness absence, both due to any illness and due to respiratory symptoms.
- 7b. Subjective respiratory health measures, such as reported allergic symptoms, chronic respiratory symptoms or work-related symptoms were more strongly associated with more absence due to respiratory symptoms, than the objective health parameters airway hyperresponsiveness and a lower level of lung function.
- 7c. Generally, smokers are more often, but not longer, absent than non-smokers. In the absence of exposure to irritants, smoking is not associated with a higher frequency of absence due to respiratory symptoms.
- 7d. The interaction of the association between age and chronic respiratory symptoms on the level of sickness absence, indicates a change in the role of these symptoms with increasing age.

* These conclusions may, to some extent, be limited by:

- the low level of the current airborne exposures;
- the higher level of airborne exposure in the past (workers with more than 10 exposure years);
- the short maximal duration of exposure (SO₂, H₂SO₄, HCl group; the relatively young age of the study population);
- pre-employment selection of workers with no asthma like symptoms in the five years prior to this study (SO₂, H₂SO₄, HCl group; oil mist and oil vapour group);
- the relatively small proportion of workers with a long duration of current exposure due to (1) reorganizations and early retirement, and (2) exclusion of older subjects with incomplete data from analysis;
- the impossibility to correct for past exposures, especially in the reference group.

This study could not demonstrate an adverse effect of exposure to low levels of airway irritants on a number of lung function outcome measures. However, the higher prevalence of chronic respiratory symptoms and work-related symptoms indicate that the exposure encountered, has inciting properties.

Samenvatting

In **hoofdstuk 1** wordt kort ingegaan op de achtergronden van het onderzoek. Beroepsmatige blootstelling aan stoffen die in de lucht voorkomen zijn van invloed op het voorkomen van obstructieve luchtwegaandoeningen, zoals astma en chronische bronchitis. Onderzoek heeft aangetoond dat blootstelling aan stof als zodanig en aan stof of dampen met allergiserende eigenschappen, deze aandoeningen kan veroorzaken. In geval van chronische blootstellingen aan gassen, dampen en rook die een irriterende werking hebben, heeft men nog niet vast kunnen stellen dat deze blootstellingen op den duur ook obstructieve longaandoeningen veroorzaken. De afgelopen jaren is veel aandacht besteed aan de vraag of het hebben van gevoelige luchtwegen (=verhoogde luchtweggevoeligheid) een risicofactor is voor het ontstaan van obstructieve longaandoeningen, of dat het alleen maar een gevolg is van een ontstekingsreactie in de luchtwegen en van een aanwezige luchtwegvernauwing. Voor beroepsmatige blootstelling aan luchtwegprikkelende stoffen (luchtwegirritantia) betekent dit dat in het eerste geval vooral personen met gevoelige luchtwegen luchtwegklachten krijgen (bijvoorbeeld piepen of kortademigheid). In het tweede geval ontstaat een verhoogde luchtweggevoeligheid tegelijk met of na het ontstaan van luchtwegklachten.

Dit proefschrift presenteert en bespreekt de resultaten van een onderzoek dat plaats heeft gevonden in de periode 1989-1992. Het is uitgevoerd bij werknemers die beroepsmatig werden blootgesteld aan luchtwegirritantia. Voor de bepaling van de luchtweggevoeligheid werd gebruik gemaakt van een test waarbij het aërosol histamine in oplopende concentraties wordt ingeademd, totdat er een te meten luchtwegvernauwing optreedt. Het proefschrift behandelt de volgende onderzoeksvragen:

1. Is voor de bepaling van de luchtweggevoeligheid het gebruik van een histamine inhalatie test in een onderzoek bij werknemers, veilig en acceptabel en in welke mate komen bijwerkingen van de test voor?
2. Komt bij personen die blootgesteld zijn aan luchtwegirritantia vaker een verhoogde luchtweggevoeligheid voor dan bij niet blootgestelde personen en is er een verband met roken, het hebben van chronische luchtwegklachten en het hebben van allergieklachten?
3. Hebben personen die blootgesteld zijn aan luchtwegirritantia vaker chronische luchtwegklachten of een lager longfunctieniveau dan bij niet blootgestelde personen en is er een verband met roken, een verhoogde luchtweggevoeligheid en allergieklachten?

4. Rapporteren personen die blootgesteld zijn aan luchtwegirritantia vaker werkgerelateerde klachten van de luchtwegen, neus en ogen dan bij niet blootgestelde personen en is er een verband met roken, een verhoogde luchtweggevoeligheid en het hebben van allergieklachten?
5. Verzuimen personen die blootgesteld zijn aan luchtwegirritantia, rokers, personen met chronische luchtwegklachten, met een verhoogde luchtweggevoeligheid of met allergieklachten, vaker en/of langer en verzuimen zij ook vaker en/of langer wegens aandoeningen van de luchtwegen?

Voor de beantwoording van de vragen 1 tot en met 4 zijn de gegevens gebruikt van het eerste onderzoek dat in 1989 heeft plaatsgevonden. Voor de beantwoording van vraag 5 is gebruik gemaakt van ziekteverzuimgegevens die betrekking hebben op de periode oktober 1989 tot oktober 1991.

In **hoofdstuk 2** worden het bedrijf en de onderzoeksgroep beschreven. De produktielokatie waar het onderzoek heeft plaatsgevonden bestaat uit vijf produktiebedrijven en het maakt synthetische garens en vezels. In 1989 zijn in totaal 909 werknemers gevraagd om mee te doen aan het onderzoek. De werknemers zijn op basis van hun functie en de werkplek waar ze werkten, ingedeeld in zeven groepen. De groepen onderscheiden zich van elkaar in het type blootstelling aan luchtwegirritantia.

1. *Controle groep*: Werknemers die niet blootgesteld zijn;
2. *Witte boorden groep*: Kantoorpersoneel en werknemers die niet direct betrokken zijn bij de produktie van garens en vezels (o.a. ploegbazen);
3. *SO₂, H₂SO₄, HCl groep*: Werknemers die blootgesteld kunnen worden aan zwaveldioxide (SO₂) en zoutzuur (HCl) dampen en zwavelzuur (H₂SO₄) en HCL aërosolen;
4. *Polyesterdamp groep*: Werknemers die blootgesteld kunnen worden aan dampen van thermodegradatieproducten van het geproduceerde polyester polymeer, zoals aldehyde dampen, Verder is blootstelling mogelijk aan diphenyl-diphenylexide - en aan ethyleen glycol dampen;
5. *Oliemist en oliedamp groep*: Werknemers die blootgesteld kunnen worden aan oliemist en oliedamp, afkomstig van (synthetische) olie die op het garens is aangebracht;

6. *Polyamide- en polyesterdamp groep:* Werknemers die blootgesteld kunnen worden aan dampen van thermodegradatieproducten van het polyester- en polyamide polymeer en aan lactam dampen;
7. *Multipale blootstelling groep:* Onderhoudsmonteurs die blootgesteld kunnen worden aan verschillende typen luchtwegirritantia, afhankelijk van het type werk en de werkplek.

In het algemeen waren de gemeten blootstellingsniveaus laag en gemiddeld lager dan de wettelijke vastgestelde Maximale Aanvaarde Concentraties (MAC-waarden) die gelden voor werkplekken waar stoffen in de lucht voorkomen.

In hoofdstuk 3 wordt het gebruik van een inhalatie test om de gevoeligheid van de luchtwegen te meten, geëvalueerd. Voor dit onderzoek werd een bestaand onderzoeksprotocol, waarbij oplopende histamine concentraties van 1, 2, 4,...,32 mg/ml worden verneveld, verkort. Het doel hiervan was om een test te gebruiken die sneller en minder vermoeiend was dan de bestaande. De volgende wijzigingen zijn aangebracht: (1) personen bij wie geen verdenking bestond dat zij gevoelige luchtwegen zouden hebben, begonnen met een hogere histamine concentratie; (2) als na de longfunctietest bleek dat het volume dat men in de eerste seconde maximaal kon uitblazen (= FEV₁), minder dan 6% was afgenomen, werd een concentratie overgeslagen en (3) de test werd gestopt als het FEV₁ minstens 18% was gedaald in plaats van het algemeen gebruikte criterium van minstens 20%. Voor de evaluatie van de test, waren gegevens beschikbaar van 697 personen.

Nagegaan is of er grote dalingen van het FEV₁ optraden (meer dan 30%) en wat de tijdswinst was. Het bleek dat alle personen die bij 4 mg/ml histamine een FEV₁ daling hadden van 20% of meer (PC₂₀ ≤ 4 mg/ml), waren geselecteerd om met de 1 mg/ml te beginnen. Er waren geen plotselinge grote FEV₁ dalingen opgetreden na een verviervoudiging van de concentratie. Bij 20 personen werd een grotere FEV₁ daling voorkòmen doordat zij moesten stoppen nadat het FEV₁ 18-19% was afgenomen. Bij vijf personen kwamen zeer grote FEV₁ dalingen voor (FEV₁ daling ≥ 40%-50%), maar die waren opgetreden na een verdubbeling van de concentratie. De tijdswinst was maximaal bij 56% van de personen die een inhalatie schema hadden van controle vloeistof, gevolgd door 4, 16 en 32 mg/ml histamine.

Tijdens het onderzoek in 1989 zijn de waargenomen bijwerkingen genoteerd. Aan de deelnemers was niet systematisch gevraagd of men last had gekregen van de test. Gedurende het onderzoek in 1991 werd dit wel aan alle deelnemers gevraagd. In 1991 werd bij 702 personen de gevoeligheid van de luchtwegen gemeten. In totaal rapporteerde 41% één of meer bijwerkingen. Een benauwd gevoel op de borst kwam het vaakst voor (26%). De anderen klachten waren roodheid in het gezicht (18%), forse hoestreactie (5%), heesheid (4%), kloppend gevoel in het hoofd (1%) en onwel worden (1%). Benauwd gevoel op de borst, ten gevolge van de luchtwegvernauwing, en onwel worden als gevolg van het herhaald uitvoeren van geforceerde blaasmanoeuvres, zijn klachten die inherent zijn aan de test. De andere klachten waren waarschijnlijk minder vaak voorgekomen als in plaats van histamine, methacholine was gebruikt.

In **hoofdstuk 4** wordt de vraag behandeld of blootstelling aan luchtwegirritantia samengaat met het meer voorkomen van een verhoogde luchtweggevoeligheid bij de werknemers. In totaal hebben 790 personen meegedaan aan het onderzoek (opkomst van 87%). Van 668 personen waren de gegevens compleet. Een verhoogde luchtweggevoeligheid, gedefinieerd als een 20% daling van het FEV₁ bij een histamine concentratie van 32 mg/ml of minder, was aanwezig bij 23% van de personen. Werknemers die blootgesteld waren aan luchtwegirritantia hadden niet vaker een verhoogde luchtweggevoeligheid. Personen met een relatief kleine FEV₁ waarde, allergieklachten of chronische luchtwegklachten, hadden significant vaker een verhoogde luchtweggevoeligheid. Personen van de SO₂ groep en van de oliemist groep die hoogstens vijf jaar in deze groep werkzaam waren, hadden beduidend minder vaak een verhoogde luchtweggevoeligheid. Dit was zeer waarschijnlijk het gevolg van de gehanteerde procedure bij de aanstellingskeuring voor werknemers van deze groepen in de periode 1984-1989. Aan de andere kant kwam een verhoogde luchtweggevoeligheid ongeveer twee maal zo vaak voor bij personen van de polyesterdamp groep en de oliemist groep die meer dan vijf jaar in de huidige groep werkzaam waren.

In **hoofdstuk 5** wordt nagegaan of blootgestelde werknemers vaker chronische luchtwegklachten (hoesten, slijm opgeven, perioden met bronchitis klachten, kortademigheid, frequent piepen en/of ooit asthma aanval) hadden en of de longfunctie minder was dan bij de niet-blootgestelde werknemers. Gemeten longfunctiewaarden zijn FVC (totale volume), FEV₁ (volume dat in één seconde kan worden uitgeblazen) en MMEF

(snelheid van uitblazen). In totaal rapporteerde 26% één of meer chronische luchtwegklachten. Werknemers van de SO₂, HCl, H₂SO₄ groep hadden minder vaak luchtwegklachten dan de controle groep. Dit komt hoogst waarschijnlijk door de aanstellingskeuring procedure die gehanteerd werd voor deze groep in de periode 1984-1989. Door de andere groepen werden 1,5 tot 2,5 maal zo vaak luchtwegklachten gerapporteerd. Het verband tussen blootstelling en het vaker voorkomen van luchtwegklachten, was sterker bij de rokers dan bij de nooit- en ex-rokers. Dit verschil tussen rokers en niet-rokers was het duidelijkst bij de polyesterdamp groep en de polyamide- en polyesterdamp groep. Er waren geen aanwijzingen dat de aanwezigheid van een verhoogde luchtweggevoeligheid of allergieklachten het verband tussen blootstelling en het vaker voorkomen van luchtwegklachten, beïnvloedden. Wel rapporteerden rokers, personen met een verhoogde luchtweggevoeligheid of allergieklachten vaker chronische luchtwegklachten. Dit was echter onafhankelijk van blootstelling aan luchtwegirritantia.

Werknemers die blootgesteld waren hadden geen verlaagd longfunctieniveau. Dit resultaat veranderde niet als rekening werd gehouden met het feit dat blootgestelde werknemers vaker chronische luchtwegklachten hadden. Er waren ook geen aanwijzingen dat een combinatie van blootstelling aan irritantia met roken, met een verhoogde luchtweggevoeligheid of met het hebben van allergieklachten, in verband gebracht zou kunnen worden met een verlaagd longfunctieniveau. De duur van de blootstelling is mogelijk wel van belang. Werknemers van de polyesterdamp groep en de oliemist groep met meer dan 10 blootstellingsjaren, hadden een verlaagd longfunctieniveau. Het aantal personen in deze groepen was echter wel klein.

In **hoofdstuk 6** worden resultaten weergegeven die betrekking hebben op de vraag of werknemers die blootgesteld zijn aan luchtwegirritantia tijdens het werk vaker oog-, neus of luchtwegklachten hebben. In totaal rapporteerde 9% hoesten, 6% slijm opgeven, 7% kortademigheid, 2% piepen, 16% oogklachten en 15% neusklachten. Vergeleken met de niet-blootgestelde werknemers, rapporteerden de blootgestelde werknemers significant vaker de genoemde klachten. Dit was onafhankelijk van het feit of ze rookten, gevoelige luchtwegen, allergieklachten of chronische luchtwegklachten hadden. Verder is nagegaan of bij blootstelling rokers, of werknemers met een verhoogde luchtweggevoeligheid of met allergie klachten, vaker klachten rapporteerden dan werknemers die niet één van deze kenmerken hadden. Om dit te onderzoeken is de onderzoeksgroep gesplitst in twee

groepen, wel en geen blootstelling. Het bleek dat in geval van blootstelling, personen met een verhoogde luchtweggevoeligheid vaker last hadden van oog-, neus-, en luchtwegklachten. Rokers hadden vergeleken met de nooit-rokers en de ex-rokers, (alleen) meer last van piepen en/of kortademigheid. Werknemers met allergieklachten hadden ook vaker klachten op het werk dan personen zonder allergieklachten. Een opvallende bevinding was dat ook niet-blootgestelde werknemers met allergieklachten relatief vaak klachten hadden op het werk.

In **hoofdstuk 7** zijn de ziekteverzuimgegevens weergegeven. Net als bij de werkgerelateerde klachten, is de onderzoeksgroep gesplitst in wel en geen blootstelling. Van 653 personen waren de verzuimgegevens over een periode van twee jaar beschikbaar. Jaarlijks verzuimde elke werknemer gemiddeld twee maal. Per jaar werd er 6,7% van de kalenderdagen verzuimd wegens ziekte. Verzuim wegens luchtwegklachten was de meest voorkomende reden van ziekteverzuim (28%).

Werknemers die blootgesteld waren aan luchtwegirritantia verzuimden niet vaker of langer dan niet blootgestelde werknemers. Dit gold zowel voor het totale ziekteverzuim als voor verzuim wegens luchtwegklachten. Er waren aanwijzingen dat bij de blootgestelde werknemers rokers vaker verzuimden wegens luchtwegklachten dan de niet-rokers. Bij de werknemers die niet waren blootgesteld, verzuimden de rokers juist minder vaak dan de niet-rokers. Naarmate het longfunctieniveau van werknemers lager was, verzuimde men vaker. Maar als rekening gehouden werd met de aanwezigheid van een verhoogde luchtweggevoeligheid, dan was dit verband niet meer aanwezig. De frequentie van het verzuim wegens luchtwegklachten was hoger bij personen met allergieklachten, met een verhoogde luchtweggevoeligheid, of met werkgerelateerde luchtwegklachten. Voor ouderen gold dat personen met chronische luchtwegklachten vaker verzuimden dan personen zonder luchtwegklachten. Voor jongeren was dit niet zo. Een bekend gegeven met betrekking tot ziekteverzuim is, is dat ouderen minder vaak verzuimen dan jongeren. Dit gold ook bij deze onderzoeksgroep, maar dan alleen voor personen die geen chronische luchtwegklachten rapporteerden. Voor personen met chronische luchtwegklachten nam de verzuimfrequentie niet af, maar ook niet toe met de leeftijd.

Wat betreft het totale ziekteverzuim, bleek dat allergieklachten, een verhoogde luchtweggevoeligheid, en werkgerelateerde klachten, geassocieerd waren met een hogere verzuimfrequentie. Dit verband was wel minder sterk dan bij het verzuim wegens

luchtwegklachten. Rokers verzuimden vaker dan niet-rokers en dit was onafhankelijk van de blootstelling aan luchtwegirritantia.

Van de onderzochte kenmerken was leeftijd de enige die significant geassocieerd was met de duur van het verzuim. Naarmate men ouder wordt, verzuimt men gemiddeld langer.

In **hoofdstuk 8** is een algemene discussie opgenomen naar aanleiding van het onderzoek. Factoren die de resultaten van dit onderzoek hebben kunnen beïnvloeden, worden besproken, zoals de karakterisering van de expositie (expositiegroepen versus expositiemetingen), de grootte van de onderzoeksgroep, selectie (bijvoorbeeld personen met klachten veranderen van werk) en het ontbreken van onderzoeksgegevens van een aantal personen (geen bepaling van de luchtweggevoeligheid). De samenvattende conclusies van het onderzoek zijn de volgende:

1. De gebruikte testmethode met histamine om de luchtweggevoeligheid te bepalen is veilig en goed te gebruiken in een onderzoek bij werknemers. Het percentage personen dat klachten kreeg door de test was, echter, hoog.
- 2a*. De blootstelling zoals die in dit onderzoek voorkwam, was geassocieerd met het meer vòòrkomen van chronische luchtwegklachten bij de werknemers. Er kon echter geen verband worden aangetoond met een verlaagd longfunctieniveau of het vaker voorkomen van verhoogde luchtweggevoeligheid.
- 2b*. De blootstelling zoals die voorkwam bij de polyesterdamp groep en de oliemist groep kan mogelijk wel een verlaagd longfunctieniveau en een verhoogde luchtweggevoeligheid veroorzaken bij werknemers, mits de blootstellingsduur lang genoeg is (meer dan 10 jaar).
- 3*. Er waren geen aanwijzingen dat verhoogde luchtweggevoeligheid een risicofactor is voor het ontstaan van nadelige effecten van blootstelling op de gezondheid van longen en luchtwegen.
4. Blootgestelde rokers hebben een grotere kans voor het krijgen van chronische luchtwegklachten dan blootgestelde niet-rokers.
- 5a. De luchtwegirritantia veroorzaken werkgerelateerd hoesten, slijm opgeven, kortademigheid, piepen, neusklachten en oogklachten. Personen met allergieklachten of een verhoogde luchtweggevoeligheid hebben meer last (=vaker klachten) dan personen zonder deze gezondheidskenmerken.

- 5b. Blootgestelde rokers hebben ook meer last dan blootgestelde niet-rokers, maar dit geldt alleen voor de klachten kortademigheid en piepen.
- 6a. Personen die blootgesteld waren aan luchtwegirritantia verzuimden niet vaker of langer dan personen die niet waren blootgesteld. Blootgestelde personen waren ook niet vaker of langer afwezig als gevolg van verzuim wegens luchtwegklachten.
- 6b. Blootstelling aan luchtwegirritantia gaat in combinatie met roken, wel gepaard met het vaker optreden van verzuim wegens luchtwegklachten.
- 7a. Personen met chronische luchtwegklachten, met werkgerelateerde klachten, met allergieklachten, of met een verhoogde luchtweggevoeligheid, verzuimen vaker dan personen zonder één van deze kenmerken. Dit geldt zowel voor het totale verzuim als voor het verzuim wegens luchtwegklachten.
- 7b. Subjectieve gezondheidskenmerken, zoals het rapporteren van allergieklachten, chronische luchtwegklachten of werkgerelateerde klachten zijn sterker geassocieerd met meer ziekteverzuim wegens luchtwegklachten dan de objectieve kenmerken verhoogde luchtweggevoeligheid en een verlaagd longfunctieniveau.
- 7c. Rokers verzuimen in het algemeen vaker, maar niet langer dan niet-rokers. In afwezigheid van irritantiablootstelling is er echter geen verband tussen roken en vaker voorkomen van ziekteverzuim wegens luchtwegklachten.
- 7d. De interactie tussen leeftijd en chronische luchtwegklachten met betrekking tot het ziekteverzuim duidt op een verandering van de betekenis van het hebben van deze klachten bij toenemende leeftijd.

* Deze conclusies zijn, tot op zekere hoogte, mogelijk beperkt door:

- het lage huidige expositie niveau aan de luchtwegirritantia;
- hogere blootstellingsniveaus in het verleden (werknemers met meer dan 10 blootstellingsjaren);
- het kleine aantal jaren dat men blootgesteld is geweest (SO₂, H₂SO₄, HCl groep; groot aantal werknemers is jong);
- de selectie van personen zonder luchtwegklachten bij de aanstellingskeuring gedurende de vijf jaren die aan dit onderzoek vooraf gingen (SO₂, H₂SO₄, HCl groep en de oliemist groep);
- het relatief kleine aantal werknemers met meer dan 10 blootstellingsjaren, waarmee gerekend kon worden als gevolg van (1) reorganisaties en de VUT

- regeling en (2) het ontbreken van bepaalde onderzoeksgegevens bij ouderen; het feit dat geen rekening gehouden kon worden met vroegere blootstellingen, met name bij werknemers uit de controle groep.

Deze studie heeft niet aan kunnen tonen dat blootstelling aan in lage concentraties voorkomende luchtwegirritantia op lange termijn nadelige gezondheidseffecten heeft op een aantal longfunctie kenmerken. Getuige het sterker vòòrkomen van chronische luchtwegklachten en werkgerelateerde klachten zijn irriterende effecten wel degelijk aanwezig.

Acknowledgement

This thesis could never have been written without the help and support of many people. I am particular grateful to all the workers of the synthetic fibre plants who participated for their cooperation in the two surveys; the production floor managers of the shifts and the clerical staff of the plants for their cooperation during the fieldwork, the workers of the medical department, the engineering department, the personnel department and the statistical department for their support during the fieldwork. They made the fieldwork possible.

Teake Pal, head of the Health Department of Akzo Nobel Fibers BV, site Emmen, and former colleague at the University Groningen, for his enthusiasm, the discussions we had on the relevance of this study for occupational medicine and on the mechanistic background of the respiratory health problems encountered in this study. Thanks to his support and extra efforts, I got the assistance I needed for the fieldwork.

Bert Rijcken, for the fruitful discussions we had on the outcomes of analyses, the critical comments on the statistical interpretations of the study results and the useful comments on different parts of this thesis.

Prof. dr. Gerard Koëter for his valuable comments on structure and contents of this thesis.

Prof. dr. Jan de Monchy for his support in developing the histamine challenge protocol as it was used in this study, and for his comments on different parts of this thesis. His enthusiasm stimulated me more than once to persevere.

The members of the reading committee of this thesis: Prof. Dr. J.S.M. Boleij, Prof. Dr. J.H.B.M. Willems and Prof. Dr. D. Post for critically reading the manuscript.

Jan Schouten for his help with statistical problems encountered.

Rick Stigter and Johanna Veltman for their help with the statistics.

Vaclav Fidler for his enthusiasm and great help regarding the statistical analysis of the sickness absence data.

Esther van Wijck for her help in sickness absence data collection and data analysis.

The members of the two survey teams Franco de Wolff, Gerda Swart, Marette Oldenziel, Marjan Kerkhof, Watze Schaafsma and Martin Bakker for their contribution.

Thanks to the cooperation of Jan de Monchy (Department of Allergology, University Hospital Groningen), Tom van der Mark (Department of Lung Function, University Hospital Groningen) and Hennie Postmus (Department of Lung Function, Beatrixoord,

Haren) they, and I, got the training we needed to perform spirometry and histamine challenge tests.

My colleagues of the 'Working Group Industrial Lung Diseases' for their interest in the progress of the performed study.

Karin Boer (Institute for Social Medicine, Department of Occupational Medicine, University Nijmegen), Lily Hartmans, Martin Roest, Evelyn Tjoe Ny, Bernie Gouders, Harold van Til and Dirk Paardekoper (Department of Air Quality and Department of Epidemiology and Public Health, University Wageningen), for their efforts in taking exposure measurements. Jan Boleij and Dick Heederik (University Wageningen), thanks to their support the occupational hygiene studies could be performed at the time of my survey.

My former colleagues at the University Groningen, Department of Epidemiology and Statistics and the Department of Social Medicine, my present colleagues at TNO-Prevention and Health for their continuing interest in the progress of this thesis.

My current employer, TNO-Prevention and Health, especially the Division of Labour and Health, for giving me the support to complete this thesis.

My family and friends who supported me and who had every confidence in me finishing this thesis.

About the author

Anja Kremer was born on December 9th, 1959 in Zevenhuizen. She finished secondary school (Atheneum-B) at the Wesselgansfort College, 1978 in Groningen. She studied astronomy at the University Groningen from 1978 to 1979, and medicine from 1979 to 1986.

From 1987 to 1989 she worked at the Department of Epidemiology and Public Health of the Agriculture University in Wageningen. From 1989 to 1994 she was appointed to the Department of Epidemiology and Statistics at the Faculty of Medicine, Groningen University. In 1989 she started the work that was described in this thesis.

Since April 1994, she is appointed to the Division Working Environment and Health of the TNO-Prevention and Health (TNO-PG) in Leiden.

