AN INTERDISCIPLINARY APPROACH TO OCCUPATIONAL RESPIRATORY DISORDERS

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An Interdisciplinary Approach to Occupational Respiratory Disorders

Een interdisciplinaire benadering van arbeidsgerelateerde respiratoire aandoeningen
(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
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het college voor promoties in het openbaar te verdedigen op
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door

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“liceat quoque interrogationem hanc adjicere, & quam Artem exerceat”

Bernardino Ramazzini (1633-1714)

“I may venture to add one more question: what occupation does he follow”

CONTENTS

CHAPTER 1

General Introduction

GENERAL INTRODUCTION

The knowledge that occupational exposures can lead to respiratory symptoms has been known for centuries. Hippocrates' (circa 460-377 BC) writings include observations of metal workers who were breathing heavily. Agricola (1494-1555), author of the De Re Metallica, dealt with every aspect of mining, smelting, and refining of gold and silver in his Twelve Books on Mining and Smelting (1556) including development of diseases. Bernardo Ramazzini (1633-1714), author of De Morbis Artificum Diatriba (1713) is regarded as the father of occupational medicine. He is known for his detailed clinical descriptions of occupational diseases including respiratory disease in a wide variety of workforces. De Morbis Artificum Diatriba was essentially a study in clinical epidemiology, social medicine and industrial toxicology and hygiene and created the discipline of occupational medicine with its emphasis on preventive measures rather than ineffective remedies.[1-3]

Nowadays we still are being confronted with the impact of occupational exposures from the recent past. For example, the incidence of malignant mesothelioma is still rising due to exposure to asbestos in the past and the number of deaths is predicted to peak in the next decades in several EU member states.[4] Occupational respiratory diseases seem to be a never ending story. Regularly new occupational exposures are associated with respiratory diseases like occupational asthma as a result of various exposures such as biotechnologically produced and highly purified enzymes and many other sensitising agents,[5] the Ardystil syndrome associated with Acramin FWN,[6] flock worker's lung associated with synthetic micro fibres[7-9] and popcorn worker's lung associated with diacetyl.[10 11]

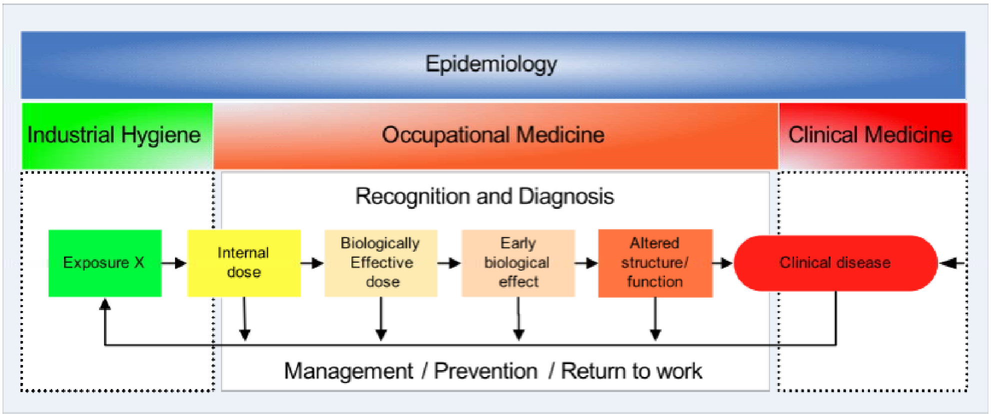
Common occupational respiratory tract diseases are rhinitis and laryngitis, tracheitis, bronchitis and bronchiolitis, asthma due to sensitizers and irritants, chronic obstructive pulmonary disease (COPD), cancer and interstitial lung diseases (ILD) like asbestosis, silicosis, hypersensitivity pneumonitis, and granulomatous disease.[12] The World Health Organization (WHO) estimates that worldwide about 50 million new cases of these occupational respiratory diseases emerge every year. Without preventative action, the burden of occupational diseases is expected to increase.[13] Pneumoconioses were the most prevalent occupational lung diseases as a result of industrialization. However, the prevalence in Western countries has been decreasing during the past decades and obstructive lung diseases increasingly have gained importance.[14] More recently, occupational asthma has become the most common occupational lung disease in many Western industrialized countries.[15 16] Point estimates based on data from occupational disease registries of several industrialized countries indicate an incidence of occupational asthma between 2 and 15 cases per 100.000.[17] An American Thoracic Society review of the literature until 2000 demonstrated that approximately 15% of all adult onset asthma and COPD cases is likely to be work related.[18] Epidemiological studies, on which these estimates are based, do not allow a distinction between occupational asthma (caused by work) and work exacerbated asthma (pre-existing or concurrent asthma worsened by work factors). Toren and Blanc recently evaluated the scientific literature in a systematic analysis and found that a value of at least 15%, and potentially as high as 20%, to be the most accurate range of the likely population burden of adult onset asthma attributable to occupational exposures.[19] Occupational chronic respiratory diseases represent a public health problem with substantial economic implications, in high-income countries, as well as in low- and middle-income countries.[20] These figures illustrate that the work environment significantly contributes to the occurrence of obstructive diseases.

For the United States, conservative estimated costs of occupational COPD and asthma were $5.0 billion for COPD and $1.6 billion for asthma in 1996. These costs probably will rise with the increasing prevalence of these diseases.[21] If these figures are to be translated to the European region this would amount to annual costs of at least € 6.4 billion.[14] Work-related asthma also has substantial socioeconomic consequences. For those affected, 25–38% of individuals with occupational asthma suffer prolonged work disruption and 42–78% report a substantial loss of income.[22] Work-exacerbated asthma is associated with a similar impact on work productivity and earning capacity.[23] The clinician must be aware of the potential occupational aetiologies for obstructive airway disease and consider them in every patient with asthma or COPD.[18]

In general, early recognition, diagnosis, management and prevention of occupational diseases is extremely important; it can possibly cure or stop progression of disease in the individual worker and may prevent mortality, morbidity and disability in other exposed workers. Further, it can save health care utilisation and socio-economic costs. Therefore, physicians seeing workers with respiratory disease should always consider an occupational origin of the respiratory disease. However, occupational lung disease remains poorly diagnosed and managed and inadequately compensated worldwide.[24] Unfortunately, there appears to be a lack of knowledge of new work-related health risks that can impede timely observation of new risks, with potentially irreversible health effects as a consequence.[25] According to The Netherlands Society of Occupational Medicine (NVAB) the occupational physician should be a key figure in the identification and diagnosis of occupational diseases, as it is one of his primary tasks.[26] However, there is a major discrepancy between the (on average) observed number of 30 cases of (occupational) asthma annually, reported by occupational physicians, and the estimated annual number of 500-2000 new cases of asthma on the basis of the size of the population at risk and the expected numbers in surrounding countries, as a result of occupational exposures in the Netherlands.[27] [28] An explanation might be, besides underreporting, that the diagnosis, management and prevention of occupational respiratory diseases is difficult and requires specific knowledge.[29-32] To support (occupational) health care professionals in the Netherlands on occupational respiratory disorders, the Netherlands Expertise Centre for Occupational Respiratory Disorders (NECORD) was founded in 2000. NECORD is comprised of four main disciplines namely, industrial hygiene, epidemiology, occupational medicine and pulmonology.

It is a centre for clinical occupational medicine with one main goal: to improve the quality of health care for workers with occupational respiratory disorders.[33 34]
In collaboration with the Netherlands Society of Occupational Medicine (NVAB), NECORD developed evidence based mono-disciplinary guidelines for work-related asthma and COPD.[35] These guidelines are practical tools for the approach to the individual worker with asthma and COPD. However, in these guidelines a population based approach to work-related asthma or COPD is summarily dealt with and an interdisciplinary approach is missing. In recent years, occupational health care professionals have frequently asked NECORD for assistance in the approach to worker populations with work-related respiratory health problems. Current occupational health care professionals appeared to experience difficulties in the approach to work-related respiratory health problems they encountered in daily practice. There appeared to be a lack of knowledge and access to the needed disciplines in the approach to the respiratory problems they encountered.
To improve the quality of health care for individuals with work-related respiratory disorders, an interdisciplinary approach is a more suitable approach for diagnosis, management and prevention of work-related respiratory disorders on an individual and population level (Figure 1).

Figure 1. An occupational health care chain: an interdisciplinary collaboration process between several distinct disciplines for an approach to work-related respiratory disorders on an individual and population level.



Adapted from: Van Damme K, Casteleyn L, Heseltine E, Huici A, Sorsa M, van Larebeke N, Vineis P. Individual susceptibility and prevention of occupational diseases: scientific and ethical issues. J Occup Environ Med. 1995;37:91-9.

Thesis:
The interdisciplinary approach to work-related respiratory diseases could be a suitable approach for recognition, diagnosis, management and prevention of work-related respiratory disorders on an individual and population level. This approach is illustrated by a series of structured case studies in this thesis.

Aims and outline of this thesis
In this thesis an alternative approach to deliver occupational health care is explored concerning work-related respiratory disorders in different worker populations.
Chapter 2: Several publications indicated a new, potentially severe occupational lung disease in workers exposed to flavourings in North American food processing industries ("popcorn worker's lung", bronchiolitis obliterans syndrome). Within the spectrum of butter flavouring vapours, the chemical diacetyl plays a prominent role. Until 2007, no cases of bronchiolitis obliterans syndrome (BOS) had been reported in the food flavouring producing industries or outside of North America. The occupational health service and the management of the plant asked for assistance to investigate the cohort of chemical workers exposed to diacetyl. The aim of our study was to investigate in a population-based approach, whether there were cases of BOS in the cohort, to examine the degree of risk, and to assess exposures.
Chapter 3: Four new cases of previously undiagnosed BOS were found in the chemical plant producing diacetyl as described in chapter 2. Exposure to an agent during diacetyl production appeared to be responsible for causing BOS in chemical process operators.
We performed an epidemiological survey of this historic cohort of workers from this diacetyl production plant. The aim of our study was to investigate and reconstruct exposures, respiratory symptoms, lung function and exposure-response relationships by modelling available exposure data.
Chapter 4: This study was occasioned by the occupational health service of a liquid detergent production plant. In a pilot study, it appeared that three out of 12 highly exposed workers were sensitised to detergent protease (Savinase). Until then, no occupational respiratory allergies had been reported in detergent production industries related to liquid detergent enzymes. The occupational health service and the management of the plant asked for assistance to investigate sensitisation among workers handling liquid detergent enzymes and secondly, the respiratory health among sensitised workers. And if there was an increased risk, how to prevent health effects in the future by exposure reduction or health surveillance.
Chapter 5: For several years, cast-house workers in an aluminium producing plant in the Netherlands reported ongoing respiratory symptoms. Several hygienic control measures were implemented already but did not lead to a decrease in reported symptoms. The occupational health service and the management of the plant asked for assistance to investigate the exact

nature and potential causes of this problem. We have studied (peak)exposures, prevalence of respiratory symptoms and lung function among aluminium cast-house workers.

Chapter 6: A (nationwide) medical surveillance program on occupational asthma among bakery workers needed an effective and efficient strategy. Practically it was not feasible to investigate the incidence of occupational astma in all bakery workers who worked scattered around the Netherlands. Sensitisation to wheat allergens is a critical step in the development of occupational asthma. A triage system by using epidemiological and diagnostic prediction principles made it feasible to select workers with a high risk of being sensitised to wheat allergens. Occupational physicians decided which selected workers should be referred for further clinical investigation by specialized outpatient clinics. In this study we clinically evaluated a population of flour- and enzyme-exposed traditional bakery workers identified by an earlier developed simple triage system.

In addition, we explored factors predictive of non-specific bronchial hyperresponsiveness (BHR) in order to optimize the triage approach in an attempt to extend it to specialized occupational respiratory clinics.

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CHAPTER 2

BRONCHIOLITIS OBLITERANS SYNDROME IN CHEMICAL WORKERS PRODUCING DIACETYL FOR FOOD FLAVOURINGS

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ABSTRACT

Rationale: Workers in microwave popcorn plants are at risk of developing bronchiolitis obliterans associated with exposure to butter flavoring volatiles, including diacetyl.

Objectives: To investigate the risk of bronchiolitis obliterans for chemical workers producing diacetyl, with exposure to less complex mixtures of chemicals.

Methods: We interviewed and conducted spirometry on 175 of 196 workers from a chemical production plant that produced diacetyl between 1960 and 2003. We used all available historical exposure data to classify all workers into three exposure groups with varying exposure profiles to diacetyl, based on frequency and level of exposure.

Measurements and Main Results: Workers with fixed airway obstruction underwent further pulmonary function testing (including diffusing capacity and lung volumes) and paired inspiratory and expiratory high-resolution computed tomography studies. We identified three cases consistent with bronchiolitis obliterans syndrome with air trapping on high-resolution computed tomography of the lungs, in the highest exposure group of 102 process operators. Two of these cases were lifelong nonsmokers. Potential exposures included acetoin, diacetyl, acetaldehyde, and acetic acid, with diacetyl exposures in the range previously reported to be associated with fixed airway obstruction in the microwave popcorn industry.

Conclusions: Exposure to an agent during diacetyl production appears to be responsible for causing bronchiolitis obliterans syndrome in chemical process operators, consistent with the suspected role of diacetyl in downstream food production.

INTRODUCTION

Several recent publications indicate a new, potentially severe occupational lung disease in workers exposed to flavorings in North American food processing industries (“popcorn worker’s lung”). These studies include clinical case studies in former employees, cross-sectional epidemiological studies among current employees, explorative exposure studies, and a few animal exposure studies. [1-9]

Carefully performed clinical case series of workers occupationally exposed to inhalable flavoring vapors documented a rare, severe lung disease, consistent with the diagnosis bronchiolitis obliterans syndrome (BOS). Within the spectrum of butter flavoring vapors, diacetyl plays a prominent role.[2 10]

Until now no cases of BOS have been reported in chemical production industries related to flavorings or outside North America. The novelty of the present study is that it was conducted in the chemical industry in a European diacetyl production plant. A cohort of workers of the plant who were potentially exposed to diacetyl in the period 1960-2003 was identified by employment records. Among these workers, cases of BOS were not previously detected or suspected by the occupational health service or otherwise.

The aim of this study was to investigate in a population-based approach whether there were cases of BOS in the cohort of workers exposed to diacetyl, to examine the degree of risk, and to assess exposures.

Some of the results of this study have been previously reported in the form of an abstract.[11]

METHODS

Study design and population

The chemical plant producing diacetyl was based in The Netherlands. The Human Resources department identified 206 workers who had potentially been exposed to diacetyl in the period 1960-2003, of whom 10 had died. Their cause of death was not investigated. We traced the remaining 196 and obtained written informed consent from 175 (89%).

Participants completed a self-administered standardized questionnaire supplemented with questions about respiratory, mucous membrane, and atopic symptoms and work history. The questionnaire is based on one with items described in NIOSH Health Hazard Evaluation Reports[12 13] and some of the questionnaire items were taken from the European Community Respiratory Health Survey (ECRHS).

Exposure assessment

Since production of diacetyl at the plant stopped in 2003, we evaluated all historical exposure data and interviewed company representatives to characterize exposure qualitatively and estimate exposure semi-quantitatively.

The plant produced diacetyl by oxidation of 2,3-butylene glycol into acetyl-methyl-carbinol (AMC; acetoin), which was further partly oxidized into diacetyl (2,3-butanedione). Acetaldehyde and acetic acid were side products of the two primary reaction products, AMC and diacetyl. Diacetyl production took place in a completely closed system in a reactor vessel at an elevated process temperature (around 360 ^{o}C). Exposure for process operators only existed at the end of the production process and they did not have exposures to heated product.

Limited routine exposure monitoring was done by company representatives using cartridges containing silica gel coated with dinitrophenylhydrazine (DNPH-cartridges), and each sample was analyzed by an external laboratory for both diacetyl and acetaldehyde using gas chromatography. A total of 26 ambient samples (sampling duration 82-219 minutes) and 4 personal task-based samples (33-90 minutes) taken between 1995 and 2003 could be traced.

Spirometry

Experienced technicians obtained spirometric lung function variables in all participants according to European Respiratory Society standards[14] by using a pneumotachograph with specific software (pneumotachograph and version software 4.66; Jaeger; Wurzburg, Germany). Age- and standing height-adjusted spirometric reference values of the European Community for Steel and Coal were used.[14] We defined fixed airway obstruction as FEV_1 < 80% of predicted, FEV_1 to FVC ratio ≤ 70%, and increase in FEV_1 < 9% after bronchodilation.[15] We referred all participants with a post bronchodilator FEV_1/FVC of < 70% and an FEV_1 < 100% of predicted to a hospital for further clinical investigation.

Clinical evaluation

Referred workers underwent medical history taking and physical examination.

We used medical files of the Occupational Health Service to reconstruct case histories and collected additional information on pulmonary function including static lung volumes by body plethysmography and single-breath carbon monoxide diffusing capacity. We performed a high-resolution computed tomography (HRCT) scan of the lungs in all workers with fixed airway obstruction using a volumetric acquisition with 16x0.75mm or 64x0.625mm collimation during inspiration and dynamic expiration.

A diagnosis of BOS was made in cases with fixed airway obstruction and an HRCT scan with features of air-trapping with hypoattenuation in segmental or lobular areas and mosaic pattern of perfusion.[16 17]

Epidemiological and statistical analysis

All statistical analyses were performed using SAS software (SAS System for Windows version 8.2, SAS Institute, Cary, NC). Data of 159 male Caucasian workers (all ages) were used to compare lung function test results between different job titles within the study population using minimally exposed workers as an internal reference group. Pulmonary function parameters in different job titles were investigated by multiple linear regression analysis (PROC REG), adjusting for age, height, and smoking habits. The accuracy of regression models was examined by using Cook's influence statistic, residual plots and partial regression residual plots.

RESULTS

Characteristics of the study population

Table 1 shows the characteristics of the study population that completed a questionnaire and underwent spirometric lung function tests in 2005. Regression analysis showed that operators had significantly lower FEV_1 values (-292 ml) than workers in the internal reference-group (Table 2). Regression coefficients for age and standing height were comparable to thosefrom reference regression equations from the European Respiratory Society (ERS).[14] Current smokers generally had lower lung function compared to non-smokers, but ex-smokers did not show the expected pattern of lower lung function compared with non-smokers.

Table 1. Characteristics of diacetyl plant workers.*

Characteristic	**Value**
Sex	
Male (%)	169 (97)
Race	
Caucasian (%)	163 (93)
Job title	
Process operator (%)	102 (58)
Quality Control Lab (%)	23 (13)
Technical service (%)	21 (12)
Other jobs (%)†	29 (17)
Age - yr (sd)	
Median	51 (9.5)
Range	25 - 78
Smoking status (%)	
Current smoker	27
Former smoker	41
Never smoked	33
FEV_1 % pred (sd)	103.9 (18.1)
FVC % pred (sd)	107.2 (16.4)
PEF % pred (sd)	123.7 (21.9)
FEV_1/FVC % (sd)	77.8 (7.4)

*(n = 175).
† The category 'Other jobs' includes: logistics (n=11); health, safety & environment workers (n=3); and a diversity of other jobs (e.g. management and research & development) (n=15).

Table 2. Multiple linear regression analysis of pulmonary function variables on age, standing height, smoking and job in a population of diacetyl plant workers.*

Determinant	FEV_1 (ml)		FVC (ml)		FEV_1/FVC %		MEF_{50} l/s	
	ß	SE	ß	SE	ß	SE	ß	SE
Intercept	21	1601	-4502†	1817	146†	17	6.91‡	3,62
Age	-34†	6	-29†	7	-0.28†	0.07	-0.06†	0.01
Height	3275†	810	6208†	919	-29†	9	0.45	1.83
Smoking status (%)§								
Current smoker	-284†	138	-288‡	156	-0.77	1.49	-0.34	0.31
Former smoker	259†	130	271‡	148	1.61	1.41	0.53‡	0.29
Jobs ¦								
Process operator	-292†	144	-182	164	-3.08‡	1.56	-0.51	0.33
Quality Control Lab	-247	203	-200	231	-1.69	2.19	-0.76‡	0.46
Technical service	-260	197	-100	223	-2.89	2.13	-0.82‡	0.44
Adjusted R^2 (%)	37		41		12		13	

Definition of abbreviation: SE = standard error; MEF_{50} = mean expiratory flow at 50% of FVC.
*(n = 159), only male Caucasians.
†$p<0.05$; ‡ $p<0.10$.
§Never smoked as reference group.
¦The job title 'other jobs' as reference group.

Exposure assessment

The air concentrations, as determined by area sampling, ranged from 1.8 to 351 mg/m^3 for diacetyl and from 0.4 to 29 mg/m^3 for acetaldehyde. Control measures taken in 2001 with the aim to enclose the process, led to a reduced exposure for both diacetyl (Geometric Mean (GM) change from 10.0 to 5.8 mg/m^3) and acetaldehyde (GM change from 7.6 to 0.7 mg/m^3). During production, process operators were potentially exposed to diacetyl during several tasks but discharge of diacetyl in containers had the highest exposure potential for process operators. Personal task-based sampling results during this activity ranged from 3-396 mg/m^3 diacetyl and 0.2-14 mg/m^3 acetaldehyde. These exposure data were collected for compliance testing of acetaldehyde exposure. Although exposure to diacetyl was mainly relevant for process operators, workers with several other occupational titles were also potentially exposed to diacetyl. Maintenance workers were likely to be exposed to diacetyl but exposure was highly variable. Laboratory workers were potentially exposed to diacetyl but no further qualitative or quantitative information was available. All other occupational titles (transport, health & safety, and management and research and development personnel) had low exposure potential for diacetyl and, if they had exposure, it was always of short duration.

The diacetyl production plant was one of several plants in operation at the production site. Most production workers, including all operators, also worked in other chemical plants on the production site. As a result, all workers were also potentially exposed to other chemical agents, including irritants such as ammonia and chlorine.

Clinical investigation

Six workers with suspected fixed airflow obstruction were referred. Two workers turned out not to have fixed airways obstruction. Both had an $FEV_1 \geq 80$ % predicted. In one subject, lung function normalized after treatment, and the diagnosis asthma was made. In the other, a former smoker (29 pack-years), no respiratory abnormalities were found. The remaining four workers were eligible for HRCT, one of whom refused. He was a 52- year old smoker (29 pack-years) and had an FEV_1 of 71.8 % predicted and an FEV_1/FVC of 63.8 %. Three workers underwent HRCT and all three were diagnosed as BOS cases (Table 3).

All three subjects had been process operators. Two of them were life-long nonsmokers, and the third was a 59 year-old smoker with a cumulative smoking history of 14 pack-years. Their symptoms had started 10 to 20 years earlier, on average after 5 years of employment at the diacetyl plant (Table 3). None had ever been hospitalized for a pneumonia or an infection, showed signs of a connective tissue disorder or colitis, used medication known to cause bronchiolitis obliterans or undergone radiotherapy in the past.

All three subjects had previously been diagnosed by chest physicians as having COPD or asthma, for which they were treated by inhaled beta-agonists and corticosteroids.

Case 1 used a long-acting anticholinergic agent; none received maintenance oral corticosteroid therapy.

Table 3. Characteristics of cases with radiological signs of bronchiolitis obliterans.

	Case no.		
	1	2	3
Age at time of diagnosis	55	72	59
Age at symptom onset years	45	52	39
Sex	M	M	M
Smoking pack-years	0	0	14
Process Operator	+	+	+
Year started at the diacetyl plant	1993	1971	1985
* Year of symptom onset	1994	1985	1985
Year stopped at the diacetyl plant	2003	1987	2001
Wheeze	+	-	+
Fever	+	-	-
Fatigue	+	+	-
Night sweats	-	-	+
Eye irritation	+	-	+
Nasal irritation	-	-	+
Skin irritation	+	-	-
Crackles on chest examination	-	-	-
Initial diagnosis	COPD	COPD	Asthma, COPD
Lung function at time of examination			
†FEV_1 % pred	35.1	37.4	42.3
†FVC % pred	65.2	65.0	57.7
†FEV_1/FVC %	42.9	43.8	57.8
‡Reversibility	-	-	-
TLC % pred	110	94	99
RV % pred	157	132	140
RV/TLC % pred	131	125	130
TLco % pred	85	70	61
Kco % pred	108	117	76

Definition of abbreviations: FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; TLC = total lung capacity; RV = residual volume; TL_{CO} = diffusing capacity for carbon monoxide; K_{CO} = transfer coefficient for carbon monoxide; % pred = percentage of the predicted value.
*Based on medical history.
†Post bronchodilator.
‡Reversibility defined as ≥ 9 percent increases in FEV_1 after bronchodilation.
+ = present, - = not present.

Lung function tests were available for cases from the Occupational Health Service through 1994 and thereafter from hospital records (Figure 1). The average FEV_1 decline during employment was 175 ml/yr for case 1 (1995 to 2003) and 55 ml/yr for case 3 (1986 to 2001). No lung function data were available for case 2 during employment. All cases reported exertional dyspnea as the first symptom and none had an acute onset or reported coughing or phlegm.

All three workers had confounding exposure from other production facilities within the plant during the same time period. Cases 1 and 2 reported no inhalation accidents. Case 3 reported a 1997 inhalation accident 12 years after his first reported chest symptoms and after commencement of accelerated FEV_1 decline. He was exposed to acetaldehyde in the diacetyl production process during a few minutes without respiratory protection after which he immediately became dyspneic. In 1998, he consulted a chest physician because symptoms worsened.

Figure 1. Change in FEV_1 over time in bronchiolitis obliterans syndrome cases.

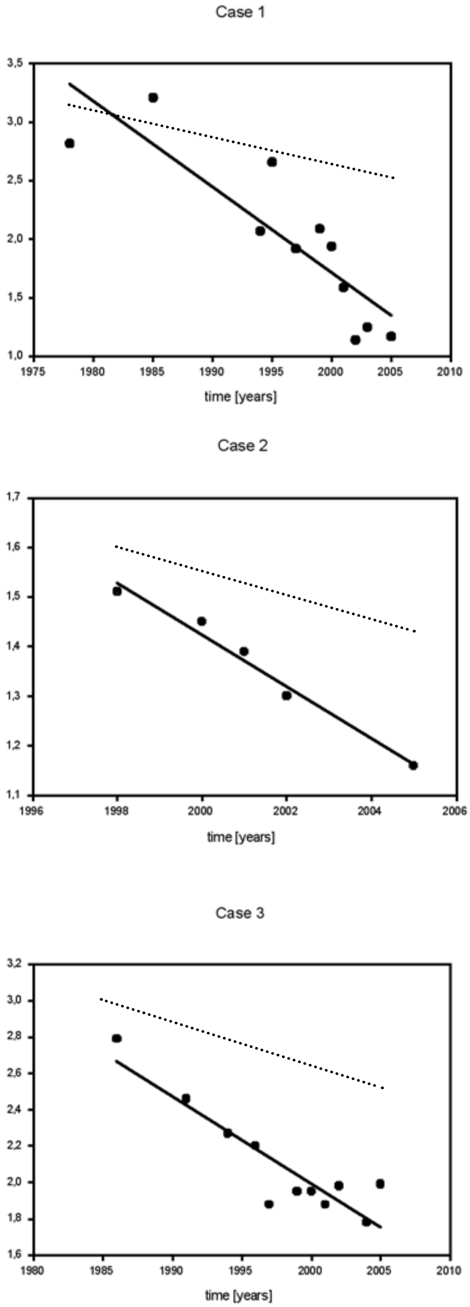

Figure 1 shows forced expiratory volume in one second (FEV_1) as a function of time for cases in comparison with expected decline. FEV_1 values as shown were available from occupational health records before 1995 and from hospital records since 1995. Expected decline .....; FEV_1 data points • ; observed decline —.

Lung function

All three cases showed a fixed airway obstruction. An increased residual volume (RV) as well as an increased RV to TLC (total lung capacity) ratio, together with a decreased FVC indicated hyperinflation in all cases. Diffusing capacity for carbon monoxide (Tlco) was below the normal range in two cases, and transfer coefficient for carbon monoxide (Kco) in one case was below normal.

Radiology

Multislice HRCT showed slight inhomogeneity of the lung attenuation during inspiration; on expiratory scans, air trapping was visible in all three cases. None of the cases demonstrated major centrilobular or paraseptal emphysema compatible with COPD as seen in smokers (Figure 2). In case 1, HRCT showed a mosaic pattern with air trapping compatible with bronchiolitis obliterans (Figure 2). In case 2, air trapping was less geographic and mainly localized in the lower lobes and the posterior portions of the upper lobe. There was mild bronchial wall thickening and focal accentuation of centrilobular structures. In case 3, the inhomogeneity of the lung parenchyma accentuated on the expiratory scan with air trapping especially in central and ventral portions of the lung. The lung periphery, lung apex and the basal lungs showed a normal increase in lung density during expiration. This effect was combined with an almost complete collapse of the central bronchi (main and lobar bronchi) during expiration. Modest bronchial wall thickening was present.

Figure 2. High-Resolution CT scans in bronchiolitis obliterans syndrome cases.

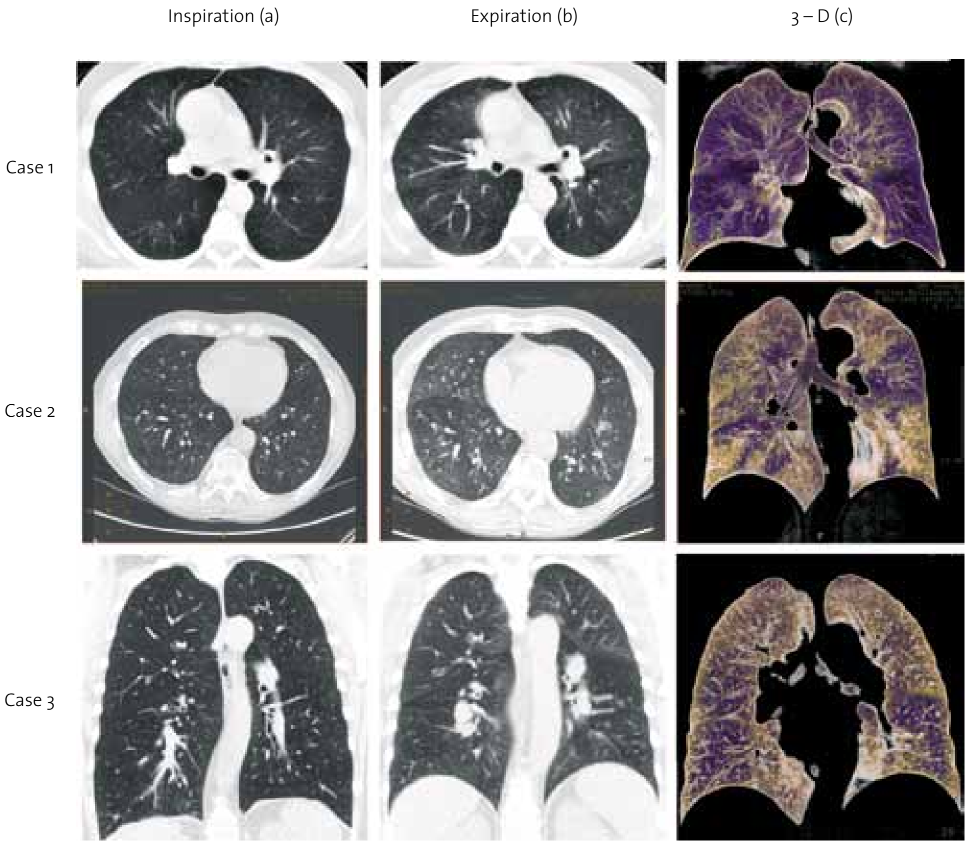

Figure 2 shows Multislice High-Resolution CT scans of the lungs during inspiration (a) show inhomogeneity of the lung attenuation during inspiration. In case 1 a slight mosaic pattern of the lung parenchyma is already present during inspiration. During expiration (b) a mosaic pattern is visible in all three cases.

Note that areas in which lung density remains virtually unchanged are indicative of substantial air trapping. In expiratory 3 dimensional (3 D) color-rendering of coronal 3cm thick sections of the lungs (c) inhomogeneity is even more pronounced with purple areas due to air trapping. Findings are compatible with bronchiolitis obliterans.

Thoracic lung biopsy

Case 1 underwent video-assisted thoracoscopic lung biopsy, with wedge biopsies taken from the right upper and lower lobe. Histology showed no signs of constrictive bronchiolitis. In some sections of the biopsies emphysema and chronic bronchiolitis was present, reflecting nonspecific small airway disease.

DISCUSSION

Our study found a cluster of BOS cases in a diacetyl production plant. This supports the conclusion that an agent in the diacetyl production process has caused BOS in process operators. The clinical characteristics and physiological and imaging features of the cases are consistent with the cases identified in a popcorn plant in the United States.[4] The third case, a modest smoker, had an unusual pattern of air trapping combined with a nearly complete collapse of the central bronchial tree during expiration. He did not have an active smoking history or physiology sufficient to explain COPD. A case with similar features in a diacetyl-exposed group was reported by Kreiss et al.[2]

Lung biopsies obtained in one case showed nonspecific small airway disease.

The main histological finding in bronchiolitis obliterans is a constrictive bronchiolitis as seen in patients with connective tissue disease and in bone marrow and (heart-)lung transplants. Because lesions are often patchy or may present as centrilobular emphysema, the diagnosis may be missed.[18] When pathology is lacking, the term obliterative bronchiolitis may more accurately describe the clinical syndrome - that is, airway obstruction due to bronchiolitis.

In the study of Akpinar-Elci et al.[4], three cases underwent thoracoscopic lung biopsies. In only one case, histology supported a diagnosis of constrictive bronchiolitis. The other two cases showed severe airway obstruction and mosaic patterns on HRCT, but bronchiolitis was not found in the lung biopsies, which was attributed to a sampling error. Although bronchiolitis obliterans is a histological diagnosis, the typical features on HRCT obviate the need for biopsy in those with occupational exposure to a recognized agent. Moreover, the risk of surgical intervention and sampling error should be weighed against the need for a histological diagnosis. Cases of bronchiolitis obliterans are easily missed.[4] HRCT may be normal during inspiration as BOS requires expiratory HRCT to visualize air trapping. In smokers under middle age and especially in nonsmokers with chronic airway obstruction, a diagnosis other than COPD should be considered. Clusters of such cases in work environments provide opportunities to identify new etiologies of bronchiolitis obliterans.

Population at risk

Process operators were the highest exposed group to diacetyl in this study and had significantly lower FEV_1 values than workers in the internal reference group.

The decline of FEV_1 value of cases was higher than expected in periods in which they worked at the diacetyl plant. Typically, FEV_1 shows average declines of 24 ml/year in nonsmokers and 28 ml/year in smokers in longitudinal studies.[19] The excess declines may have been affected by spirometry measured in different settings with different devices and technicians, but each of the cases had quite consistent declines despite different data sources.

Exposure

This is the first study where cases of BOS were found in a chemical plant producing diacetyl. Although the information regarding exposure levels was limited, available data suggest that diacetyl exposure was in the same range as in several popcorn plants with similar cases of BOS.[9] Before 2001, the diacetyl exposure in the production plant was as high as in the index microwave popcorn plant where the first cases of BOS were described.[2] After several control measures were implemented, diacetyl levels were significantly lower but still in the range found in other microwave popcorn plants with cases of BOS.[9] In a separate analysis, no clear relationship between lung function and cumulative exposure was observed.[11] Estimated historic exposure levels are subject to considerable measurement error and it is likely that exposure misclassification obscured exposure-response relationships.

Causal relationship between bronchiolitis obliterans syndrome and diacetyl exposure

In addition to working in the diacetyl production plant, cases also worked in other plants on the same production site during the same time period, and were potentially exposed to other agents. Among the gaseous chemicals identified in the plants, only ammonia and chlorine were of potential concern for bronchiolitis obliterans[20], but none of the cases reported having had significant exposures to these agents. Furthermore, these two known causes of bronchiolitis obliterans are based on reports of the disease after inhalation accidents and not on the slow evolution of BOS.[21-23] It is unlikely that other chemicals were responsible for the cases because none reported inhalation accidents before they became symptomatic. Case 3 reported an inhalation accident in 1997 (to acetaldehyde) but he had been symptomatic since 1985 and had accelerated decline during employment. In the symptomatic presentation of these cases, there were slowly evolving symptoms and pulmonary function abnormalities, similar to the endemic pattern seen in the microwave popcorn industry.

In this study, as in the study by Kreiss et al.[2], diacetyl may either be a cause of respiratory disease or a marker of another causative exposure. The spectrum of exposures is much smaller in this production plant compared with the popcorn processing plants where a wide range of chemicals was identified. Consistent with animal inhalation studies showing airway injury with diacetyl vapor[10], our study suggests a causal role of diacetyl. However, we cannot rule out a possible contribution of acetoin or even acetaldehyde[24] either as causative or contributing agents.

Study limitations

The study population was small, and this limited statistical power in internal comparisons especially after correction for confounding variables in multiple regression modeling. Selection bias is unlikely given the high participation rate. There was no evidence of confounding, either by smoking status or age.

Moreover, our analyses of exposure have not addressed the potential importance of short-term or peak exposures among workers because such information was lacking. By not pursuing decedents and not obtaining clinical evaluation of one case of fixed airway obstruction, we may have underestimated the number of BOS cases. Indeed, an additional case was found after the study among the ten nonparticipants among the former workers at the plant. This post-study case was a 63-year old nonsmoking process operator who worked from 1968-1970 and stopped working in 1970 when he became symptomatic and was diagnosed with severe COPD (FEV_1 31% predicted, FEV_1/FVC 37%). The 2006 HRCT scan of the lungs was compatible with a diagnosis of bronchiolitis obliterans. Thus, at least four cases of clinical bronchiolitis obliterans arose in 206 workers employed in this diacetyl manufacturing plant.

This population-based survey establishes the presence of BOS, or popcorn worker's lung, in chemical workers manufacturing a flavoring ingredient with exposures to diacetyl, acetoin, and acetaldehyde. Any or all of these exposures may contribute to the risk of this emerging occupational lung disease.

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Chapter 3

A CROSS-SECTIONAL STUDY OF LUNG FUNCTION AND RESPIRATORY SYMPTOMS AMONG CHEMICAL WORKERS PRODUCING DIACETYL FOR FOOD FLAVOURINGS

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ABSTRACT

Objectives: Four diacetyl workers were found to have bronchiolitis obliterans syndrome. Exposures, respiratory symptoms, lung function and exposure–response relationships were investigated.

Methods: 175 workers from a plant producing diacetyl between 1960 and 2003 were investigated. Exposure data were used to model diacetyl exposure. Lung function and questionnaire data on respiratory symptoms were compared to a general population sample and respiratory symptoms to an internal reference group.

Results: Workers were potentially exposed to acetoin, diacetyl, acetaldehyde and acetic acid. Historic diacetyl exposure ranged from 1.8 to 351 mg/m3, and from 3 to 396 mg/m3 for specific tasks. Diacetyl workers reported significantly more respiratory symptoms compared to the general population sample (continuous trouble with breathing (prevalence ratio (PR) = 2.6; 95% CI 1.3 to 5.1), daily cough (PR = 1.5; 95% CI 1.1 to 2.1), asthma attack (ever) (PR = 2.0; 95% CI 1.2 to 3.4), doctor diagnosed asthma (PR = 2.2; 95% CI 1.3 to 3.8) and asthma attack in the last year (PR = 4.7; 95% CI 1.9 to 11.4) and to a minimally exposed internal reference group (ever trouble with breathing (PR = 2.8; 95% CI 1.1 to 7.0) and work-related shortness of breath in the last year (PR = 7.5; 95% CI 1.1 to 52.9). Lung function did not differ between groups. A positive relationship between exposure and FEV_1 was found.

Conclusion: The excess of respiratory symptoms in this retrospective cohort suggests that diacetyl production poses an occupational hazard. Limited historical exposure data did not support a quantitative individual diacetyl exposure–response relationship, but our findings suggest that preventive measures are prudent.

INTRODUCTION

Fixed airway obstruction consistent with bronchiolitis obliterans syndrome (BOS, “popcorn workers lung”) was first reported among workers in the microwave popcorn production industry in relation to inhalatory exposure to airborne butter-flavouring chemicals.[1] Diacetyl, a predominant chemical in butter flavouring, is suggested to play a prominent role.[1-4]

In the index plant an exposure-response relationship was reported between cumulative exposure to diacetyl (using quartiles of increasing exposure) and the proportion of workers with abnormal spirometric lung function results including airway obstruction.[1] Analyses of aggregated data of current workforces in the microwave popcorn industry indicated a wide spread risk for occupational lung disease from exposure to butter-flavouring chemicals. Workers mixing oil and butter flavourings had medical findings consistent with BOS, and workers with more than 12 months’ mixing experience had a higher prevalence of respiratory symptoms and airway obstruction and lower mean percent predicted FEV_1 compared with workers who had less than 12 months’ experience, indicating a relationship with exposure.[4]

Elsewhere, we have previously reported four new cases of unsuspected BOS in a chemical plant producing diacetyl, where exposure to an agent during diacetyl production appeared to be responsible for causing BOS in chemical process operators.[5]

In this article we present our findings from a epidemiological survey of a historic cohort of workers from a diacetyl production plant and investigate and reconstruct exposures, respiratory symptoms, lung function and exposure-response relationships by modelling available exposure data.

This investigation was conducted in the same plant previously examined and the epidemiologic description of the cohort in this study complements the case reports of BOS.[5]

METHODS

Study population

We performed a cross-sectional study in 2005 in a cohort of former workers in a chemical plant producing diacetyl in The Netherlands in the period 1960-2003. The plant was closed in 2003. The human resources department identified 206 workers who potentially had been exposed to diacetyl in that period. Ten of these workers had died, but we traced the remaining 196 and obtained written, informed consent from 175 (89%).[5]

Some of the items in the questionnaire were based on questions from NIOSH Health Hazard Evaluation Reports and while others were taken from the European Community Respiratory Health Survey (ECRHS).[5]

The questionnaire had several detailed items on work history and work-related symptoms, both in the diacetyl plant (job title, duration and number of days/week) and other plants at the production site (type of plant, type of exposure, duration and number of days/week). In addition, workers were asked if they experienced exposure incidents, for example during maintenance and/or process disturbances.

Experienced technicians obtained spirometric lung function variables in all participants according to European Respiratory Society standards[6] using a pneumotachograph with specific software (Pneumotachograph with 4.66 software, Jaeger; Wurzburg, Germany). Age- and standing height-adjusted spirometric reference values of the European Community for Steel and Coal were used.[6]

Reversibility was measured after bronchodilation with 400 micrograms salbutamol (metered dose inhaler) and defined as ≥ 9% increase in FEV_1 predicted.[7]

We used data from the Dutch part of the ECRHS, a general population sample, as a reference.[8]

To compare symptom prevalence between the two groups, we used data from male subjects aged between 30 and 70 (n = 159 diacetyl production workers and n = 1125 subjects from the EHRCS population). For analysis of lung function data, we only used data from Caucasian males aged 30-70 (n = 149 diacetyl production workers and n = 1084 subjects from the EHRCS population) as there were too few non-Caucasian workers in the diacetyl population.

Exposure estimates

We evaluated all historical exposure data and interviewed company representatives to characterize exposure qualitatively and estimate exposure semi-quantitatively.[5]

The working schedule varied considerably among workers as some worked in the diacetyl plant for five successive days, whereas others were scheduled to work in the diacetyl plant for one day per week. Company representatives thought that all process operators worked on average an equal number of days per year in the diacetyl plant, but some individual differences may have existed among workers. We used three different exposure proxies to study diacetyl exposure-response relationships: (1) the number of years in the diacetyl plant, (2) the number of years in the diacetyl plant before 1995, and (3) an exposure estimate in which both the duration of exposure and the level of diacetyl were taken into account. Three crucial changes must be noted. First, in the mid-1980s, diacetyl production was changed from batch production to a continuous production process. Second, in 1995, several hand-operated processes were automated and, as a result, operators only had to be present in the diacetyl plant for 2 hours per day instead of 8 hours. Third, in 2001, exposure to diacetyl and other relevant chemical agents was considerably reduced when the installation was enclosed (Table 1). We translated these process changes into exposure multipliers resulting in a relative cumulative exposure estimate for each worker, using the most recent time episode as the reference period. We estimated exposure between 1995-2000 to be about four times higher compared to 2001-2003, based on the arithmetic mean of environmental area sampling results. We estimated exposure between 1986-1994 to be about four times higher compared to 1995-2000, based on the time present in the plant (8 versus 2 hours). We estimated exposure between 1960-1985 to be about half compared to 1986-1994, based on the change in production volume. Thus, the relative cumulative diacetyl exposure for each worker was calculated as: 8x(years between 1960-1985) + 16x(years between 1986-1994) + 4x(years between 1995-2000) + (years between 2001-2003). The period before 1995 had the highest diacetyl exposure.

Statistical analysis

All statistical analyses were performed using SAS software (SAS System for Windows version 9.1, SAS Institute, Cary, NC). Data of 159 male white workers, with ages between 30 and 70 years were used to compare the prevalence of respiratory symptoms among workers with the general population sample. Workers were assigned different job titles based on the main job in their self reported work history. Data of 159 male white workers (all ages) were used to compare the prevalence of respiratory symptoms among different job titles within the study population using minimally exposed workers as an internal reference group. We calculated prevalence ratios (PR) and 95% confidence intervals by log-binomial regression analysis.[9]

A starting value of -4 for the intercept was used to prevent convergence problems.[10] PR were adjusted for age and smoking habits (categorical: never-, ex-, or current smoker).

Analysis of variance was used to compare the personal characteristics and spirometric test results of workers with the general population sample. Self-reported data on job history in the diacetyl plant were used to assess associations among process operators between lung function variables and duration of work in the diacetyl plant.

Two-sided p values of 0.05 or less were considered to represent associations unlikely to be due to chance. For internal comparisons among small subgroups, we examined marginally significant p values of 0.1 or less.

RESULTS

Characteristics of the workers

In 2005, 175 (89 %) workers completed a questionnaire and underwent spirometric lung function tests. The majority (97.6 %) of participants was male. The mean age was 51 and ranged from 25-78 years. There were 27% current smokers and 41 % former smokers, and 33 % had never smoked. Overall, 102 participants had ever worked at the diacetyl plant as a process operator for on average, 10.4 years with a range of 1-29 years.

Reconstruction of the exposure profile

Limited routine exposure monitoring was carried out by company representatives using cartridges containing silica gel coated with dinitrophenylhydrazine (DNPH-cartridges), and each sample was analyzed externally for both diacetyl and acetaldehyde using gas chromatography. Twenty six area samples (mean sampling duration 120 minutes; range 82-219 minutes) and four personal task-based samples (mean 65 minutes; range 33-90 minutes) for the period 1 995-2003, could be traced (Table 1). All area samples had been taken in locations in the plant where operator activities were performed. Control measures taken in 2001 to enclose the process led to a reduced exposure for both diacetyl (geometric mean (GM) change from 10.0 to 5.8 mg/m^3) and acetaldehyde (GM change from 7.6 to 0.7 mg/m^3).
During production, process operators were potentially exposed to diacetyl while quality checking, discharging to buffer vessel, checking process parameters in the plant, charging batch column, discharging into 50 kg and in 2.5 l containers, and cleaning activities. According to the company representatives, discharge of diacetyl into containers had the highest exposure potential, and for this reason, task based samples were available for this specific activity. Although exposure to diacetyl was mainly relevant for process operators, workers with several other occupational titles were also potentially exposed. Maintenance workers were likely to be exposed but exposure was highly variable. Laboratory workers were potentially exposed but no further qualitative or quantitative information was available. 'other jobs' (transport, health and safety, and management and research and development personnel) had low exposure potential for diacetyl and, if they had exposure, it was always for a short time.[5]

Table 1. Environmental area sampling results in the diacetyl production plant by historic period.

	N	AM	GM	GSD	Range
Diacetyl (mg/m^3)*					
All samples	26	27.9	8.1	3.9	1.8-351
Samples 1995 to 2001	16	38.7	10.0	4.5	1.9-351
Samples after 2001	10	10.6	5.8	2.9	1.8-51
Acetaldehyde (mg/m^3)†					
All samples	26	6.2	3.1	3.8	0.4-29
Samples 1995 to 2001	16	9.6	7.6	2.1	1.6-29
Samples after 2001	10	0.9	0.7	1.7	0.4-2.3
Personal task-based sampling results during tapping containers of diacetyl.					
Diacetyl (mg/m^3)*					
All samples	4	122.0	38.4	7.5	3-396
Samples 1995 to 2001	3	152.0	40.8	11.7	3-396
Samples after 2001	1	32	32	-	-
Acetaldehyde (mg/m^3)†					
All samples	4	3.8	0.9	7.4	0.2-14
Samples 1995 to 2001	3	4.8	0.8	11.6	0.2-14
Samples after 2001	1	1.0	1.0	-	-

Definition of abbreviations: N = number of samples; AM = Arithmetic mean; GM = Geometric mean; GSD = Geometric standard deviation; Range = lowest and highest sampling results.

*1 mg/m^3 = 0.21 ppm

†1 mg/m^3 = 0.56 ppm

Questionnaire and spirometry

Compared to the Dutch ECRHS population, diacetyl plant workers reported significantly more continuous trouble with breathing, daily cough, self-reported asthma attacks, physician-diagnosed asthma attacks, and having had an asthma attack in the last year (Table 2).

Compared with a minimally exposed internal reference group, operators (including three workers with BOS) and quality control lab workers reported significantly more ever trouble with breathing, and operators reported also significantly more shortness of breath in the last year.

Exposure incidents (ever) were reported by 74/95 operators (78%), 11/18 technical service workers (61%), 6/11 quality laboratory workers (35%) and 15/28 of the internal reference group (54%). Operators reported significantly more exposure incidents (mostly spills and leakages) compared with the minimally exposed internal reference group (PR = 1.5; 95% CI 1.0 – 2.1). The occurrence of these exposure incidents was borderline significantly ($p = 0.06$) associated with cough symptoms but not with any other respiratory symptom. The association with cough disappeared after adjusting for smoking and age.

Table 2. Prevalence (%) and adjusted Prevalence Ratios (PR) with 95% confidence interval (CI) of respiratory symptoms in diacetyl plant workers and a general Dutch population sample of the European Community Respiratory Health Survey and adjusted PR with 95% CI of jobs compared with an internal reference group ('Other jobs').

	Comparison with external reference population*			Comparison with internal reference population†						
	Diacetyl plant workers	*General population*		*'Óther jobs'*	*Process operator*		*Technical service*		*Quality Control Lab*	
	n = 159	n = 1125		n = 28	n = 95		n = 19		n = 17	
	%	%	PR (95% CI)	%	%	PR (95% CI)	%	PR (95% CI)	%	PR (95% CI)
Trouble with breathing										
Ever	37.1	18.8	2.1 (1.6-2.6)‡	14.3	40.0	2.8 (1.1-7.0)‡	26.3	1.8 (0.6-5.8)	47.1	3.1 (1.1-8.6)‡
Continuously	6.9	2.7	2.6 (1.3-5.1)‡	0.0	9.5	- (-)	5.3	- (-)	5.9	- (-)
Repeatedly	10.7	7.2	1.6 (1.0-2.6)§	0.0	14.7	- (-)	5.3	- (-)	5.9	- (-)
Cough symptoms (last year)										
Cough (work-related)	26.4	NA		25.0	29.5	1.3 (0.5-3.6)	21.1	0.9 (0.2-4.6)	11.8	0.5 (0.1-4.1)
Daily cough	21.4	15.4	1.5 (1.1-2.1)‡	17.9	23.2	1.3 (0.5-3.0)	15.8	0.9 (0.2-3.0)	17.7	1.0 (0.3-3.4)
Daily cough with phlegm	15.7	11.8	1.4 (1.0-2.1)§	7.1	15.8	2.1 (0.5-8.7)	26.3	3.5 (0.8-15.5)	11.8	1.7 (0.3-10.7)
Shortness of breath (SOB) and wheezing (last year)										
SOB (work-related)	20.8	NA		3.6	27.4	7.5 (1.1-52.9)‡	15.8	4.4 (0.5-38.9)	11.8	3.6 (0.4-36.7)
Exercise induced SOB	23.3	19.6	1.2 (0.9-1.7)	17.9	24.2	1.4 (0.6-3.3)	31.6	1.8 (0.7-5.1)	11.8	0.7 (0.2-3.1)
Awakened due to SOB	7.6	6.1	1.3 (0.7-2.3)	0.0	9.5	- (-)	10.5	- (-)	11.8	- (-)
Wheezing	20.8	24.3	0.9 (0.7-1.3)	10.7	22.1	2.0 (0.7-5.8)	26.3	2.0 (0.6-6.8)	11.8	1.3 (0.3-6.6)
Wheezing (work-related)	15.7	NA		3.6	19.0	5.2 (0.7-36.3)§	21.1	5.3 (0.7-42.0)	5.9	1.8 (0.1-25.6)
Wheezing with SOB	13.8	14.8	1.0 (0.7-1.5)	7.1	14.7	2.1 (0.5-8.5)	15.8	2.0 (0.4-10.5)	11.8	1.9 (0.3-11.7)
Awakened due to chest tightness	15.1	12.6	1.2 (0.8-1.8)	14.3	15.8	1.2 (0.4-3.3)	10.5	0.8 (0.2-3.8)	5.9	0.4 (0.0-3.3)
Chest tightness (work-related)	13.2	NA		3.6	15.8	4.9 (0.7-35.7)	15.8	4.8 (0.5-42.2)	17.7	5.0 (0.6-44.0)
Asthma										
Asthma attack (ever)	10.1	5.0	2.0 (1.2-3.4)‡	3.6	11.6	3.3 (0.4-24.6)	10.5	2.8 (0.3-28.8)	5.9	1.6 (0.1-23.5)
Asthma attack, doctor diagnosed	10.7	4.6	2.2 (1.3-3.8)‡	3.6	12.6	3.7 (0.5-27.3)	10.5	2.9 (0.3-29.4)	5.9	1.6 (0.1-23.6)
Asthma attack in the last year	5.0	1.1	4.7 (1.9-11.4)‡	0.0	5.3	- (-)	10.5	- (-)	0.0	- (-)

Definition of abbreviation: NA = Not available.
*Men only, age between 30 and 70.
†All only male Caucasians (n = 159).
‡$p < 0.05$, §$p < 0.10$; adjusted for age and smoking habits (categorical: never-, ex-, or current smoker)
- (-) prohibited to calculate due to nihil subjects in the reference group.

Spirometric test results of 149 Caucasian male diacetyl plant workers showed no significant differences (percentage of the predicted value) compared to a general Dutch population sample after adjusting for smoking habits (Table 3).

Table 3. Personal characteristics and spirometric test results of diacetyl plant workers versus a general Dutch population sample of the European Community Respiratory Health Survey (ECRHS).

	Diacetyl plant workers*	General population†
Age – yr, mean (sd)	51 (7.7)	50 (11.4)
Smoking status (%)		
Current smoker	29	41
Former smoker	42	40
Never smoked	30	19
FEV_1 % pred (sd)	105.4 (18.0)	104.9 (18.1)
FVC % pred (sd)	108.9 (15.9)	108.4 (15.0)
FEV_1/FVC % (sd)	77.5 (7.1)	77.9 (8.6)
‡Reversibility (%)	10 (6.7)	NA
Body Mass Index in kg/m2 (sd)	26.5 (3.9)	25.7 (3.2)

Definition of abbreviations: yr = year; sd = standard deviation; FEV_1 = forced expiratory volume in one second;
FVC = forced vital capacity; FEV_1/FVC = forced expiration ratio; NA= not available.
% pred = percentage of the predicted value.
*n = 149, Caucasian males only, age between 30 and 70.
†n = 1084, Caucasian males only, age between 30 and 70.
‡Reversibility = increase in $FEV_1 \geq 9\%$ predicted.

Exposure-response relationship

There was no clear association between FEV_1 (% predicted) and exposure to diacetyl (Figure 1). Multiple linear regression analysis of pulmonary function variables on exposure in process operators (Table 4) showed a significant increase in actual FEV_1 of 28 ml per year for those working in the diacetyl plant before 1995 (95% CI 3 - 53) and a significant increase in FEV_1 of 2 ml per cumulative weighted number of years in the diacetyl plant (95% CI 0 – 4).

Figure 1.

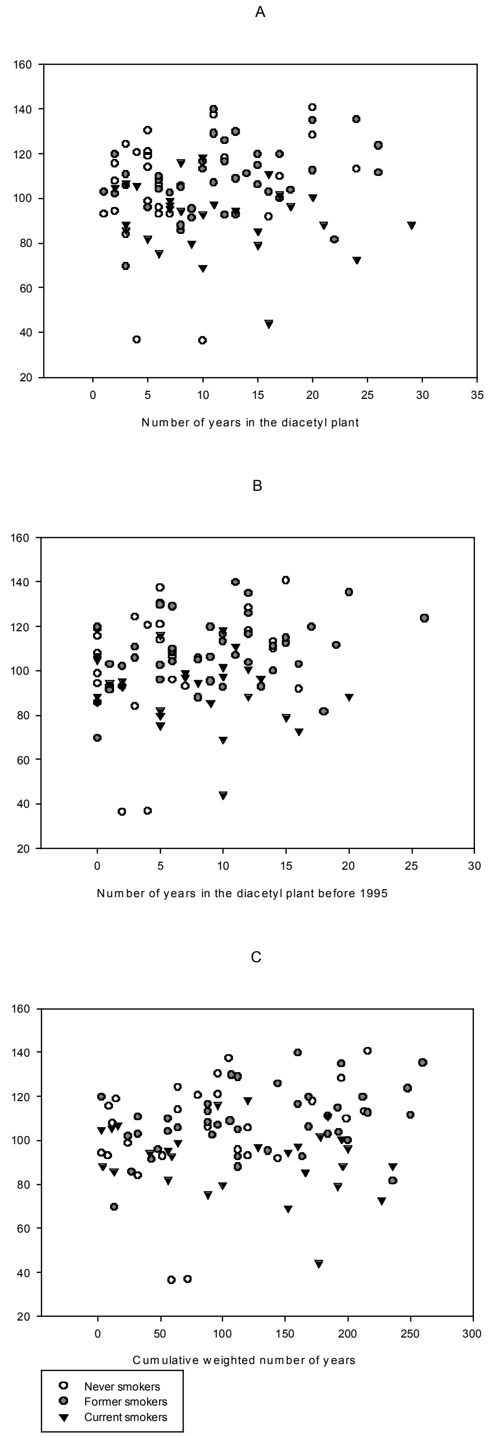

Figure 1. Percent predicted FEV_1 value of process operators (n=95), and: A) the total number of years that process operators had tasks in the diacetyl plant; B) the number of years before 1995 that process operators had tasks in the diacetyl plant (if the number of years is 0, then process operators started after 1995); and C) cumulative weighted number of years that process operators had tasks in the diacetyl plant.

Table 4. Multiple linear regression analysis of pulmonary function variables on exposure in process operators producing diacetyl.*

		FEV_1 (ml)		FVC (ml)		FEV_1/FVC %	
Exposure†	**Range**	**ß**	**SE**	**ß**	**SE**	**ß**	**SE**
Total years	1 - 29	19§	11	14	11	0.150	0.125
Years before 1995	0 - 26	28‡	13	18	14	0.307‡	0.149
Cumulative weighted number of years	3 - 260	2‡	1	1	1	0.019	0.012

*n = 95, only male Caucasians.
Definition of abbreviation: SE = standard error.
†adjusted for age, height, and smoking habits.
‡$p<0.05$; § $p<0.10$.

DISCUSSION

Exposure

During production of diacetyl, process operators were potentially exposed to acetoin, diacetyl, acetaldehyde and acetic acid. Diacetyl levels ranged from 1.8 - 351 mg/m^3 and acetaldehyde levels from 0.4 - 29 mg/m^3. Diacetyl exposure levels could not be evaluated in relation to an occupational standard as no Dutch occupational exposure limit ("MAC value") or international equivalent is available. Average levels of acetaldehyde were low compared to the previous Dutch MAC-value of 180 mg/m^3 and the new Dutch 2007 health standard value of 37 mg/m^3.[11] A detailed comparison could not be made because sampling times were relatively short, and the MAC value is based on an eight hour time weighted average (TWA).

Although exposure data were limited, available data suggest that diacetyl exposure before 2001 in the production plant was as high as in the index microwave popcorn plant where the first cases of BOS were described.[1] In this index plant, mixers had a mean area exposure of 180 mg/m^3 diacetyl, with a range to 467 mg/m^3, as determined by full-shift area sampling.[3]

In the microwave popcorn industry, diacetyl was the predominant chemical among many in air sampling of volatiles and was used as a proxy for flavouring exposure.[3] The spectrum of potential causative agents in this production plant is much smaller than in the index microwave popcorn plant.[3] After several control measures were implemented in the diacetyl plant to enclose the process, diacetyl levels were lower but still in the range found in microwave popcorn plants where cases of BOS were found.[4] This supports the conclusion that the diacetyl concentration in our study was high enough to be potentially associated with cases of BOS.

Respiratory symptoms and spirometry

Workers at the diacetyl production plant reported significantly more respiratory symptoms and self reported asthma compared to the Dutch ECRHS population, and process operators reported significantly more respiratory symptoms compared to an internal reference group.

There were no significant differences in spirometric abnormalities compared to the Dutch ECRHS population.

It seems unlikely that recall of symptoms is greatly different across the specific job titles. However, overestimation of symptoms in workers can not be excluded , and recall bias may have affected comparisons with the general population.

The general population data were obtained using the same procedures and devices, and have the same age range and distribution, but were not restricted to a working subpopulation. As the general population sample also included non-active workers who were not fit enough to be active in the workforce, the differences in respiratory status between exposed workers and the general population are likely to be underestimated.

In addition, data in the general population sample were obtained earlier (1991-1992) and so socioeconomic characteristics may be different. We did not correct for socio-economic status and education level, which were around the average for the Dutch workforce. Theoretically there could be a cohort effect but practically this is expected to be marginal for a period of less than 15 years.

The finding of significantly more respiratory symptoms among workers compared to a general population sample is consistent with the findings at the micro-wave popcorn plant.[1]

Persistence of symptoms despite plant closure that differ among groups is consistent with permanent injury. The marginally significant finding of work-related wheezing in the last year in operators is compatible with asthma, and many have high adjusted prevalence ratios despite low power to detect differences. With asthma as a possible outcome, as shown in a NIOSH health hazard evaluation report of a popcorn plant, one would not necessarily expect pulmonary function abnormalities.[12]

Three robust results support the previous finding that diacetyl is an occupational hazard: 1) the highest exposed group, the process operators, had significantly more respiratory symptoms than other occupational groups, and the plant population as a whole had excess symptoms compared to the general population; 2) a previously published spirometric analysis internal to the cohort showed that process operators had a job title-related decrement in FEV_1 (-292 ml);[5] and 3) all severe BOS cases occurred in process operators. In addition to these robust findings, our analyses confirm (marginally) significant excesses of respiratory symptoms in diacetyl workers (from table 2).

Exposure-response relationships

The number of years that operators had tasks in the diacetyl plant, the numbers of years they had worked there before 1995, and an exposure weighted estimate of years of exposure was positively associated with effects on lung function.

These findings seem inconsistent with the results of the study of Kreiss et al. where the estimated cumulative exposure to diacetyl was correlated with chronic effects on lung function, in terms of both the rate of abnormalities on spirometry and the average decreases in FEV_1 in quartiles of increasing cumulative exposure.[1]

Several explanations may account for our findings and all related to possible misclassification of biologically-relevant exposure, which would obscure exposure-response relationships. First, exposure to diacetyl in this study population changed considerably over time, and it is likely that changes occurred that were not captured by the estimates based on the 30 exposure measurements taken in the 1995-2003 period. Second, time spent in this process also changed over time. Since workers rotated among different plants, the time spent in the diacetyl plant had to be crudely estimated on the basis of questionnaires. Third, the population in the present study was engaged in a range of chemical production processes with different qualitative exposure profiles, and therefore substantial misclassification of exposure might have occurred. Fourth, duration of exposure might not be the most relevant measure of exposure. Our study results document higher risks for BOS, respiratory symptoms and lung function decrements within highly exposed groups of workers but not in relation to exposure estimates which incorporate duration of exposure.

The finding that pulmonary function increased with increasing exposure proxies might be due to a healthy worker effect (HWE) bias. In cross-sectional studies the healthy worker effect is a common type of bias which can obscure exposure-response effects.[13] Although our retrospective survey is less sensitive to a potential HWE survivor bias as it includes inactive and active workers, affected workers may have migrated to lesser exposed jobs over time. This bias is difficult to assess quantitatively because of a lack of exposure data for all jobs involved. We had no data on either symptoms onset times or past exposures which would have allowed a historical cohort design and thus would have corrected for selection bias. Alternatively, no cumulative exposure-response relationship may exist, and peak exposures could play a role. Operators reported significantly more exposure incidents compared to the internal reference group and had (marginally) significantly more respiratory symptoms. However there was no association between symptoms and ever having experienced an exposure incident, which may be a result of recall bias.

Hendrick reported a case of bronchiolitis obliterans in the food industry related to accidental diacetyl exposure,[14] although the presented radiological patterns did not agree with criteria for BOS.[15]

Exposed workers in our study developed BOS following 0-14 years' exposure to diacetyl, an observation which is consistent with findings of Akpinar-Elci et al. who showed that workers first exhibited symptoms between 5 months and 9 years after starting work in the plant.[16] Thus, incident cases occur with a short exposure period or a low cumulative exposure. Such cases might be explained by specific exposure patterns involving short high peaks during spills or specific tasks. Thus far, the possible importance of short-term, peak exposures or host factors which may play a role in the development of BOS related to diacetyl exposure have not been studied.

There was no evidence of confounding, either by smoking status or age. Potentially, there may have been some confounding by exposure to other agents. Most workers have at some point in time been exposed to several other chemicals including irritants such as ammonia and chlorine. Confounding exposures were not considered relevant for the four cases of BOS which we described earlier.[5]

In conclusion, this epidemiological study supports the finding that the production of diacetyl presents a respiratory hazard in the plant where four cases of severe BOS were found and indicates a process associated risk. A cumulative diacetyl exposure–response relationship could not be demonstrated or did not exist. The job title-related risk suggests that further attention should be given to peak exposures and to host factors among the susceptible in high-risk jobs. The research on diacetyl-exposed populations to date suggests that preventive measures should be taken.

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Chapter 4

A CROSS-SECTIONAL STUDY AMONG DETERGENT WORKERS EXPOSED TO LIQUID DETERGENT ENZYMES

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ABSTRACT

Objectives: To investigate sensitisation and respiratory health among workers who produce liquid detergent products and handle liquid detergent enzymes.

Methods: We performed a cross-sectional study among 109 eligible workers of a detergent products plant. 108 were interviewed for respiratory and allergic symptoms and 106 blood samples were taken from them to examine sensitisation to enzymes. Those, sensitised to one or more enzymes were referred for clinical evaluation. Workers and representatives were interviewed to characterise exposure qualitatively and estimate exposure semi-quantitatively. Workers were classified into three exposure groups with varying exposure profiles to enzymes, based on frequency, duration and level of exposure.

Results: Workers were exposed to proteases, α-amylase, lipase and cellulase. The highest exposures occurred in the mixing area. Liquid spills with concentrated enzyme preparations and leakage of enzymes during weighing, transportation and filling were causing workplace contaminations and subsequently leading to both dermal and inhalation exposure for workers. Workers with the highest exposures reported significantly more work-related symptoms of itching nose (prevalence ratio PR = 4.2, 95% CI 1.5-12.0) and sneezing (PR = 4.0, 95% CI 1.5-10.8) and marginally significant more symptoms of wheezing PR = 2.9 (95% CI 0.9-8.7) compared with the least exposed group. Fifteen workers (14.2 %) were sensitised to one or more enzymes. A marginally statistically significant gradient in sensitisation across the exposure categories was found (p=0.09). There was a clinical case of occupational asthma and two other with probable occupational rhinitis.

Conclusions: Workers exposed to liquid detergent enzymes are at risk of developing sensitisation (14 %) and respiratory allergy.

INTRODUCTION

Occupational asthma (OA) in the detergent industry was first reported in 1969 and associated with exposure to dust of proteolytic enzymes.[1 2] Occupational allergies were considered to be under control as a result of encapsulation of enzymes and improved hygiene in the 1970s[3 4] and evidence exists for a reduction of OA risk.[5 6] Despite these measures, sensitisation could not be totally prevented [4] and new outbreaks of OA have been reported due to detergent enzymes exposure.[7 8]

This study was occasioned by the occupational health service of a liquid detergent production plant which, in a pilot study, reported that three out of 12 highly exposed workers were sensitised to detergent protease (Savinase).

As far as we know, no occupational respiratory allergies have been reported in detergent production industries related to liquid detergent enzymes. The novelty of the present study is that it was conducted in a detergent plant producing liquid detergents using only liquid enzymes. The plant never produced powdered detergent products and neither used powdered nor encapsulated enzymes. This study was conducted among all workers in the plant who were potentially exposed to liquid detergent enzymes. The first aim of this study was to investigate sensitisation among workers handling liquid detergent enzymes and secondly the respiratory health among sensitised workers.

MATERIAL AND METHODS

Study design, setting and participants

In March 2006 we conducted a cross-sectional study among 109 eligible workers who were potentially exposed to liquid detergent enzymes in a plant producing liquid detergents. We obtained written, informed consent from 108 (99%) workers who completed the questionnaire. From 106 (97%) blood samples were taken. One worker refused for personal reasons to participate in the study and two other workers who completed the questionnaire refused to provide a blood sample.

Before 1992 the plant produced several liquid based but enzyme-free, detergents and cleaning products such as shampoo, liquid abrasives and washing-up liquid. Liquid enzymes were first introduced around 1992 to improve the cleaning power of the liquid detergents. Granulated enzymes have never been used in this company.

The plant produces only liquid detergents (+ 60.000 metric tons in 2005) and uses proteases, amylases, lipase and cellulases (table 1) (totally 540,883 kg in 2005). The production of detergents includes (a) weighing and transporting ingredients to the tubs including concentrated liquid enzymes; (b) adding the ingredients to the tubs and mixing with water; and (c) filling of bottles. Several meetings were held to inform workers about the goal of the study.

Table 1. Characteristics and amount of enzymes used in liquid detergent production and the number of sensitised workers per enzyme.

	Enzymes	**Bacterial/fungal**	**Kilogram used in 2005**	**Number of sensitised workers**
Proteases:				
a	Alcalase 2.5 L	bacterial	112.595	5
b	Alcalase ultra	bacterial	19.564	5
c	Purafect	bacterial	224.586*	4
d	Savinase	bacterial	10.150	4
e	Everlase	bacterial	*	4
α-Amylases:				
f	Purastar	bacterial	30.802	13
g	Termamyl	bacterial	135.735	13
h	Stainzyme	bacterial	<200	8
Lipase:				
i	Lipex 100 L	fungal	<100	1
Cellulases:				
j	Carezyme	fungal	5.055	4
k	Endolase	fungal	2.096	2

* Total kilogram of Purafect and Everlase

Exposures

Historic exposure data were not available and exposure to enzymes at this point in time could not be measured because appropriate immune assays for these allergens were not available. As a consequence, a semi-quantitative exposure assessment was performed. We observed the workplace and interviewed workers and representatives to characterise current exposure to enzymes qualitatively and estimate exposure semi-quantitatively. We identified all tasks with potential enzyme exposure and scored them by frequency, duration of exposure and enzyme concentration of the handled product. Both inhalation and dermal exposure were considered. Subsequently, we created several groups of workers with various levels of enzyme exposure based on this semi-quantitative exposure assessment, by assigning all tasks to different job categories.

Exposure was assigned blindly to the workers' status of sensitisation. All workers were classified into three groups with, respectively, high, moderate and low exposure to enzymes. The high exposure group handled concentrated enzyme products and was potentially exposed during the entire working day. The moderate exposure group handled diluted enzyme products and exposure was limited to a few tasks during the working day. The low exposure group was only incidentally exposed to enzyme products.

Besides exposure to detergent enzymes some other potentially harmful exposures occurred. Some ingredients have been labelled as irritants (e.g. perfumes and preservatives used in the detergents). Other sensitizers can not be excluded in a few products (especially some preservatives), but compared to the liquid enzymes, the amounts used are low and these substances have been reviewed as potential causes of sensitization in individual clinical cases.

Questionnaire

Participants completed a self-administered standardized questionnaire supplemented with questions about respiratory, mucous membrane, atopic symptoms and work history. The questionnaire was based on items described in the detergent industry [9] and some of the questionnaire items were taken from the European Community Respiratory Health Survey (ECRHS).

Serology

We assessed total serum IgE and specific IgE reactions to a panel of common environmental allergens (house dust mites, cat, and dog, grass and birch pollen).[10] A total IgE of > 100 kU/l and/or at least one positive reaction to common allergens was defined as atopy. For some of the enzymes no validated serology tests were available and therefore two different approaches were taken to assess sensitisation. First, by a low cost "in-house" developed enzyme immunoassay and second, by a customized ImmunoCAP system at the German Social Accident Insurance (BGFA), Institute of the Ruhr University of Bochum in Germany.

For the In-house assay all liquid enzyme solutions, except Carezyme and Endolase, were dia lyzed against PBS using dialysis hoses 8000 MWCO (Spectrapor Cat. No. 132131) Spectrum Laboratories Inc., Rancho Dominguez, USA) to remove low molecular weight additives. The dialyzed supernatants were harvested and stored at -20°C. A microtiterplate- based enzyme-linked immunoassay was applied, using a polyclonal rabbit anti-human IgE/swine anti rabbit-horseradish peroxidase IgE detection system. The optical density was used as readout relative to blank samples where levels more than four times the standard deviation were considered as positive.

ImmunoCAP system

Specific IgE to the enzymes was measured using Streptavidin ImmunoCAPs and fluorescent enzyme immunoassay on a ImmunoCAP 250 system (Phadia, Uppsala, Sweden) as described previously.[11] All enzymes were biotinylated with a five-fold molar excess of D-biotinoyl-ε-aminocaproic acid N-hydroxysuccinimide ester (NHS-Biotin) in 10 mM carbonate buffer (pH 8.5), after estimating protein concentration (Bradford assay, Biorad, München, Germany) and the average molecular weight of each enzyme preparation by SDS-PAGE using pre-casted NuPAGE gels (Novex, San Diego, CA, USA). For a first screening, mixtures of biotinylated enzymes with similar function and protein pattern (each with an OD_{280} of 1.5) were bound to Streptavidin ImmunoCAPs and tested: alpha-amylases (Purastar, Termamyl, Stainzyme), cellulases (Carezyme, Endolase),

Alcalases (Alcalase 2,5 L, Alcalase ultra 2,5L), Subtilisins (Purafect, Savinase, Everlase). Single enzymes were then bound (OD_{280} of 1.5) and tested: with Lipex 100L all sera, with the other enzymes only sera which had been positive in the first screening with the respective mixture were measured.
Streptavidin ImmunoCAPs with alpha-amylases had been incubated in acidic buffer (50 mM citric acid, 50 mM Na_2HPO_4, pH 4.2) for 1 h at 50°C and washed extensively before measurements to abolish unspecific reactions in fluorescent enzyme immunoassay.
Values ≥ 0.35 kU/l were defined positive, indicating sensitisation.
Because a validated test system is not yet available, workers who were positive in the in-house assay or the immunoCAP system were considered sensitised to detergent enzymes.

Clinical evaluation

Workers sensitised to one or more enzymes underwent further clinical investigation including clinical history taking, nasal examination, spirometry and assessment of non-specific bronchial hyperresponsiveness (NSBH) to histamine within 24 hours after exposure after a continuous period of working of at least 2 weeks.
A diagnosis of OA was excluded if there were no indications of asthma in the medical history and a worker showed no NSBH within 24 hours after exposure while working uninterrupted for two weeks.[12 13]
Spirometry was obtained by experienced technicians according to European Respiratory Society standards[14] by using a pneumotachograph with specific software (Pneumotachograph and 4.66 software, Jaeger; Würzburg, Germany). Histamine was administered during a controlled inspiratory capacity breathing dosimeter technique using the Aerosol Provocation System with a Medic-Aid nebulizer (Jaeger; Würzburg, Germany), starting with diluent and followed by doubling doses of histamine from 0.026 mg to a maximum dose of 2.5 mg. The test was stopped when a fall of 20% in FEV_1 was observed (PD20) or the maximum cumulative dose was reached. If necessary, bronchoconstriction was treated with inhalation of salbutamol.[15]
All workers with NSBH when at work performed serial peak expiratory flow rate (SPEFR) measurements during 2 weeks at work and 2 weeks away from work after which histamine challenge with assessment of NSBH was repeated. A change of one doubling dose increase in PD20 was regarded as significant. SPEFR measurements were interpreted using direct visual analysis by a panel of two experienced physicians. A diurnal variation in PEFRs of ≥ 20% was considered as diagnostic criterion.[16] The diagnosis of work-related asthma was based on the American College of Chest Physicians (ACCP) consensus statement.[16]
The medical diagnosis of OA was based on four criteria according to the ACCP: (A) diagnosis of asthma; and (B) onset of asthma after entering the workplace; and (C) association between symptoms of asthma and work; and (D) one or more of the following criteria: (D1) workplace exposure to an agent known to give rise to OA; or (D2) work-related changes in forced expiratory

volume in one second or peak expiratory flow rate, or (D3) work-related changes in bronchial responsiveness.[17] The diagnosis of work-related rhinitis was based on a position paper of the EAACI Task force on Occupational Rhinitis. A suggestive clinical history of occupational rhinitis associated with sensitisation to detergent enzymes was considered as probable occupational rhinitis.[18]

Epidemiological and statistical analysis

All statistical analyses were performed using SAS software (SAS System for Windows version 9.1, SAS Institute, Cary, North Carolina, United States). Questionnaire data for 108 workers and serological data of 106 workers were used to compare the prevalence of respiratory symptoms and sensitisation between different exposure groups within the study population using low exposed workers as an internal reference group. We calculated prevalence ratios (PRs) and 95% confidence intervals by log-binomial regression analysis.[19] A starting value of -4 for the intercept was used to prevent convergence problems.[20] PRs were adjusted for age and smoking habits (pack years). The trend in sensitisation was investigated by logistic regression analysis (PROC LOGISTIC) by entering exposure group (1,2,3) as a continuous variable in the regression model using the Wald Chi-square test. We calculated the phi coefficient as a measure of the degree of association between the outcomes of the two different serology tests. Two-sided p values of 0.05 or less were considered to represent associations unlikely to be due to chance. For internal comparisons among small subgroups, we examined marginally significant p values of 0.1 or less.

RESULTS

Participants

In table 2 the personal characteristics of the detergent workers are given, including the median years of employment and the number of workers in the exposure groups.

Table 2. Characteristics of 108 detergent workers.

Characteristic	Number
Sex	
Male (%)	88(81.5)
Age - yr	
Mean (sd)	40 (7.9)
Range	24 - 60
Smoking status (%)	
Current smoker	54 (50.0)
Former smoker	23 (21.3)
Never smoked	31 (28.7)
Duration of employment (years)	
Median	8.0
Range	1 – 34
Exposure group	
1. Low (%)	54 (50.0)
2. Moderate (%)	37 (34.3)
3. High (%)	17 (15.7)

Exposure assessment

The highest exposure to liquid detergent enzymes occurred in the mixing area. Spills and leakages of enzymes during weighing, transporting and filling of the tubs were sources of potential workplace contamination with high concentrated enzyme preparations, and workers were exposed via skin (splashes) and inhalation (aerosols). In addition, high-pressure cleaning of the floor and machines generated inhalable aerosols likely to contain enzymes.

Changing products on the production lines was the most important activity in the filling area, leading to spills and leakages of product containing enzymes in the workplace. Workers were potentially both directly exposed to the product (skin) and via aerosols (inhalation). Cleaning with high pressure (air) was also a possible source of inhalable aerosols containing diluted enzymes. Respirators were not used both in the mixing and in the filling area and workers often wore short sleeves.

Symptoms and sensitisation

Of 108 workers 5 (5%) reported having constantly problems with breathing, 2 of them (40%) were sensitised to detergent enzymes, 14 (13%) reported wheezing, 5/13 (39%) were sensitised to detergent enzymes, 27 (25%) reported to have an allergy including hay fever, 7 of them (26%) were sensitised to detergent enzymes, 15 (14%) reported work-related symptoms of an itching nose, 4 of them (27%) were sensitised to detergent enzymes, and 17 (16%) reported work-related sneezing, 5 of them (29%) were sensitised to detergent enzymes. Symptoms were significantly more prevalent in the high exposure group than in the low exposure group. Workers in the high exposure group reported significantly more work-related symptoms of an itching nose (PR = 4.2, 95% CI 1.5-12.0) and sneezing (PR = 4.0, 95% CI 1.5-10.8) (Table 3). The PR associated with wheezing was marginally significant at 2.9 (95% CI 0.9-8.7).

Table 3. Prevalence (%) and adjusted prevalence ratios (PRs) with 95% confidence interval (CI) of respiratory symptoms in exposure groups compared with an internal reference group (Low exposed) and sensitisation.

Exposure group	**Low (n = 54)**	**Moderate (n = 37)**		**High (n = 17)**	
	(%)	(%)	PR (95% CI)	(%)	PR (95% CI)
Symptoms					
Trouble with breathing					
Ever	10 (18.5)	8 (21.6)	1.1 (0.5-2.6)	5 (29.4)	1.4 (0.6-3.6)
Repeatedly	4 (7.4)	7 (18.9)	2.5 (0.8-8.1)	3 (17.7)	2.3 (0.6-9.1)
Cough last year	7 (13.0)	3 (8.1)	0.5 (0.1-2.0)	2 (11.8)	0.7 (0.2-2.9)
Shortness of breath (SOB) and wheezing (last year)					
SOB	8 (14.8)	2 (5.4)	0.3 (0.1-1.3)	0 (0.0)	- (-)
Exercise induced SOB	6 (11.1)	3 (8.1)	0.6 (0.1-2.4)	0 (0.0)	- (-)
Wheezing	5 (9.3)	4 (10.8)	1.1 (0.3-3.8)	5 (29.4)	**2.9 (0.9-8.7)#**
Asthma					
Asthma attack last year	3 (5.6)	2 (5.4)	0.7 (0.1-4.5)	0 (0.0)	- (-)
Asthma attack, doctor diagnosed	2 (3.7)	1 (2.7)	0.5 (0.0-6.4)	2 (11.8)	2.9 (0.5-18.1)
Allergies					
Allergy (including, hay fever)	17 (31.5)	6 (16.2)	0.6 (0.3-1.3)	4 (23.5)	0.9 (0.3-2.1)
Doctor visit last year due to allergic symptoms	5 (9.3)	4 (10.8)	1.2 (0.1-9.2)	3 (17.7)	2.3 (0.3-16.3)
Work-related respiratory symptoms (last year)					
SOB	3 (5.6)	1 (2.7)	0.5 (0.0-4.3)	0 (0.0)	- (-)
Chest tightness	1 (1.9)	3 (8.1)	4.3 (0.5-40.6)	1 (5.9)	2.7 (0.2-41.0)
Cough symptoms	5 (9.3)	3 (8.1)	0.8 (0.2-3.3)	2 (11.8)	1.0 (0.2-4.6)
Itching nose	5 (9.3)	4 (10.8)	1.3 (0.4-4.5)	6 (35.3)	**4.2 (1.5-12.0)***
Sneezing	6 (11.1)	4 (10.8)	1.1 (0.3-3.6)	7 (41.2)	**4.0 (1.5-10.8)***
Serology					
Sensitised to ≥ 1 common allergen/total IgE > 100 kU/l	20 (37.0)	12 (32.4)	0.9 (0.5-1.7)	6 (40.0)†	1.0 (0.5-2.1)
Sensitised to detergent enzymes (%)	5 (9.3)	6 (16.2)	1.5 (0.5-4.9)	4 (26.7)†	**2.8 (0.9-9.0)#**
Sensitised to detergent enzymes (%) highest exposure ever	3 (6.7)	7(17.5)	2.4 (0.6-10.3)	5(23.8)†	**3.8 (1.0-14.1)***

CI = confidence interval.
*Significant $p<0.05$, #Significant $p<0.10$ adjusted for age and smoking habits (pack years).
- (-) prohibited to calculate due to nihil subjects in group.
†n = 15, two participants refused serology testing.

Of 106 workers, 15 (14%) were sensitised to one or more enzymes, mainly to bacterial α-amylases and proteases (Table 1). The agreement between the two different assay methods was very good (phi coefficient = 0.83). Thirty-eight workers (36%) were atopic. None of the sensitised workers had previously worked in another (related) industry with exposure to enzymes. Of workers who were sensitised, 11 (73%) were atopic and 8 (53.3%) were current smokers. The median of years of employment was 8.0 years (range 1-20) which was not associated with sensitisation (PR = 0.96, 95% CI 0.89-1.04). Atopics were 4.9 times more likely to be sensitised to detergent enzymes than non-atopics (PR = 4.92, 95% CI 1.68-14.39). Sensitisation was not associated with smoking (PR = 0.99, 95% CI 0.95-1.03).

A linear trend test showed a marginally significant ($p = 0.09$) gradient in sensitisation across the exposure categories (Table 3).

Workers in the high exposure group were 2.8 times (marginally significant, $p = 0.08$) more likely to be sensitised to detergent enzymes than workers in the low exposure group (Table 3).

Five workers reported to have changed their employment within the plant from the high to the low exposure group and four workers from the moderate moved to the low exposure group. Of these nine workers, two workers reported to have changed job during their employment at this plant as a result of work-related symptoms. One of them was case 5 (Table 4) and the other was not sensitised.

An additional analysis was conducted with workers classified according to the highest exposure group they had ever worked in. Workers in the high exposure group were 3.8 times (significant, $p<0.05$) more likely sensitised to detergent enzymes than workers in the low exposure group (Table 3).

Table 4. Characteristics of workers sensitised to one or more detergent enzymes.

Case number	Sex	Job Category	Smoking	Common allergens	Total IgE (kU/l)	Enzyme sensitisation				Work-related respiratory symptoms		NSBH PD20mg		Clinical diagnosis
						protease	α-amylase	lipase	cellulase	lungs	nose	During work	Away from work	
1	M	1	0	H	126		g			-	-	NA	NA	
2	M	1	2	H,G,B	359		f,g			-	-	> 2.6		
3	M	1	0	-	116		f,g,h			-	-	> 2.6		
4	M	1	1	-	81				j	-	+	> 2.6		Non-specific symptoms
5	M	1	2	G	80	a,b	f,g,h			-	-	1.14	0.46	Asthma
6	F	2	2	-	160		f			-	-	> 2.6		Asthma
7	M	2	1	-	33	c,d,e	f,g,h			-	-	> 2.6		
8	M	2	2	-	68		f,g			-	-	> 2.6		
9	F	2	2	-	511	a,b,c,d,e	f,g,h			+	+	NA	1.81	NA
10	F	2	0	G	191		f,g.			-	-	1.30	0.82	Work exacerbated rhinitis
11	M	2	2	G	142		f,g,h			-	-	1.16	1.34	COPD
12	M	3	0	H,G	444	a,b,c,d,e	f,g,h	i	j,k	+	-	0.18	0.64	Occupational asthma
13	M	3	0	H	111	a,b	f,g,h		j	+	+	> 2.6		Probable occupational rhinitis
14	M	3	2	-	35		f,g			-	+	1.14	1.06	Probable occupational rhinitis
15	M	3	2	H,G	552	a,b,c,d,e	f,g,h		j,k	-	+	contra indicated		Asthma/COPD

Abbreviations: F = female, M = male; + = present, - = not present; a,b,c,d,e,f,g,h,i,j, refer to enzymes in table 1 and NA = not available; PD20, provocative dose of histamine producing a 20% fall in forced expiratory volume in 1 s.
Job category: 1 = low, 2 = moderate, 3 = high exposure.
Smoking: 0 = never, 1 = ex-, 2 = current smoker.
Common allergens: sensitised to: H = House dust mite, G = Grass mix, B = Birch, - = not sensitised to common allergens.

Clinical investigation

Fifteen sensitized workers underwent further clinical investigations (table 4). All cases except case 15 had lung function values within normal range. NSBH was assessed in 12 cases of whom five (42%) showed NSBH while at work (Table 4). In case 1 it was impossible to assess NSBH for technical reasons, case 9 was on sickleave and in case 15 FEV_1 was too low (≤ pred - 3 SD). Six out of 15 cases (40%) had work-related respiratory symptoms. Four cases of asthma were found of whom one was work-related. Case 5 was treated for asthma and had no work-related symptoms. Case 12 met the criteria for OA. Case 15 was a smoker with inadequately treated asthma and persistent airway obstruction. He was strongly suspected of having occupational rhinitis and OA but did not finish the diagnostic work-up, so an occupational allergy could not be confirmed. Three cases were diagnosed as rhinitis and two of them as work-related. Case 10 had pre-existing allergic rhinitis (hay fever) and although sensitised to workplace agents only experienced work-related symptoms when also having seasonal symptoms. Case 13 and 14 had probable occupational rhinitis. Case 13 had childhood asthma, and pre-existing allergic rhinitis. Although he was sensitised to detergent enzymes, he claimed that parmatol and/or acticide (containing ethylisothiazolinone) was the cause of his work-related upper airway symptoms.

Thus, at least three cases (12,13,14) out of 106 were diagnosed as having an (probable) occupational allergy.

DISCUSSION

This study shows that working in the liquid detergent production industry is associated with sensitisation to liquid detergent enzymes and likely with occupational respiratory allergies. The prevalence of sensitisation was 14.2% and at least three cases of (probable) occupational airway allergy were clinically confirmed. Workers were exposed to liquid detergent enzymes and specific tasks could be identified during which exposure was relatively high. All exposed workers were at risk for sensitisation but there appeared to be a trend toward a relatively increased number of sensitised workers with higher exposures. In addition high, exposed workers had significantly more upper airway symptoms and marginally significant lower airway symptoms compared with low exposed workers.

Study limitations

The study population was small, and this limited statistical power in internal comparisons, especially after adjusting for confounding variables in multiple regression modeling.

Two women were classified as low exposed, 18 as moderate and none as high, limiting the possibility to adjust for gender. However, patterns were similar in the whole population as in men only.

The in-house assay made use of the liquid enzyme solutions from the detergent industry. These were utilized without purification of the products used. Therefore, theoretically sensitisation to possible contaminants can not be excluded.

Information was collected in a standard manner and exposure was assigned blind to the serology test results. As a result, misclassification will likely to be non-differential and exposure-response relationships might have been underestimated.

The healthy worker effect is a potential source of bias in cross-sectional studies when restricted to actively employed workers. Leaving employment or job transfer to lower exposure as a result of disease may have led to underestimation of the effects of exposure.[21 22] According to the additional analysis job transfer may have led to an underestimation of exposure-response relationships, although only two workers reported to have changed job during their employment at this plant as a result of work-related symptoms.

There was no evidence of confounding, either by smoking status or age.

Symptoms and sensitisation

Workers in the highest exposure group reported (marginally) significant more respiratory symptoms. The excess of symptoms in the high exposure group could not be explained by allergic reactions to enzymes only as we identified only three workers with clinically confirmed airway allergy. False negative serology test results may be an explanation. Irritant effects of detergent enzymes or exposure to other allergens or irritants may have induced symptoms as well. However, respiratory symptoms and allergy may develop through separate pathways as suggested by Skjold at al. in their prospective cohort study among baker apprentices. They showed that the occurrence of new airway symptoms was not always paralleled by sensitisation to occupational allergens.[23]

In the present study the prevalence of sensitisation was 14% according to results of two different serology tests. When only one serology test had been used to estimate sensitisation, the prevalences would be 13 % for the "in-house assay" and 11% for the ImmunoCAP system, respectively. Workers were most often sensitised to bacterial α-amylase probably due to the higher turnover for this bulk chemical. Cross-reactivity between some detergent enzymes may be possible, but earlier experiences indicate that enzymes have distinctly different epitopes.[24]

In the detergent industry a prevalence between 6.7 and 11.6 % has been reported using a skin prick test method for Alcalase, Termamyl and Subtilisin B at a liquid detergent manufacturing site. These workers were also exposed to granulated detergents.[25] The novelty of our study is that workers were exposed to liquid detergent enzymes only and never had been exposed to granulate detergents, indicating the occupational risk of exposure to liquid detergent enzymes for sensitisation.

Sensitised workers were found in every exposure group but a trend toward a relatively increased number of sensitisation with higher exposures is suggestive for an exposure-response effect. It is not clear when workers became sensitised as both data about the introduction of specific enzymes and exposure periods are lacking.

Atopy was significantly associated with sensitisation to enzymes and this is consistent with some but not all earlier findings.[6 26]

Clinical investigation

A minority of sensitised workers showed NSBH while at work. A diagnosis of OA was excluded if there were no indications of asthma in the medical history and a worker showed no NSBH within 24 hours after exposure while working uninterrupted for two weeks.[12 13]

According to Fishwick et al,[27] a normal result from a test of NSBH is not sufficiently useful to exclude OA and as a result cases of OA will be missed. This is in contrast with Tarlo et al., who considered a methacholine challenge within 24 hours after exposure as useful, having a high predictive value in excluding OA.[12 28]

Two cases of occupational allergy were clinically confirmed. The prevalence of occupational allergies is likely to be underestimated because in two sensitised workers with work-related symptoms the diagnostic work up could not be completed.

One of these had asthma with a strong suspicion of an occupational allergy. He and the two workers who refused serology testing belonged to the high exposure group.

Prevention

The current production process was not designed to avoid contact with enzymes. Workers were not aware of the risk of exposure to liquid enzymes, so there was no trigger to avoid exposure at any level of the organisation within the plant. For example high-pressure cleaning generated inhalable aerosols likely to contain enzymes and could have played a crucial role in becoming sensitised. This lack of exposure and risk awareness resulted in workers' exposure to liquid detergent enzymes and sensitisation to liquid detergent enzymes. Sensitisation is an essential step towards allergy and should be avoided.[29] Most important problem-solving directions are to implement technical control measures to prevent the regular spills and leakages by enclosure and automation of the weighing, transporting and mixing process and enclosure of machineries during product changes. In addition, education and creation of awareness among workers about the health risks of exposure to enzymes and working in a more hygienic way should be initiated. Using high pressure for cleaning activities should definitely be banned, first of all by preventing process leakages and the subsequent cleaning activities. A health surveillance program should especially be implemented when a 'no observed adverse effect level' for detergent enzymes cannot be identified. The approach in this study can be seen as the first round of surveillance and is an example of a population based approach leading to diagnosis in individuals.[30]

In conclusion, exposure to liquid detergent enzymes should be regarded as an occupational hazard leading to sensitisation and occupational allergy. To prevent sensitization and airway allergies as a result of exposure to liquid detergent enzymes, exposure should be minimised and health surveillance should be offered to exposed workers. Development of non-commercial validated immunoassays for specific enzyme allergens in the liquid enzyme industry is warranted for screening and monitoring purposes.

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Chapter 5

A CROSS-SECTIONAL STUDY OF EXPOSURES, LUNG FUNCTION AND RESPIRATORY SYMPTOMS AMONG ALUMINIUM CAST-HOUSE WORKERS

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ABSTRACT

Objectives: To investigate exposures, respiratory symptoms, lung function and exposure–response relationships among aluminium cast-house workers.
Methods: We performed a cross-sectional study among 182 aluminium cast-house workers. Exposure data was used to model exposure to irritants. Lung function and questionnaire data on respiratory symptoms were compared to a general population sample and an internal reference group. Blood samples were taken from 156 workers to examine total IgE, eosinophils and sensitisation to common allergens.
Results: The average daily mean exposures to inhalable dust, metals, hydrogen fluoride, fluor salts and sulphur dioxide were relatively low compared to reference values. Airflow patterns in the plant were disturbed regularly and resulted in spreading of pot emissions with high concentrations of fluorides around the workplace. Occasionally peak exposures to chlorine gas occurred due to production process disturbances. Workers reported significantly more respiratory symptoms (continuous trouble with breathing (prevalence ratio (PR) = 2.5; 95% CI 1.2 to 5.3), repeatedly trouble with breathing (PR = 1.8; 95% CI 1.1 to 3.0), wheezing (PR = 1.4; 95% CI 1.1 to 1.8), asthma attack (ever) (PR = 2.8; 95% CI 1.7 to 4.6), doctor diagnosed asthma (PR = 2.6; 95% CI 1.5 to 4.4), and showed in regression analysis significantly lower FEV_1 values (-195 ml) and FVC values (-142 ml) compared to a general population sample. Workers in the highest exposed group reported significantly more eye symptoms during their work compared to a minimally irritant exposed internal reference group, (PR = 5.5; 95% CI 1.2 to 24.9). The moderately exposed group reported significantly more chest tightness upon waking up (PR = 3.0; 95% CI 1.1 to 8.2). Lung function did not differ between groups.
Conclusion: This epidemiological study indicates that there is a respiratory hazard for cast-house workers in the aluminium industry. Exposure-response relationships could not be demonstrated but this study supports the prudence of taking preventive measures in the work-environment with a focus on (peak)exposures to irritants.

INTRODUCTION

Respiratory health effects and diseases are well known in the aluminium industry.[1-5]
Exposure to irritants in the aluminium industry is associated with respiratory symptoms and asthma.[6-10] Associations between respiratory symptoms and exposure to particulates and gaseous fluorides have been reported in potroom workers,[11] and between respiratory symptoms and total fluorides and inhalable dusts in aluminium smelters.[12] Bronchial responsiveness in aluminium potroom workers reporting work-related asthmatic symptoms was found to be related to fluoride plasma levels, but the mechanism has yet to be elucidated.[2]
Respiratory symptoms among aluminium smelter workers are not only reported by potroom workers but are reported by ingot mill and anode workers as well.[13] Until now, working as an aluminium cast-house worker was not associated with adverse respiratory health effects. Presently, only a few cross-sectional studies among cast-house workers have been published.[14-16]
Field found that the prevalence of asthma-like symptoms in potroom workers in the aluminium industry ranged from 20-57% and found a similar range in aluminium casting workers.[14]
Godderis et al. found among 30 workers from an aluminium casting plant no significant differences in any of the categories of the respiratory questionnaire and in spirometry results between cast house personnel and referents.[15]
Despite modernization of an aluminium production factory in Bosnia and Herzegovina aimed to reduce the amount of harmful substances at work, high concentration of chlorine in the cast-house remained the biggest problem.[16]
We performed a study among aluminium cast-house workers with respiratory symptoms and for whom currently implemented hygienic measures did not decrease respiratory complaints.
The aim of our study was to assess (peak)exposures, the prevalence of respiratory symptoms, and lung function among aluminium cast-house workers in an aluminium producing plant in the Netherlands.

METHODS

Study design, participants and setting

In the summer of 2008, we conducted a cross-sectional study among 182 aluminium cast-house workers who were eligible if they were potentially exposed to airway irritants in an aluminium producing plant in the Netherlands. We obtained written, informed consent from 157 (86%) of the workers. 151 (96%) completed the questionnaire, 155 (99%) underwent spirometric lung function tests and blood samples were taken from 156 (99%). 25 (14%) did not participate in the study and only few of them gave a reason for not participating, like suffering from a chronic illness or leaving the plant for another job.

We used data from the Dutch contribution to the European Community Respiratory Health Survey (ECRHS)[17], a general population sample, to compare symptom prevalence between the two groups. We used data from males aged between 30 and 65 (n = 144 aluminium cast-house workers and n = 1000 subjects from the EHRCS population). For analysis of lung function data, we only used data from Caucasian males aged 30–65 (n = 138 aluminium cast-house workers and n = 972 subjects from the EHRCS population). We excluded females and non-Caucasian workers from the study population as there were too few of them in the aluminium cast-house workers population.

Production process

Alumina (aluminium oxide) arrives in the plant and is transported into furnaces which are filled with liquid electrolyte (a salt containing fluorine). Aluminium production is based on the electrolysis process. Alumina is dissolved at 960 °C and subsequently 140,000 A of current are sent through the solution. In this process, aluminium oxide is reduced to the pure metal. The aluminium sinks to the bottom of the furnace, where it is taken out and transported to the foundry/cast house in transport ladles. Aluminium is cleaned and mixed with other materials to obtain the right quality and properties to meet the customers' requirements. The aluminium is then cast in the form of rolling ingots or extrusion billets in vertical casting machines. The plant produces 160,000 tonnes of aluminium annually (110,000 tonnes of new aluminium and another 50,000 tonnes through remelting and recycling).

Exposure assessment

Personal full-shift inhalable dust samples were collected in the worker's breathing zone using PAS-6 sampling heads and mixed cellulose ester filters at a flow rate of 2 l/min. One personal sample and two area sedimentation samples were analyzed for several metals using Inductively Coupled Plasma (ICP) analysis.

Workers' exposure to fluorides was assessed by short-term (18-55 min) and full-shift (6-8 hours) personal and area sampling of gaseous and particulate fluorides, using standardised method MDHS 35/2.[18] Particulate and gaseous fluorides were captured and analysed separately using disposable three-piece plastic filter cassettes. In addition, during two working days, all eligible cast-house workers and 13 controls were asked to provide a urine sample before and after each shift in a collection cup pre-treated with 0.2 gram EDTA. In total 55 samples were collected and analyzed according to NIOSH Method 8308 with results expressed as milligrams fluoride per gram of creatinine.[19] To assess exposure emissions within the cast-house area, real-time Hydrogen fluoride (HF) concentrations were measured with Tunable diode laser (TDL) technology, using a commercially available TDL-based instrument (GasFinder; Boreal Laser, Spruce Grove, AB, Canada). Sulphur dioxide (SO_2) and chlorine (Cl_2) were measured during walk-through sessions on several days using a commercially available real-time instrument with substance-specific toxic sensors (QRAE+; RAE Systems BeNeLux BV, Capelle a/d IJssel, The Netherlands).
Based on the current job title, the relative distance to emission sources of respiratory irritants, and the expected duration of presence of each job title in the cast-house area during a day, all workers were divided into three exposure groups with increasing (expected) exposure to respiratory irritants.

Questionnaire
Participants completed a self-administered standardized questionnaire supplemented with questions about respiratory, mucous membrane, and atopic symptoms, smoking habits and work history. Some of the questionnaire items were taken from the European Community Respiratory Health Survey (ECRHS).

Spirometry
Spirometry was performed by experienced technicians according to European Respiratory Society standards by using a pneumotachograph with specific software (Pneumotachograph and 4.66 software, Jaeger; Würzburg, Germany).[20] Age- and standing height-adjusted spirometric reference values of the European Community for Steel and Coal were used.[20]
Non-specific bronchial hyperresponsiveness (BHR) was assessed by metacholinebromide challenge. Metacholinebromide was administered during a controlled inspiratory capacity breathing dosimeter technique using the Aerosol Provocation System with a Medic-Aid nebulizer (Jaeger; Würzburg, Germany), starting with a diluent and followed by doubling doses of metacholinebromide from 0.12 mg to a maximum dose of 1.87 mg. The test was stopped when a fall of 20% in FEV_1 was observed (PD20) or the maximum cumulative dose was reached. If necessary, bronchoconstriction was treated with inhalation of salbutamol.[21]
We defined airway obstruction as a FEV_1 < 80% of predicted FEV_1 and a FEV_1 to FVC ratio < 70%.

Serology and eosinophil count

Blood samples were cooled and transported to a nearby hospital laboratory for analyses. The concentration of eosinophils was measured with Cell-Dyn Sapphire, Abbott. An increased concentration of eosinophils was defined as $\geq 0.4 \times 10^9$/l. We assessed total serum IgE and specific IgE reactions to a panel of common environmental allergens (house dust mites, cat, and dog, grass and birch pollen).[22] Workers with a total IgE of > 100 kU/l and/or at least one positive reaction to common allergens were defined as atopic.

Epidemiological and statistical analysis

All statistical analyses were performed using SAS software (SAS System for Windows version 9.1, SAS Institute, Cary, NC). Data for 144 male workers aged between 30 and 65 years were used to compare the prevalence of respiratory symptoms among workers with the general population sample. Data for 138 Caucasian male workers aged between 30 and 65 years were used to compare spirometric test results among workers with the general population sample. Multiple linear regression analysis was used to compare personal characteristics and spirometric test results of workers with the general population sample, adjusting for age and height. Spirometric test results were also investigated by multiple linear regression analysis (PROC REG), adjusting for age, height, and smoking habits (categorical: never-, former- or current smoker).
Workers were assigned to different exposure groups based on their current job in their self-reported work history. Respiratory symptoms and spirometric test results of Caucasian male workers (all ages, n = 140 and 139, respectively) were compared between different exposure groups within the study population using minimally irritant exposed workers as an internal reference group. Spirometric test results in different exposure groups were also investigated by multiple linear regression analysis (PROC REG), adjusting for age, height, and smoking habits. For all questionnaire items, we calculated prevalence ratios (PR) and 95% confidence intervals (CI) by log binomial regression analysis.[23] A starting value of -4 for the intercept was used to prevent convergence problems.[24] PR were adjusted for age and smoking habits. Two-sided p values of 0.05 or less were considered to represent associations unlikely to be due to chance.

RESULTS

Participants

In table 1 the personal characteristics of the aluminium cast-house workers are given, including the number of workers in the exposure groups, the median years of employment, and the spirometry and blood test results.

Table 1. Characteristics of aluminium cast-house workers.*

n	151
Male (%)	150 (99.3)
Caucasian (%)	141 (93.4)
Age - yr	
Median (sd)	45 (9.0)
Range	24 - 63
Smoking status (%)	
Current smoker	76 (50.3)
Former smoker	42 (27.8)
Never smoked	33 (21.9)
Exposure to irritants (%)	
High	45 (29.8)
Moderate	51 (33.8)
Low	55 (36.4)
Duration of employment in years† (sd)	16.7 (10.6)
Range	0 - 40
Spirometry‡	
FEV_1 % pred (sd)	103.1 (14.4)
FVC % pred (sd)	108.7 (13.8)
PEF % pred (sd)	115.2 (20.3)
FEV_1/FVC % (sd)	77.2 (6.9)
BHR§ (%)	17 (11.4)
Blood test	
Atopy ¦ (%)	50 (32.1)
Total IgE > 100 kU/l	18 (11.5)
Sensitised to ≥ 1 common allergen	15 (9.6)
Tot. IgE > 100 kU/l & ≥ 1 common allergen	17 (10.9)
Eosinophils** ≥ 0.4 x 109/l (%)	18 (12.0)

*(n = 151), †(n = 148), ‡(n = 155), §(n = 149), ¦(n = 156), **(n = 150).

Exposure assessment

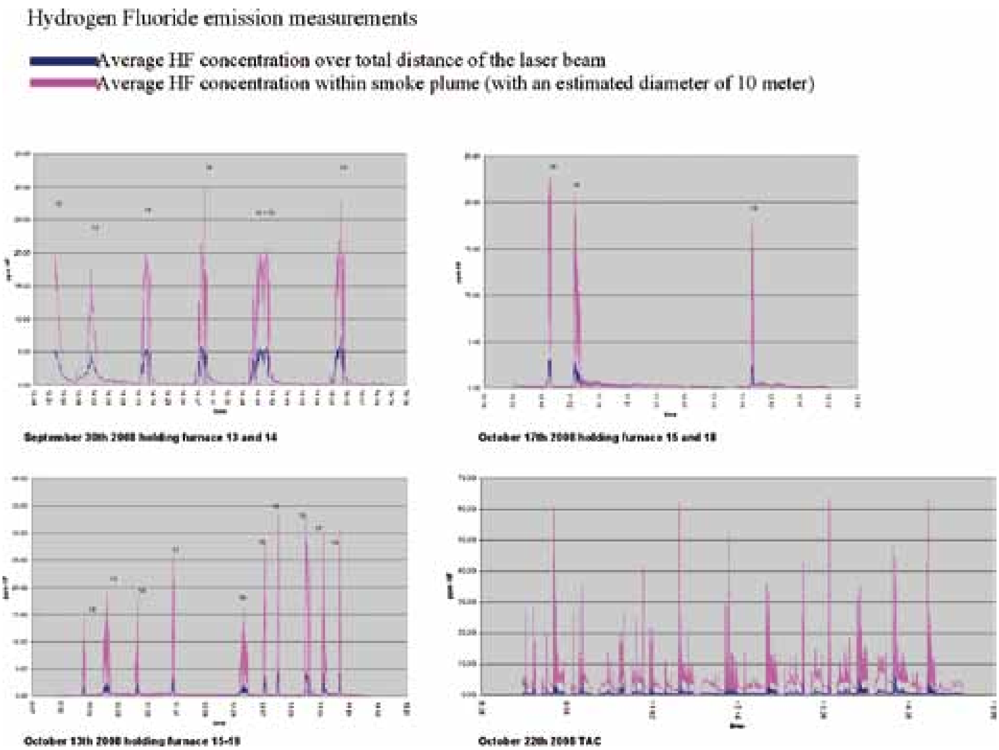
In total 88 personal inhalable dust samples were taken (GM=0.76 mg/m^3; GSD=2.35; range 0.05-5.79 mg/m^3). All samples were below the occupational exposure limit (OEL) for inhalable dust (10 mg/m^3), with an overall probability of exceeding the OEL of 0.1%.

Metal analyses in personal and sedimentation dust revealed that the main metals in the dust were aluminium (47-90%), iron (15-18%), magnesium (2-14%), and sodium (1-15%). In addition, small amounts (0.1-3%) of other metals were found (borium, chromium, copper, manganese, selenium, and titanium). No detectable levels of beryllium were found.

Full-shift personal fluoride exposure of workers (N=6) showed detectable but relatively low fluoride exposure levels (range of total fluoride exposure, 0.021-0.261 mg/m^3), in which the hydrogen fluoride accounted for 53-63% of the total fluoride exposure (gaseous and particulate). The full-shift fluoride area samples (N=6) were well below the Dutch 8-hr OELs (1.5 mg/m3 for HF, and 2.5 mg/m^3 for inorganic fluorides), except for one sample taken high (approx. 8 meters above ground level) in the cast-house area, directly above one of the melting/mixing furnaces. All short-term fluoride area samples (N=17) were below the detection limit. The low average fluoride concentrations were confirmed by the urine samples (N=55), with urine concentrations up to a maximum of 1.81 mg fluoride/g creatinine. Post-shift fluoride urine values were slightly elevated for most workers compared with the pre-shift values, but all values were well below the American Conference of Governmental Industrial Hygienists -Biological Exposure Indices (ACGIH-BEI) or German Biologische Arbeitsplatztoleranzwerte (BAT) values for urinary fluorides. HF emissions, measured with the real-time TDL-based instrument, are shown in figure 1. Each time a transport ladle was emptied into the melting/mixing furnaces, high levels of HF could be measured in the smoke plume above the furnaces which were much higher than the Short-Term Exposure Limit (STEL) for HF of 1.5 ppm, and occasionally up to 60 ppm. Similar peak emissions occurred every few minutes within the cast-house area. The amount of smoke generated during this activity was highly varied, but the height of the HF peak did not vary much and seemed to be independent of (visible) smoke generation.

Real-time walk-through monitoring sessions showed no detectable levels of sulphur dioxide within the cast-house area. Chlorine concentrations were low during most walk-through monitoring sessions, but did rise to 8.8-11.8 mg/m^3 (3-4 ppm) on several occasions when workers were taking test samples out of the induction oven (a daily activity taking only a few minutes). On one occasion a chlorine peak of 88.5 mg/m^3 (30 ppm) was measured which appeared to be due to a leakage in one of the chlorine ducts, and during this sampling session workers reported that similar leakages occurred on a regular basis.

Figure 1 HF measurements over time showing peak exposures during furnace filling and sodium cleaner (TAC). (averaging time of the sampler 2 seconds)



Questionnaire and spirometry

Compared with the Dutch ECRHS population, cast-house workers reported significantly more continuous and repeated trouble with breathing, exercise-induced shortness of breath, wheezing, self-reported asthma attacks, and physician diagnosed asthma attacks (table 2).

Spirometric test results of 138 Caucasian male aluminium cast-house workers showed significant differences in FEV_1 and FEV_1/FVC values (percentage of the predicted value) compared to a general Dutch population sample after adjusting for smoking habits (table 3).

Regression analyses showed that aluminium cast-house workers had significantly lower FEV_1 values (-195 ml) and FVC values (-142 ml) compared to a general Dutch population sample after adjusting for age, standing height and smoking habits (table 4). Regression coefficients for age and standing height were comparable to those from reference regression equations from the European Respiratory Society. Current and former smokers generally had lower lung function compared with non-smokers.

Table 2. Adjusted Prevalence Ratios (PR) with 95% confidence interval (CI) of respiratory symptoms in cast house workers and a general Dutch population sample of the European Community Respiratory Health Survey.

	Comparison with external reference population		
	Aluminium cast-house workers* (n = 144)	General population* (n = 1000)	
	n (%)	%	PR (95% CI)
Trouble with breathing			
Ever	53 (36.8)	18.9	1.9 (1.5-2.5)‡
Continuously	9 (6.3)	2.7	2.5 (1.2-5.3)‡
Repeatedly	18 (12.5)	6.9	1.8 (1.1-3.0)‡
Cough symptoms			
Daily cough	22/55 (40)	14.7	
Daily cough with phlegm	18/51 (35.3)	11.2	
Shortness of breath (SOB) and wheezing			
Exercise-induced SOB	46 (31.9)	19.4	1.7 (1.3-2.3)‡
Awakened due to SOB	11 (7.6)	6.1	1.4 (0.7-2.6)
Wheezing	47 (32.6)	24.1	1.4 (1.1-1.8)‡
Wheezing with SOB	37 (25.7)	14.6	1.8 (1.3-2.5)‡
Awakened due to chest tightness	20 (13.9)	12.4	1.2 (0.8-1.8)
Asthma			
Asthma attack (ever)	20 (13.9)	5.2	2.8 (1.7-4.6)‡
Asthma attack, doctor diagnosed	17 (11.8)	4.8	2.6 (1.5-4.4)‡

*Males only, age between 30 and 65.
‡$p < 0.05$; adjusted for age and smoking habits (categorical: never-, ex-, or current smoker)

Table 3. Personal characteristics and spirometric test results of aluminium cast-house workers versus a general Dutch population sample of the European Community Respiratory Health Survey (ECRHS).

	Aluminium cast-house workers* (n = 138)	General population* (n = 972)
Age – yr, mean (sd)	47 (8.1)	48 (10.2)
Smoking status (%)		
Current smoker	48	42
Former smoker	30	38
Never smoked	22	20
FEV_1 % pred (sd)	102.8 (14.2)†	106.0 (17.2)
FVC % pred (sd)	108.6 (13.5)	109.2 (14.4)
PEF % pred (sd)	115.9 (20.8)	115.6 (21.9)
FEV_1/FVC % (sd)	76.8 (7.0)†	78.5 (8.3)
‡Airway obstruction	6 (4.3)	51 (5.2)

Definition of abbreviations: yr = year; sd = standard deviation; FEV_1 = forced expiratory volume in one second;
FVC = forced vital capacity; PEF = peak expiratory flow; FEV_1/FVC = forced expiration ratio.
% pred = percentage of the predicted value.
*Caucasian males only, age between 30 and 65.
†$p<0.05$; adjusted for smoking habits.
‡Airway obstruction (FEV_1/FVC < 70% and FEV_1 < 80% pred).

Table 4. Multiple linear regression analysis of pulmonary function variables on age, standing height, smoking in a population of cast-house workers.*

Determinant	FEV_1 (ml)		FVC (ml)		PEF (ml/s)		FEV_1/FVC %	
	β	SE	β	SE	β	SE	β	SE
Intercept	-3329	498	-6223	535	-2849	1578	111	6
Age	-38†	2	-33†	2	-64†	6	-0.26†	0.03
Height	5204†	262	7290†	281	9263†	830	-11†	3
Smoking status (%)§								
Current smoker	-236†	48	-124†	51	-424†	151	-2.66†	0.62
Former smoker	-31	50	-42	53	209	158	0.12	0.65
Cast house Workers¦	-195†	56	-142†	60	-155	178	-1.26‡	0.73
Adjusted R^2 (%)	51		54		24		11	

Definition of abbreviation: SE = standard error.
*n = 138, Caucasian males only, age between 30 and 65.
†$p<0.05$; ‡$p<0.10$.
§Never smoked as reference group.
¦ General population as reference group, n = 972, Caucasian males only, age between 30 and 65.

Exposure-response relationship

Workers in the high exposure group reported significantly more eye symptoms during their work (PR = 5.5, 95% CI 1.2-24.9) and workers in the moderate exposure group reported significantly more symptoms of chest tightness upon awaking (PR = 3.0, 95% CI 1.1-8.2), compared to an internal reference group. Further, there were no significant differences in self-reported respiratory symptoms among exposure groups. There also were no significant differences among exposure groups in BHR, atopy, and eosinophils ≥ 0.4 x 10^9/l.

Spirometric test results of 139 Caucasian male aluminium cast-house workers showed no significant differences (percentage of the predicted value) compared to a minimally exposed internal reference group after adjusting for smoking habits (table 5). Regression analysis also showed no significant differences compared to a minimally exposed internal reference group after adjusting for age, standing height and smoking habits.

Table 5. Association between lung function test results and exposure to irritants adjusted for smoking status of cast-house workers.*

	High exposure	Moderate exposure	Low exposure (internal reference group)
n	43	43	53
Age - yr (sd)	44 (9.1)	45 (10.2)	48 (7.4)
Smoking status (%)			
Current smoker	58.1	51.2	43.4
Former smoker	30.2	25.6	30.2
Never smoked	11.6	23.3	26.4
FEV_1 % pred sd)	104.3 (13.8)	102.2 (14.8)	101.3 (13.8)
FVC % pred (sd)	108.2 (11.6)	108.5 (13.5)	107.3 (12.6)
PEF % pred (sd)	117.5 (21.3)	111.1 (18.7)	115.2 (20.0)
FEV_1/FVC % (sd)	78.2 (5.9)	76.6 (8.2)	76.1 (6.7)
†Airway obstruction	1 (2.3)	3(7.0)	2(3.8)

*n = 139, Caucasian males only
†Airway obstruction (FEV_1/FVC < 70% and FEV_1 < 80% pred)

Work-related airway symptoms

Of 151 cast-house workers, 21 (13.9%) reported an asthma attack (ever). 10/21 (47.6%) reported having had an asthma attack (ever) before they started working at the plant; 8/21 (38.1%) after they started working at the plant, and 3/21 (14.3%) could not remember if they had had asthma attacks before or after they started working at the plant. 75/151 (49.7%) reported having work-related upper and/or lower airway symptoms, 16 (21.3%) of those reported an asthma attack (ever) and 14 (18.7%) reported that they changed jobs as a result of their symptoms. Of these 14 cast-house workers, 10 (71.4%) reported having had an asthma attack (ever) and 4/10 (40%) of them after they started working at the plant. Of this group with work-related upper and/or lower airway symptoms, 64/69 (92.8%) reported that their symptoms improved on non-working days.

An additional analysis of Caucasian males (n = 140) showed that cast-house workers who reported work-related upper and/or lower airway symptoms reported significantly more asthma attacks (ever) (PR = 3.7, 95% CI 1.3-10.6), after adjusting for age and smoking habits, compared to those who did not report upper and/or lower work-related airway symptoms.

In additional interviews with the 14 job changers, 13/14 (92.9%) cast-house workers confirmed that they had changed jobs as a result of their work-related upper and/or lower airway symptoms. One worker reported to have had work-related upper and/or lower airway symptoms and an asthma attack (ever) but had changed his job as a result of the Ménière syndrome. 5/13 (38.5%) reported having experienced an exposure incident of whom 3 reported a chlorine gas incident. 9/13 (69.2%) confirmed that they had asthma and used asthma medications; 8/9 were treated by a pulmonologist and 1/9 by a general physician. 7/9 reported that they had no asthma symptoms when they started working at the plant. Of the other 4/13 workers, one had COPD and 3 had no clear diagnosis.

DISCUSSION

Aluminium cast-house workers reported significantly more respiratory symptoms and showed significantly lower spirometric values compared to a sample of the Dutch ECRHS population.
The average daily mean exposure to inhalable dust, metals, hydrogen fluoride, fluor salts and sulphur dioxide was relatively low compared to reference values. However, high emission levels of fluoride occurred above the furnaces. The ventilation in the cast-house consisted of a natural ventilation system with automatically opening and closing ventilation grids. When ventilation grids were open, the outside wind influenced the airflow patterns within the cast-house, disturbing the upward airflow patterns above the ovens. This resulted in the spreading of pot emissions with high concentrations of fluorides around the workplace. Measurements showed that peak exposures to chlorine gas occurred as a result of production process disturbances.
Compared to a minimally irritant exposed internal reference group, cast-house workers in the highest exposed group reported significantly more eye symptoms during their work, and workers in the moderate exposed group reported significantly more symptoms of chest tightness upon awaking. No differences in spirometric values were found between exposure groups.
Cast-house workers who reported work-related airway symptoms reported significantly more asthma attacks compared to workers without work-related airway symptoms. The majority of cast-house workers who reported a job change due to their symptoms also reported having asthma.
The average daily mean exposures to inhalable dust, metals, hydrogen fluoride, fluor salts and sulphur dioxide were relatively low compared to reference values. However peak emissions of hydrogen fluoride and fluoride salts occurred in the cast-house area when aluminium was poured from transport ladles into the furnaces. On a regular basis, normal airflow patterns in the workplace were disturbed and as a result, emissions from transport ladles with high concentrations of hydrogen fluoride and fluoride salts were spread around the workplace. So, peak exposures to hydrogen fluoride and fluoride salts are very likely but were difficult to measure due to their unpredictable nature.
Measurements showed that peak exposures to chlorine gas can occur as a result of specific production process disturbances. This was confirmed by workers during walk-through surveys and during the medical interviews with workers who changed jobs due to symptoms. Thus, intermittent exposures to irritants are relevant for cast-house workers. Particularly exposures to fluorides were not restricted to certain tasks or jobs but depended on weather conditions and airflow patterns in the workplace and as a result were quite homogeneous for all cast-house workers within the cast-house area.
Godderis et al. did not find, a significant difference in any of the categories of the respiratory

questionnaire and in the results of the spirometry in their study among 30 cast-house workers and 17 controls. They concluded that there was no indication for respiratory health problems in cast-house personnel compared to the referent population.[15]

We also did not find a significant difference in any of the categories of the respiratory questionnaire and in the spirometry results between cast-house personnel and internal referents. In addition, spirometry results were not associated with duration of employment, which was evaluated as a proxy for cumulative exposure to irritants [data not shown].

However, cast-house workers did have respiratory health problems compared to a general population sample and these problems are likely to be underestimated.

Godderis et al. concluded that exposure in cast-houses seemed to be acceptable but that the possibility of peak exposure to fumes could not be excluded. Our study shows that exposures measured in the workplace are, on average, within acceptable limits, but that peak exposures to respiratory irritants occurred on a regularly basis as a result of disturbances in the airflow pattern and common, occasional exposures to chlorine gas.

Our study suggests that these peak exposures to irritants may explain the respiratory health effects in exposed cast-house workers in comparison to the general population.

In an internal comparison of exposure groups to irritants, the highest exposed group reported significantly more eye symptoms during their work, and workers in the moderate exposed group reported significantly more symptoms of chest tightness upon waking up. These symptoms may be the result of irritation by fluorides and/or chlorine.[25 26] The homogeneous character of exposures among cast-house workers may explain why we did not find more differences in respiratory symptoms among exposure groups.

Further, cast-house workers who reported work-related airway symptoms reported significantly more asthma attacks compared to workers without work-related airway symptoms, and the majority of those who reported to have changed jobs due to their symptoms also reported having asthma.

Most workers with physician diagnosed asthma reported they had no asthma symptoms when they started working at the plant. These findings may be an indication that exposures in cast-house workers either caused or aggravated asthmatic symptoms. After all, exposure to irritants can aggravate and probably cause asthma.[27] Kipen et al. reported cases of nonsensitization adult-onset asthma in settings of exposure to noticeable but distinctly "tolerable" levels of inhalation irritants, and Taiwo et al. demonstrated a significant relationship between mean gaseous fluoride exposure and the incidence rate of asthma but were unable to show any significant association between short-term HF exposure and asthma incidence in their study population. [28 10]

Whether asthmatic cast-house workers in this study had "pot room asthma", as has been previously described in aluminium potroom workers[1], can not be concluded because cases were not further evaluated. But even if cases had been evaluated for potroom asthma, the causative agent of potroom asthma has not yet been elucidated.[2] The study population was small, and this limited statistical power in internal comparisons, especially after adjusting for confounding variables in multiple regression modelling.

Information was collected in a standard manner and exposure was assigned blind to the questionnaire and test results. As a result, misclassification will likely to be non-differential and exposure-response relationships might have been attenuated.

Cast-house workers reported significantly more respiratory symptoms and showed significantly lower spirometric values compared to the Dutch ECRHS population. However, overestimation of symptoms in workers cannot be excluded, and recall bias may have affected comparisons with the general population. Nevertheless, workers also showed significantly lower spirometric values which are a more objective outcome. Reversibility in FEV_1 was not measured, so it was not possible to evaluate the nature of the spirometric changes.

The general population data were obtained with the same procedure and device, with same age and distribution, but not restricted to a working subpopulation. The general population sample also included non-active workers who were not fit enough to be active in the workforce; therefore the differences in respiratory status between exposed workers and the general population are likely to be underestimated.

The healthy worker effect is a potential source of bias in cross-sectional studies when restricted to actively employed workers. Leaving employment or job transfer to a position involving lower exposures as a result of symptoms may have led to underestimation of the effects of exposure.[29 30]

Job transfer may have led to an underestimation of exposure-response relationships in this study, because 14 workers reported having changed jobs during their employment at this plant as a result of work-related airway symptoms.

In conclusion, this epidemiological study supports that there is a respiratory hazard for cast-house workers in the aluminium industry. Although an exposure-response relationship could not be demonstrated, this study offers evidence that taking preventative measures would be prudent in the work-environment of cast-house workers with a focus on (peak)exposures to irritants. Exposure should be minimized and health surveillance should be offered to exposed workers.

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Chapter 6

CLINICAL EVALUATION OF A POPULATION OF FLOUR AND ENZYME EXPOSED TRADITIONAL BAKERY WORKERS IDENTIFIED BY A SIMPLE TRIAGE SYSTEM

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ABSTRACT

Objectives: The aim of this study was to describe the clinical characteristics of a large sample of traditional bakery workers referred by occupational physicians through a formalized simple triage system and to explore factors predictive of occupational asthma, in order to optimize the triage approach in the future for specialized occupational respiratory clinics.

Methods: A cross-sectional study was conducted among 161 bakery workers at risk of occupational asthma, who were referred by occupational physicians to an outpatient clinic for occupational respiratory disorders for a diagnostic work-up.

Predictors of non-specific bronchial hyperresponsiveness (BHR) were explored to make the clinical work-up more efficient in diagnosing (occupational) asthma. Respiratory symptoms that were associated with BHR (univariable p values < 0.15) were selected for backward stepwise logistic regression to explore a prediction model.

Results: The overall prevalence of (probable) occupational respiratory allergy among referred workers was 45%. Most of them (71%) were categorised in the high probability group of being sensitised by an earlier developed prediction model. Of all referred workers, 11% were diagnosed with occupational asthma (OA) and 44% with probable occupational rhinitis or rhinoconjunctivitis.

The strongest predictors of BHR were: wheezing, respiratory symptoms or eye symptoms when exposed to pets, problems with breathing due to transition from warm to cold circumstances and when exposed to baking/frying odours. The discriminative ability of the model, determined with the area under the receiver operating characteristic curve, was 0.77 (95% CI 0.68-0.85).

Conclusion: This study shows that a simple triage system is capable of detecting occupational asthma cases among bakery workers that likely otherwise would not have been detected.

Improvement of prediction models for occupational asthma in the clinical setting seems possible but more research in a larger sample is needed.

INTRODUCTION

Occupational allergies are commonly reported illnesses among bakery workers. An occupational allergy is a significant problem because the symptoms are often progressive and may become irreversible due to ongoing exposure.[1] Moreover, socio-economic consequences of occupational allergies are usually serious in terms of reduced income and quality of life.[2] Workers' health should therefore be protected by reducing allergen exposure. However, for many sensitizers there is not a no-observed-adverse-effect-level, which means that even at very low exposure levels, there is a residual risk for occupational allergy. Therefore, early detection of sensitised workers by means of periodic screening is warranted in combination with exposure reduction.[3]
Ideally, every bakery worker exposed to inhaled sensitizers should be offered periodic screening. However, logistic difficulties may make universal screening very expensive in small traditional bakeries. A simple triage system could facilitate the control of both costs and efficacy.[4 5]
Recently a surveillance scheme has been set up for bakery workers in The Netherlands which has been described elsewhere.[6]
The aim of this study was to describe the clinical characteristics of a large sample of traditional bakery workers referred to specialized occupational respiratory clinics by occupational physicians through a formalized simple triage system. The triage system is based on a diagnostic rule which predicts sensitisation.[4] In addition, we explored factors predictive of non-specific bronchial hyperresponsiveness (BHR) in order to optimize the triage approach in an attempt to extend it to specialized occupational respiratory clinics. BHR was chosen because it is considered to be a hallmark of asthma and BHR is present in both occupational and non-occupational asthma.

METHODS

Study design, setting and participants

In the first round of surveillance, more than 3000 traditional bakers filled out a questionnaire, which stratifies workers by a prediction score for being sensitised to wheat allergens according to a diagnostic model.[4] Bakery workers with medium and high scores were referred to an occupational physician of a regional occupational health service. Some patients required a more detailed diagnostic work-up according to the occupational physician and were referred to two specialized occupational respiratory clinics in the middle (Utrecht) and North (Groningen) of the country.
From January 1st 2007 until July 1st 2008, 184 bakery workers were referred by occupational physicians for clinical evaluation. 161 (87.5%) bakery workers were referred to our outpatient occupational health clinic in Utrecht. Blood samples were taken from 137 bakery workers

for serology testing. Reasons for non-participation were often not clear. Workers referred to Groningen are not included in this analysis because the clinic did not use the same clinical work-up.

Serology

Total IgE was determined by using ImmunoCAP. Specific IgE to common allergens was determined by Phadiatop and specific IgE to common bakery allergens was determined by ImmunoCAP (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden). Values of ≥ 0.35 kU/l were defined positive, indicating sensitisation. Workers sensitised to one or more common allergens were considered to be atopic.

Clinical evaluation

All referred workers underwent further clinical investigation including clinical history, nasal examination, serology testing, spirometry and assessment of BHR to histamine within 24 hours after exposure to during a continuous working period of at least 2 weeks. A diagnosis of occupational asthma (OA) was excluded if there was no indication of asthma in the medical history and a worker showed no BHR within 24 hours after exposure while working uninterrupted for two weeks.[7] [8] Spirometry was obtained by experienced technicians according to European Respiratory Society standards[9] by using a pneumotachograph with specific software (Pneumotachograph and 4.66 software, Jaeger; Würzburg, Germany). Histamine challenge was not performed within 6 weeks of an exacerbation or change in the use of asthma medication. Histamine was administered during a controlled inspiratory capacity breathing dosimeter technique. We used the Aerosol Provocation System with a Medic-Aid nebulizer (Jaeger; Würzburg, Germany), starting with diluent and followed by doubling doses of histamine from 0.026 mg to a maximum dose of 2.5 mg. The test was stopped when a fall of 20% in forced expiratory volume in one second (FEV_1) was observed (PD20) or the maximum cumulative dose was reached. If necessary, bronchoconstriction was treated with inhalation of salbutamol.[10]

All workers with BHR when at work performed serial peak expiratory flow rate (SPEFR) measurements after 2 weeks at work and after 2 weeks away from work, after which histamine challenge with assessment of BHR was repeated. A change of at least one doubling dose increase in PD20 was regarded as significant. SPEFR measurements were independently interpreted using direct visual analysis by a panel of two experienced physicians. Discrepancies were resolved by consensus. A diurnal variation in PEFRs of ≥ 20% was considered a diagnostic criterion.[11] The diagnosis of work-related asthma was based on the American College of Chest Physicians (ACCP) consensus statement.[11]

The medical diagnosis of OA was based on four criteria according to the ACCP: (A) diagnosis of asthma; and (B) onset of asthma after entering the workplace; and (C) association between symptoms of asthma and work; and (D) one or more of the following criteria: (D1) workplace exposure to an agent known to give rise to OA; or (D2) work-related changes in FEV_1 or peak expiratory flow rate, or (D3) work-related changes in bronchial responsiveness.[12] The diagnosis of work-related rhinitis was based on a position paper of the EAACI Task force on Occupational Rhinitis. A suggestive clinical history of occupational rhinitis associated with sensitisation to common bakery allergens was considered as probable occupational rhinitis.[13]

Statistical analysis

All statistical analyses were performed using SPSS 15.0 for Windows (Statistical Package for Social Sciences, Chicago Il). We explored predictive factors of BHR using questionnaire data of referred workers at the time of triage using a short questionnaire. Respiratory symptoms that were associated with BHR (univariate p values < 0.15) were selected for backward stepwise logistic regression (likelihood ratio). Further, we used a backward stepwise procedure (p <0.16) to select the strongest predictors for BHR. We used the area under the curve (AUC) of the receiver operator characteristic (ROC) curve as an indication of the performance of the prediction model.

RESULTS

Participants and characteristics

Of the 161 eligible traditional bakery workers referred to the outpatient health clinic in Utrecht, 140 (87.0%) finished the clinical assessment within a year and a half from the start of this study and were included. Characteristics of study participants (n = 140) are given in table 1.

Most traditional bakery workers (92.1%) were male. The majority of referred workers reported work-related nose (80.7%) and eye (52.9%) symptoms and 75 out of 138 (54.3%) were atopic. 12.1% had asthma before they started working as a bakery worker (pre-existent asthma). 59 out of 137 (43.1%) workers were sensitised to wheat and 21 out of 137 (15.3%) were sensitised to fungal α-amylase. In the end, 45.0% of the traditional bakery workers were diagnosed with occupational allergic respiratory disease. 45 out of 63 (71.4%) were previously stratified as belonging to a high probability of sensitisation group.

Table 1. Clinical characteristics of traditional bakery workers referred to the outpatient clinic Utrecht across probability groups (n = 140).

	All	Low probability	Moderate probability	High probability
Number of patients	140	4	48	88
Characteristics n (% within column)				
Bread baker	48 (34.3)	2 (50.0)	18 (37.5)	28 (31.8)
Confectioner	39 (27.9)	1 (25.0)	11 (22.9)	27 (30.7)
Bread baker and confectioner	42 (30.0)	1 (25.0)	14 (29.2)	27 (30.7)
Miscellaneous	11 (7.9)	0 (0.0)	5 (10.4)	6 (6.8)
Age, mean in years (standard deviation)	37.5 (10.7)	37.5 (10.1)	36.1 (10.2)	38.2 (11.0)
Work duration, mean in years (standard deviation)	20.8 (11.1)	21.5 (10.9)	19.3 (10.8)	21.6 (11.4)
Male	129 (92.1)	4 (100.0)	43 (89.6)	82 (93.2)
Ex-smoker	28(20.0)	1 (25.0)	8 (16.7)	19 (21.6)
Current smoker	37 (26.4)	0 (0.0)	16 (33.3)	21 (23.9)
Pre-existent asthma	17 (12.1)	0 (0.0)	4 (8.3)	13 (14.8)
Taking asthma medication	40 (28.6)	1 (25.0)	7 (14.6)	32 (36.4)
Work related symptoms				
Chest	55 (39.3)	4 (100.0)	12 (25.0)	39 (44.3)
Nose	113 (80.7)	3 (75.0)	37 (77.1)	73 (83.0)
Eyes	74 (52.9)	3 (75.0)	22 (45.8)	49 (55.7)
Sensitisation				
Total IgE > 100kU/l	67/134 (50.0)	1/2 (50.0)	19/46 (41.3)	47/86(54.7)
Common environmental allergens (≥ 1)	75/138 (54.3)	3/3 (100.0)	18 (37.5)	54/87 (62.1)
Wheat	59/137 (43.1)	2/2 (100.0)	14 (29.2)	43/87 (49.4)
Fungal α-amylase	21/137 (15.3)	0/2 (0.0)	2 (4.2)	19/87 (21.8)
Soya	12/137 (8.8)	0/2 (0.0)	5 (10.4)	7/87 (8.0)
Rye	24/33 (72.7)	- (-.-)	4/7 (57.1)	20/26 (76.9)
BHR at work	57/130 (43.8)	1 (25.0)	15/44 (34.1)	41/82 (50.0)
Significant changes in BHR	15/32 (46.9)	1/1 (100.0)	1/6 (16.7)	13/25 (52.0)
Work-related pattern in Serial PEFR	7/40 (17.5)	0/1 (0.0)	1/8 (12.5)	6/31 (19.4)
Diagnosis				
Occupational allergic respiratory disease	63 (45.0)	3 (75.0)	15 (31.3)	45 (51.1)

Definition of abbreviation: BHR = non-specific bronchial hyperresponsiveness; PEFR = peak expiratory flow rate.

Table 2. Characteristics of traditional bakery workers according to different categories (n = 140).

	Work-related chest symptoms	*Sensitised to Wheat	*Sensitised to Wheat/ Fungal α-amylase	Occupational allergic asthma (medical diagnosis)
Number	55	59/137	62/137	15
Age, mean in years (standard deviation)	37.3 (10.3)	38.6 (9.8)	38.5 (9.6)	38.4 (9.0)
Work duration, mean in years (standard deviation)	20.7 (10.6)	21.8 (9.9)	21.7 (9.7)	21.3 (9.7)
Total IgE > 100kU/l	31/53 (8.5)	47/58 (81.0)	48/61 (78.7)	11/14 (78.6)
Sensitisation				
Common environmental allergens (≥ 1)	30/53 (56.6)	41/58 (70.7)	44/61 (72.1)	10/14 (71.4)
Wheat	29/53 (54.7)	59 (100.0)	59 (95.2)	13/14 (92.9)
Fungal α-amylase	12/53 (22.6)	18 (30.5)	21 (33.9)	6/14 (42.9)
Soya	6/53 (11.3)	12 (20.3)	12 (19.4)	3/14 (21.4)
Rye	14/16 (87.5)	20/21 (95.2)	21/22 (95.5)	7/7 (100.0)
BHR at work	31/53 (58.5)	32/55 (58.2)	34/58 (58.6)	15/15 (100.0)
Significant changes in BHR	13/21 (61.9)	13/23 (56.5)	13/25 (52.0)	13/15 (86.7)
Work-related pattern in Serial PEFR	6/24 (25.0)	5/27 (18.5)	5/29 (17.2)	6/14 (42.9)
Diagnosis				
Asthma:	31 (56.4)	34 (57.6)	35 (56.5)	15/15 (100.0)
Pre-existent	4 (7.3)	8 (13.6)	9 (14.5)	1 (6.7)
Asthma medication	21 (38.2)	25 (42.4)	25 (40.3)	8 (53.3)
Occupational allergic asthma	15 (27.3)	13 (22.0)	13 (21.0)	15
Non-confirmed occupational asthma	4 (7.3)	8 (13.6)	8 (12.9)	0
Work-exacerbated asthma	2 (3.6)	1 (1.7)	2 (3.2)	0

*ImmunoCAP values of ≥ 0.35 kU/l
Definition of abbreviation: BHR = non-specific bronchial hyperresponsiveness; PEFR = peak expiratory flow rate.

Work-related respiratory symptoms and sensitisation

Of all 140 workers, 132 (94.3%) reported nose symptoms. Of those workers with nose symptoms, 113 (85.6%) reported work-related nose symptoms. Serology test results were available from 111 of those 113 workers. 54 out of 111 (48.6%) were sensitised to wheat, and 19 (17.1%) to fungal α-amylase, and 16 out of 111 (14.4%) were sensitised to both.

Of all 140 workers, 93 (66.4%) reported chest symptoms. Of those workers with chest symptoms, 55 (59.1%) reported work-related chest symptoms. Serology test results were available from 53 of those 55 workers. 29 out of 53 (54.7%) were sensitised to wheat, 12 out of 53 (22.6%) to fungal α-amylase, and 10 out of 53 (18.9%) were sensitised to both. Of the 93 workers who reported chest symptoms, 88 (94.6%) also reported nose symptoms and 73 out of those 88 (83.0%) reported work-related nose symptoms.

Clinical diagnosed occupational allergic asthma cases

15 (10.7%) cases of OA were diagnosed out of the group of 140 referred workers. Among them, five were bread bakers, five confectioners and four bread bakers and confectioners, and one was a dough maker. One of the OA cases had asthma in childhood. Two OA cases had been diagnosed earlier by an allergist. Eight OA cases used asthma medication but no association with work had been diagnosed earlier. 14 (93.3%) out of 15 OA cases were also diagnosed with probable occupational rhinitis. Ten (71.4%) out of 14 OA cases were sensitised to one or more common allergens and diagnosed as atopic. One case was regarded as sensitised to wheat but was not tested with ImmunoCAP. 14 out of 15 (93.3%) OA cases were sensitised to wheat and one out of 15 to rye. Six out of 14 (42.9%) were also sensitised to fungal α-amylase, and all six were also sensitised to wheat. During the clinical investigation 13 out of 15 (86.7%) OA cases showed significant changes in BHR after 2 weeks at work and after 2 weeks away from work. In six out of 14 (42.9%) a work-related pattern was identified in serial PEFR measurements.

Table 3. Respiratory diagnosis of traditional bakery workers referred to the outpatient clinic in Utrecht across probability groups, n (% in columns).

	All	**Low probability**	**Moderate probability**	**High probability**
Number of patients	140	4	48	88
Asthma	51 (36.4)	2 (50.0)	9 (18.8)	40 (45.5)
Non-work-related asthma	23 (16.4)	1(25.0)	5 (10.4)	17 (19.3)
Work-related asthma				
Occupational asthma	15 (10.7)	1 (25.0)	1 (2.1)	13 (14.8)
Non-confirmed occupational asthma	9 (6.4)	0 (0.0)	3 (6.3)	6 (6.8)
Work-exacerbated asthma	4 (2.9)	0 (0.0)	0 (0.0)	4 (4.5)
Rhinitis	91 (65.0)	3 (75.0)	22 (45.8)	66 (75.0)
Non-work-related rhinitis	29 (20.7)	0 (0.0)	7 (14.6)	22 (25.0)
Probable occupational rhinitis	13 (9.3)	0 (0.0)	3 (6.3)	10 (11.4)
Probable occupational rhino conjunctivitis	49 (35.0)	3 (75.0)	12 (25.0)	34 (38.6)
Miscellaneous	8 (5.7)	0 (0.0)	6(4.3)	2(1.4)

An exploration of predictors of BHR

Table 4 shows the respiratory symptoms from the short questionnaire used in the triage system that were associated with BHR (univariate p values < 0.15) and selected for backward stepwise logistic regression (likelihood ratio). The predictors of BHR in the multivariate regression model were: dyspnoea after walking at a normal pace, wheezing (in the past year), chest tightness upon waking up (past year), and symptoms when exposed to pets, change of temperature from warm to cold, or baking/frying odours (Table 4). The Area Under the Curve was 0.77 (95% CI 0.68-0.85) (Figure 1).

Figure 1 .

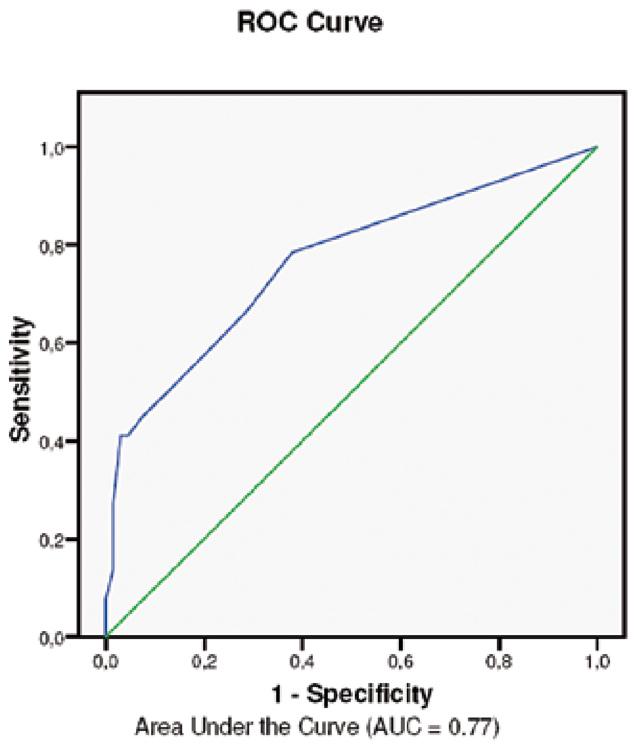

Table 4. Univariate association (p < 0.15) between symptoms (questionnaire) and non-specific bronchial hyper-responsiveness (BHR) and predictors of BHR in a multivariate model.

	Number (%)	Univariate OR (95.0% CI)	p value	Multivariate OR (95.0% CI)	p value
Wheezing (past year)	46/134 (34.3)	5.8 (2.6-13.1)	0.000	4.4 (1.7-11.4)	0.002
Asthma attack (past year)	42/135 (31.1)	6.8 (2.8-16.2)	0.000		
Chest tightness upon waking up (past year)	30/134 (22.4)	7.4 (2.6-21.5)	0.000		
Respiratory symptoms or eye symptoms when exposed to:					
- house dust	52/132 (39.4)	2.3 (1.1-4.8)	0.026		
- pets	26/128 (20.3)	3.0 (1.2-7.4)	0.018	2.9 (1.0-8.1)	0.044
Problems with breathing:					
- due to warm to cold transitions	30/134 (22.4)	4.2 (1.7-10.6)	0.002	3.2 (1.1-9.7)	0.041
- due to fog	23/133 (17.3)	2.4 (0.9-6.2)	0.081		
- when exposed to baking/frying odours	12/131 (9.2)	5.7 (1.2-28.3)	0.032	6.5 (1.1-37.1)	0.036
Dyspnoea during work	32/131 (24.4)	3.3 (1.4-7.9)	0.007		
Chest tightness during work	33/129 (25.6)	3.5 (1.4-8.3)	0.005		
Chest tightness after work	24/133 (18.0)	3.0 (1.1-8.1)	0.028		

OR: Odds Ratio ; CI: confidence interval

DISCUSSION

The overall prevalence of (probable) occupational respiratory allergy in this group of referred traditional bakery workers was 45%. Of all referred workers, 11% were diagnosed as occupational asthma cases and 44 % as probable occupational rhinitis or rhinoconjunctivitis cases. Most of them had been stratified in the high probability of sensitisation group by the prediction model. The triage model appeared not to differentiate well between work-related and non-work-related asthma and rhinitis cases as there were 23 out of 53 (45%) non-work-related asthma cases and 29 out of 91 (32%) non-work-related rhinitis cases.
One of the objectives of this study was to describe the clinical characteristics of a large sample of traditional bakery workers referred by occupational physicians through a formalized triage system. The triage system was based on the probability of being sensitised to wheat/fungal α-amylase. Sensitisation in the clinic was assessed by serology testing and 44% of the referred workers were sensitised to wheat/fungal α-amylase. Most workers (86%) who were sensitised to fungal α-amylase were also sensitised to wheat. As a result of the triage, almost 4 times as many wheat-sensitised workers were identified in the referred population than in a general bakery population. In the general bakery population, specific wheat flour IgE was detected in 107 (12%) workers.[14] This finding indicates that the triage system was able to concentrate workers who were sensitised to wheat in a population at risk. Many referred workers had respiratory symptoms, which is not remarkable, because the triage model used symptoms as predictors for sensitisation.[6] However, there was a discrepancy between work-related symptoms and sensitisation. Only half of the workers with work-related symptoms were sensitised to wheat/fungal α-amylase. False negative serological test results may be an explanation, but also exposure to other allergens or irritant effects of dust may explain our findings. The latter is in accordance with the findings of Skjold et al.[15] They showed in their prospective cohort study among baker apprentices that the occurrence of new airway symptoms was not always accompanied by sensitisation to occupational allergens. They concluded that not all work-related symptoms have an allergic basis. Work-related symptoms maybe reflect the development of an inflammation rather than the production of a specific immunoglobulin E pathway, as sensitisation to occupational allergens was rarely observed.[15]
This simple triage model for screening of occupational asthma among bakery workers is based on predicting sensitisation to wheat allergens. From a clinical point of view it would be preferable to be able to predict OA as an outcome as well. A diagnostic model for OA might improve the efficiency of the clinical work-up process in the specialized referral clinic. The model might eventually even be used as alternative triage approach instead of or next in parallel with a triage for work-related sensitisation, to further support physicians in the field and in the clinic. Unfortunately, the study size and the numbers of OA in our study were too small to develop such a model with OA as an outcome. Therefore an alternative model for BHR was explored because

BHR is considered as an important hallmark of (occupational) asthma.[16 17] A negative BHR test practically excludes (occupational) asthma in symptomatic workers who are still exposed in the workplace.[7 8]
Of all referred workers, 44% had BHR at work. The predictors of BHR (wheezing, respiratory symptoms or eye symptoms when exposed to pets, problems with breathing due to transition from warm to cold circumstances, and when exposed to baking/frying odours) were quite different from the predictors of sensitisation in the triage model (asthma attacks, rhinitis symptoms, conjunctivitis symptoms, during work symptoms).[6] This exploration predicted clinically assessed BHR in a group of referred traditional bakery workers based on questionnaire data used in the pre-clinical setting of the triage system. It would probably be more efficient to predict BHR in the population under surveillance, making the referral protocol more effective. This would require a large survey in this population with BHR as the outcome variable.
Fifteen cases of clinically confirmed asthma were diagnosed by using a specific clinical work-up which included the assessment of specific sensitisation to wheat and α-amylase. Van Kampen et al. predicted specific challenge test results in bakers with work-related symptoms (rhinitis, conjunctivitis, cough, chest tightness, shortness of breath or wheezing).[18] The positive predictive value was 100% for specific inhalation provocation test confirmed OA when a minimal cut-off value of 2.32 kU/l was used for sensitisation to wheat flour.[18] Of the 118 bakery workers in our study with the same work-related symptoms, 55 (46.6%) were sensitised to wheat. 35 (63.6%) out of those 55 sensitised workers had a wheat-specific IgE concentration > 2.32 kU/l. Nine (69.2%) out of 13 OA cases due to wheat sensitisation had a wheat-specific IgE concentration of > 2.32 kU/l. According to the study of van Kampen et al. 35 cases in our study would have been diagnosed as OA cases due to wheat flour exposure. This suggests that our work-up underestimated the number of OA cases. However, bakery workers in the study of van Kampen et al. were examined within the scope of claims for compensation due to OA and criteria for referral and inclusion might have differed from our study inclusion criteria. Brant et al. used work-related chest symptoms with serum specific IgE to either flour or fungal a-amylase as a workable definition of baker's asthma in routine surveillance and cross-sectional survey.[19] In our study 31 out of 53 (58.5%) workers with work-related lower respiratory symptoms were sensitised to wheat/fungal α-amylase. Further supporting that our work-up underestimated the number of OA cases. However, the workable definition used by Brant et al. is probably more sensitive than the more specific clinical definition we used.
Despite the limitations of the triage system, more occupational asthma cases were detected among bakery workers than reported to the national surveillance scheme in the preceding two years. A report by the Netherlands Centre for Occupational Diseases in 2007 showed that, on average, 30 cases of (occupational) asthma were reported annually by occupational physicians in the Netherlands. Ten cases of baker's asthma were reported in 2005 and among the 24 cases of "(occupational) asthma" reported in 2006, there were no cases of

baker's asthma.[20] Compared to our findings this is an indication that baker's asthma is under reported or underdiagnosed by occupational physicians in the Netherlands. Thus, the triage system identified more occupational asthma cases than contemporary occupational health care, indicating that the triage model worked well. Nevertheless, the costs of this approach still have to be assessed. This approach is a start for early detection of occupational asthma cases in bakery workers as suggested by Malo and Gautrin,[21] transforming population approach into diagnostic process leading to identification of OA cases.

In the future, more sophisticated diagnostic models for different clinical entities of occupational respiratory allergy need to be developed and validated for screening purposes and also for cost-effectiveness purposes. For screening on occupational allergies, we still face significant challenges ahead.

In conclusion, this study shows that a simple triage system is capable of detecting occupational asthma cases among bakery workers that otherwise would not have been detected.

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Chapter 7

GENERAL DISCUSSION

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Towards an interdisciplinary approach

This thesis describes a series of studies on existing respiratory health problems in a range of industrial settings in the field of occupational medicine. These respiratory health problems were the result of occupational exposures to allergens and irritants, which potentially caused a range of respiratory diseases including COPD, bronchiolitis obliterans syndrome (BOS) and occupational asthma. Most occupational health services employ industrial hygienists, safety engineers, occupational health nurses and occupational physicians among their staff. These professionals usually work together to recognize and manage work-related diseases among many other tasks. They had, however, problems identifying and managing the outlined work-related respiratory health problems in this thesis, which they encountered in daily practice. The reason that the occurrence of disease was not recognized in these concrete situations is a combination of many factors and will be discussed below.

The studies described in this thesis explore work-related respiratory health problems in an interdisciplinary way by integrating concepts from industrial hygiene, occupational medicine, epidemiology and clinical health care. The character of the interdisciplinary collaboration differed between the studies and was dependent on the encountered problems and questions to be answered.

The occupational physician played a key role in overseeing in the collaboration process and integrating different elements.

As described in individual chapters, the interdisciplinary approach had synergistic effects on the collaboration process owing to a common focus on work-related respiratory health problems and intensive communication between the disciplines involved. The approach led to a higher level of knowledge in all disciplines and a more common way of approaching respiratory problems. "The whole appeared to be greater than the sum of its parts for each of the disciplines".[1 2] This thesis shows that there is a clear need for more awareness of work-related respiratory disorders and we do need more research facilities to investigate these diseases properly. All studies started where current occupational health care professionals appeared to experience difficulties in the approach to work-related respiratory health problems they encountered in daily practice. The interdisciplinary approach appeared to be essential in elucidating respiratory health problems in the work environment which fall outside the usual competence of the common occupational health service.

Interdisciplinary collaboration with appropriate infrastructure delivered the knowledge necessary to investigate individual workers and populations in a systematic way, leading to recognition, diagnosis and management of occupational respiratory health problems. The collaboration also instigated the implementation of preventative measures. In his own way, Ramazinni already integrated clinical epidemiology, social medicine, industrial toxicology and hygiene in the Morbis Artificum.[3] Despite this example from ancient literature, the application of the interdisciplinary approach, as outlined in this thesis, is relatively new in current occupational health care practice in the Netherlands.

Current health care in the Netherlands

One may wonder why the health care system and the occupational health care system were not able to recognize work-related disease as outlined in this thesis. Further, why the occupational health care system was not able to address these issues once recognized, despite the fact that the different disciplines already collaborate within the existing occupational health care structures. Although these topics were not the primary topic of this thesis, they are part of the context and a few points can be made:

- **Occupational respiratory disease and health care:**
  First of all, physicians should at least be aware that a work-related disorder might be possible in a certain situation. Further, general practitioners should consult an occupational physician in cases of complex work-related disorders. However, in a study of van der Burg et al., in only 41 % of 501 general physician consultations the (possible) relationship between presented complaints and work was discussed and in only three consultations a (possible) consultation with an occupational physician came up.[4]
  As far as clinical specialists are concerned, 80% would like to improve collaboration with occupational physicians.[5] However, many clinical specialists appear to have a blind spot for work-related disorders and the implications.[6] Also in a study among bakery workers (chapter 6), many were already treated for their symptoms, but in many cases, no association with work was made. Several initiatives have been undertaken in recent years to improve the collaboration between clinical health care and occupational health care professionals.[6-12] Despite these initiatives, the collaboration between occupational physicians and clinical physicians in the Netherlands is developing with great difficulty as a result of different funding and focal points. Clinical health care is funded by public means and focused on curing while occupational health care is focused on return to work and is funded by private means.[13] As far as chest physicians are concerned, only a limited number of the approximately 35 cases of respiratory diseases per year were reported by chest physicians since 2003, when a national registration system ("Peilstation Arbeidsgerelateerde Longaandoeningen") was set up. The number increased to 104 in 2007, when the national surveillance program was started among bakery workers as discussed in chapter 6.[14] This indicates that a passive system as it exists now identifies a limited number of the cases which actually seem to exist. There is a demand among chest physicians for collaboration. They came in second place after occupational physicians for referring 20% of all cases of a total of 300 to a specialized centre for occupational respiratory disorders.[1]

- **Occupational respiratory diseases and recognition in occupational health care:**
  Even if clinical health care professionals would be more aware of work-related (respiratory) disorders and if collaboration with occupational health care would improve, a problem would still remains to be solved: Occupational heath care professionals do not always recognize the respiratory health problems adequately. Especially occupational physicians should be aware that a work-related disorder might be possible in a certain situation and hygienists should recognize the potential for exposure and health risks to a known respiratory hazard. Current occupational health care is nowadays seldom focused on recognizing and preventing work-related disorders. At least two main developments have contributed to the erosion of occupational health care in the Netherlands as it existed earlier:

  - First, current occupational health care is hardly focused on occupational disease prevention. As a result of the privatisation of part of the social insurance system in 1994, employers became more financially responsible and accountable for sick leave and work disability. Parallel with this development, the occupational health service system was reformed and professionals had to work more and more in a commercial environment from that moment on. As a result of supply and demand, occupational health care in the Netherlands became mainly focused on sickness absence and disability in the last two decades, and hardly contributed to the prevention of occupational diseases. Over 90% of the contracts of companies with occupational health services consisted either entirely or largely of sickness absence guidance. Because the high sickness absence rates and disability figures in most companies have been substantially reduced in the last years, many occupational health services are currently in a process of re-orientation, seeking new possibilities to show their added value with regard to prevention.[15 16]
  - Second, current occupational medicine has drifted away from clinical practice. Recently, Soethout published the results of a survey among 125 medical students in the last phase of their training in the Netherlands about their career preference, showing that a career preference for occupational health medicine was extremely rare. Even 74% of the male students and 82% of the female students did not or absolutely did not prefer a career in occupational medicine. The most attractive features of practicing medicine and becoming a physician were diagnosing diseases, visible results and knowledge of pathology, but these features were found less applicable to the current profession of an occupational physician.[17]

These observations show that change is required in current occupational health care in the approach to work-related (respiratory) health problems.

Examples of interdisciplinary progress

In chapter 2, in the study among diacetyl workers, none of the four identified cases of BOS had been recognized earlier as bronchiolitis obliterans or as occupationally-related by (occupational) physicians or the usual health care system. In three cases the diagnosis COPD was accepted by the chest physician solely based on lung function without further evaluation, despite the fact that the workers never smoked. In addition, an accelerated decline in FEV_1 was not detected, as the occupational physician and chest physician did not exchange lung function results. This impeded preventive measures for the population at risk. This observation is in line with the 2002 report of the Social and Economic Council of the Netherlands (SER) that mentions the lack of knowledge of new work-related health risks. The report concludes that this lack of knowledge can impede timely observation of new risks, with potentially irreversible health effects as a consequence.[18]

Although physicians should need to consider the work-relatedness of disease, it appears difficult in practice (this thesis). An important message of the study in chapter 2 is, that in smokers under middle age and especially in non-smokers with chronic airway obstruction, a diagnosis other than COPD should be considered, including occupational disease.

Specific methodological knowledge contributed to different elements of this thesis. In the study in chapter 2, the discipline of epidemiology and the clinical setting played a crucial role in identifying BOS cases by transforming a population approach into a diagnostic process. Without this work up, using epidemiological principles, it would have been practically unfeasible and likely too expensive to investigate all workers with HRCT. Besides, also unnecessary X-ray exposure could be avoided with this work up. BOS cases are easily missed.[19] HRCT may be normal during inspiration as BOS requires expiratory HRCT to visualize air trapping. The clinical setting provided the opportunity to investigate workers with HRCT during in- and expiration, which is not a standard procedure. This illustrated the need for close collaboration between occupational health care and clinical health care, otherwise, likely many cases would have been missed, impeding the possibility for prevention. Despite the availability of spirometric data in the study in chapter 2, change in lung function had not been evaluated over time. Even though the spirometric data were measured in different settings with different devices and technicians, each of the cases had quite consistent declines despite different data sources. Looking back, this probably could have been an indication for a hazard in the workplace when change in lung function had been evaluated over time, even if diacetyl had not been identified as a respiratory hazard. However, longitudinal evaluation of spirometric data is still not a common practice among occupational health care professionals while it has been proven to be useful and instrumental.[20]

The interdisciplinary approach also realized opportunities for preventive measures.

Although the plant in chapter 2 had been closed before the study started, it delivered evidence that exposure to an agent during diacetyl production appeared to be responsible for causing BOS in chemical process operators. This finding was consistent with the suspected role of diacetyl in downstream food production and further underpinned the need for preventive measures to limit workers' exposures in the microwave popcorn and flavouring manufacturing industries.[21]

In chapter 4, in the study among detergent workers, the occupational physician considered occupational allergic disease. A lack of knowledge concerning the population-based epidemiological approach, and poor access to diagnostic facilities to investigate the population at risk as a whole contributed to the problem. The main problem was the absence of validated serological tests or skin prick tests for some detergent enzymes to identify sensitised workers. A problem that has also been raised by the Dutch Health Council.[22] Working in collaboration with two different laboratories, it was possible to create a solution for this problem and provide the possibility for serology testing.

The approach used in this study to identify sensitised workers could be perceived as the first round of surveillance. Nowadays the plant is using the serological approach as a base for an occupational health surveillance program to promote the health, safety and quality of life of workers exposed to liquid detergent enzymes.

In the study among aluminium cast-house workers (chapter 5), neither the occupational health service nor other professionals succeeded in identifying and solving the current respiratory health problems despite several attempts in the past to do so. Despite the fact that the exact cause of the occupational respiratory health problems among cast-house workers could not be identified in the study, the epidemiological survey suggested that preventive measures should be taken to reduce peak exposures to irritants. Cast-house workers could not be clinically diagnosed in a specialized outpatient clinic for occupational respiratory disorders at the time of study due to lack of funding and absence of a sense of urgency of the management of the plant. Workers were advised to contact their own occupational or general physician for further clinical evaluation.

The study among traditional bakery workers in chapter 6 described the clinical results of an occupational health surveillance program based on a diagnostic model for workers exposed to wheat allergens.[23] Without the triage system, which was developed by using epidemiological and diagnostic prediction principles, investigating all bakery workers would have been practically unfeasible and most likely too expensive as they worked scattered around the Netherlands. Furthermore, the specialized outpatient clinics played a crucial role in identifying occupational respiratory allergies in this surveillance scheme.

This study clearly supports the added value of the interdisciplinary approach in secondary prevention by forming an occupational health care chain for the recognition, diagnosis, and management of occupational respiratory diseases in bakery workers and consequently the possibility of prevention. More occupational asthma cases were detected among bakery workers during this study than were reported to a national surveillance scheme in the preceding two years. This, despite an obligation for occupational physicians in the Netherlands to report occupational disease. This is an indication that bakers' asthma is underreported, not recognized or under diagnosed by occupational physicians in the Netherlands.

This thesis shows that the interdisciplinary approach by a specialized centre can be a solution to those difficulties in contemporary (occupational) health care concerning the approach to work-related respiratory health problems. The interdisciplinary approach in health care clearly showed its benefits in all studies as outlined before. However, in the present situation, such interdisciplinary approaches can only develop in more specialized units in the occupational health care system or in more specialized expertise centres as were established in different university centres under the Minister of Health, Ms. Borst, in 1999. However, over recent years, these centres do not receive any public funding and are fully dependent on private funding, which will be highlighted later on. Despite these practical and financial constraints, interdisciplinary collaboration, as it developed for occupational respiratory diseases did create new opportunities, including:

- the availability of specific epidemiological and clinical knowledge and expertise to recognize, diagnose and manage work-related respiratory disorders;
- the opportunity to investigate workers with specific diagnostic facilities;
- the recognition of the need for exposure assessment by specialized industrial hygienists.
- the realization of opportunities for prevention.

How should present gaps in occupational health be solved?

In 2003 the Advisory Council for Health Research (RGO) drew up an inventory of the knowledge gaps in the Public Health area. It was concluded that the potential for research in occupational medicine in the Netherlands is relatively limited, especially considering the research required to improve the quality of medical care and the magnitude of the social problems that this care is facing.[24] Their conclusions were (among others) that:

1. Physicians working in occupational health services are given little opportunity to participate in scientific research together with academic and non-academic institutions.
2. There is only limited exchange between the research community and those working in the field. The collaboration between research institutions and institutions whose mission is to disseminate the results of research could be improved considerably.
3. Within the present training programme for medical officers there is a lack of more extensive and more flexible facilities for training in scientific research.
4. In the basic curriculum of most medical training programmes, little or no attention is given to occupational medicine.

By integrating epidemiology, industrial hygiene, clinical and occupational medicine, this interdisciplinary approach provided the opportunity to participate in scientific research in the field of occupational medicine together with academic and non-academic institutions. It also improved the contact between the research community and those working in the field. NECORD is a specialized centre in work-related respiratory disorders and plays a key role in the interdisciplinary approach. Further, the interdisciplinary approach provides the possibility to transfer knowledge in the field of occupational medicine. For example, the developed knowledge could be incorporated in the basic curriculum of medicine and occupational medicine in order to close the gap between the academic world and occupational health practice. These effects are comparable to the intended goal of so called "Academic workplaces" in Public Health. These workplaces were used as instruments to improve the collaboration infrastructure between science and practice in the Netherlands, with the difference that the interdisciplinary approach is not funded by public means.[25] There appears to be no public means for further developing this kind of specific occupational health care in the Netherlands. Similarly, occupational health also has become isolated on the European level since there is no access to European research funds because programmes in occupational health do not exist. This leads to a fragmented, nationally-oriented health care with limited access to research facilities, and this will eventually limit research and development in the years to come.

In summary, the interdisciplinary approach to work-related respiratory health problems should not be ignored and is a suitable approach in the field of occupational medicine to improve the quality of medical care available to workers facing work-related respiratory health problems.

Future needs

Despite the benefits of the interdisciplinary approach to work-related respiratory disorders and progress made to date, concerns remain. Future needs include a change of attitude among occupational physicians towards collaboration with clinical health care professionals, improvement of knowledge, a good infrastructure and funding for occupational health care. The Netherlands Society of Occupational Medicine (NVAB) characterizes occupational physicians as the medical specialists on occupational medicine in medical health care.[26 27] However, if occupational physicians truly want to achieve that place in medical health care with respect to respiratory diseases, they should change their attitude towards collaboration with clinical health care and improve their knowledge and expertise on work-related disorders. In case of COPD for example, more knowledge led to an improved chance of recognition, diagnosis and management of the disease in occupational medicine. However, the intended effect of collaboration with chest physicians fell short of expectations due to a lack of a sense of urgency among the majority occupational physicians.[12] Maybe the efforts and possibilities to diagnose work-related diseases and collaboration with clinical health care will improve if (occupational) physicians are funded by insurance companies or by public means for their efforts to diagnose work-related diseases. As a consequence, current and former workers would have free access to the occupational physician or specialized clinical occupational centres, independent of whether employers or others were willing to pay the costs (chapter 5).

Nevertheless, as far as knowledge transfer is concerned there are some rays of hope. First of all, there is the active involvement of the NVAB in developing multidisciplinary guidelines in collaboration with other (para)medical professionals.[28 29] This development provides the opportunity to integrate occupational health care into regular clinical health care.

Another promising development in the collaboration between occupational medicine and clinical health care is the founding of the Netherlands Association of Clinical Occupational Medicine (NVKA) in 2007. Clinical occupational medicine was defined as the domain of medicine in which specific occupational medicine knowledge is applied to patients in a clinical or multidisciplinary setting for whom the factor work is relevant for diagnosis, therapy or prognosis.[30]

Not only is there a need for clinical occupational medicine in the field of occupational respiratory diseases in the Netherlands (this thesis), but there also is a need for clinical occupational medicine in cases of rheumatoid arthritis, gonarthrosis, diabetes mellitus, hearing impairment, psychological symptoms and cardiovascular disorders as well. It appeared that the factor work hardly was considered in the treatment of patients, indicating a gap between occupational and clinical medicine. [31] Specialized centres for clinical occupational medicine can play a role in bridging this gap (this thesis). In recent years the number of occupational clinical centres arose in the Netherlands. However, unfamiliarity with the existence of these occupational clinical centres and the lack of structural funding seems to obstruct further development of such centres.[32]

Therefore, in order to improve the quality of occupational health care, the infrastructure of current occupational health care and funding of occupational health care centres should be improved in order to bridge the gap between occupational medicine and current clinical health care.

Áll stakeholders involved, including employees, employers, government, insurance companies and occupational health professionals, are faced with huge challenges to develop this kind of integrated occupational health care. Even more so in the perspective of the ongoing public debate regarding sustainable employability in work due to plans to raise the age of retirement under the General Old Age Pensions Act (AOW) to 67. This puts occupational health back on the agenda. However, occupational health care in its present form, focussing mainly on sick leave, will not be able to play a relevant role and will have little relevant added value.

In conclusion: current clinical and occupational health care encounter difficulties in their a pproach to work-related respiratory health problems. An interdisciplinary approach, which includes specialized clinical occupational health centres playing a key role, can improve the quality of health care. However, obtaining adequate funding is one of the major problems to ensure free access for workers. Therefore, all stakeholders involved should invest in inter-disciplinary collaboration to achieve sustainable employability in work for those at risk for work-related respiratory health problems.

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Summary

SUMMARY

The knowledge that occupational exposures can lead to respiratory symptoms has been known for centuries. Nowadays we still are being confronted with the impact of occupational exposures from the recent past. For example, the incidence of malignant mesothelioma is still rising due to exposure to asbestos in the past and the number of deaths is predicted to reach a peak in the next decades in several EU member states. Common occupational respiratory tract diseases are rhinitis and laryngitis, tracheitis, bronchitis and bronchiolitis, asthma due to sensitizers and irritants, chronic obstructive pulmonary disease (COPD), cancer and interstitial lung diseases (ILD) like asbestosis, silicosis, hypersensitivity pneumonitis, and granulomatous disease. Occupational respiratory diseases seem to be a never ending story. The World Health Organization (WHO) estimates that worldwide about 50 million new cases of these occupational respiratory diseases emerge every year. Without preventive action, the burden of occupational diseases is expected to increase.

Pneumoconioses were historically the most prevalent occupational lung diseases as a result of industrialization. However, the prevalence in Western countries has been decreasing during the past decades and obstructive lung diseases have increasingly gained importance. More recently, occupational asthma has become the most common occupational lung disease in many Western industrialized countries. Occupational chronic respiratory diseases represent a public health problem with substantial economic implications.

In general, early recognition, diagnosis, management and prevention of occupational diseases is extremely important and possibly can cure or stop progression of disease in the individual worker and may prevent mortality, morbidity and disability in other exposed workers. Further, These steps can save health care utilisation and socio-economic costs. Therefore, physicians seeing workers with respiratory disease should always consider an occupational origin of the respiratory disease. However, occupational lung disease remains poorly diagnosed and managed and inadequately compensated worldwide.

Unfortunately, there appears to be a lack of knowledge of new work-related health risks that can impede timely observation of new risks with potentially irreversible health effects as a consequence. According to The Netherlands Society of Occupational Medicine (NVAB), the occupational physician should be a key figure in the identification and diagnosis of occupational diseases, as it is one of her primary tasks. However, there is a major discrepancy between the (on average) observed number of 30 cases of (occupational) asthma annually, reported by occupational physicians, and the estimated annual number of 500-2000 new cases of asthma on the basis of the size of the population at risk and the expected numbers in surrounding countries, as a result of occupational exposures in the Netherlands. An explanation might be, besides underreporting, that the diagnosis, management and prevention of occupational respiratory diseases is difficult and requires

specific knowledge. In recent years, occupational health care professionals regularly asked the Netherlands Expertise Centre for Occupational Respiratory Disorders (NECORD) for assistance in the approach to worker populations with work-related respiratory health problems. Current occupational health care professionals appeared to experience difficulties in the approach to work-related respiratory health problems they encountered in daily practice. There appeared to be a lack of knowledge and access to the needed disciplines in the approach to the respiratory problems they encountered. To improve the quality of health care for individuals with work-related respiratory disorders, we think that an interdisciplinary approach is a more suitable approach for diagnosis, management and prevention of work-related respiratory disorders on an individual and population level. In this thesis an alternative approach to deliver occupational health care is explored concerning work-related respiratory disorders in various worker populations. This approach is illustrated by a series of structured case studies.

Chapter 2

Several publications indicated a new, potentially severe occupational lung disease in workers exposed to flavourings in North American food processing industries ("popcorn worker's lung", bronchiolitis obliterans syndrome). Within the spectrum of butter flavouring vapours, the chemical diacetyl plays a prominent role. Until 2007, no cases of bronchiolitis obliterans syndrome (BOS) had been reported in the food flavouring producing industries or outside of North America. The occupational health service and the management of the plant asked for assistance to investigate the cohort of chemical workers exposed to diacetyl. The aim of the study was to investigate in a population-based approach whether there were cases of BOS in the cohort, to examine the degree of risk, and to assess exposures.

Three cases of BOS consistent with air trapping on high-resolution computed tomography of the lungs were identified in the highest exposure group of process operators. Two of these cases were lifelong non-smokers. Potential exposures included acetoin, diacetyl, acetaldehyde, and acetic acid, with diacetyl exposures in the range previously reported to be associated with fixed airway obstruction in the microwave popcorn industry.

It was concluded that exposure to an agent during diacetyl production appears to be responsible for causing BOS in chemical process operators, consistent with the suspected role of diacetyl in downstream food production.

Chapter 3

At the end of the study, four new cases of unsuspected BOS were found in the chemical plant producing diacetyl as described in chapter 2. The study in chapter 3 describes an epidemiological survey of a historic cohort of workers from this diacetyl production plant. The aim of the study was to investigate and reconstruct exposures, respiratory symptoms, lung function and exposure–response relationships by modelling available exposure data.

Diacetyl workers reported significantly more respiratory symptoms compared to the general population sample and to a minimally exposed internal reference group. Lung function did not differ between groups. A positive relationship between exposure and lung function (FEV_1) was found.
The excess of respiratory symptoms in this retrospective cohort suggests that diacetyl production poses an occupational health hazard. Limited historical exposure data did not support a quantitative individual diacetyl exposure-response relationship, but the findings suggest that it would be prudent to take preventative measures.

Chapter 4

This study was occasioned by the occupational health service of a liquid detergent production plant. In a pilot study, it appeared that highly exposed workers were sensitised to a detergent enzyme (Savinase). Until then, no occupational respiratory allergies had been reported in the literature in detergent production industries related to liquid detergent enzymes. The occupational health service and the management of the plant asked for assistance to investigate sensitisation among workers handling liquid detergent enzymes and the respiratory health among sensitised workers. Furthermore, if an increased risk were to be found, how best to prevent health effects in the future.
Workers were exposed to different detergent enzymes like proteases, α-amylase, lipase and cellulase. The highest exposures occurred in the mixing area. Liquid spills with concentrated enzyme preparations and leakage of enzymes during weighing, transportation and filling were causing workplace contaminations and subsequently leading to both dermal and inhalation exposure for workers. Workers with the highest exposures reported significantly more work-related symptoms of itching nose and sneezing and marginally significant more symptoms of wheezing compared with the lowest exposed group. Fifteen workers were sensitised to one or more detergent enzymes. A marginally statistically significant gradient in sensitisation across the exposure categories was found. There was a clinical case of occupational asthma and two others with probable occupational rhinitis.
It was concluded that workers exposed to liquid detergent enzymes are at risk of developing sensitisation and respiratory allergy. The approach used in this study to identify sensitised workers could be seen as the first round of surveillance. Nowadays the plant is using the approach as a basis for an occupational health surveillance program to promote the health, safety and quality of life of workers exposed to liquid detergent enzymes.

Chapter 5

For several years, cast-house workers in an aluminium producing plant in the Netherlands reported ongoing respiratory symptoms. Several hygienic control measures had already been implemented but they did not lead to a decrease in reported symptoms. The occupational

health service and the management of the plant asked for assistance to investigate the exact nature and potential causes of this problem. We have studied (peak)exposures, prevalence of respiratory symptoms and lung function among aluminium cast-house workers.
The average daily mean exposures to inhalable dust, metals, hydrogen fluoride, fluor salts and sulphur dioxide were relatively low compared to reference values. Airflow patterns in the hall were disturbed regularly and resulted in spreading pot emissions with high concentrations of fluorides around the workplace. Occasionally, peak exposures to chlorine gas occurred due to production process disturbances. Workers reported significantly more respiratory symptoms and showed in regression analysis significantly lower lung function (FEV_1 and FVC values) compared to a general population sample. Workers in the highest exposed group reported significantly more eye symptoms during their work compared to a minimally irritant-exposed internal reference group. The moderately exposed group reported significantly more chest tightness upon awakening. Lung function did not differ between groups.
This epidemiological study indicated that working in the cast-house of the aluminium plant poses a respiratory hazard. Exposure-response relationships could not be demonstrated but this study supports the prudence of taking preventive measures in the work-environment with a focus on (peak)exposures to irritants.

Chapter 6

A (nationwide) medical surveillance program on occupational asthma among bakery workers needed an effective and efficient strategy. Practically it was not feasible to evaluate all bakery workers who worked scattered around the Netherlands. Sensitisation to wheat allergens is a critical step in the development of occupational asthma. A triage system which made use of epidemiological and diagnostic prediction principles made it feasible to select workers with a high risk of being sensitised to wheat allergens. Occupational physicians decided which selected workers should be referred for further clinical investigation in specialized outpatient clinics. In the study in this chapter, we clinically evaluated a population of flour and enzyme exposed traditional bakery workers identified by an earlier developed simple triage system. In addition, we explored factors predictive of non-specific bronchial hyperresponsiveness (BHR) in order to optimize the triage approach in an attempt to extend it to specialized occupational respiratory clinics.
The overall prevalence of (probable) occupational respiratory allergy among referred workers was 45%. Most of them were categorised in the high probability group of being sensitised by an earlier developed prediction model. Of all referred workers, 11% were diagnosed with occupational asthma (OA) and 44 % with probable occupational rhinitis or rhinoconjunctivitis.
The strongest predictors of BHR were: wheezing, respiratory symptoms or eye symptoms when exposed to pets, problems with breathing associated with warm to cold transitions and when exposed to baking/frying odours.

It was concluded that this study shows that a simple triage system is capable of detecting occupational asthma cases among bakery workers that likely otherwise would not have been detected. Improvement of prediction models for occupational asthma in the clinical setting seems possible but more research in a larger sample is needed.

In general, the studies described in this thesis explore work-related respiratory health problems in an interdisciplinary way by integrating concepts from industrial hygiene, occupational medicine, epidemiology and clinical health care. Most occupational health services employ industrial hygienists, safety engineers, occupational health nurses and occupational physicians among their staff. Although these disciplines usually work together to recognize and manage work-related diseases, among many other tasks, they had problems identifying and managing the outlined work-related respiratory health problems in this thesis. The reason that the occurrence of disease was not recognized in these concrete situations is a combination of many factors. Important factors were the lack of collaboration between occupational physicians and clinical physicians and that current occupational health care is seldom focused on recognizing and preventing work-related disorders.
This thesis shows that there was a clear need for knowledge on and research facilities for occupational medicine concerning respiratory disorders. The outlined interdisciplinary approach appeared to be essential in elucidating respiratory health problems in the work environment beyond the competence of the common occupational health service.
Interdisciplinary collaboration delivered the necessary knowledge and infrastructure to investigate individual workers and populations in a systematic way leading to recognition, diagnosis and management of occupational respiratory health problems. The collaboration also provided an impulse to implement preventive measures.
However, in the present situation, such interdisciplinary approaches can only develop in more specialized units in the occupational health care system or in more specialized expertise centres. Despite practical and financial constraints, interdisciplinary collaboration, as it developed for occupational respiratory diseases in the Netherlands, did create new opportunities, including:

- the availability of specific epidemiological and clinical knowledge and expertise to recognize, diagnose and manage work-related respiratory disorders;
- the opportunity to investigate workers with specific diagnostic facilities;
- the recognition of the need for exposure assessment by specialized industrial hygienists.
- the realization of opportunities for prevention.

Unfortunately, there appears to be no public monetary means for further developing this kind of specific occupational health care in the Netherlands. Similarly, occupational health also becomes isolated on the European level since there is no access to European research funds because programmes in occupational health do not exist. This leads to a fragmented, nationally oriented health care system with limited access to research facilities, and this will eventually limit research and development in the years to come.

In summary, the interdisciplinary approach to work-related respiratory health problems should not be ignored and is a suitable approach in the field of occupational medicine to improve the quality of medical care available to workers facing work-related respiratory health problems.

Despite the benefits of the interdisciplinary approach to work-related respiratory disorders and progress made, concerns remain. Future needs are a change of attitude among occupational physicians towards collaboration with clinical health care, improvement of knowledge, a good infrastructure and funding for occupational health care.

Therefore, in order to improve the quality of occupational health care, the infrastructure of current occupational health care and funding of health care centres should be improved.

All stakeholders involved employees, employers, government, insurance companies and occupational health professionals are faced with huge challenges to develop this kind of integrated occupational health care. Even more so in the perspective of the ongoing public debate regarding sustainable employability in work due to plans to raise the age of retirement under the General Old Age Pensions Act (AOW) to 67. This puts occupational health back on the agenda. However, occupational health care in its present form, focussing mainly on sick leave, will not be able to play a relevant role and will have little relevant added value.

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Samenvatting

SAMENVATTING

Dat beroepsmatige blootstellingen tot respiratoire klachten kunnen leiden is al eeuwen bekend. Tegenwoordig worden we nog steeds geconfronteerd met de gevolgen van beroepsmatige blootstellingen uit het verleden. De incidentie van het maligne mesothelioom bijvoorbeeld stijgt nog steeds als gevolg van asbestblootstelling in het verleden en het aantal doden zal naar alle waarschijnlijkheid in de komende decennia een piek bereiken in verscheidene EU lidstaten. Veel voorkomende arbeidsgerelateerde respiratoire aandoeningen zijn, rhinitis, laryngitis, tracheitis, bronchitis, bronchiolitis, astma als gevolg van sensibiliserende stoffen en irritantia, COPD, kanker en interstitiële longziekten zoals asbestose, silicose, extrinsieke allergische alveolitis en granulomateuze aandoeningen. Respiratoire aandoeningen als gevolg van beroepsmatige blootstellingen lijken een "never ending story" te zijn.

De 'World Health Organization' (WHO) schat dat wereldwijd elk jaar ongeveer 50 miljoen nieuwe gevallen van arbeidsgerelateerde respiratoire aandoeningen zich voor zullen doen. Zonder preventieve maatregelen zal de omvang van beroepsziekten alleen maar toenemen.

Historisch gezien waren pneumoconiosen (stoflongen) als gevolg van industrialisatie de meest voorkomende arbeidsgerelateerde respiratoire aandoeningen.

Echter, de prevalentie is in de westerse landen de laatste decennia afgenomen en het aandeel van obstructieve longaandoeningen is aanzienlijk belangrijker geworden.

Inmiddels is beroepsastma de meest voorkomende arbeidsgerelateerde respiratoire aandoening in de westerse geïndustrialiseerde wereld geworden.

Chronische arbeidsgerelateerde respiratoire aandoeningen vormen een maatschappelijk gezondheidsprobleem met aanzienlijke economische gevolgen.

In zijn algemeenheid is vroege herkenning, diagnose, aanpak en preventie van beroepsziekten uitermate belangrijk. Als gevolg daarvan kan mogelijk de ziekte in individuele gevallen worden genezen of gestopt en sterfte, ziekte en beperkingen bij andere blootgestelde werkenden worden voorkomen. Verder kunnen deze stappen besparingen opleveren op het gebruik van gezondheidszorg en sociaal-economische kosten. Daarom moeten artsen die werkenden zien met respiratoire klachten altijd bedacht zijn op een arbeidsgerelateerde oorzaak. Echter, arbeidsgerelateerde respiratoire aandoeningen worden wereldwijd slecht gediagnosticeerd, behandeld en onvoldoende gecompenseerd.

Helaas blijkt er een gebrek aan kennis te zijn van nieuwe arbeidsgerelateerde gezondheidsrisico's waardoor nieuwe risico's te laat worden herkend met mogelijk onherstelbare gezondheidseffecten als gevolg.

Volgens de Nederlandse Vereniging voor Arbeids- en Bedrijfsgeneeskunde (NVAB) zou de bedrijfsarts een sleutelfiguur moeten zijn bij de herkenning en diagnostiek van beroepsziekten aangezien het gaat om een van zijn/haar kerntaken.

Echter, er bestaat een grote discrepantie tussen het jaarlijks aantal gemelde gevallen van

(arbeidsgerelateerd) astma door bedrijfsartsen en het geschatte aantal nieuwe gevallen van beroepsastma in Nederland op basis van gegevens uit de omringende landen.

Een verklaring daarvoor zou kunnen zijn, naast het feit dat gevallen niet worden gemeld, dat de diagnose, aanpak en preventie van arbeidsgerelateerde respiratoire aandoeningen moeilijk is en specifieke kennis behoeft.

In de afgelopen jaren hebben professionals in de bedrijfsgezondheidszorg regelmatig een beroep gedaan op het Nederlands Kenniscentrum Arbeid en Longaandoeningen (NKAL) om ze te helpen bij de aanpak van werknemerpopulaties met arbeidsgerelateerde respiratoire klachten. De huidige professionals in de bedijfsgezondheidszorg bleken moeilijkheden te ervaren in de aanpak van arbeidsgerelateerde aandoeningen die ze in hun dagelijkse praktijk tegen kwamen. Er bleek een gebrek aan kennis te zijn en toegang tot de noodzakelijke disciplines om de respiratoire problemen die men tegenkwam adequaat aan te pakken.

Om de kwaliteit van gezondheidszorg voor individuen met arbeidsgerelateerde respiratoire aandoeningen te verbeteren, denken we dat een interdisciplinaire benadering een meer geschikte aanpak is voor de diagnose, aanpak en preventie van arbeidsgerelateerde respiratoire aandoeningen op zowel een individueel als populatieniveau.

In dit proefschrift wordt een alternatieve benadering van bedrijfsgezondheidszorg verkend voor wat betreft arbeidsgerelateerde respiratoire aandoeningen in verschillende werknemerpopulaties.

Deze benadering wordt geïllustreerd aan de hand van een aantal studies.

Hoofdstuk 2

Verscheidene wetenschappelijke publicaties beschreven aanwijzingen voor een mogelijk ernstige beroepslongaandoening ("popcornwerkers long", bronchiolitis obliterans syndroom) in de Noord-Amerikaanse voedingsmiddelenindustrie die in verband werd gebracht met blootstelling aan diacetyl.

In het spectrum van boteraroma dampen, speelt het chemische diacetyl een belangrijke rol. Tot 2007 werden er geen gevallen van het bronchiolitis obliterans syndroom (BOS) gerapporteerd in de smaakstoffen industrie buiten Noord-Amerika.

De Arbo-dienst en het management van de fabriek vroegen om hulp om de groep werknemers te onderzoeken die waren blootgesteld aan diacetyl. Het doel van de studie was om te onderzoeken of er gevallen van BOS in de blootgestelde groep werknemers aanwezig waren, het risico te bepalen en de blootstelling in kaart te brengen.

Drie gevallen van BOS werden met behulp van beeldvormend onderzoek (HRCT) onderzoek gevonden in de hoogst blootgestelde groep van procesoperators. Twee van deze gevallen hadden nog nooit gerookt. Er was sprake van mogelijke blootstelling aan acetoine, diacetyl, aceetaldehyde en azijnzuur. De blootstellingniveaus aan diacetyl waren vergelijkbaar met de niveaus zoals gerapporteerd in de popcornindustrie die in verband waren gebracht met irreversibele luchtwegobstructie. Een stof gedurende de diacetyl productie bleek verantwoordelijk te zijn voor het veroorzaken van BOS in de groep procesoperators in de chemische industrie. De verdachte rol van diacetyl daarin was overeenkomstig de bevindingen in de voedingsmiddelen industrie.

Hoofdstuk 3

Uiteindelijk werden er in de chemische fabriek die diacetyl produceerde zoals beschreven in hoofdstuk 2 vier nieuwe gevallen van BOS gevonden.

De studie in hoofdstuk 3 beschrijft een epidemiologisch onderzoek van een groep (ex)werknemers van de diacetylfabriek. Het doel van de studie was om blootstellingen te reconstrueren en respiratoire klachten, longfunctie en blootstelling-reponse relaties te onderzoeken.

De diacetyl werknemers rapporteerden significant meer respiratoire klachten in vergelijking tot de algemene bevolking en in vergelijking met een interne referentiegroep.

De longfunctie verschilde niet tussen de diverse groepen werknemers. Er werd een positieve relatie gevonden tussen blootstelling en longfunctie (FEV_1).

De overmaat aan respiratoire klachten in de groep diacetyl werknemers suggereert dat de productie van diacetyl een arbeidsgebonden risico met zich meebrengt.

De beperkte historische blootstellinggegevens ondersteunde niet een blootstelling-respons-relatie, maar de bevindingen suggereren wel dat het verstandig zou zijn om preventieve maatregelen te treffen.

Hoofdstuk 4

Deze studie werd mogelijk gemaakt door de Arbo-dienst van een vloeibare wasmiddelen fabriek. Uit een pilotstudy bleek dat hoog blootgestelde werknemers gesensibiliseerd waren voor het wasmiddel enzym (Savinase).

Tot dan toe waren er geen gevallen van respiratoire allergie in de literatuur beschreven in verband met blootstelling aan vloeibare wasmiddel enzymen in de wasmiddelen industrie.

De Arbo-dienst en het management van de fabriek vroegen om hulp voor onderzoek naar sensibilisatie en respiratoire problematiek onder werknemers die met vloeibare wasmiddel enzymen in aanraking kwamen.

Als er een verhoogd risico op gezondheidseffecten zou worden gevonden dan wilde men weten hoe men het beste gezondheidseffecten in de toekomst kan voorkomen.

De werknemers werden aan verschillende enzymen blootgesteld zoals, protease, α-amylase, lipase en cellulase. De hoogste blootstelling deed zich voor bij het mengen. Het morsen van vloeibare geconcentreerde enzympreparaten en het lekken van enzymen gedurende het wegen, transporteren en het vullen besmette de werkvloer en leidde vervolgens tot huid- en respiratoire blootstelling van werknemers. Werknemers met de hoogste blootstelling rapporteerden significant meer arbeidsgerelateerde klachten van jeuk in de neus en niezen, en marginaal significant meer klachten van piepen op de borst in vergelijking tot de laagst blootgestelde groep werknemers. Vijftien werknemers waren voor een of meerdere wasmiddelenzymen gesensibiliseerd. Er werd een marginaal significante blootstelling-responsrelatie gevonden tussen de mate van blootstelling en sensibilisatie.

Er werd een geval van beroepsastma gevonden en twee gevallen van (waarschijnlijk) beroepsrhinitis.

Er werd geconcludeerd dat werknemers die werden blootgesteld aan vloeibare wasmiddelenzymen het risico lopen om gesensibiliseerd te raken en respiratoire allergie te ontwikkelen. De aanpak in de studie om gesensibiliseerde werknemers op te sporen kon worden gezien als de eerste ronde van een periodiek arbeidsgezondheidskundig onderzoek. Tegenwoordig gebruikt de fabriek de aanpak als basis voor een gezondheidsbewakingsprogramma om de gezondheid, veiligheid en kwaliteit van leven van werknemers die blootgesteld worden aan vloeibare wasmiddelenzymen te bevorderen

Hoofdstuk 5

Al verscheidene jaren rapporteerden aluminiumgieters in een aluminium producerend bedrijf in Nederland respiratoire klachten. Ondanks allerlei arbeidshygiënische interventies leidden de getroffen maatregelen niet tot een afname van respiratoire klachten. De Arbo-dienst en het management van het bedrijf vroegen om hulp om de aard en mogelijke oorzaken van dit probleem te onderzoeken. We hebben daarop (piek)blootstellingen, de prevalentie van respiratoire klachten en longfunctie van aluminiumgieters onderzocht.

De gemiddelde dagblootstelling aan inhaleerbaar stof, metalen, waterstoffluoride, fluorzouten en zwaveldioxide waren relatief lag in vergelijking tot referentiewaarden.

De luchtstroom in de werkhal werd regelmatig verstoord met als gevolg dat emissies uit de pannen met hoge concentraties fluoride over de werkvloer werden verspreid. Zo nu en dan deden er zich piekblootstellingen aan chloorgas voor als gevolg van storingen in het productieproces.

De werknemers rapporteerden significant meer respiratoire klachten en hadden in een regressieanalyse een significant slechtere longfunctie in vergelijking tot een steekproef uit de algemene bevolking. De hoogst blootgestelde groep werknemers rapporteerden significant meer oogklachten gedurende hun werk in vergelijking tot werknemers die nauwelijks werden blootgesteld aan irriterende stoffen. De matig hoog blootgestelde groep rapporteerde significant meer benauwdheidsklachten bij het wakker worden. Er werden geen verschillen gevonden in longfunctie tussen de blootstellingsgroepen.

De epidemiologische studie leverde aanwijzingen op dat het werken in de aluminiumgieterij van het bedrijf een risico met zich meebracht voor de luchtwegen. Blootstellings-respons relaties konden niet worden aangetoond maar de bevindingen van deze studie suggereren wel dat het verstandig zou zijn om preventieve maatregelen te treffen op de werkvloer met het oog op (piek)blootstellingen aan irriterende stoffen.

Hoofdstuk 6

Een (nationaal) gezondheidsbewakingssysteem voor bakkerij werknemers voor wat betreft beroepsastma behoefde een effectieve en efficiënte aanpak. Praktisch gezien was het niet haalbaar om alle bakkerij werknemers te onderzoeken aangezien ze verspreid werkten over heel Nederland. Sensibilisatie voor meelstofallergenen is een kritische stap op weg naar het ontwikkelen van beroepsastma. Een triage methodiek die gebruik maakte van epidemiologische en diagnostische voorspellende principes maakte het mogelijk om werknemers te selecteren met een hoog risico om gesensibiliseerd te zijn voor meelstof. Bedrijfsartsen beslisten welke geselecteerde werknemers moesten worden verwezen voor vervolgonderzoek naar een gespecialiseerde polikliniek. In dit hoofdstuk beschrijven we een klinisch geëvalueerde populatie die is blootgesteld aan meel en enzymen in ambachtelijke bakkerijen en zijn opgespoord door een eerder ontwikkeld eenvoudig triage systeem. Vervolgens, hebben we voorspellers van aspecifieke bronchiale hyperreactiviteit (BHR) verkend, in een poging om de triage methodiek te optimaliseren en door te trekken naar de gespecialiseerde poliklinieken op het gebied van arbeidsgerelateerde respiratoire aandoeningen.

De prevalentie van (waarschijnlijk) arbeidsgerelateerde respiratoire allergie in de groep verwezen werknemers was 45%. De meesten waren ingedeeld in de groep met de hoogste waarschijnlijkheid om gesensibiliseerd te zijn op basis van het eerder ontwikkelde predictiemodel. Van alle verwezen werknemers was er 11% gediagnosticeerd met beroepsastma en 44% met waarschijnlijk beroepsrhinitis of rhinoconjunctivitis.

De sterkste voorspellers voor BHR waren: piepen, respiratoire - of oogklachten als men werd blootgesteld aan huisdieren, problemen met ademhalen van warme naar koude omstandigheden en als men werd blootgesteld aan bak- en braadlucht.

Er werd geconcludeerd dat een eenvoudig triage systeem in staat is om gevallen van beroepsastma op te sporen bij bakkerij werknemers die anders waarschijnlijk niet zouden zijn ontdekt. Verbetering van predictiemodellen voor beroepsastma in de klinische setting lijkt mogelijk maar meer onderzoek in een grotere steekproef is nodig.

In zijn algemeenheid exploreren de studies zoals beschreven in dit proefschrift, arbeidsgerelateerde respiratoire problemen op een interdisciplinaire wijze. Dit door concepten uit de arbeidshygiëne, arbeidsgeneeskunde, epidemiologie en klinische gezondheidszorg te integreren. De meeste Arbo-diensten beschikken over arbeidshygiënisten, veiligheidskundigen, Arbo-verpleegkundigen en bedrijfsartsen. Hoewel deze disciplines gewoonlijk samenwerken om naast andere taken, arbeidsgerelateerde ziekten te herkennen en aan te pakken, had men toch problemen om de geschetste arbeidsgerelateerde respiratoire problemen te identificeren en aan te pakken. De reden dat de ziekten niet werden herkend in deze concrete situaties heeft te maken met een combinatie van factoren. Belangrijke factoren waren het gebrek aan samenwerking van bedrijfsartsen met de curatieve gezondheidszorg en dat de huidige bedrijfs-

gezondheidszorg zelden gefocust is op het herkennen en voorkomen van arbeidsgerelateerde aandoeningen.
Dit proefschrift laat zien dat er een behoefte bestaat aan kennis en onderzoeksfaciliteiten voor arbeids- en bedrijfsgeneeskunde als het om arbeidsgerelateerde respiratoire problematiek gaat. De geschetste interdisciplinaire benadering bleek van essentieel belang te zijn om de arbeidsgerelateerde respiratoire problemen op te helderen die het competentie niveau van de gemiddelde Arbo-dienst overstijgt. Interdisciplinaire samenwerking leverde de noodzakelijke kennis en infrastructuur om zowel werkenden individuen en populaties op een systematische wijze te onderzoeken en arbeidsgerelateerde respiratoire aandoeningen te herkennen, te diagnosticeren en aan te pakken. De samenwerking gaf ook een impuls om preventieve maatregelen te implementeren.
Echter, in de huidige situatie, kunnen zulke interdisciplinaire benaderingen alleen maar ontwikkelen in meer gespecialiseerde eenheden binnen de bedrijfsgezondheidszorg of in meer gespecialiseerde expertisecentra.
Ondanks de praktische en financiële beperkingen creëerde de interdisciplinaire benadering voor arbeidsgerelateerde respiratoire aandoeningen in Nederland nieuwe kansen zoals:

- De beschikbaarheid van specifieke epidemiologische en klinische kennis en expertise om arbeidsgerelateerde respiratoire aandoeningen te herkennen, te diagnosticeren en aan te pakken.
- De gelegenheid om werkenden te onderzoeken met specifieke diagnostische faciliteiten.
- De herkenning van de noodzaak om de blootstelling in kaart te brengen door gespecialiseerde arbeidshygiënisten.
- De realisatie van kansen voor het treffen van preventieve maatregelen.

Helaas blijken er geen publieke geldmiddelen beschikbaar te zijn voor de verdere ontwikkeling van deze specifieke vorm van bedrijfsgezondheidszorg.
Ook op Europees niveau komt de bedrijfsgezondheidszorg in een isolement daar er geen toegang is tot Europese onderzoeksgelden omdat bedrijfsgezondheidsprogramma's niet bestaan. Dit leidt tot een gefragmenteerd, nationaal georiënteerd gezondheidszorgsysteem met beperkte toegang tot onderzoeksfaciliteiten. Als gevolg hiervan zullen op termijn onderzoek en inhoudelijke ontwikkeling op dit terrein stagneren.

Samenvattend, de interdisciplinaire benadering van arbeidsgerelateerde respiratoire problematiek moet niet worden genegeerd en is een geschikte benadering binnen de bedrijfsgezondheidszorg om de kwaliteit van zorg voor werkenden te verbeteren voor wat betreft arbeidsgerelateerde respiratoire problematiek.
Ondanks de voordelen van de interdisciplinaire benadering van arbeidsgerelateerde respiratoire aandoeningen en de vooruitgang die is geboekt, blijven er zorgen.

De attitude van bedrijfsartsen met betrekking tot samenwerking met de curatieve gezondheidszorg zal moeten veranderen, het kennisniveau zal moeten toenemen en er zal een goede infrastructuur en financiering moeten komen.
Om de kwaliteit van de bedrijfsgezondheidszorg te verbeteren zal de infrastructuur van de huidige bedrijfsgezondheidszorg en de financiering van gezondheidscentra moeten verbeteren. Alle betrokken aandeelhouders – werknemers, werkgevers, de overheid, verzekeringsmaat-schappijen en professionals in de bedrijfsgezondheidszorg – staan voor een grote uitdaging om deze vorm van integrale bedrijfsgezondheidszorg te ontwikkelen.
Zeker in het perspectief van het publieke debat, dat gaande is betreffende duurzame inzet-baarheid in werk en plannen om de AOW-leeftijd te verhogen naar 67 jaar.
Dit zet bedrijfsgezondheidszorg weer op de agenda.
Echter, bedrijfsgezondheidszorg in zijn huidige vorm, voornamelijk gericht op ziekteverzuim, zal niet in staat zijn om een relevante rol te spelen en zal weinig toegevoegde waarde hebben.

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Curriculum Vitae

Frits van Rooy werd op 8 augustus 1961 te Valkenswaard geboren.
In 1980 behaalde hij zijn VWO diploma aan het Carolus Borromeus College te Helmond. Vervolgens deed hij in 1980 een colloquium doctum scheikunde om in 1981 te kunnen starten met zijn studie geneeskunde aan de toenmalige Katholieke Universiteit Nijmegen.
In 1988 voltooide hij de opleiding geneeskunde en vervulde aansluitend zijn militaire dienstplicht bij de Koninklijke Luchtmacht (Klu) als officier-arts. Na zijn dienstplicht heeft hij nog tot 1992 als officier-arts bij de Klu gewerkt. Vanaf 1991-1994 specialiseerde hij zich in de arbeids- en bedrijfsgeneeskunde te Nijmegen. Op zoek naar de toegevoegde waarde van de arbeids- en bedrijfsgeneeskunde kwam hij in 1999 in contact met Prof.dr. H.Th.M. Folgering. Het gevolg daarvan was dat hij vanaf 2000-2005 werkzaam is geweest bij het Nederlands Kenniscentrum Arbeid en Longaandoeningen (NKAL) te Groesbeek op het gebied van de klinische arbeidsgeneeskunde. In die tijd is contact gelegd met Prof.dr. D.J.J. Heederik en is de samenwerking ontstaan met het Institute for Risk assessment Sciences (IRAS) van de Universiteit Utrecht. In samenwerking met IRAS, NKAL en Prof.dr. J-W.J. Lammers van het Universitair Medisch Centrum Utrecht (UMCU) startte hij in 2004 met het promotietraject dat heeft geresulteerd in dit proefschrift. Na het stopzetten van de subsidiering van het NKAL door de overheid, is het NKAL in 2005 voortgezet als Stichting Nederlands Kenniscentrum Arbeid en Longaandoeningen. Hij maakt tot op de dag van vandaag daar nog onderdeel van uit. Parallel aan al deze ontwikkelingen is hij vanaf 1992 werkzaam geweest voor bedrijfsgezondheidsdiensten. Op dit moment werkt hij bij de Arbo Unie waaronder het Expertise Centrum Toxische Stoffen. Daarnaast is hij vanaf 1999 lid van de medisch toxicologische commissie van het chemiekaartenboek, participeert hij vanaf 2009 in het International Chemical Safety Cards project van de World Health Organization/ International Labour Organization en is hij sinds 2010 in opleiding voor gezondheidskundig adviseur gevaarlijke stoffen (GAGS).

Frits van Rooy is an occupational physician with a focus on occupational respiratory disorders. He is working at the Institute for Risk Assessment Sciences (IRAS) at Utrecht University, the Netherlands Expertise Centre for Occupational Respiratory Disorders (NECORD), and Arbo Unie.

This thesis describes a series of studies in the field of occupational medicine on respiratory health problems that have occurred in different industrial settings. These studies explore an interdisciplinary approach to occupational respiratory health problems by integrating concepts from industrial hygiene, occupational medicine, epidemiology and clinical health care.