Exposure intervention and health impact assessment

The example of baker's asthma

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The example of baker's asthma

Blootstellinginterventies en een beoordeling van de impact op gezondheid *Bakkersastma als een voorbeeld*

(met samenvatting in het Nederlands)

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Chapter 1

General introduction

Occupational flour dust exposure and related health effects

In the past two decades several studies have been performed in the Dutch bakery sector assessing occupational exposure levels and its relationship with occupational (allergic) respiratory diseases. In the early nineties Houba et al. published several papers describing occupational exposure levels to flour dust, wheat allergen and fungal α-amylase in bakery workers[1,2]. As a result, the first epidemiological study could be performed evaluating specific exposure-response relationships between exposure to occupational allergens and occupational allergy and respiratory symptoms[3,4]. The studies showed strong exposure-sensitization relationships for exposure to both allergens and a strong indication for exposure-response relationship with respiratory symptoms. They also showed that work related sensitization is associated with the risk of developing allergic respiratory symptoms. Studies are often difficult to compare because exposure and symptoms have been measured differently and study populations vary. Overall, conclusions of the Dutch studies were consistent with findings from the UK, Germany and several other developed countries[5-26].

Generally, occupational exposure levels in bakeries are substantial for both flour dust and specific allergens, especially high peak exposures occur during specific production activities[27]. Exposure levels seem to be comparable between countries for flour dust but can be very different for allergen levels. In the Netherlands primarily wheat flour is used in the production of bread and pastry and the use of other grains is negligible in studies on work related exposure. For other countries, for example Germany where rye flour is one of the predominantly used products, this might be very different[28]. The exposure levels presented in the numerous studies performed throughout the years do not indicate that occupational exposure has been changing substantially over time. This was confirmed in a recent study by Creely et al. evaluating occupational exposure trends for a large variety of compounds and industries[29]. They identified no exposure trends for flour dust. This is contrary to what is observed in most other industries where downward exposure trends of 5-10% annually are common. These trends are often ascribed to generic technical advancements in these industries or the setting of occupational exposure limits, but can generally not be related to specific interventions[29,30].

In the Netherlands the study of Houba and colleagues created awareness of the potential disease burden related to occupational exposure to flour dust. The study resulted in questions in the Dutch Parliament on adverse health effects of flour dust exposure and limits for occupational exposure, eventually leading to several (research) initiatives. In 2000/2001 the possibilities for deriving exposure limits for occupational allergens from available data was explored. Dutch epidemiological data for wheat allergens were re-analyzed as an example[31-33]. These data indicated that sensitization and symptoms can occur even at very low exposure levels, suggesting the absence of a “no effect level” for high molecular weight allergens including wheat allergens and fungal α-amylase. At the same time a new study was initiated to investigate exposure to flour dust and related occupational allergens as well as the prevalence and severity of associated occupational diseases[34,35]. Furthermore, insight had to be obtained into the state of the art with respect to control measures. The results of these studies preceded the start of a covenant in 2001. The covenant was an agreement between the major flour processing sectors (bakeries, flour mills and ingredient producers) and social partners with the main goal to decrease occupational exposure and disease.

Covenants in the Netherlands

In the past decade covenants were introduced in over 50 sectors in the Netherlands covering approximately 50% of Dutch workforce. Covenants were introduced in a large diversity of occupational sectors like construction industry, hairdressing sector, cleaning sector, hospitals, and agricultural sector. The main aims of the covenants were to improve occupational health and safety and decrease sickness absence. Through involvement of employers, labor organizations, the government and other stakeholders, a strong support base was created to set goals and implement agreed changes in a particular sector. In most covenants quantitative goals were set with respect to exposure and/or disease reduction, as well as more general issues like worker education on occupational exposure risks. Both qualitative and quantitative monitoring was performed to evaluate the final results and changes at the end of most covenants. Data obtained in these covenants in some cases provided a good opportunity for research initiatives on occupational exposure and (their relationship with) occupational diseases.

An example of a covenant study is a recently performed probabilistic analysis of the impact of interventions on oncology nurses' exposure to antineoplastic agents in Dutch hospitals[36] [Appendix 1 of this thesis]. In this study data from several exposure surveys combined with questionnaire data on contextual information were used to get detailed insight in changes in the population exposure distribution related to the introduction of various interventions at the workplace (i.e. control measures, elimination of tasks, changes in organization structure). This evaluation learned that several of the initiatives taken in this particular covenant were very successful in reducing population exposure (e.g., elimination of high risk tasks), whereas other interventions, like the introduction of personal protective equipment (i.e. gloves), had only a very limited effect on the exposure distribution. Unfortunately, at the time of this study, no data was available to expand the analysis to health of the oncology nurses.

The covenant in the Dutch flour processing industries focused on reduction of exposure to flour dust and related allergens and reduction of disease burden from occupational respiratory diseases. It included a health surveillance system, set up to monitor the presence of disease in the population at large. The first step in this health surveillance system was the screening of workers for work related sensitization, using a short questionnaire, as a predictor for high risk of developing respiratory symptoms[37,38] . As part of the development of a diagnostic tool a validation dataset was created with extensive serological and symptomatic data on over 850 workers. Workers identified are currently referred for a detailed clinical evaluation to determine severity of their work related symptoms. Diagnosis of severe work related symptoms results in medical and/or hygienic intervention.

The covenant included quantitative aims for exposure reduction of up to 50% in average population exposure levels for flour dust in most of the sectors. To realize this goal, an intervention program was enrolled including education of employers and employees on the risk of occupational exposure and also development and dissemination of state of the art guidelines with respect to control measures. The changes in exposure were evaluated by means of a pre- and post covenant exposure measurement survey. These surveys also contained information on the use of control measures. Contrary to what was the case for the hospital covenant, detailed information on workers health and exposure- response relationships was obtained from the validation dataset and was also available from earlier studies in this sector.

The fact that up till 2000 initiatives to control exposure had failed to substantially decrease occupational exposure in the bakery sector, created the need for a stronger evidence base for effective intervention strategies. First, to provide an evidence base, detailed information on determinants as well as information on effective control measures to reduce occupational exposure needs to be available. Second, to be able to determine the health impact of exposure reduction and compare the effectiveness of different intervention strategies a quantitative health impact assessment model was needed. The availability of data and an advanced understanding of etiology of the diseases of interest provided a good basis for development of a methodology to quantitatively assess health impact of interventions.

Health impact assessment and burden of disease studies in the work environment

Health impact assessment is primarily used in the public health domain as a methodology to assess health consequences from large scale projects or developments (transport, housing, air pollution) affecting large populations[39,40]. In many of these cases health impact assessment involves a wide range of potential health effects and will often be combined with environmental impact assessment. Usually, these assessments are performed in a qualitative or semi-quantitative way and often the evidence base to perform complex analyses is limited[41]. Quantification of effects in health impact assessment is relatively rare as are methodologies to do so[42]. Health impact assessment could benefit from a more quantitative approach but this will require availability of data and access to valid, usable, simulation models.

The first step in estimating effects of changes to the occupational health status of a population is the estimation of the (baseline) disease burden[43,44]. Burden of disease studies are most common in the public health domain and are often performed as input for cost-benefit analysis. In most cases these assessments are performed on a global or national population level using generic indicators of ill health, like DALY'S. One of the best known examples is the global burden of disease study initialized by the World Health Organization[45-51]. But there is also a large variety of examples on the national level available[52-54]. Data are most likely obtained from (inter)national statistics (registries) or population studies. In some cases health policies are prospectively evaluated providing insight in their potential health impact[55-57].

Health impact assessment has hardly penetrated occupational health research. Almost a decade ago the applicability of health impact assessment for (complex) worker situations was emphasized by Rosenberg and colleagues[58]. They advocated "work environment impact assessment" as a methodological framework that should evaluate intended and unintended effects of work place interventions beyond the scope of worker health (e.g. socio-economic effects). Unfortunately, since then very limited development is observed in this field. The field of occupational health continuous to focus primarily on conducting classical exposure assessment surveys and epidemiological studies. Information from the two disciplines is rarely combined to perform (health) impact assessment in light of primary prevention.

Recently several global scale assessments of the occupational disease burden were performed in the occupational health domain[59]. These studies describe the contribution to global disease burden of specific occupational exposures like carcinogens or airborne exposures[60-62]. The results reveal the huge disease burden related to occupational diseases including occupational asthma. In the Netherlands an exploratory study was recently performed assessing the disease burden related to nine selected diseases resulting from occupational exposure to chemicals. This study estimates the disease burden to be approximately 47000 DALY's annually including 1900 deaths[63]. The results contained a substantial amount of uncertainty (approximately a factor 5 for the DALY estimate), although an explicit uncertainty analysis was not given.

The main aim of many of these studies is to assess the magnitude of an (occupational) health problem and to provide guidance to policy makers (i.e. national governments, UN WHO) on emerging issues and priorities in the global or national health programs. Although essential to draw attention to the (occupational) disease burden, the used methodologies clearly have some limitations. The use of (inter)national statistics likely make these studies vulnerable to underreporting of the prevalence's of disease[44,59]. Furthermore the association between exposure and disease in these analyses is generally very crude, not taking into account exposure-response relationships[64]. These approaches can be used to estimate the potential effect of only very general interventions scenarios (e.g. dealing with complete cessation of exposure from populations)[65].

It is clear that these approaches only have limited meaning when evaluating subtle primary preventive measures, resulting in (small) long term exposure reductions. If one wants to move towards primary prevention and management of occupational disease it is important to obtain an evidence base for effective means of interventions. Models need to be more specific taking into account information on exposure (control). Insight in mechanisms of disease development, and exposure-response relationships seems vital[66]. In the case of occupational respiratory diseases, especially occupational asthma, the classic approach of advising complete cessation of exposure lacks a conclusive rationale for its effectiveness as well as having large social-economic implications[67-69]. The potential for occupational exposure reductions may in many cases prove to be a much more (cost) effective approach, especially in small and medium enterprises where relocation of workers will not be an option[70]. Here quantitative health impact assessment can be an important tool for decision makers to obtain (prospective) insight in the potential impact of changes implemented in the work environment. This insight is of importance to ensure decisions will actually result in substantial changes. Quantitative information on health improvement will also assist decision makers to convince both employers and employees to implement the necessary changes. This will be even more the case when information from a health impact assessment is used as input for cost-benefit analyses. Lastly, information from a health impact assessment might inform both policy makers and researchers on achievable goals that can be set within certain time frames with respect to health improvement in occupational populations.

Research objective

Based on the above presented information some specific aims were formulated in this thesis:

1) To develop a generic methodology for quantitative occupational health impact assessment that makes optimal use of available data.
2) To provide an evidence base for effective interventions to decrease the occupational disease burden in Dutch bakeries.
3) To evaluate the impact of the recently implemented covenant program on workers health in Dutch bakeries.

Outline of this thesis

Figure 1 is a diagram showing the different compartments of the study, related to the development of a quantitative health impact assessment model. Basically three main elements can be distinguished in this thesis. First, the information from the covenant studies and other sources is analyzed to obtain detailed information on exposure levels, exposure-response relationships and efficacy of exposure control measures. Detailed insight in the population characteristics is obtained. Furthermore, the baseline situation in the bakery sectors and the results of the covenant program is described. Secondly, the quantitative health impact model is developed. This quantitative approach is referred to as dynamic population-based model and integrates information on the population exposure distributions, exposure-disease relationships and population information. Third, available information is gathered to develop and evaluate a variety of intervention strategies. As shown in the figure the resulting intervention scenarios change the input parameters for the dynamic population based model, allowing the estimation of changes in disease burden related to different scenarios over time.

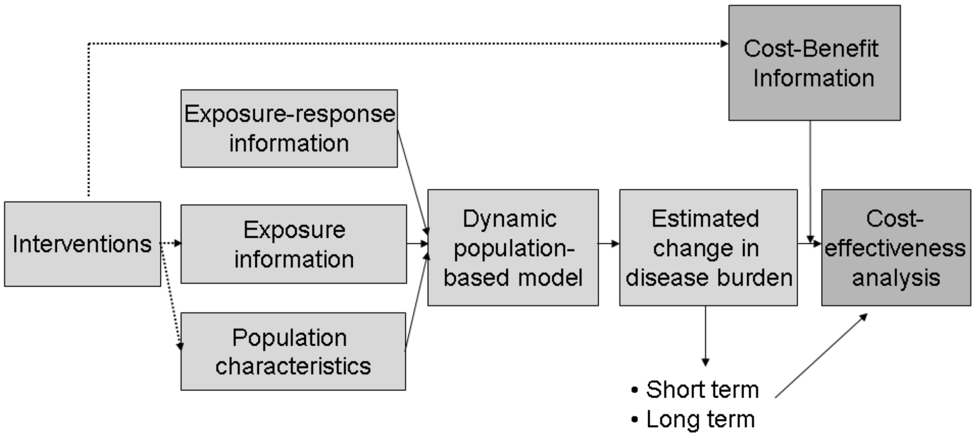

Figure 1. Box diagram for the development of a methodology for occupational health impact assessment

The diagram also contains a box on cost-effectiveness analysis and although this will not be subject of this thesis, it should be acknowledged that in the end an assessment of the health impact from interventions will be only a first, but very important, step in deciding what changes can and need to be made in the work environment.

Chapter 2 of this thesis describes the analyses of the pre-covenant exposure measurement dataset. This study provides the baseline population distribution of exposure levels to flour dust and fungal α-amylase used in several following studies. It also provides detailed information on main determinants of exposure and a limited evaluation of control measures. Predictive exposure models were developed for the different flour processing sectors.

In **Chapter 3** a dataset with real time peak exposure measurements was used to estimate efficacy of a range of control measures on task exposure level. In this study we also presented some examples of how this information can be used to assess the effect of interventions on population exposure levels.

Chapter 4 describes a dataset of 860 bakery workers included in the health surveillance system with detailed information on serology and symptoms. The individual exposure estimates in the study population were generated with the exposure models described in chapter two. The dataset was used to evaluate the shape of dose-response relationships between occupational exposure and work related sensitization and upper and lower respiratory symptoms (including occupational asthma). Mechanistic insight from this study was used in the development of the health impact model (Chapter 6).

Chapter 5 describes the evaluation of the effect of the covenant intervention program on the occupational exposure levels of flour dust and fungal α-amylase in all four flour processing sectors in the Netherlands. The results of this paper were used as the baseline intervention scenario for the bakery sector in the health impact simulations described in Chapter 7.

In **Chapter 6** we describe the development of the quantitative health impact assessment methodology: i.e., the dynamic population-based model. Information from the studies described in the earlier chapters as well as information from additional studies was used to assess input parameters for this model. The resulting model simulates the onset and progression of work related upper and lower respiratory symptoms as well as the occurrence of work related sensitization as a function of individual exposure levels in a population of bakery workers. The dynamic population-based model takes into account time effects as well as population dynamics.

The application of this model to perform a comparison of potential health impacts of a variety of intervention strategies is demonstrated in **Chapter 7**. Health impact of different intervention scenarios was evaluated. Insight was obtained in changes of disease prevalence and incidence figures as well as some other population characteristics (i.e. duration till disease) over a 20 year period. The comparisons of these results give an indication of the most effective design for decreasing the occupational respiratory disease burden in bakery workers and may provide more generic lessons for intervention research.

Chapter 8 discusses the results of this thesis and gives the perspective of the developments in light of current state of the art. It also proposes further developments with respect to quantitative occupational health impact assessment and provides elements for a future research agenda in occupational intervention research.

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CHAPTER 2

Modelling exposure in flour processing sectors in the Netherlands: a baseline measurement in the context of an intervention program

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Abstract

Introduction: Recent studies have shown that even low exposure levels to flour dust and related allergens can cause severe respiratory symptoms. In the Netherlands, the Dutch government and responsible branch organizations (from bakeries, flour mills and bakery ingredient producers) signed a covenant to reduce exposure to flour dust and decrease the prevalence of work related occupational airway disease. This paper describes a sector wide survey to measure exposure to flour dust, wheat allergens and fungal α-amylase. The results are being used to underpin various elements of the covenant.
Methods: A dataset containing 910 personal measurements was compiled from four field studies containing information on exposure and potential determinants. The dataset represents a baseline estimate of exposure for four major flour processing sectors in the Netherlands. Exposure models for all sectors and agents were generated, based on job, tasks and company size, taking into account worker and company as random effect components. Use of control measures and, where possible, their effect were evaluated.
Results: Flour dust and enzyme exposures vary strongly between sectors. The job performed and specific tasks were identified as important determinants of exposure. The number of identified control measures during walk-through surveys, and their effectiveness in reduction of dust exposure was generally limited. The exposure models explained significant exposure variability between companies and workers but performed poorly in explaining day to day differences in exposure.
Discussion: The dataset serves as a baseline estimate and will be compared with a post intervention survey in the near future. The information obtained on control measures can be used to optimize the intervention scenarios that will be implemented in the different sectors by external occupational hygienists. The predictive exposure models will provide a relevant measure of average personal exposure that will be used in the sector wide health surveillance system.

Introduction

Exposure to flour dust and related allergens is one of the most observed causes of occupational airway diseases and occupational asthma in Western Europe[1]. Several studies show that prevalence of sensitization for wheat allergens and fungal α-amylase, and prevalence of occupational airway diseases and occupational asthma are high among workers exposed to flour dust[2-8].

In the Netherlands over 10.000 workers in bakeries, flour mills and baking ingredient production[6] are potentially exposed to high levels of flour dust (>>1mg/m^3) and related allergens. From this group 28 percent is estimated to be sensitized against allergens present in the flour, compared to 2-4 % in the general population. Prevalence of respiratory symptoms among workers exposed to flour can be as high as 60 % of the population depending on the definition of the symptom and the (sub)population under investigation. An analysis of epidemiological survey data[6] showed no conclusive evidence for the existence of an exposure threshold for specific wheat sensitization. The epidemiological analysis indicated that even low inhalable flour dust levels (below 0.5 mg/m^3) might lead to sensitization of workers and cause occupational airway diseases. Yet, the probability of sensitization and development of symptoms increases with increasing exposure[3,6,7,9,10].

Previous studies confirm that exposure to both flour dust and allergens can be high (>>1 mg/m^3 for flour dust, >>10µg/m^3 for wheat allergens and >>10 ng/m^3 for fungal α-amylase)[11-15]. Since recent studies show that time trends do not indicate a decrease in exposure[11,16], more rigorous interventions in baking and flour processing sectors are needed. In the Netherlands the Ministry of Social Affairs and Employment signed a covenant with branch organisations representing the baking industry (traditional and industrial), flour mills and baking ingredient producers with the main goal to reduce exposure to flour dust and decrease the prevalence of work related occupational airway diseases. Key elements of this covenant are: inform workers about hazards, reduce exposure by implementation of a sector wide intervention program, and the installation of a health surveillance system (HSS) with the aim to detect allergic diseases in an early stage by using a formalized questionnaire approach. The underlying rationale of the questionnaire approach to determine individual probabilities of becoming sensitized has been described elsewhere[17].

The overall aim of this paper was to use available exposure measurements from several recently performed exposure surveys to create an extensive exposure database with information on personal exposure to flour dust, wheat allergen and fungal α-amylase in the four main flour processing industries in the Netherlands. This database serves as a baseline population exposure estimate in the occupational hygiene intervention program and will be used to evaluate its effectiveness. Furthermore, this database can be used to develop exposure models based on jobs and tasks performed to enable the generation of individual exposure estimates within the HSS. The database will also be used to obtain insight into the presence and use of control measures in the different sectors and where possible evaluate their effectiveness.

Methods

Population

The database described in this paper consists of measurement data from four exposure surveys performed between 2000 and 2005. The largest survey was carried out in 2000/2001 in four major flour processing sectors in the Netherlands: bakeries (traditional and industrial), flour mills and bakery ingredient producers. This exposure study was performed as part of a large epidemiological study that investigated the respiratory effects related to occupational exposure to flour dust and related allergens among workers in the four sectors. The main aim of the exposure study was to obtain a detailed overview of personal exposure levels across all jobs performed. In addition, the study was set up to explore the current use of control measures. For the epidemiological study a random selection of companies from all four sectors was approached to participate. When agreeing to participate a random selection of workers from each company was asked to fill in an epidemiological questionnaire. In total 692 workers returned a questionnaire. Of these workers approximately 70% also agreed to participate in the exposure assessment survey. To increase the number of exposure measurements, all other workers in the visited companies were also approached to participate in the exposure survey. Eventually, 551 workers in 84 companies in were sampled between 1-3 times, resulting in 638 personal exposure measurements. In addition, three smaller surveys investigating exposure levels in one or several companies were added to the database. The majority of workers in these companies were included in the surveys. The studies were performed in 2005 and contained 47 (flour mill), 39 (traditional bakeries) and 186 (industrial bakeries) personal exposure measurements, respectively. Companies and workers involved are a representative cross-section of the total working population in the four sectors, including all relevant jobs and activities performed in the four sectors. In total 910 personal exposure samples were included in the database. Repeated samples were available from approximately 23% of the population (170 workers). Table 1 gives a description of the four sectors and the different jobs per sector.

Table 1. Description of sectors and jobs within sectors with their main activities

Sector with related jobs	Job description with most important tasks
Traditional bakeries	Also known as craft bakeries, generally low grade of automation, large variety of bread and confectionary products (>>100) in low quantities.
- bread baker	Bread production process, weighing ingredients, dumping ingredients (bagged or from silo) operating mixers (preparing dough), processing dough, operating ovens. Often also cleaning and wrapping activities.
- confectioner	Pastry production process, weighing ingredients, preparing dough, using sheeter, large part of the work is generally finishing of pastry and cakes (decorating).
- general baker	Combination of tasks from the two above.
Industrial bakeries	Bakeries with a high grade of automation often specialized in specific products (bread or pastry). Nevertheless still has many activities with flour and/or dough products.
- bread baker	Works along the bread production lines, dough making, operating machinery (dough line) processing dough, control of process, troubleshooting.
- confectioner	Works along the pastry production line, majority of work is finishing/decorating pastry. Also production of cookies and cakes. Control of processes.
- dough maker	Makes batches of dough, weighing ingredients, operates mixers, dumping of ingredients, sometimes small cleaning activities, troubleshooting.
- cleaner	All cleaning activities, vacuuming, sweeping, mopping, cleaning with pressures air.
- maintenance worker	Periodical maintenance of machinery, incidental repair of machinery when malfunctioning.
- 'low exposed job'	Group of jobs not directly involved in production process (flour handling) or performing substantial cleaning or maintenance work like, oven operators, wrappers, administrative personal, etc.
Flour mills	Involved in milling grains, corn, soy, etc. Also increasingly producing pre-mixes (with all kind of additives) directly for the baking industry. Some have very specialized additional processes (e.g. producing food fibers).
- quality controller	Primarily involved in checking the quality of both ingredients and end products. Taking samples throughout the production process, lab analysis, test baking, small cleaning activities.
- cleaner	All cleaning activities, vacuuming, sweeping, mopping, cleaning with pressures air.
- foreman/boss	Generally leads a team of workers often takes part in (some of) the regular activities but also responsible for planning and administrative activities.
- mill operator	Operates the mills, large part of the work takes place from an (enclosed) operating room. But also often hands on activities on the work floor around the mills. Small cleaning activities, small maintenance, trouble shooting.
- operator bagging	Operates the bagging lines, can be control work or hands on filling of bags. Also palletizing bags, closing bags (sewing).
- storage worker	Works in ingredient or end product storage. Weighing of ingredients, supplying of several departments, small cleaning work, palletizing of products, administrative work.
- general operator	Primarily working in general operating rooms overlooking (several) processes. Administrative work. Occasionally assistance on work floor in any of the processes.
- maintenance workers	Periodical maintenance of machinery, incidental repair of machinery when malfunctioning.

- loader/unloader	Loading and unloading of trucks/ships, driving fork lift trucks (occasionally), operating silos, unloading grain ships, operating crane.
- chauffeur	Driving of trucks, driving of fork lift trucks (major part of the work day).
- silo builder	Technical worker specialized in building and maintenance of storage silo's.
Ingredient producers	Producing ingredients for baking industry, primarily pre-mixes based on flour or other bulk and specialized additive mixtures for bread or pastry. Also other additives grease, pastes, sugar mixtures, fruit mixtures etc.
- quality controller	Primarily involved in checking the quality of both ingredients and end products. Taking samples throughout the production process, lab analysis, test baking, small cleaning activities.
- production worker	Gives assistance throughout the production processes, often a lot of conveyer belt work. Majority of work in grease/paste department but also occasionally other departments.
- foreman/boss	Generally leads a team of workers often takes part in (some of) the regular activities but also responsible for planning and administrative activities.
- operator bagging	Operates the bagging lines, can be control work or hands on filling of bags. Also palletizing bags, closing bags (sewing).
- storage worker	Works in ingredient or end product storage. Weighing of ingredients, supplying of several departments, small cleaning work, palletizing of products, administrative work.
- maintenance worker	Periodical maintenance of machinery, incidental repair of machinery when malfunctioning.
- weigher	Weighs and mixes ingredients (additives) that are send to different departments to be mixed to batch flour or other bulk products
- dumper (ingredients)	Empties bulk products (from silo or big bags) and bags of additives in large mixers.
- general operator	Primarily working in general operating rooms overlooking (several) processes. Administrative work. Occasionally assistance on work floor in any of the processes.
- loader/unloader	Loading and unloading of trucks/ships, driving fork lift trucks (occasionally), operating silo's, operating crane.

Personal exposure measurements and walk-through survey

Personal air samples were obtained from a random sample of workers from companies in each sector. The number of observations per individual ranged from 1 to 3. The dust samples were collected using a portable pump (Gillian GilAir5) with a flow rate of 2 l/min and a Teflon filter (Millipore, PTFE, pore size 1.0 micron) mounted in a PAS6 sampling head. Sampling was performed in the breathing zone of the worker for 4-10 hours (full shift).
Dust levels were determined by weighing (analytical balance: Mettler AX 105 DR) the filters in a climate-controlled weighing room where the filters were conditioned for 24 hours prior to weighing (40% humidity, 22°C and 1020 Pa air pressure). The limit of detection (LOD) was assessed as the average weight difference of the blank filters plus three times the standard deviation, amounting to 0.17 mg dust on the filter. A few samples had values below the analytical limit of detection. These samples were assigned with a value two thirds of the LOD prior to statistical analysis. The concentration of wheat allergens and fungal α-amylase were determined in the majority of samples using specific immuno-chemical analysis (specific EIA). In these analyses proteins were extracted from the dust on the filters through a variety of extraction and elution steps. Subsequently, extraction fluid was analyzed using

specific enzyme immunoassay (EIA) as described in detail by Bogdanovic et al.[18,19]. The same assay was used for analysis of allergens in all four surveys.

A walk-through survey was carried out in all companies, using a standardized checklist to register relevant exposure determinants (job and tasks performed, specific control measures). Workers were followed throughout their shift and information on tasks performed and specific work characteristics was registered. The information was obtained independently for each measurement day. For three tasks (weighing ingredients, processing dough (sprinkling flour), and cleaning) process characteristics were identified that could influence exposure. For processing of dough these were: use of stainless steel tables, use of oil and dust free flour. During the weighing of ingredients, the use of a silo with closed mixing tub and the absence of bagged ingredients were evaluated as control measures. For cleaning, the effect of the use of a vacuum cleaner instead of brooms or pressured air was evaluated. Finally, we evaluated the effect of local exhaust ventilation (LEV).

Exposure modelling

Descriptive statistics (histograms, normal probability plots) were applied to determine exposure distributions. Log-transformed data were used for further analysis. Spearman correlation coefficients between exposure to flour dust and allergens were calculated using the PROC CORR procedure in SAS v8.2 (SAS Institute Inc.). The geometric mean and standard deviation were calculated, stratified by sector and job. Based on these results and observations in the field, some jobs in industrial bakeries were grouped because of comparable (low) exposure levels. This ‘low exposed’ job category consisted of: oven operators, wrappers, quality controllers, boss/foreman and storage workers. Bakeries were also classed according to their size for both traditional and industrial bakeries.

Mixed effects models (PROC MIXED) were used to study associations between exposure to flour dust, wheat allergens, fungal α-amylase and covariates as well as random effects[20]. Job, tasks and company size were considered as covariates. Random effect components considered were worker and company. Homogeneity of variance components between sectors was checked using log-likelihood ratio testing[21-23]. For other determinants (e.g. jobs) the number of repeated measurements per strata was too small to perform a detailed analysis of homogeneity of variance components. A compound symmetric covariance structure was assumed.

Model building comprised of two steps. In the first step, univariate analyses were used to determine which variables were associated with exposure to flour dust, wheat allergens and/or fungal α-amylase. In the second step, stepwise model building was used starting with the variable which explained the most variance. Variables with a p-value of 0.1 or smaller were included. The increase in explained variability compared to the previous model was calculated as the difference in -2 log likelihood. Statistical significance was established using the likelihood ratio test. If the model fit did not improve, expansion was stopped. Graphical analyses of residuals were performed to evaluate assumptions of homoscedasticity.

Control measures were evaluated after adjustment for job performed and related tasks. Measurements with missing data for a specific factor were left out of the analysis causing slight changes in the total number of measurements taken into account in the various analyses. Missing contextual data of measurements remained relatively small during analyses (generally <5% of measurements).

Results

Exposure measurements

The final dataset comprised of 910 personal inhalable dust samples from 735 subjects and 99 companies. The database contained repeated measurements from 170 subjects. Table 2 shows the average exposure levels for each sector (geometric means and standard deviations). Exposure to dust and wheat allergens is highest in flour mills, whereas workers in baking ingredient production plants are exposed to the highest levels of fungal α-amylase. For wheat allergens and fungal α-amylase in particular, a wide range in exposure levels is often found within sectors and jobs, resulting in a large GSD. The overall correlation between exposure to flour dust and wheat allergens was 0.8 (range 0.71-0.83 for different sectors). The correlation between exposure to fungal α-amylase and flour dust was low, overall 0.4 (range 0.30-0.43 for different sectors).

Table 2. Mean exposure to total dust, wheat allergen and α-amylase in bakeries, flour mills and ingredient producers

Sector	k	n	r	N	Inhalable dust (mg/m3) GM (GSD)[1]	Range	N	Wheat allergens (µg/m3) GM (GSD)	Range	N	α-Amylase (ng/m3) GM (GSD)	Range
Traditional bakeries	65	174	26	200	1.5 (2.7)	0.2-318	171	7.4 (8.3)	0.1-5365	169	0.8 (6.5)	0.1-115
Industrial bakeries	20	303	75	381	1.0 (3.5)	0.2-292	346	3.6 (10)	0.1-7571	344	0.4(6.0)	0.1-910
Flour mills	7	154	47	203	2.7 (4.5)	0.2-1837	185	10.4 (8.5)	0.1-3874	142	8.4 (9.7)	0.2-30009
Ingredient producers	7	104	22	126	2.0 (5.8)	0.0-627	113	4.2 (12.1)	0.1-1517	113	33.5 (22.4)	0.2-889054

k=number of companies visited
n=number of subjects sampled
r=number of subjects with repeated measurements
N=total number of personal air samples taken
[1] geometric mean (geometric standard deviation)

Mixed effects models
Table 3-6 shows the results from the mixed effects models with job, tasks and company size as covariates. Variance components with their respective confidence intervals and the total explained variance are given. The results of the different models are discussed below.

Traditional bakeries
Table 3 shows that exposure to all three agents was significantly higher for bread- and general bakers. Working in a large traditional bakery (>10 workers in production) was associated with a significantly higher exposure to flour dust and wheat allergens (approximately a factor 1.5). Dough making, sprinkling flour, weighing and cleaning increased exposure to one or more of the agents, while oven work and wrapping was associated with lower exposure to fungal α-amylase. Depending on the agent, models explained 15-50% of day to day variability and explained 10-35% of between company variability, respectively.

Industrial bakeries
Table 4 indicates that exposure differed with a factor 1.6 to 5 depending on the job performed and the agent of interest. Working in a large industrial bakery (>100 workers) is associated with a higher exposure to flour dust. Furthermore, tasks such as dough making, sprinkling flour and processing dough are associated with higher exposure levels to one or more agents, while wrapping and cleaning are associated with lower exposure levels to wheat allergens and/or fungal α-amylase. Between worker differences were for a large part (>60%) explained by our final models. On the other hand, day to day differences in exposure are poorly explained. For amylase almost 90% of total variability was associated with day to day differences in the final model.

Flour mills
Table 5 shows that exposures differed with a factor of 1.2-7 (flour dust), 2-35 (wheat allergens) and 3.5-24 (fungal α-amylase) respectively, compared to baseline exposure depending on the job performed. Workers who performed storage work, loading/ unloading of goods, unloading grain and cleaning grain had a significantly lower exposure to flour dust and/or wheat allergens. Cleaning was associated with higher exposure levels for all three exposures, whereas mixing ingredients only increases the exposure to α-amylase.
Most of the variability in exposure to flour dust and wheat allergen was associated with differences between workers, of which the final models explained 50% and 30% respectively. The remainder was day to day variability which was poorly explained by the final mixed effects models. For amylase all variability was assigned to differences between working days, of which approximately 15% was explained by our model.

Table 3. Estimates of model variables in final mixed effects model of the log transformed exposure to flour dust, wheat allergens and fungal α-amylase among traditional bakers. Company is included as random effect for all models.

			Flour Dust		Wheat allergen		α-amylase	
Model Variables (Fixed Effects)		**k[4]**	**β**	**P-value**	**β**	**P-value**	**β**	**P-value**
Intercept[1]		-	-0.74	0.00	-1.05	0.01	-0.83	0.01
Jobs[2]	Bread baker	86	0.82	0.00	1.87	0.00	1.31	0.00
	General baker	65	0.46	0.01	1.00	0.01	1.37	0.00
Company size[3]	Large bakery	116	0.42	0.01	0.90	0.01	-	-
Tasks	Dough making	122	0.57	0.00	0.99	0.00	-	-
	Sprinkling Flour	93	0.31	0.03	0.85	0.00	-	-
	Weighing ingredients	112	-[5]	-	0.52	0.08	-	-
	Cleaning	93	-	-	0.48	0.06	0.54	0.03
	Oven work	96	-	-	-	-	-0.64	0.00
	Wrapping	65	-	-	-	-	-0.71	0.01
Var_b_C (CI)[6]		-	0.19 (0.09-0.64)		1.08 (0.63-2.28)		1.61 (1.02-2.90)	
Var_b_w (CI)[7]		-	[9]		[9]		[9]	
Var_w_w (CI)[8]		-	0.67 (0.54-0.89)		1.67 (1.29-2.24)		1.43 (1.11-1.93)	
Total explained variability		-	27%		39%		9%	

[1] the intercept gives the exposure level working as a confectioner in a small bakery not performing any of the tasks in the model.
[2] job confectioner is reference group
[3] small bakeries are reference group
[4] number of observations with factor present
[5] not in model, not significant at the α=0.10 level
[6] variance component between companies (confidence interval)
[7] variance component between workers (confidence interval)
[8] variance component within workers (confidence interval)
[9] random effect not significant in final model

Table 4.Estimates of model variables in final mixed effects model of the log transformed exposure to flour dust, wheat allergens and fungal α-amylase among industrial bakers. Company and worker are included as random effects for flour dust and wheat allergens analyses, only company is included as a random effect for α-amylase analyses.

			Flour Dust		Wheat allergen		α-amylase	
Model Variables (Fixed Effects)		**k[4]**	**β**	**P-value**	**β**	**P-value**	**β**	**P-value**
Intercept[1]			-1.08	0.00	-0.33	0.24	-1.14	0.00
Jobs[2]	Bread baker	87	1.19	0.00	1.60	0.00	1.07	0.00
	Confectioner	23	1.08	0.00	1.30	0.01	-0.67	0.10
	Dough maker	100	1.08	0.00	1.46	0.00	0.35	0.19
	Cleaner	12	0.53	0.09	0.06	0.93	-0.40	0.47
	Maintenance worker	21	1.05	0.00	1.18	0.01	0.41	0.28
Company size[3]	Large bakery	155	0.37	0.01	-	-	-	-
Tasks	Dough making	123	0.51	0.00	1.46	0.00	0.93	0.00
	Sprinkling flour	43	0.46	0.01	0.73	0.02	-	-
	Processing dough	147	-[5]	-	0.39	0.09	-	-
	Wrapping	68	-	-	-0.47	0.08	-0.79	0.00
	Cleaning	147	-	-	-	-	-0.48	0.01
Var_b_C (CI)[6]			[9]		0.37 (0.15-1.91)		0.27 (0.12-1.10)	
Var_b_w (CI)[7]			0.35 (0.16-0.54)		1.34 (0.71-1.97)		[9]	
Var_w_w (CI)[8]			0.70 (0.55-0.91)		1.73 (1.33-2.34)		2.22 (1.92-2.62)	
Total explained variability			36%		42%		9%	

[1] the intercept gives the exposure level working in a 'low exposed' job in a small bakery not performing any of the tasks in the model
[2] job confectionary is reference group
[3] small bakeries are reference group
[4] number of observations with factor present
[5] not in model, not significant at the α=0.10 level
[6] variance component between companies (confidence interval)
[7] variance component between workers (confidence interval)
[8] variance component within workers (confidence interval)
[9] random effect not significant in final model

Table 5. Estimates of model variables in final mixed effects model of the log transformed exposure to flour dust, wheat allergens and fungal α-amylase among flour millers. Worker is included as random effect for flour dust and wheat allergens analyses, no random effect is included in α-amylase analyses.

Model Variables (Fixed Effects)		k[3]	Flour Dust		Wheat allergen		α-amylase	
			β	P-value	β	P-value	β	P-value
Intercept[1]			0.00	0.99	1.05	0.33	-0.27	0.80
Jobs[2]	Quality controller	20	0.21	0.76	0.79	0.51	1.33	0.27
	Cleaner	19	1.98	0.00	1.80	0.16	2.24	0.09
	Foreman/ Boss	19	0.69	0.31	1.12	0.35	2.51	0.03
	Mill operator	24	1.98	0.00	2.35	0.05	3.16	0.01
	Operator bagging	18	1.88	0.01	2.82	0.02	2.07	0.10
	Storage worker	35	1.98	0.00	3.55	0.00	1.69	0.17
	Operator (general)	34	0.88	0.19	1.11	0.36	3.14	0.01
	Maintenance worker	10	0.82	0.20	0.42	0.72	1.37	0.23
	Loader/unloader	4	1.66	0.03	1.55	0.23	1.78	0.16
	Chauffeur	4	0.17	0.84	2.11	0.17	1.24	0.41
	Silo builder	5	0.74	0.52	1.01	0.58	-	-
Tasks	Cleaning	78	0.39	0.08	0.73	0.06	0.85	0.08
	Storage work	24	-0.97	0.01	-1.19	0.05	-	-
	Unloading grain	17	-1.46	0.00	-2.09	0.00	-	-
	Cleaning grain	17	-1.42	0.00	-1.59	0.02	-	-
	Loading/unloading	27	-[4]	-	-1.03	0.03	-	-
	Mixing	18	-	-	-	-	1.46	0.02
Var_b_C (CI)[5]			[8]		[8]		[8]	
Var_b_w (CI)[6]			1.11 (0.66-1.57)		2.36 (1.21-3.50)		[8]	
Var_w_w (CI)[7]			0.57 (0.38-0.93)		1.41 (0.88-2.61)		[8]	
Total explained variability			29%		22%		15%	

[1] the intercept gives the exposure performing an office job, not performing any of the tasks in the model.
[2] job office worker is reference group
[3] number of observations with factor present
[4] not in model, not significant at the α=0.10 level
[5] variance component between companies (confidence interval)
[6] variance component between workers (confidence interval)
[7] variance component within workers (confidence interval)
[8] random effect not significant in the final model

<u>Baking ingredient producers</u>

Table 6 indicates that exposure levels varied with a factor of 3-46 (flour dust), 1.3-40 (wheat allergens) and 2.7-200 (fungal α-amylase) respectively, depending on the job performed. Cleaning, weighing ingredients and bagging was associated with higher flour dust exposure. Packing pallets and weighing ingredients were associated with higher wheat allergen exposures. Paste/grease production significantly reduced exposure to wheat allergens and fungal α-amylase (with a factor 54 and 65 respectively).

Table 6. Estimates of model variables in final mixed effects model of the log transformed exposure to flour dust, wheat allergens and fungal α-amylase among baking ingredient production workers. No random effects were significant in the final models.

			Flour dust		Wheat allergens		α-amylase	
Model Variables (Fixed Effects)		**k[3]**	**β**	**P-value**	**β**	**P-value**	**β**	**P-value**
Intercept[1]			-1.93	0.02	-0.85	0.56	0.92	0.54
Job[2]	Quality control	13	2.03	0.03	2.75	0.09	1.28	0.45
	Production worker	11	1.43	0.12	3.70	0.06	3.86	0.07
	Foreman/Boss	4	1.06	0.33	1.69	0.34	1.75	0.38
	Operator bagging	20	2.42	0.01	2.42	0.11	1.01	0.53
	Storage worker	13	1.25	0.17	0.23	0.88	2.52	0.14
	Maintenance worker	2	3.09	0.02	-[5]	-	3.62	0.13
	Weigher	6	3.83	0.00	2.77	0.12	5.29	0.01
	Dumper (ingredients)	19	3.50	0.00	3.63	0.02	5.18	0.00
	General operator	16	2.04	0.02	2.00	0.20	3.24	0.05
	Loader/unloader	3	2.49	0.00	0.44	0.79	3.29	0.05
Tasks	Cleaning	30	0.98	0.00	-	-	-	-
	Weighing ingredient	16	0.88	0.05	2.11	0.00	-	-
	Packing pallets	19	-[4]	-	2.11	0.00	-	-
	Grease/paste production	13	-	-	-4.02	0.00	-4.20	0.00
	Mixing ingredients	9	-	-	-	-	1.88	0.06
Total explained variability[6]			37%		32%		31%	

[1] the intercept gives the exposure performing an office job, not performing any of the tasks in the model.
[2] office workers are reference group
[3] number of observations with factor present
[4] not in model, not significant at the α=0.10 level
[5] no wheat analysis results for this job
[6] no random effects were significant in final model

Control measures

Potential control measures were not often observed and their actual use was generally limited. Some of the control measures were used but only to such a limited extent that it was not feasible to evaluate their effect. Some examples of control measures that were incidentally encountered were: use of liquid or paste bread improver (enzymes) instead of powder form, use of palletized additives instead of powder additives, use of closed bag compressors, elimination of use of pressured air, use of only wet cleaning methods instead of brushing and sweeping, extensive LEV throughout the factory. An extensive list of potential control measures in bakeries is described in the manual for dust control in bakeries[24].Table 7 and 8 give results of a small set of identified control measures that were evaluated quantitatively.

Table 7. Impact of identified control measures and other determinants on exposure to flour dust for traditional and industrial bakeries

Task	**Control measure of interest**	**Use**	**Traditional bakeries**		**Industrial bakeries**	
			N (k=200)	**β (p-value)**	**N (k=381)**	**β (p-value)**
Sprinkling flour	Use of substitutes for dusting flour[1]	No sprinkling of flour	106	-0.39 (0.01)	314	-0.36 (0.08)[4]
		Use of substitutes	41	-0.17 (0.40)	30	-0.82 (0.00)[4]
		No use of substitutes	51	[2]	29	[2]
Dumping of flour	Use of closed silo and no bagged ingredients	No dumping of flour	57	-0.68 (0.00)	245	-0.51 (0.00)
		Closed silo	14	-0.43 (0.10)	12	-0.36 (0.25)
		Silo open and/or bags	129	[2]	124	[2]
Cleaning	Use of vacuum cleaner	No cleaning	-	[3]	238	-0.09 (0.46)
		Use of vacuum cleaner	-	[3]	33	-0.37 (0.08)
		No use of vacuum	-	[3]	109	[2]

N= # measurements; k= total number of observations in that sector
[1] use of oil, dust free flour and/or stainless steel worktables
[2] reference group
[3] no data available on this control measure for this sector
[4] only use of stainless steel table was observed

Table 7 shows that control measures in bakeries were primarily identified during activities such as the weighing of ingredients and processing of dough, and also for cleaning activities at industrial bakeries. The statistical analyses show that dumping of flour when weighing ingredients is associated with higher exposure. Use of a closed silo system largely eliminates this exposure. Use of dusting flour also leads to significantly higher exposure to flour dust. These eposures decreased when substitutes like oil, dust-free flour or a stainless steel worktable were used. For industrial bakeries the use of a vacuum cleaner (instead of a broom) reduced exposure. For the other sectors no data on specific control measures were obtained.

Table 8. Impact of local exhaust ventilation on exposure to flour dust for all four flour processing industries

Use of LEV	**Traditional bakeries**		**Industrial bakeries**		**Flour mills**		**Bakery ingredient producers**	
	N (k=200)	**β (p-value)**	**N (k=381)**	**β (p-value)**	**N (k=203)**	**β (p-value)**	**N (k=126)**	**β (p-value)**
yes	29	-0.30 (0.18)	46	0.26 (0.14)	108	-0.08 (0.83)	68	**-0.82 (0.00)**
no	171	[1]	335	[1]	95	[1]	58	[1]

[1] reference group

Table 8 indicates the results of local exhaust ventilation and its use. In less then 20% of the sampled bakeries proper LEV was present. In general, no significant effect on the average daily exposure to flour dust in bakeries was observed when LEV was installed. At flour mills LEV was present in approximately 50% of the measured situations, especially at points where flour products were bagged or tapped. No overall protective effect was observed from LEV in flour mills. Only for ingredient producers, where LEV was observed more frequently (54% of measured situations), a significant effect on flour dust exposure was observed.

Discussion

In this paper we describe a comprehensive measurement database containing detailed information on exposure levels to flour dust, wheat allergens and fungal α-amylase for all four major flour processing industries in the Netherlands. The levels found in this study show no trend in exposure compared to previous Dutch studies[25-27] and generally are comparable[2,9,12] or somewhat lower[14] to what is found in recent studies in other countries. Some caution has to be taken when comparing results of different countries since sampling methods and analytical methods might vary. In addition, the organization of the industry, especially the baking industry, varies widely between countries, creating differences in job types and work characteristics. Finally, large differences in dust contents with respect to the presence of wheat allergens[28] and/or additives (e.g. enzymes) can be expected.

A small part (10%) of our measurements for traditional bakeries had a sampling time of half a shift (4 hours). Excluding this data did not change the final exposure models. This is reassuring and is likely due to the fact that work is very cyclical (same activities are repeated most of the shift).

In general, the database provides detailed baseline estimates of exposure that can be used to evaluate the impact of the covenant by comparison with a post intervention exposure survey. The fact that the measurement scheme was elaborate, taking substantial numbers of samples for each job/task combination, a large variety of companies and repeated measurements over a time span of several months implies that our database contains exposure information on the majority of the potential exposure situations encountered in these sectors. Therefore we believe the models provide good individual estimates of exposure among workers in these sectors. The information on variance components can be used to optimize the measurements schemes to evaluate and quantify changes in exposure due to interventions[29,30].

The models generated in our study performed moderately in explaining total variability in our populations. Overall the exposure models explained a significant proportion of between company and between worker variability. The explained day to day variability, which for all sectors was a significant part of total variability, is considerably lower. Earlier work on exposure in bakeries and flour mills reported a smaller relative contribution of within worker component to total variability[15,31,32]. However, the different approaches in sampling design and grouping makes detailed comparisons between studies difficult.

The fact that our models are poor in explaining day to day variability is related to the fact that frequency and time spend on activities performed was not taken into account, which is likely to be an important source of day to day variability. Other studies that take into account the time spend on different activities perform better and explain up to 70% of total dust exposure variability[33,34]. Results in explained variability were comparable for dust and wheat allergen exposure, whereas for fungal α-amylase the explained variability was much lower (except for ingredient producers). This outcome may be explained by the fact that fungal α-amylase exposure is highly dependant on the ingredients used and the α-amylase concentration in that ingredient, two variables that were not available from our database. For ingredient producers this factor is closely associated with the task performed, therefore the model for this sector explain more variability for fungal α-amylase.

We have collected questionnaire information on jobs and tasks for the total population in the four sectors (~ 10,000 workers). This information in conjunction with the exposure models described in this manuscript enables us to generate individual exposure predictions for the total population at risk in the Netherlands. These can be used for the predictive diagnostics work in the context of the health surveillance system as described by Suarthana et al.[17]. The predictions can also serve as background information for occupational health physicians and hygienists to obtain a general idea of a workers average exposure. Although the models only explained a relatively small proportion of exposure variability, we believe the exposure predictions represent an essential part of the health surveillance system. The value of exposure information in diagnostic and prognostic rules has been shown in earlier work on laboratory animal workers[35,36].

The third aim of this paper was to obtain insight into the state of the art of control measures and, where possible, evaluate the effect of control measures currently in place. The complex of tasks and presence of a wide range of exposure sources made it difficult to identify and evaluate potential control measures. A disappointing number of effective control measures were identified. When control measures were present their use was often limited to a few cases or control measures were not consequently introduced in all tasks. This strongly limited the power of this study with respect to evaluation of control measures. Furthermore, the effect of a control measure on exposure during a single short-term task may be obscured in our analysis of shift-based measurements. Nevertheless, the analysis presented in this paper provides conclusive information for a limited number of control measures. The lack of data caused by limited use of control measures in all four sectors is, in itself, an important conclusion. It suggests that more emphasis should be placed on the introduction and maintenance of control measures in these sectors.

Our analysis reveals a rather low reduction effect when the dusting flour is substituted, based on 8-hour time weighted average exposure. This is contradictory to what was found by Burstyn et al.[33,34] that showed a 30 fold decrease in exposure when substituting dusting flour with oil. This discrepancy could be explained by the fact that substitution was often ‘partially’ introduced; in almost all cases substitutes were introduced whilst dusting flour was still used in part of the production process. It is also likely that the effect was underestimated in this study since we pooled several substitutes into one category (less dusty flour and oil) which are probably not equally effective. Unfortunately the low number of cases in which we observed these substitutes did not allow separate analysis. Nevertheless the results suggest that elimination of dusting flour, as it is currently performed in bakeries in the Netherlands, will only result in a small reduction of TWA exposure. Studies in other sectors have also shown disappointing reduction in exposure levels due to the substitution of dusty products with less dusty materials[37]. Our evaluation showed that control measures introduced during weighing of ingredients, especially limiting the use of bagged flour products and the enclosure of silo’s (when dumping flour), strongly decrease exposure. Observational information from the field suggests that training of workers in dust-free work practices (no shaking of bags/ silo-hose, use of a bag compressor, wet cleaning instead of dry, etc.) will reduce peak exposures.

Data obtained during walk-through surveys indicate that, with some exceptions, not much attention is given to LEV systems in the bakeries that participated in this study. Integrated LEV systems in flour mills often had an insufficient capacity to reduce dust emissions. Local exhaust ventilation only had a significant effect on flour dust exposure in the baking ingredient producing companies. This sector often applied advanced LEV systems for various processes and activities. Evidence is available from the literature showing significant reductions in worker exposure due to the introduction of LEV systems. For example, LEV fitted or integrated on equipment may produce reductions of more than 90%[38-40]. However, the protective effect is limited and highly depends on the way it is installed and used by the workers[41]. Our results clearly indicate that more attention should be paid to proper use and maintenance of LEV in the various flour processing sectors.

Information obtained on control measures will be used to optimize the intervention scenarios that will be implemented in the different sectors. Communication of proper control measures to workers will for a large part be based on a recently published dust control manual for bakery sectors[24]. This manual was compiled using the contextual information gathered during the exposure measurements and walk through surveys as described in this paper.

In conclusion, the results described in this paper will be used to underpin the covenant with flour processing branches. A broad range of exposure models were developed enabling the prediction of average exposure estimates based on job and tasks performed for a large population of workers in all major flour processing sectors in the Netherlands. The information obtained from this study will be used in the sector wide health surveillance system. A disappointing number of effective control measures were identified, indicating the importance of introducing adequate control measures in these sectors in the Netherlands.

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CHAPTER 3

Evaluation of peak exposures in the Dutch flour processing industry: implications for intervention strategies

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Abstract

Introduction: To effectively decrease occupational exposure to flour dust and related allergens, detailed information on exposure determinants and effectiveness of control measures is essential. In this paper we use personal real time exposure measurements to get more insight into the relationship between specific work characteristics, including the use of control measures, and (peak) exposure to flour dust. The study has three objectives; (a) identify tasks and activities related to peak exposure, (b) identify control measures and other important exposure determinants and (c) assess the potential impact of these control measures on the (peak) exposure to flour dust.
Methods: A dataset containing 82 real time exposure measurements in combination with information from detailed observations was used to study the association between peak exposures and different tasks, activities and other determinants such as control measures. Descriptive statistics of peak exposure on job level were generated as well as information on contribution of task specific peak exposures to TWA exposure levels. Finally we evaluated the efficacy of a variety of control measures on task exposure by comparing exposure levels of groups of workers with and without controls.
Results: In workers included in this study more then 75% of time-weighted-average (TWA) exposure is directly associated with peak exposures during a limited set of well defined tasks/activities. The impact of a single task on population TWA exposure is generally limited (less then 40%). Worker behavior seems an important determinant in effective exposure control for many tasks.
Conclusions: Data from real time measurements provides important detailed information with respect to exposure determinants and control measures, not obtainable from conventional measurement studies focusing on TWA exposure. This information is essential to perform prospective impact assessments of intervention strategies on the populations' exposure distribution.

Introduction

Exposure to flour dust is among the most observed causes of occupational airway disease and asthma[1]. Recent time trend studies do not show a decline in occupational exposure[2], indicating that rigorous interventions are needed to reduce the disease burden in the flour processing industry. To effectively decrease occupational exposure to flour dust and related allergens, detailed insight in exposure determinants, and especially effectiveness of control measures, is essential. Yet, although occupational exposure to flour dust has been studied extensively in a range of occupational industries, most studies evaluated average daily exposure in relation to descriptive variables such as sector or job[3-6]. Few studies also evaluated exposure determinants in a more detailed level.

A recent study in the Netherlands comprised over 900 full shift personal exposure measurements. The variability in exposure in this study could only to a limited extend be explained by job and tasks variables and only a few effective control measures were identified[5]. In Canada, studies of Burstyn et al.[7,8] also identified effective control measures in only a few activities. Likewise only generic characteristics such as having appointed a safety representative were associated with lower exposure levels in the United Kingdom[9].

A result of the findings in these studies is that a clear starting point for intervention strategies is absent. The question arises to what extent effects of existing control measures on exposure actually can be detected by statistical modeling of eight hour measurements. Workers may perform several tasks at different production lines, all with specific characteristics that might influence exposure during a shift. Production cycles are relatively short and tasks are preformed repeatedly over a workday. Generic questionnaires to monitor tasks performed and time spent on certain tasks may not be accurate enough. Hence, measurement error in these independent variables will very likely lead to underestimation of the effect of determinants on exposure. As a result exposure assessment strategies based on 8-hour exposure measurements (time weighted average (TWA) exposure) may not always be sensitive enough to identify (task) specific determinants of exposure, including the effect of control measures.

Nieuwenhuijsen et al.[10] showed that for bakery workers in the UK time-weighted average exposure levels to a large extend are determined by peak exposures that can be associated with specific work activities. This suggests that it would be sensible to direct intervention strategies towards the conditions and tasks that contribute most to peak exposures. In this case, real time exposure measurements are needed for allocating control measures in an optimal manner. Several examples from occupational settings are available where real time measurements were used to characterize personal exposure[11-14].

In the present paper we analyzed data from personal real time exposure measurements to get detailed understanding of the relationship between specific activities, work characteristics, including use of control measures, and (peak) exposure to flour dust. This study was conducted in the context of a sector wide intervention program to reduce exposure and related occupational airway diseases among workers in the baking and flour processing industry in the Netherlands. The collection of the real time measurements was part of a large occupational hygiene survey that is described elsewhere[5]. The study has three main objectives; (a) identification of tasks and activities related to peak exposure within jobs and sectors, (b) identification of control measures and other important exposure determinants and (c) assessing the potential impact of these control measures on the (peak) exposure to flour dust.

Methods

Exposure measurements

Real time exposure measurements were performed in three cross sectional exposure surveys. In total 82 ‘real time’ measurements were obtained in different companies from 57 workers across different jobs in bakeries, flour mills and ingredient production plants. Measurements were performed using a DataRam (model pDR-1000, Thermo Electron Ltd). This device measures particle concentrations in air, moving through a detection chamber through ambient air movement, by means of light scattering[15]. The DataRam has an effective measurement range of 0.001-400 mg/m^3 and is calibrated for dust with particle sizes with aerodynamic diameters up to 10 µm. The DataRam was mounted in the breathing zone of the worker and was worn for a period of 4-8 hours. Airborne concentration of flour dust was logged every three seconds to obtain a high resolution in exposure data.

Parallel to each DataRam measurement a personal air measurement was performed using a PAS6 inhalable dust sampler. PAS6 samplers were located at the side of the preferred working hand (generally right side) and DataRam on the opposite side. Both samplers were placed on similar height in the breathing zone (around the collarbone) for each measurement. PAS6 samples were analyzed for dust, wheat allergens and fungal α-amylase, for this paper only dust results were used in comparisons with DataRam data. Details on PAS6 measurements and exposure levels for wheat allergens and fungal α-amylase, as well as processing of filters are described in a previous paper[5].

Classification of tasks, activities, and control measures

During measurements a trained occupational hygienist observed the worker and documented all main tasks performed. Within these tasks performance of specific activities was also registered (e.g. shaking of bags, use of pressured air, etc.). Finally detailed information was obtained on presence of control measures (e.g. use of local exhaust ventilation). A trained occupational hygienist conducted all surveys using a standardized checklist. Based on checklist information, all 82 measurements were split up into tasks and activities in conjunction with control measures nested within tasks/activities. Tasks, activities and control measures taken into account were selected prior to the surveys based upon information from earlier studies. In incidental cases this information was supplemented with additional situations observed on site.

Processing of data

Data from the DataRam device was uploaded to a computer and imported into Excel. Peak exposure plots were created for all DataRam measurement series to visually explore peak exposure patterns. Peaks were identified using a peak detection limit, arbitrarily set at 1 mg/m^3 of dust. This is approximately equal to the population average exposure level[5]. This approach was earlier used by Preller et al.[16]. Several other studies used comparable concentration levels as peak detection levels for dust exposures[11,13]. For each identified peak exposure a variety of descriptive statistics (maximum peak concentration, average exposure concentration, peak duration) are calculated. Subsequently, a range of descriptive statistics was calculated for each measurement using a macro in Excel; i.e. arithmetic mean, number of peaks, time between peaks, maximum peak concentration, total peak exposure, total peak exposure per task and activity.

Data from the real time measurements were manually linked to the workplace survey information. All identified peaks were labeled with the task and/or activity a worker was performing. For each peak the average exposure intensity (concentration) and the peak exposure duration (duration for which exposure was above 1 mg/m^3) was calculated. We calculated a “cumulative peak exposure” metric, by multiplying average peak exposure intensity with peak exposure duration. Within each measurement cumulative peak exposures associated with a single task or activity were summed.

Since job and task profiles and exposure levels are fairly similar between traditional and industrial bakeries and between flour mills and ingredient production workers, measurements were grouped into two sectors: i.e. a bakery sector and the ingredient production sector. Bakery sector includes both traditional and industrial companies involved in bread and/or pastry production. Ingredient production sector includes companies involved in production of flour (milling) and premixes/bread improvers. A detailed description of job titles can be found in Meijster et al.[5].

Statistical analyses

The final Excel database was important into SAS v9.1 for statistical analyses. Correlation between average exposure values of DataRam - and PAS6 measurements were explored per sector using PROC CORR and scatter plots. A ratio of the DataRam versus PAS6 results was calculated for each measurement to evaluate (structural) differences between both methods. To correct the DataRam measurements for structural underestimation of the inhalable dust concentration the median of the ratio’s of the individual measurements was used as a correction factor before further analysis. For each job within each sector an overview was made of the descriptive statistics with respect to peak exposure (i.e. number of peaks/hour, max peak intensity, median peak duration, max peak duration). The effect of exposure control technologies was evaluated by stratified analysis, comparing average cumulative peak exposure related to tasks and activities among workers with and without a particular control measure. A reduction factor was calculated as percentage difference of average cumulative peak exposure with and without control measure.

Scenario analysis
To get insight into the impact of task-based interventions on TWA exposure we evaluated two hypothetical examples. First we evaluated the impact of eliminating the peak exposure during sprinkling of flour for an individual worker. The peak exposure periods were eliminated from the exposure measurement and descriptive statistics were recalculated to evaluate the impact on the TWA exposure.

In the second example we evaluated the effect of a hypothetical control strategy in the whole set of bakery workers in our study population (n=59). The strategy comprised of implementing the state of the art with respect to control measures upon this population. In other words we looked at the work practice of all 59 bakery workers and, where not present, assumed implementation of the control measures as listed in this paper. Exposure levels were then reduced according to the corresponding average reduction factor(s) and time weighted averages recalculated.

Results

The correlation between inhalable dust and real time measurements is high (correlation coefficient= 0.79, Figure 1a). Nevertheless the DataRam significantly underestimates the concentration of dust in air compared to the PAS6 inhalable dust sampler. Overall the median exposure measured with the DataRam sampler was 0.21 mg/m^3 and 1.63 mg/m^3 for PAS6 measurements. Figure 1b shows box plots of the ratios of PAS6 and DataRam results per sector, with median ratio's and outliers indicated. Generally the ratio was fairly similar across sectors and measurements. The median ratio between DataRam and PAS6 results for all measurements was approximately a factor 0.12 (DataRam underestimates exposure with a factor 8 compared to PAS6).

Figure 2 gives a typical selection of real time measurement plots with labeled peaks. Peaks are generally relatively short exposure moments of seconds to minutes, sometimes occurring with a high frequency. Highest levels are in excess of 100 mg/m^3. The plots indicate that the concentration of dust in air between peaks is in most cases negligible. In these periods workers generally perform tasks that are associated with low exposures, such as wrapping or administrative work. Alternatively, tasks with "high" exposure might be performed with use of effective control measures.

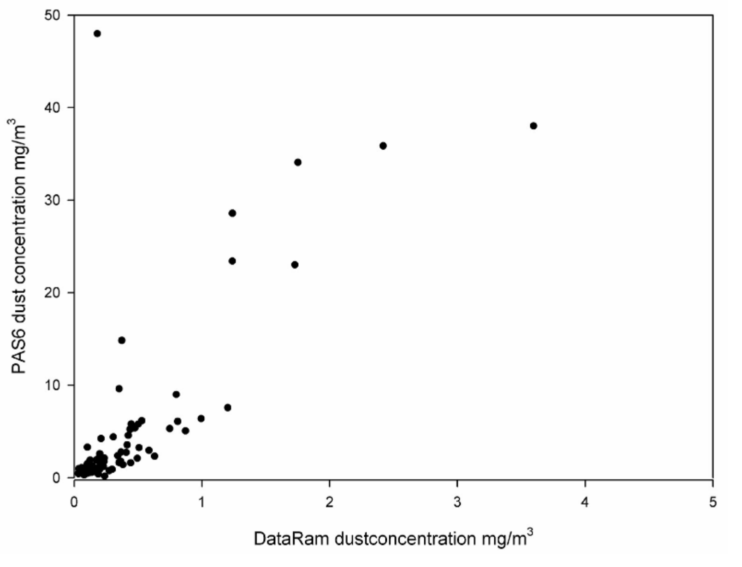


Figure 1a. Scatter plot of correlation between dust concentrations measured with DataRam versus dust concentration measured with PAS6

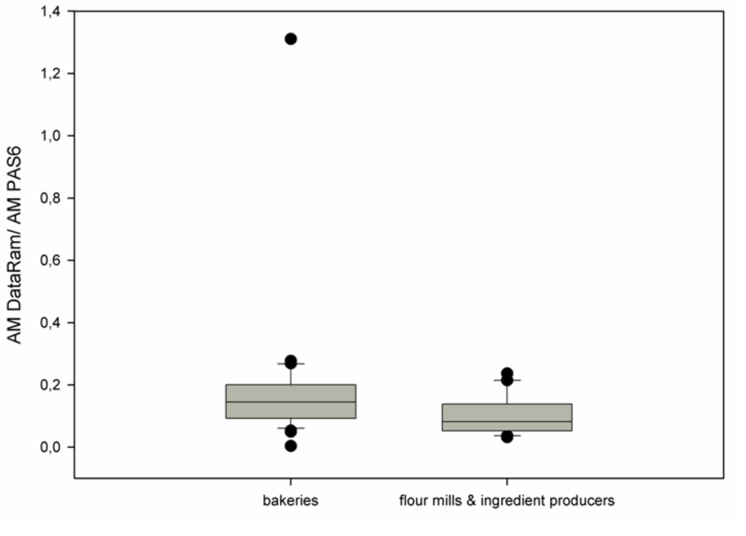
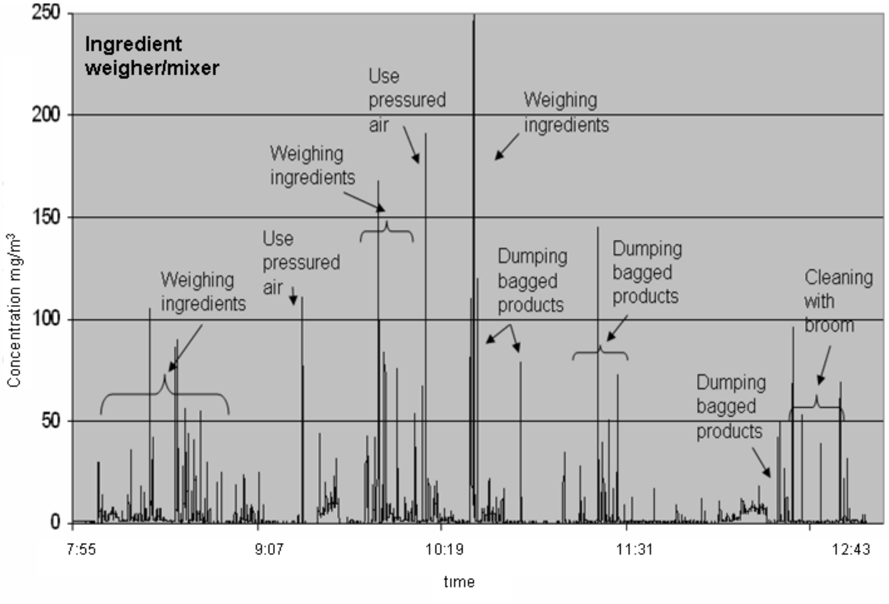
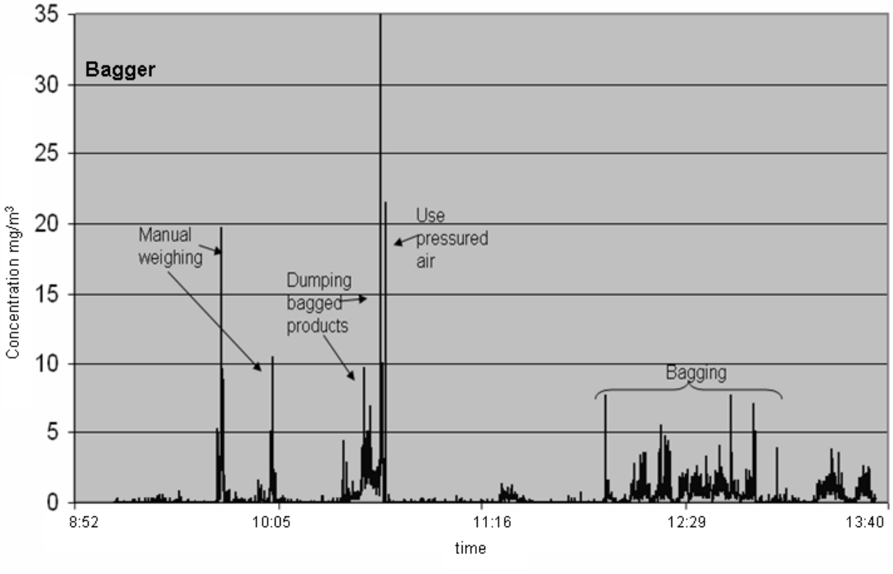


Figure 1b. Box plots of the ratio between the AM of the DataRam measurement vs. the PAS6 measurement for both bakeries and ingredient producers (boxplot shows; median, 10-90-percentiles and outliers)


Ingredient weigher/mixer
Concentration mg/m3
250
200
150
100
50
0
7:55
9:07
10:19
11:31
12:43
time
Weighing ingredients
Use pressured air
Weighing ingredients
Use pressured air
Weighing ingredients
Dumping bagged products
Dumping bagged products
Dumping bagged products
Cleaning with broom


Bagger
Concentration mg/m3
35
30
25
20
15
10
5
0
8:52
10:05
11:16
12:29
13:40
time
Manual weighing
Dumping bagged products
Use pressured air
Bagging

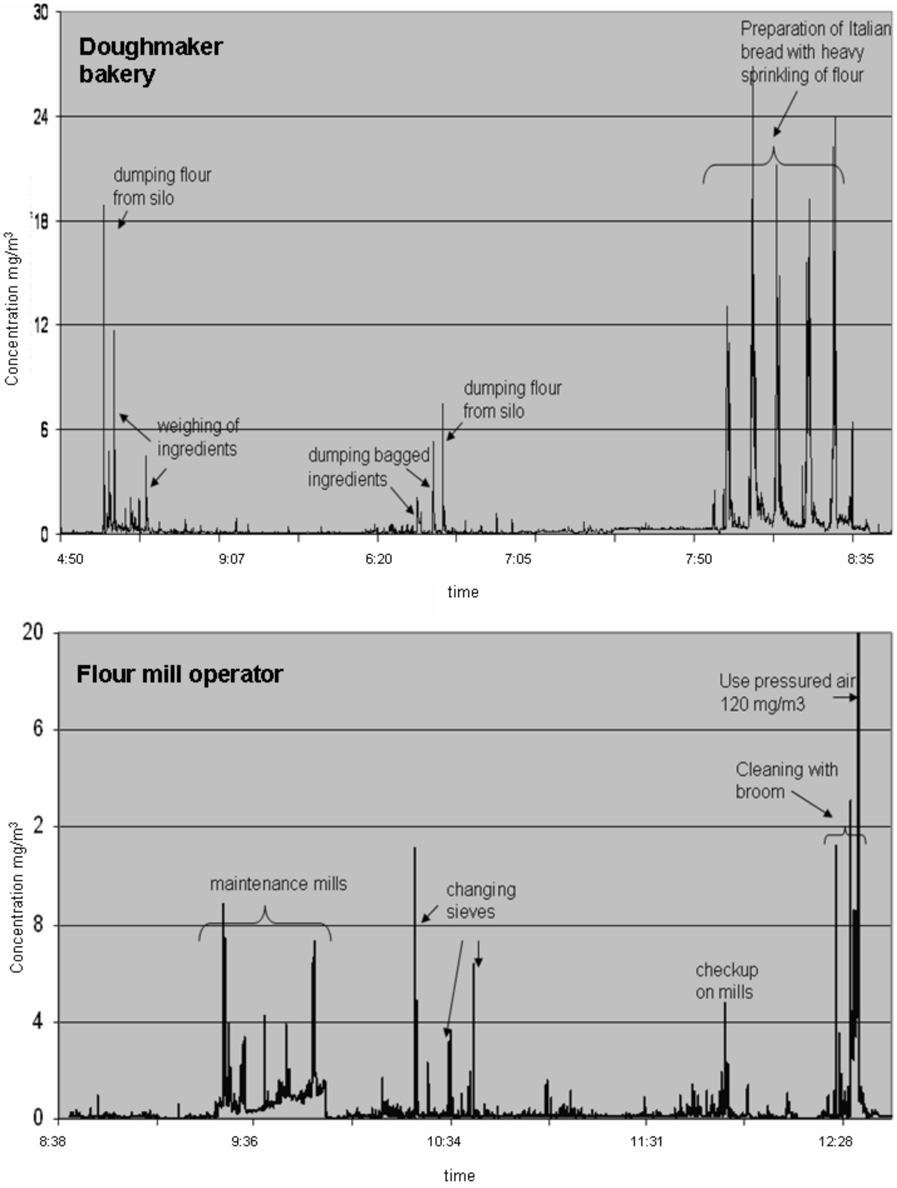


Figure 2. Plots from (partial) real time measurements showing specific labeling of type of peak exposure for different jobs

The latter is illustrated by the graphs in Figure 3a-c. Here some specific examples are given of reduced exposures as a result of implementation of specific control measures. Figure 3a shows the effect of replacing flour sprinkling by use of oil; nevertheless high peak exposures still occur during the sprinkling of flour where substitution with oil is not possible. Figure 3b represents a situation where weighing of ingredient was performed in a laminar flow cabinet. Dust exposure under these circumstances is negligible, contrary to the examples in Figure 2 where high peak exposures occurred during weighing without control measures. Finally, Figure 3c shows an example of a worker using a vacuum cleaner instead of a broom or pressured air during cleaning (see Figure 2).

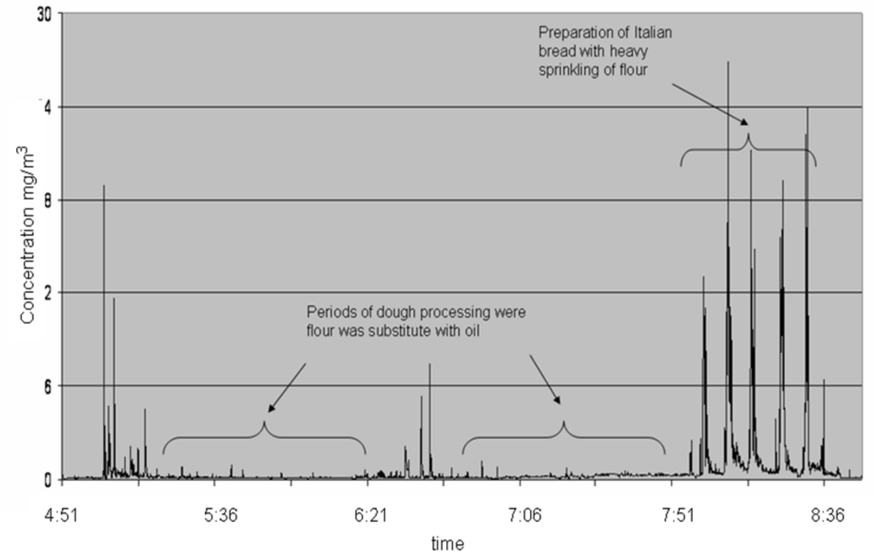


Figure 3a. The potential effect of substitution of flour sprinkling with use of oil when processing dough

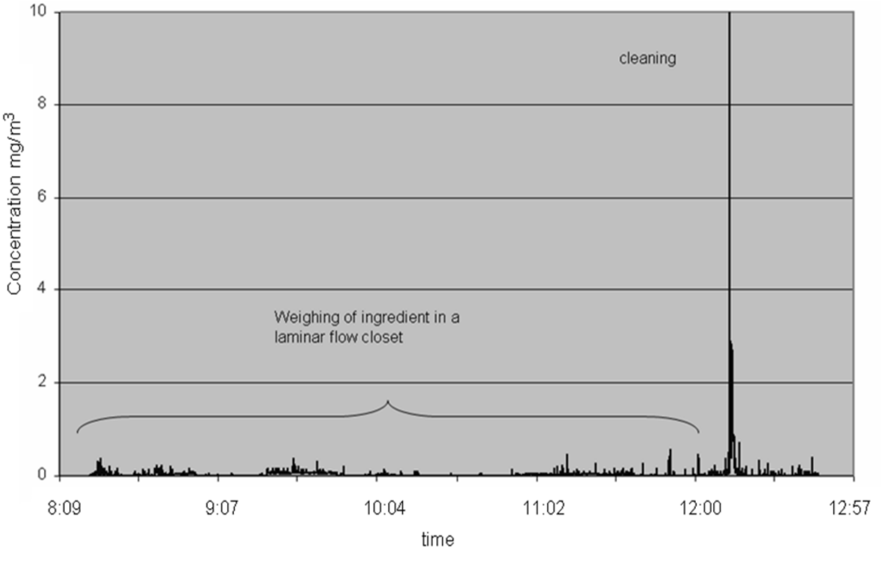


Figure 3b. Elimination of peak exposures when weighing ingredients by performing weighing activities in a laminar flow closet

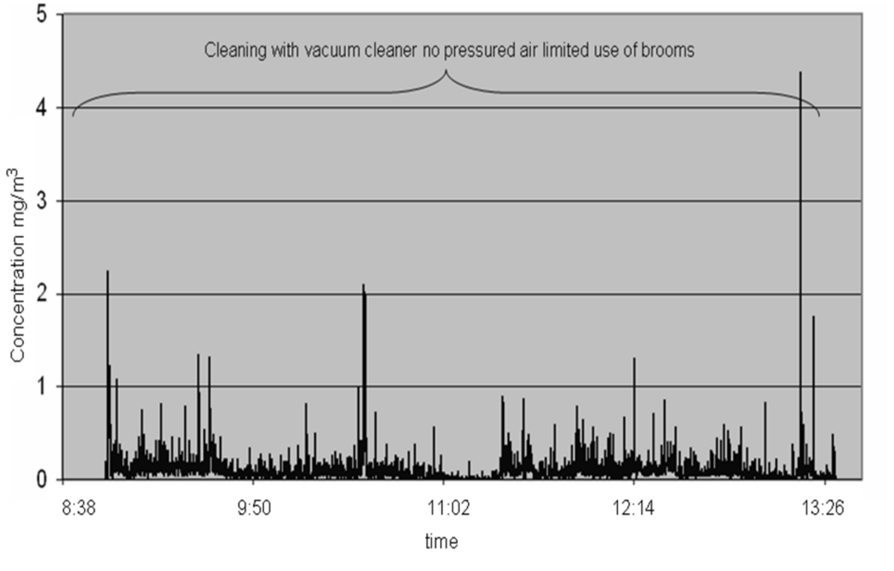


Figure 3c. Limited peak exposure when cleaning flour spill in a flour mill with vacuum cleaner instead of broom

Table 1 gives the number of peaks per hour as well as peak intensity and duration, which varies substantially between jobs. In some cases many peaks are observed, more then 20 peaks per hour sometimes in combination with very high concentrations, in excess of 100 mg/m^3. For all jobs extensive periods of peak exposure are identified, often peak exposures have a duration of more then 10 minutes and occasionally periods over 1 hour are observed.

Table 1. Descriptive peak exposure statistics and average exposure levels (PAS6) per sector and job

Sector	Job	N	PAS6 AM (mg/m^3)	average number of peaks/ hour	max peak intensity (mg/m^3) [1]	median duration (sec.) [2]	Max. peak duration (sec.) [3]
Bakeries	Breadbaker	30	4.49	26	371	53	9441
	Pastrybaker	4	0.49	27	117	34	2478
	Dough maker	16	1.82	33	203	29	2637
	All baker	8	2.02	30	400	54	4890
	Storage worker	1	2.32	18	400	179	5883
Ingredient producers	Weigher/Mixer	7	14.9	20	317	172	8700
	Bagging operator	1	0.65	17	20	39	939
	Mill operator	5	10.60	29	258	32	1971
	General operator	1	1.19	30	28	44	1449
	Dumper ingredients	2	19.47	18	231	180	2459
	Cleaner	3	10.23	42	165	71	1368
	Foreman/boss	1	1.64	13	222	88	1749
	Storgage worker	3	0.78	8	161	16	6542

[1] maximum peak intensity observed within that job over all measurements
[2] median duration of the peak exposures averaged over all observed peaks in all measurements for that job
[3] maximum peak duration, longest single peak exposure observed over all measurements for this job

Table 2 shows the number of measurements where peak exposure was observed during a specific task, as well as the relative contribution of this task peak exposure to the TWA exposure. Contribution of peak exposure during individual tasks to TWA exposure in bakeries is substantial for dough making, dough processing and to lesser extend cleaning and limited for the other tasks. In individual cases the contribution of peak exposures during most tasks and activities can be substantial, up to 100%. In bakery workers on average approximately 76% of TWA exposure could be assigned to peak exposures associated with specific tasks.

For ingredient producers contribution of the different tasks to TWA exposure was more evenly distributed. Weighing of ingredients, dumping of ingredients and cleaning were activities that caused most peak exposure. On average 78% of TWA exposure was related to peak exposure during the defined tasks.

Table 2 Relative contribution of task/activity peak exposure to total TWA exposure

Sector	**Activities and main tasks**	**k**[1]	**Contribution to time weighted average exposure (%)**	
			AM	**range**
Bakeries	Preparing dough	48	39	0-100
	Processing dough	45	24	0-99
	Cleaning	34	6	0-43
	Pastry work	8	1	0-18
	Wrapping	6	1	0-31
	Storage work	14	1	0-7
	Maintenance	11	1	0-15
	Control work	28	3	0-33
	Total peak exposure	59	76	32-100
Ingredient producers	Bagging	6	6	0-58
	Dumping	14	13	0-49
	Cleaning	17	16	0-95
	Maintenance work	6	4	0-53
	Weighing of ingredients	15	26	0-98
	Control work	16	4	0-2
	Storage work	19	9	0-100
	Total peak exposure	23	78	8-100

[1] number of measurements where peak exposures occurred during this task

Potential control measures identified were; enclosure of mixing tub at silo, no shaking of bags and silo hose when dumping or weighing ingredients, use of local exhaust ventilation (LEV) at different tasks, elimination of use of sprinkling flour, and performing wet cleaning instead of sweeping or pressured air use. Average and ranges of cumulative peak exposure vary substantially between tasks as does the effectiveness of the different control measures (Table 3).

Table 3. Impact of control measures on task/activity peak exposure in bakeries and ingredient production facilities.

Control measure	Sector	Short description of control measure	Task/activity	No control measure			Control measure[1]			Average reduction in peak exposure
				N[2]	cumulative peak exposure		N[2]	cumulative peak exposure		
					average[3]	range		average[3]	range	
A	Bakery	No shaking of cotton hose attached to flour silo	Dumping flour from silo	10	3389	0-9154	7	518	0-2689	85%
B		Closed tub and local exhaust ventilation	Dumping flour from silo	7	518	0-2689	16	405	0-2089	22%
C		No shaking of bags when dumping bagged ingredients in mixing tub	Dumping bagged flour	28	3373	0-17590	22	2071	0-10303	39%
D		No shaking of bags	Weighing ingredients	28	4568	0-21971	22	1456	0-12365	68%
E		Substitute normal flour with dust free flour when dusting	Flour sprinkling	28[4]	6459	0-46827	6[4]	2921	0-14897	55%
F		Partially substitute flour dusting with oil	Processing dough	28[5]	14105	0-65274	3	22109	9591-46986	NR[6]
G		No flour dusting	Processing dough	28[5]	14015	0-65274	10	2823	0-12032	80%
H		Eliminate use of pressured air	Cleaning	8	4979	10-14995	23	2173	0-10801	56%
I		Use vacuum cleaner where possible	Cleaning	23	2173	0-10801	5	1666	477-1324	30%
J		Only perform wet cleaning activities	Cleaning	5	1666	477-1324	6	140	0-676	92%
K	Ingredient producers	Use of local exhaust ventilation	Bagging	3	58038	0-174115	5	6034	0-28720	90%
L		Use of local exhaust ventilation	Dumping	3	66827	0-112799	6	23246	0-94467	65%
M		No shaking of bags	Dumping	3	66827	0-112799	6	3069	9-6877	95%
N		Eliminate use of pressured air	Cleaning	10	27129	79-180497	10	1344	0-7141	95%
O		Eliminate use of pressured air	Maintenance	4	10042	0-20867	3	9	0-26	100%
P		Use of local exhaust ventilation	Weighing ingredients	3	127545	4100-222244	6	64009	2944-333707	50%
Q		No shaking of bags	Weighing ingredients	6	64009	2944-333707	6	38845	145-173575	39%

[1] indicated in the first column (e.g. A, B, C, etc.) [2] N=number of measurements in this group [3] arithmetic mean [4] not including workers that partially substitute sprinkling flour with oil [5] only workers that sprinkle with normal flour [6] NR= no reduction

In general, reductions of peak exposures in both sectors were in most cases above 50% (between 22-100%), except for partial substitution of sprinkling flour with oil where no reduction on task level was observed. Most effective control measures (with respect to percentage reduction) in bakeries were; no shaking of cotton hose attached to flour silo, no flour dusting, perform only wet cleaning. For ingredient production sector the elimination of use of pressured air, installation of LEV when bagging and not shaking bags when dumping ingredients were most effective control measures.

The above data show that significant reductions in exposure can be achieved on a task level. For an individual worker the impact on exposure depends on the time spend on the task and performance of other activities. In a hypothetical example we eliminate the peak exposures during sprinkling of flour from the exposure pattern shown in figure 3a, the TWA exposure of this individual decreases from 4.2 mg/m^3 to 1.6 mg/m^3. This represents a reduction of 62%.

The information on efficacy of control measures can also be used to prospectively evaluate the impact of intervention strategies. A hypothetical intervention strategy that beheld structural implementation of best practices (as presented in table 3) for all bakery workers in our study population was evaluated. At individual level reductions in flour dust exposure ranged between 0-80%. As expected, relatively low reductions were observed in individuals with TWA exposures already below 1 mg/m^3, on average 17% exposure reduction was observed in this group. These workers generally performed less of the high exposure tasks or already implemented control measures in their daily work practice. For workers with exposures between 1-3 mg/m^3 the average exposure reduction was 36% and for workers with exposure above 3mg/m^3 average reduction was 47%. The median TWA group exposure decreased from 1.45 mg/m^3 before to 0.88 mg/m^3 after the hypothetical interventions. The GSD decreased from 2.10 to 1.98.

Discussion

This paper describes the use of real time exposure measurements to associate tasks/activities and related control measures to (reduction in) peak exposure. This study shows that the real time measurement data combined with detailed observational information on worker performance can provide quantitative information on the influence of determinants on TWA exposure levels. It also gives information on effectiveness of specific control measures in reducing task-based peak exposures. In general the results show that contribution of one or a few specific task exposures and associated control measures can be large on an individual level but that a broader range of tasks is important for the overall population TWA exposure. Hence, interventions in this sector should cover a range of tasks to have substantial impact on the population exposure distribution.

The control measures identified in this study show that worker behavior during several of the tasks/activities has a large impact on exposure. The importance of worker behavior, skills and hygiene on exposure is generally acknowledged in studies on exposure control and interventions[9,17,18]. Quantitative information on impact of interventions specifically focusing on worker behavior related to the tasks and activities observed in our study is, to our knowledge, not available from scientific literature. Some comparison data is available for specific control measures. For cleaning, one study evaluated the effect of wet cleaning (sweeping) instead of dry sweeping and found reductions up to 99%[19]. This is comparable to the reduction figures found in our study for substituting sweeping with wet cleaning. Several studies showed that use of pressured air (significantly) increased exposure, but non quantified exposure reductions when eliminating this task[20-22]. For substitution of sprinkling flour with oil Burstyn et al.[7] found significant reduction in exposure whilst the present study found no effect on task level. This is primarily caused by the fact that substitution is in most cases only partial in Dutch bakeries, as figure 3a also shows, having only limited effect on task level. Where sprinkling flour was eliminated, substantial reductions in exposure were observed.

Local exhaust ventilation (LEV) is by far the most studied exposure control technology. Effectiveness ranges substantially, depending on type of LEV (integrated in process, mobile, etc), process characteristics, and worker behavior (e.g., working exactly below the LEV or at a distance). For efficacy of integrated LEV when dumping bagged product, one study in mining was identified. This study showed reductions in exposure of 80-90% during bag filling[23], comparable to the reduction observed in ingredient factories. A Dutch study on evaluation of effectiveness of LEV during dumping of powders found exposure reductions between 55-99%, all >75% except for one situation with poor design[24]. This is a little higher then 65% reduction found in the ingredient sector, where LEV was generally limited to a flow hood above the dumping site. For weighing of ingredients Heinonen et al.[25] found exposure reductions of LEV up to almost 100% depending on the design and flow rate, considerably higher then the figures we found in our study. In general, the use of LEV and therefore the effectiveness at the processes observed in both bakeries and ingredient sector was in many cases not optimal. Ineffective design and use (i.e. large distance from the source, relative position of worker and LEV system, weak airflow, poor maintenance) was the most observed reason for LEV not to be very effective in controlling exposure.

This study identified a large variety of tasks, activities and control measures associated with peak exposures that were not identified in an earlier study among the same population, focusing at determinants of full shift TWA exposure[5]. This is likely caused by the limitations of the contextual data and measurement error in the previous study. The time series presented in this paper in combination with detailed observations show that exposure to flour dust in the studied sectors is a complex phenomenon; workers perform many tasks often for very short time periods and have a large mobility within the production facility. The use of control measures can be very fragmented, being implemented for one task, but not for another task conducted during the same shift. Furthermore, as our study shows, on a population level the influence of a single task or control measure on the TWA exposure is limited. The use of general, often post measurement interview based questionnaires, results in crude generalizations about tasks performance and the presence of specific determinants (i.e. control measures). This limited contextual information leads to misclassification error in these variables. Consequently, although 8-hour TWA exposure measurements provide invaluable information on variability and major determinants of exposure[26] they lack sensitivity (in these situations) to evaluate effectiveness of (task) specific control measures.

The opposite placement of the samplers on the worker might have been a potential source of bias in our comparisons[27]. Nevertheless two recent studies show that the difference of measured concentration between parallel samplers placed on the left and right side of a worker are minimal. For styrene a recent study did not find any significant difference in sampled concentration[28]. A study performed in the rubber industry, looking at exposure to dust and rubber fumes found a small difference of 30% between measured concentration with PAS6 samplers placed on the left and right shoulder[29]. Although no comparisons results are available specifically for bakery workers we believe these results indicate the effect of opposite placement has been limited.

Our results allow calculation of the effect of control measures on peak exposures into so called reduction factors. The presented reduction factors give an indication of the average potential impact on task/activity exposure. Actual reduction varies substantially between companies and individual work areas. In the occupational hygiene literature, large variations are observed in effectiveness of control measures across studies[30].

In this study information on the evaluated control measures is based on small numbers of observation and might change substantially if more data would become available. Especially for ingredient production industry numbers are very small and therefore results should be interpreted with caution. Although the number of workers included in the study is limited we do believe our sample provides a good representation of the work performed in the different branches.

In observational studies environmental factors that can have an impact on exposure, might differ between groups of workers that are compared, in our case workers with and without control measures. Contrary to what is the case in experimental or intervention studies where these factors are as much as possible controlled[30]. This might have lead to bias in our estimated reduction factors. By defining and describing very specific tasks and activities we have tried to minimize such error in our study.

It was not possible to correct the cumulative peak exposure of the activities for differences in total time an activity was performed between groups of workers with and without control measure. Information on performance time was obtained from the survey questionnaire and was only available for the main tasks and not for the more detailed activities. As a result we might have over- or underestimated specific reduction factors. However, adjusting for the main task time did not reveal substantial changes in reduction factors. This suggests that the potential confounding effect is limited.

Although the information from real time measurements provides valuable data there are some drawbacks of the used measurement methodology. The DataRam device used in this study is primarily designed to sample dust that contains particles with an aerodynamic diameter <10 μm. Earlier studies have shown that flour particles are relatively large with a substantial amount of particles larger then 10 μm[31-33]. Particle sizes above the respirable range may not be detected by direct reading devices. This can lead to structurally underestimation of the dust concentration with a constant factor not depending on the measured concentration[15]. This indicates the use of an overall calibration factor related to the mass median aerodynamic particle diameter of the dust measured is justified. Thorpe et al. in their paper present comparable correction factors for dusts with similar characteristics as flour dust[15]. Smit et al in a study looking at seed dust also presented comparable reduction factors[13].

In conclusion this study shows that exposure to flour dust in the Netherlands is primarily caused by short term, sometimes very intensive, peak exposure moments. The impact that exposure during a specific task or activity has on TWA exposure can be substantial for an individual worker. This information is important to get a better understanding why workers have (sometimes very) high exposures and eventually to design efficient control strategies focusing on a limited set of relevant tasks. This information on peak exposure patterns will also help in explaining to workers why and how they have to change their work practice. The presented hypothetical examples show how the information from this study might be used to get insight in the potential impact of specific intervention strategies.

Nevertheless the reduction factors have to be interpreted with caution since for some interventions the number of measurements was minimal. In the near future the information from this study will be used as input for scenario analysis to predict post-intervention population distributions of exposure. This will be done in the context of a health impact assessment (HIA) study among bakeries, predicting shifts in burden of disease due to branche-specific interventions at the workplace.

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CHAPTER 4

Wheat allergen exposure and the prevalence of work-related sensitization and allergy in bakery workers

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Abstract

Background: Occupational airway diseases are common among bakers. The present study describes the association between exposure to wheat allergen levels and sensitization to wheat allergens, work-related upper and lower respiratory symptoms and asthma in bakery workers.

Methods: As part of a Health Surveillance System for early detection of (allergic) occupational airway diseases a so-called "validation study" was performed among Dutch bakers for validation of a diagnostic model that predict the likelihood of sensitization to specific workplace allergens. The present study used serology and questionnaire results of a subgroup of 860 bakers participating in the validation study. An earlier developed job-exposure matrix was used to predict average and cumulative personal exposure to wheat allergens.

Results: The prevalence of wheat sensitization, work-related respiratory symptoms and asthma increased till average wheat exposure levels of approximately 25-30 µg/m3, leveled off and decreased at higher exposure concentrations. Exposure-response curves showed a stronger pronounced bell-shape with cumulative exposure. Associations were strongest for asthma and work-related lower respiratory symptoms (PR~2 and PR~3.5-4.5 for resp. average and cumulative exposure). Associations were only found in atopics. Wheat sensitization was an important factor in the prevalence of respiratory symptoms.

Conclusion: In accordance with earlier studies, the present study showed a bell-shaped exposure- response relationship especially for cumulative wheat allergen exposure with sensitization, allergic respiratory symptoms and asthma. The healthy worker effect may be the possible explanation for the bell-shaped relationship.

Introduction

Respiratory allergies are common among bakery workers[1]. Asthma is one of the most serious manifestations of occupational airway disease in bakers. Baker's asthma can be caused by immunologic sensitization to specific work-related allergens and subsequent allergic reactions in the airways[2-7]. In other studies a considerable proportion of workers had respiratory symptoms but was not sensitized to any work-related allergen[8,9]. Rhinitis and conjunctivitis are less severe (respiratory) disorders in bakers, however, they are reported more frequently among exposed workers than occupational asthma and it has been suggested that the presence of allergic rhinitis increases the likelihood of developing occupational asthma[10].

Several cross-sectional studies and a longitudinal study show a strong association between flour dust exposure and sensitization to wheat allergens[3,5,9,11]. Similar associations have been found for rhinitis and physician-diagnosed asthma although these endpoints have been studied less extensively[12]. The shape of the exposure-response relationships for both sensitization and symptoms are not well characterized. Houba et al.[3,4] found an increasing risk for sensitization with increasing exposure. He also showed that atopy is a major determinant of specific sensitization for both wheat and fungal α-amylase allergen exposure. Heederik et al.[5] showed with smoothing that even low exposure levels to flour dust (<0.5 mg/m^3) might sensitize workers and this is possibly associated with the presence of severe respiratory symptoms with a plateau for sensitization risk at higher exposure levels. The results of this analysis showed no evidence for the existence of an exposure threshold for wheat sensitization or work-related symptoms. Others also found non-linear exposure-response relationships, however, with considerable heterogeneity between different sectors of industry[11].

There is some discussion about the explanation for the shape of the exposure-response relationship. Several studies suggest a healthy worker effect is responsible for the decline at higher exposure levels[3,5,11], few other studies indicates that tolerance might also play a role[13]. The present study describes the association between exposure to wheat allergen levels, using allergen exposure data from a large survey[14], and specific IgE-sensitization to wheat allergens, and work-related (allergic) respiratory symptoms in bakery workers. Special attention is paid to the shape of the exposure-response relationships for sensitization and symptoms. Individual (cumulative) exposure calculated on the basis of more than 900 wheat allergen measurements are included which may help improve the understanding of the possible role of the healthy worker effect on the exposure-response relationship. Furthermore, the present study is the first workforce-based study in bakeries with exposure, health outcome data and with measurements of specific IgE available for such a large population.

Methods

Study population

As part of a Health Surveillance Program for early detection of (allergic) OAD a so-called "validation study" was performed among Dutch bakers for validation of a diagnostic model that predict the likelihood of sensitization to specific workplace allergens. Between June 2005 and June 2006, 341 traditional and 28 industrial bakeries were approached randomly from the list of bakeries invited to the surveillance program, which covers more than 80% of the baking industry in the Netherlands. From these companies 64.5% (238/369) participated in the study, comprising 1249 workers to be invited for blood drawing and additional questionnaire information. Twelve bakeries no longer existed, 116 companies refused to cooperate, while 3 bakeries were withdrawn from the inviting list for different reasons. From these 1249 workers, 186 did not want to participate, 173 were not available for reason of vacation, sick leave, or leaving their employer, resulting in 890 workers for blood drawing and participation in responding to an extensive self-administered questionnaire. Twenty three of these workers refused to give blood, and seven did not have complete exposure questionnaire information leaving 860 (69%) workers for further analysis.

Exposure assessment, questionnaires and serology

A dataset comprising 910 personal exposure measurements was used to estimate individual average exposure[14]. An analysis of exposure determinants was performed taking job title, tasks performed and other work characteristics into account. Information on work characteristics obtained from the completed self-administered questionnaire was combined with the exposure models, to predict individuals average exposures to occupational allergens. Cumulative exposure was calculated by multiplying average exposure with the number of years worked in the job, no information on prior work history was available.

A self-administered questionnaire was derived from the IUATLD[15] and the MRC-ECCS[16] and contained items on employment (job, tasks, absenteeism), history of respiratory, allergic, and work-related symptoms, symptoms suggesting bronchial hyperresponsiveness, medication use and smoking habits.

Blood samples were taken from all workers. Sera were stored at -20°C until IgE analysis. Specific IgE antibodies to wheat were assessed using ELISA[17]. A sample OD>=0.1 above blank was considered being positive. Specific IgE-antibodies to common allergens (house dust mites, grass pollen, birch pollen, cat fur and dog fur) were partly detected with commercial kit (Pharmacia Unicap system, Pharmacia Diagnostics, Sweden) and with concentration of 0.35 kU/L and above defined as positive. Common allergens in the remainder samples were detected by an earlier described method[17]. Subjects were classified atopic if they had at least one positive response to house dust mite allergens, cat or dog allergens, grass or birch pollen.

Endpoint of interest

In exploring exposure-response relationships, endpoints of interest were specific IgE-sensitization to wheat, and wheat sensitization including either work-related upper – and lower respiratory symptoms and asthma. Work-related upper respiratory symptoms were defined as having at least two of the following three symptoms: the presence of sneezing, a running nose or itchy/teary eyes during work. Work-related lower respiratory symptoms were defined as at least two of the following symptoms: asthma attacks, wheezing, shortness of breath or tightness of chest during work. Asthma was classified according the ECRHS and was defined as the presence of any of the following three variables during the last 12 months: asthma attack, woken by an asthma attack or the use of asthma medication[18].

Statistical analyses

Statistical analyses were performed using SAS software (version 9). The prevalence of general characteristics, exposure and health information was analyzed by using the FREQ or UNIVARIATE procedure. Level of statistical significance was set at p=<0.10. Nonparametric regression modeling (smoothing) was performed by using generalized additive models (PROC GAM) to explore and visualize the association between exposure and health for atopic and non-atopic separately. Generalized cross validation (GCV) was used to select the degrees of freedom for the smoothing component. In a number of cases, the curves in GAM showed large fluctuations that were not biologically plausible. In those cases the degrees of freedom were limited to a maximum of 2. Estimates from the generalized additive models were exported to Sigmaplot (v9.0) to create smoothed spline plots for the different exposure-response relationships.

Results

General characteristics

Population characteristics and health information are outlined in table 1. Most workers (95 %) were male and were on average 40 years of age. Serology results showed that 288 (33%) workers were atopic, specific wheat flour IgE was detected in 107 (12%) workers and wheat IgE-sensitization was more common in atopic than in non-atopic workers (24% vs. 7%). Furthermore, 9% of the workers were asthmatic, 10% used asthma medication, 23% of the bakers reported work-related upper respiratory symptoms, while 9% suffered work-related lower respiratory symptoms. All respiratory symptoms were more prevalent in atopic than in non-atopic workers.

Table 1: Description of the general characteristics and health outcomes (n=860)

General characteristics	***N***	***Overall (n=860)***	***Non-atopic (n=572)***	***Atopic (n=288)***
Age in years (range)	853	40 (17-79)	40 (17-79)	37 (19-66)
Gender n (man) (%)	858	812 (95%)	533 (94%)	279 (97%)
Current smoker n (%)	825	291 (35%)	197 (36%)	94 (34%)
Quit smoking n (%)	825	188 (23%)	131 (24%)	57 (21%)
Years working at the company (range)	836	12 (1-54)	13 (1-54)	12 (1-44)
Health outcomes				
Serology		N (%)	N (%)	N (%)
IgE sensitization to wheat allergen	859	107 (12%)	38 (7%)	69 (24%)
Elevated total IgE (>= 100 kU/L)	848	223 (26%)	77 (14%)	146 (52%)
IgE sensitization to any common allergen (house dust mites, cat/dog fur, grass/birch pollen)	860	288 (33%)	0 (0%)	288 (100%)
Asthma	860	81 (9%)	29 (5%)	52 (18%)
Use of asthma medication	829	79 (10%)	28 (5%)	51 (18%)
Symptoms during work				
Upper respiratory symptoms	860	202 (23%)	100 (17%)	102 (35%)
Lower respiratory symptoms	860	81 (9%)	37 (6%)	44 (15%)
IgE-response to wheat and airway symptoms				
Upper respiratory symptoms (during work)	859	54 (6%)	16 (3%)	38 (13%)
Lower respiratory symptoms (during work)	859	34 (4%)	10 (2%)	24 (8%)
Asthma	859	37 (4%)	8 (1%)	29 (10%)
Use of asthma medication	829	36 (4%)	8 (1%)	28 (10%)

Exposure

Table 2 describes the exposure statistics for both average and cumulative exposure to flour dust and wheat allergens based on predicted exposure. Average exposure in the population was approximately 2 mg/m^3 for flour dust and 13 µg/m^3 for wheat allergens (GM). The average number of working years in the population was twelve years (range 1-54 years). The model to estimate α-amylase allergen exposure had a low explained variability (<10%). So, exposure prediction based on statistical models is only possible for α-amylase at the expense of considerable misclassification error. Hence, and α-amylase was not included because exposure-response modeling using these poor estimates would lead to inaccurate associations. The correlation between dust and wheat allergen exposure was very high (rho=0.95, spearman correlation), therefore all analyses were limited to wheat allergen exposure. An earlier study[14] showed that especially bread bakers and, in industrial bakeries, dough makers were exposed to high wheat levels. Furthermore, tasks, such as dough making and sprinkling flour were associated with higher exposure levels to wheat allergen.

Table 2: Description of average and cumulative exposure to dust and wheat allergens

Exposure characteristics		***AM***	***GM***	***GSD***	***Range***
Estimated average dust exposure mg/m3	860	2.1	1.8	1.7	0.3-7.3
Estimated cumulative dust exposure mg/m3 x year	860	30.5	-	-	0.8-278.0
Estimated average wheat exposure µg/m3	860	22.5	12.8	3.5	0.3-95.6
Estimated cumulative wheat exposure µg/m3 x year	860	318.5	-	-	1.0-4492.4

Sensitization and symptoms

Table 3 shows associations between IgE-sensitization to wheat allergens and the prevalence of work-related respiratory symptoms and asthma. Workers sensitized to wheat showed a higher prevalence for both work-related symptoms and asthma compared to non-sensitized workers (overall: 50% vs. 20% for upper respiratory symptoms, 32% vs. 6% for lower respiratory symptoms and 35% vs. 6% for asthma). Stratifying for atopy resulted in smaller differences in work-related symptoms between sensitized and non-sensitized workers. Wheat sensitization was strongest associated with lower respiratory symptoms and asthma (3.8-5.3 times more individuals reported lower respiratory symptoms and asthma when sensitized, compared to a factor 1.9-2.6 for upper respiratory symptoms). Atopics reported more often work-related symptoms and asthma than non-atopics (factor 1.3-2.8). Still, wheat sensitization was stronger associated with symptoms than that atopic status was.

Table 3: Prevalence of work-related symptoms and asthma in non-sensitized and sensitized bakery workers stratified by atopic status

	Total		**Non-atopic**		**Atopic**	
	Non-sensitized (N=752)	**Sensitized (N=107)**	**Non-sensitized (N=533)**	**Sensitized (N=38)**	**Non-sensitized (N=219)**	**Sensitized (N=69)**
Upper respiratory symptoms	148 (20%)	54 (50%)	84 (16%)	16 (42%)	64 (29%)	38 (55%)
Lower respiratory symptoms	47 (6%)	34 (32%)	27 (5%)	10 (26%)	20 (9%)	24 (35%)
Asthma	44 (6%)	37 (35%)	21 (4%)	8 (21%)	23 (11%)	29 (42%)

Table 4 and figure 1a-d present the results of the exposure-response modeling in atopics and non-atopics for average and cumulative exposure. Age, smoking and gender in the model did not substantially change parameter estimates for the exposure under study and were therefore excluded in final analyses. Average and cumulative exposure was significantly ($p<0.10$) associated with wheat sensitization, work-related respiratory symptoms and asthma in atopic workers when using smoothing (table 3). Figure 1a and c shows that in atopic workers increased exposure to wheat allergens was associated with a higher frequency of wheat sensitization, work-related symptoms and asthma. The prevalence of wheat sensitization as well as the prevalence of wheat sensitization in combination with work-related symptoms and asthma showed an increase up to an average wheat exposure level of approximately 25-30 μg/m^3, leveled off and decreased at higher exposure concentrations, especially for the prevalence of wheat sensitization and upper respiratory symptoms.

About 22% of the atopic workers were sensitized at very low average exposure and with increasing exposure sensitization rates rose to approximately 27%. Sensitization including upper respiratory symptoms was reported in 11% of atopics with very low average exposure and reached a maximum of 16% with increasing exposure. Lower respiratory symptoms and asthma increased from about 6-7% at low exposure to 11-13% at exposure levels above 25 μg/m^3. Cumulative exposure-response curves showed similar patterns, with a more pronounced bell-shape. The highest prevalence of symptoms was found at cumulative wheat allergen levels of 600 μg/m^3*year. Wheat allergen exposure was strongest associated with lower respiratory symptoms and asthma (PR's approximately 2 and 3.5-4.5 for respectively average and cumulative exposure). For sensitization and upper respiratory symptoms prevalence ratios were below 1.5 for average exposure and 1.5-2.5 for cumulative exposure.

In non-atopic workers only weak non-significant associations were found for wheat allergen exposure with wheat sensitization, asthma and work-related symptoms (figure1b and 1d, table 4). The prevalence of symptomatic allergies and asthma was low among low exposed (6% for sensitization and 1-3% for sensitization in combination with symptoms) but hardly increased with elevated wheat exposures. Cumulative exposure showed a linear association with asthma symptoms in sensitized non-atopic workers (figure 1d), however when the two highest exposure levels were excluded from analyses associations appeared to be non-significant.

Table 4: Association between wheat exposure, wheat sensitization, work-related respiratory symptoms and asthma analyzed by generalized additive models stratified by atopic status

	Average exposure				Cumulative exposure			
	Non-atopic		Atopic		Non-atopic		Atopic	
	Esti-mate	P-value	Esti-mate	P-value	Esti-mate	P-value	Esti-mate	P-value
Wheat sensitization								
Regression model (parametric part)								
Intercept	-2.806	<.01	-1.091	<.01	-2.778	<.01	-1.189	<.01
Linear component	0.007	0.33 (ns)	-0.002	0.83 (ns)	0.000	0.13 (ns)	0.000	0.47 (ns)
Smoothing model (non-parametric part)								
Spline component	df=0	Ns	df=1*	0.05#	df=0*	Ns	df=1*	<.01#
Wheat sensitization and upper respiratory symptoms								
Regression model (parametric part)								
Intercept	-3.717	<.01	-1.847	<.01	-3.598	<.01	-1.923	<.01
Linear component	0.007	0.51 (ns)	-0.0003	0.97 (ns)	0.000	0.66 (ns)	0.0005	0.46 (ns)
Smoothing model (non-parametric part)								
Spline component	df=0*	Ns	df=1	0.04#	df=0*	ns	df=1*	<.01#
Wheat sensitization and lower respiratory symptoms								
Regression model (parametric part)								
Intercept	-4.183	<.01	-2.434	<.01	-4.293	<.01	-2.562	<.01
Linear component	0.006	0.63 (ns)	0.002	0.84 (ns)	0.001	0.12 (ns)	0.001	0.24 (ns)
Smoothing model (non-parametric part)								
Spline component	df=0	Ns	df=1	0.10#	df=0*	Ns	df=1	<.01#
Wheat sensitization and asthma								
Regression model (parametric part)								
Intercept	-4.420	<.01	-2.279	<.01	-4.685	<.01	-2.343	<.01
Linear component	0.007	0.66 (ns)	0.005	0.62 (ns)	0.001	0.01#	0.001	0.18 (ns)
Smoothing model (non-parametric part)								
Spline component	df=0*	Ns	df=1	0.06#	df=0	Ns	df=1*	0.01#

*= degrees of freedom were selected by a generalized cross-validation method
#= significant (p<0.10) Ns=not significant

Figure 1a: Association between average wheat exposure and work-related respiratory symptoms and sensitization in atopic bakery workers (n=288) in a smoothed plot

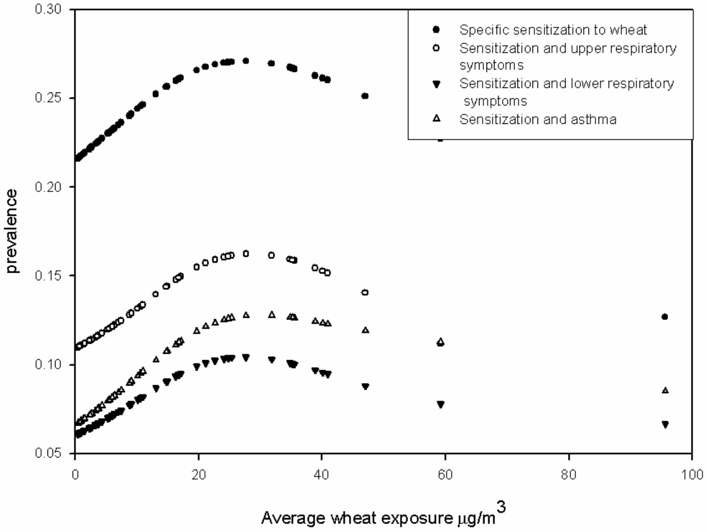

Figure 1b: Association between average wheat exposure and work-related respiratory symptoms and sensitization in non-atopic bakery workers (n=572) in a smoothed plot

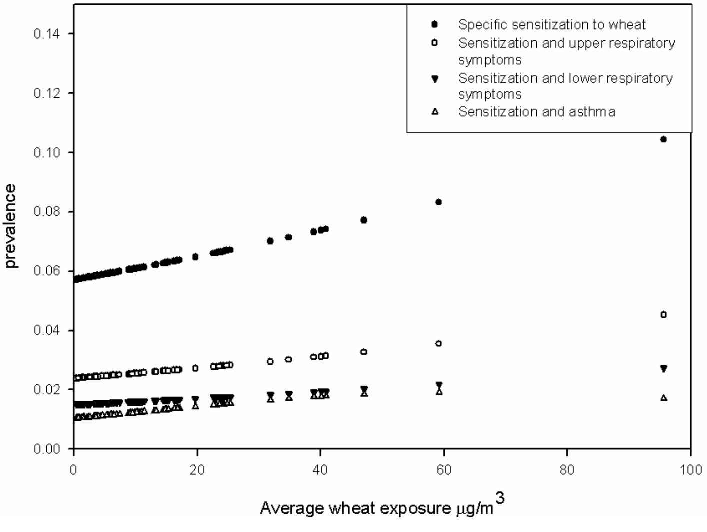

Figure 1a and b: Association between average wheat exposure and work-related respiratory symptoms and sensitization in atopic and non-atopic bakery workers

Figure 1c: Association between cumulative wheat exposure and work-related respiratory symptoms and sensitization in atopic bakery workers (n=280) in a smoothed plot

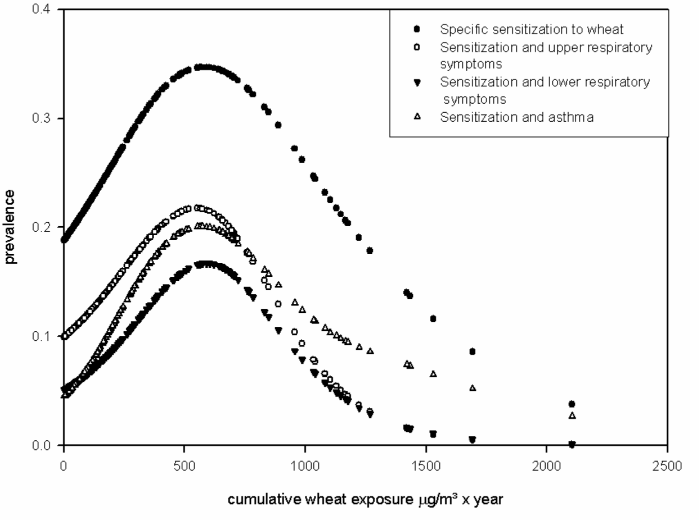

Figure 1d: Assocation between cumulative wheat exposure and work-related respiratory symptoms and sensitization in non-atopic bakery workers (n=555) in a smoothed plot

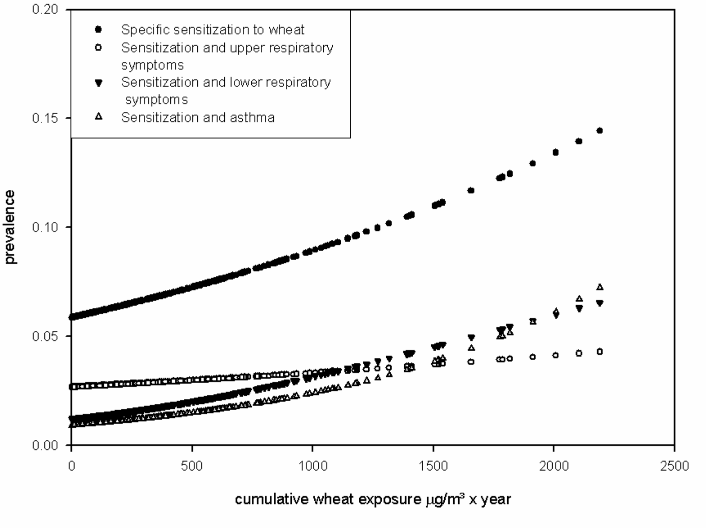

Figure 1c and d: Association between cumulative wheat exposure and work-related respiratory symptoms and sensitization in atopic and non-atopic bakery workers

Discussion

As found in earlier studies, we found strong associations between increasing occupational wheat allergen exposure and prevalence of lower respiratory symptoms and asthma, and to a lesser degree with the prevalence of specific wheat sensitization and upper respiratory symptoms. Work-related asthma is considered a critical endpoint in bakers' allergy[5,19,20]. In our study 46% of the cases (37 of 81 bakers) with general asthma according the ECRHS definitions was IgE-sensitized to wheat allergens, emphasizing the importance of occupational exposure among asthmatic bakery workers. Additional analyses showed that 49% of the cases with lower respiratory symptoms had asthma and in wheat sensitized this number was even higher (68%). The levels of asthma medication use were highly associated with prevalence of asthma, which may underline the role of occupational exposure on asthma in bakers. 79 of the 81 asthmatics used medication (98%) compared to over 80% in earlier findings[21]. A follow-up study found indications that use of anti-inflammatory drugs was highest in populations with highest proportions of severe asthmatics[22].

We found specific wheat IgE-sensitization rates of 12% and a prevalence of 23% for upper respiratory symptoms and approximately 10% for lower respiratory symptoms and asthma. Earlier studies found comparable sensitization rates (Droste et al.[23] 12%; Brant et al.[24] 11%; deZotti et al.[25] 12%). Respiratory symptoms were more difficult to compare due to different symptom definitions. Exposure-response relations, were bell-shaped, i.e. the prevalence increased with increasing exposure then flattened and eventually decreased at higher concentrations, which indicates the presence of a healthy worker effect. This effect was stronger for cumulative than for average exposure, indicating that both exposure intensity and duration of exposure play an important role in developing sensitization and symptoms and contribute to the healthy worker effect. For non-atopic workers only very weak and statistically not significant associations were found.

Two earlier studies found similar-shaped exposure-response curves as the present study. A study by Heederik[5] found increased prevalence to sensitization and symptoms till a wheat allergen level of 10 μg/m^3 and the prevalence decreased at higher exposure levels. Peretz[11] found increased probability of sensitizing till wheat levels reached 25.7 μg/m^3 and sensitization risks declined at higher exposure. So, several independent cross-sectional studies found similar associations between wheat allergen exposure and sensitization. In the longitudinal studies available, which designs are less prone to bias from the healthy worker effect, no bell-shaped exposure-response relationships was found[9,12]; higher exposure resulted in elevated incidence ratios of work-related symptoms.

There has been some debate about the explanations for the bell-shaped exposure-response curves for some indoor allergens. It has been suggested that for some allergens, tolerance may exist at higher exposure levels. IgG and IgG4 antibody responses at higher exposures without IgE sensitization are thought to play a role[13,26]. Although we did not evaluate the presence of IgG antibodies and their potential role, it seems unlikely that in the present study the bell shape can be attributed to tolerance. The study by Peretz[11] found differently shaped curves for the same wheat allergen exposure in different flour-processing industries, which argue against the occurrence of tolerance. Contextual differences between populations, like a differentially strong healthy worker effect, seem a more likely explanation. The decline at higher exposure levels was probably caused by movement of symptomatic persons to low- or non-exposed jobs. In addition, exposure-response relationships for the higher exposure levels are based on few measurements, so results of this part of the curve have to be interpreted with caution.

Earlier studies suggest that occupationally low or non-exposed individuals have a low but substantial frequency of specific sensitization to high-molecular-weight work-related allergens, which partly may be contributed to cross-reactivity by other allergens (pollens)[27]. Background prevalence of specific sensitization between 2%-5% were reported in total population groups[2,3,5,27,28] and in atopic workers specific sensitization rates up to 8% were reported[3,27]. Our study showed a high specific sensitization rate in all low exposed bakers (11%) and in low exposed atopic workers (22%). Cross-reactions probably did not play a role. No elevated prevalence of wheat sensitization in only grass or birch sensitized people was found compared to people who were sensitized to the other common allergens (24% in both groups). The most likely explanation for the high prevalence is migration of sensitized and symptomatic high exposed employees to a lower exposed job function. However, we could not assess this in our analyses because a complete job history was not available.

In our study 27% of the upper respiratory symptoms were IgE-related and for lower respiratory symptoms and asthma respectively 42% and 46% of the bakers showed wheat allergen sensitization, which was, although some endpoint definitions differed, high compared to earlier findings, where between 10%[9] and 20%[3] of work-related symptoms were IgE-related. Additional analyses showed a statistically significant ($p<0.01$) (linear) association between wheat allergen exposure and upper respiratory symptoms in non-sensitized workers (data not shown). This confirms that specific sensitization is an important condition in respiratory problems (including asthma) of especially the lower respiratory tract. A mechanism of airway irritation might also play a substantial role in upper respiratory symptoms[3,29,20].

Our results suggest atopy is an important modifier of the prevalence of allergies in bakery workers. Atopics reported more often respiratory allergies and sensitization than non-atopics (~factor 2). Furthermore, exposure-response associations were found most pronounced in atopics. This may be explained because atopics are highly predisposed to develop allergic (respiratory) disease. In addition, the time until sensitization and development of symptoms is much shorter in atopics than in non-atopics which may influence the shape of exposure response curves because the healthy worker effect influences atopics and non-atopics differently in quantitative terms[30]. Furthermore, regression analyses showed increased sensitization risks for atopics (factor 3.6-4.6, not illustrated). Earlier cross-sectional[3,5,11]and longitudinal[9] studies confirmed the role of atopy in the relationship between wheat allergen exposure and sensitization to wheat allergens, although an association with work-related symptoms was not always found[9].

Conclusions

In accordance with earlier studies, the present study showed a bell-shaped exposure-response relationship between wheat allergen exposure and allergic work-related respiratory symptoms and asthma. Specific wheat IgE-sensitization appears to be an important condition in the prevalence of respiratory problems. A possible explanation for the bell-shaped relationship is the healthy worker effect. This effect is strongest pronounced for cumulative exposure, which indicates that additionally to exposure level also time is an important determinant that contributes to the healthy worker effect. The risk of sensitization and allergic symptoms at the highest and lowest exposure levels may be confounded by migration of symptomatic high exposed employees to a lower exposed job function. This can cause underestimation of the slope of the exposure-response relationship. Longitudinal studies are required to explore the true associations between wheat exposure, specific sensitization and the development of respiratory symptoms.

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CHAPTER 5

Effect of an intervention aimed at reducing the risk of allergic respiratory disease in bakers: change in flour dust and fungal alpha-amylase levels

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Abstract

Introduction: We evaluated the effect on exposure of an intervention program, which focused on risk education and providing information on good work practices. This intervention program was enrolled as part of a Dutch covenant in the flour processing industry (industrial bakeries, flour mills, ingredient producers).
Methods: Data from several measurement surveys collected pre- and post-intervention were used to evaluate changes in exposure over time. All datasets contained personal measurements analysed for flour dust and fungal α-amylase contents and contextual information was available on process characteristics, work practice, and use of control measures.
Results: Changes in exposure over time varied substantially between sectors and jobs. For bakeries a modest downward annual trend of -2% was found for flour dust and -8% for amylase. For flour mills the annual trend for flour dust was -12%, no significant trend was observed for amylase. For ingredient producers results were generally non significant but indicated a reduction in flour dust exposure and increase in fungal α-amylase exposure. Modest increase in use of control measures and proper work practices were reported in most sectors, especially the use of LEV and decreased use of compressed air.
Conclusions: The magnitude of the observed reductions in exposure levels indicate that the sector-wide intervention strategy implemented during the covenant period had a limited overall effect. This indicates that a more rigorous approach is needed to substantially decrease the exposure levels to flour dust and related allergens and respectively the prevalence of associated occupational diseases.

Introduction

In many occupational settings exposure to hazardous substances declined the past decades[1,2]. Most suggested reasons for this are the introduction of exposure limits and technological innovations in processes[3,4]. However, the specific mechanisms which explain observed time related trends in exposure are poorly understood[5]. Almost all studies on exposure trends involve the re-analyses of existing exposure data that often results in an inability to rigorously evaluate determinants of exposure. Studies that are a priori designed to evaluate changes in exposure levels across time are very rare. A notable exception is the Minnesota Wood Dust study[6,7]. This study evaluated the effectiveness of tailored interventions on occupational exposure in small wood working shops, using a group randomized trial. A comparison was made between a group of companies receiving an extensive intervention (training of workers, technical assistance and written recommendations) and a control group only receiving written recommendation. The results showed a lower than expected effect of the extensive intervention scheme, which was attributed to the challenges related to the implementation of interventions in small enterprises.

For the bakery sector and several other flour processing sectors no decline in exposure over time was reported in recent studies[3,8]. This is an important observation since occupational exposure to flour dust is one of the most observed causes of occupational respiratory disease[9,10]. In the Netherlands approximately 12.000 workers perform work activities that have a high risk of expose to flour dust and related allergens[11,12]. To significantly reduce occupational exposure to flour dust and related allergens, and decrease the prevalence of associated occupational disease, a sector-wide intervention program was initiated in 2001.

This intervention program was implemented as part of a covenant among social partners and major flour processing industries (bakeries, flour mills and ingredient producers). The social partners of the covenant were responsible for the design and conduct of the intervention program. In the Netherlands, covenants can comprise detailed agreements to reduce exposures, introduce exposure control measures, or inform and educate workers. In the context of these covenants effectiveness of implemented control measures receives special attention. Various covenants in different sectors have been initiated in the Netherlands. An assessment of the impact of a covenant for hospitals in the Netherlands has been described elsewhere[13].

The main aim of the covenant in the major flour processing sectors was reduction of the burden of occupational respiratory diseases among workers exposed to flour dust. Workers health was monitored through the instalment of a sector wide health surveillance system. One of the major initiatives within the covenant intervention program was to inform all employers and employees on the risks of occupational exposure(s) and provide information on good work practices and control measures. This campaign included visits to all companies by a trained consultant and the distribution of a dust control manual specifically developed for this purpose[14]. This manual primarily contained information on practical control measures and work practices that are easy to implement and a limited number of more elaborate technological control measures. The content was primarily based upon general knowledge of potential control measures and lacked a sound scientific evidence base. The manual also included a dust control plan that every company had to fill in to get an overview of the current state of dust control and the plans and possibilities for future improvements. Within the covenant specific aims were set with respect to exposure reduction: i.e., all sectors committed to a 50% reduction in time weighted average exposure levels for flour dust and ingredient producers also aimed at a 50% reduction for fungal α-amylase.

To evaluate the impact of the covenant on occupational exposure levels, surveys were performed in all three sectors, both at the beginning and at the end of the covenant period. This paper describes the evaluation of time related trends in occupational exposure. The results are discussed in light of observed changes in work characteristics and use of control measures.

The presented study is one in a series of studies focusing on potential exposure reductions and their health impact in flour processing industries. The results of the time trend evaluation will be used as a baseline scenario in a health impact assessment study focusing on the population burden of disease in the flour processing industry in the Netherlands. The collated information may also provide information on potential further actions that need to be undertaken to increase awareness of risk and stimulate control of occupational exposure.

Materials and methods

Exposure data

A large database was created using two large- and three small-scale exposure assessment surveys which have been conducted during the covenant period. The covenants' baseline exposure survey, which led to agreements regarding exposure reduction included in the covenant, was performed in the three major flour processing sectors (bakeries, flour mills and ingredient producers) in 2001, and included 638 personal exposure measurements. This study is described in detail by Meijster et al.[8]. At the end of the covenant period, in 2007, another large survey was performed to evaluate the effect of the covenant. Where possible this survey included the same companies and workers as the baseline study in 2001. Traditional bakeries were not included in this survey. This study comprised 310 personal exposure measurements. The three small exposure surveys conducted during the covenant comprised of a total of 272 personal exposure measurements. These studies were performed in 2005 and included measurements from traditional bakeries, industrial bakeries and flour mills.

For the bakery sector the exposure component of an epidemiological study, performed in the early nineties, focusing on occupational exposure in relation to respiratory symptoms was also included in the analysis[15,16]. This study comprised of 550 personal exposure measurements obtained from a random sample of workers in both traditional and industrial bakeries. The final dataset comprised 1770 personal exposure measurements generally including data on flour dust and fungal α-amylase levels for most samples. Table 1 gives descriptive statistics and references for the different datasets used in the analyses.

Table 1. Descriptive statistics and references for the different datasets used in the analyses

Study period	N	k	c	Sectors			References
				bakeries	flour mills	ingredient producers	
1993	550	180	21	550	-	-	[15][16][36][37]
2001	638	99	95	356	156	126	[8]
2005	272	86	24	225	47	-	[8]
2007	310	67	23	131	88	91	-
total	1770			1262	291	217	

N= total number of samples
k= number of workers with repeated measurements
c= number of companies

Exposure assessment
In all surveys personal sampling was performed in the breathing zone of the worker. Full shift samples were obtained. During the post intervention survey, workers sampled during earlier surveys were preferentially included. If this was not possible, workers with a similar job title and task pattern were included. Measurement duration was between 4 and 10 hours with 85% of samples having more than 6 hours of sampling time. All personal air samples were obtained using a PAS6 sampling head, with a mounted glass fibre filter, connected to a Gillian GilAir sampling pump with a calibrated air flow of 2 litres/minute. Dust levels on the filters were determined by pre- and post sampling weighing of the filters after conditioning them for 24-hours in an acclimatized room. Details on personal air sampling can be found in Meijster et al.[8] After determining the dust weight samples were extracted and analyzed for their contents of fungal α-amylase using immunoassays. For all studies similar extraction and analyses techniques were used. These analyses and extracting procedures are described in detail by Houba et al.[16] and Bogdanovic et al.[17].

Contextual data
Contextual data was obtained from two sources. Information on process characteristics, work practice, and use of control measures was obtained in a walk through survey conducted during the measurement surveys by a trained field worker. We also obtained the

dust control plans that were part of the dust control manual of all companies involved in the post-covenant study. This provided a more general overview of recent and future changes in these companies, especially with respect to implementation of control measures. Additionally, a limited survey was performed in a small sample of companies from all sectors to look at the impact of the covenant with respect to familiarity of bakery workers with the risk of flour dust and their knowledge of potential control measures[18]. This survey also identified how many bakeries received the dust control manual and filled in a dust control plan.

The quality and nature of the obtained information varied substantially between the different studies. In some surveys information was very detailed and gathered for individual workers, in other surveys information was only obtained on company level or in a qualitative way (e.g. description of changes in retrospect). In some cases definitions of variables changed in-between studies initiated by insights obtained in prior studies. Where possible, changes in process characteristics, work practice and use of control measures were evaluated in a quantitative manner preferably on worker level and otherwise on company level. If data did not allow for such analysis a qualitative description of the changes is presented to give an overview of the interventions that resulted from the covenant.

Statistical analyses

The distribution of the exposure data was determined to be approximately log-normal using fit tests and visual inspection of plots of the data. Descriptive statistics (arithmetic and geometric mean, geometric standard deviation and range) were calculated for both flour dust and fungal α-amylase stratified for sector and time period. Box plots of both flour dust and fungal α-amylase levels were created stratified for sector and study year. Evaluation of exposure trends were performed with linear mixed effects models using the Proc Mixed procedure in SAS (v9). Separate time trend analyses were performed for the three sectors; i.e. bakeries, flour mills and ingredient producers.

Changes in exposure levels over time were modelled by introducing year as a continuous variable in our mixed effects models to estimate the annual relative change in average exposure[19]. Job title and sampling duration were introduced in the models as co-variable to correct for possible confounding effects. Sampling duration was introduced as a continuous variable. Co-variables were included in the final models if the maximum likelihood test showed significant improvement of model fit ($p<0.05$).

Worker and company were incorporated into the analysis as random effect variables to account for correlation in the exposure data[20]. Significance of random effect variables was tested after adding co-variables (fixed effects). If random effects were not significant they were excluded from final analysis. A compound symmetric covariance structure was assumed. The models were evaluated for heteroscedasticity using residual plots. Time trend models stratified for job (e.g. bread bakers, general bakers, pastry bakers, dough makers and low exposed jobs) were used to evaluate trends in exposure levels in more detail. Final analyses were performed looking at trends for the total time period for which data was available. For bakeries, separate analyses were performed for the covenant period only (i.e., 2001-2007) to look at effects of intervention implemented specifically during this period.

Results

The survey measuring the familiarity of bakery workers with the health risks revealed that >70% of workers were familiar with the risk of flour dust exposure. Only 35% of traditional bakeries reported to be familiar with the dust control manual, this was higher for the other sectors (between 50-100%). Only 30% of the traditional bakeries filled in a dust control plan (between 48-100% for the other sectors). This means that although the information on risk did reach the workers the actual implementation of the main tools provided was limited especially in the traditional bakeries that represent >60% of the worker population[18].

A similar picture arises from the contextual data obtained in the measurement studies. In the post covenant study 23 companies were eventually visited, 21 of these companies were also visited in the baseline exposure survey (2001). The matching of workers was not successful due to high turnover and. As an alternative, we were able to match measurements on job title within a company.

The information from the walk through survey showed that for several control measures a clear increase in use occurred. The most significant increase was observed in the use of local exhaust ventilation (LEV). In the pre-covenant period the use of LEV was negligible in both flour mills and industrial bakeries, whereas after the covenant period use of LEV was reported by approximately 40% of workers in industrial bakeries and 60% of workers in flour mills. For ingredient production LEV was already common and it further increased during the intervention from 57% to 70%. In bakeries LEV was mainly installed at flour dumping installations, often combined with (partial) enclosure of the mixing tub. For flour mills and ingredient production industry LEV was mainly installed at bagging and ingredient dumping sites as well as weighing locations.

Use of pressured air is an important factor for (peak) exposures; unfortunately this variable was only obtained in a very crude way in the pre-covenant study. In general, the dust control plans reported for many companies that use of compressed air was replaced with use of vacuum cleaning. However observational data from the post-covenant survey showed that 51%, 64% and 42% of workers still reported the use of compressed air in bakeries, flour mills and ingredient producers respectively.

In bakeries the use of liquid instead of powder bread improver (containing fungal α-amylase) increased from 30% to 50% of workers involved in dough production. Other important factors, especially related to work practice, were not evaluated in a quantitative manner. The results of the post-covenant study did suggest more attention is paid in general to dust free work practice: e.g., not shaking bags when dumping flour and/or additives, use of wet cleaning methods instead of sweeping, and a decrease in the use of dusting flour were often mentioned by the companies as implemented interventions.

Figures 1a-f show the box-plots of the overall trends in exposure not corrected for any co-variables. The plots do not show any clear changes in exposure over time for flour dust for any of the sectors. For fungal α-amylase the plot indicates a slight downward trend for bakeries. In flour mills and ingredient producers this is less obvious, for the latter one the plot clearly indicates an increase of exposure over time.

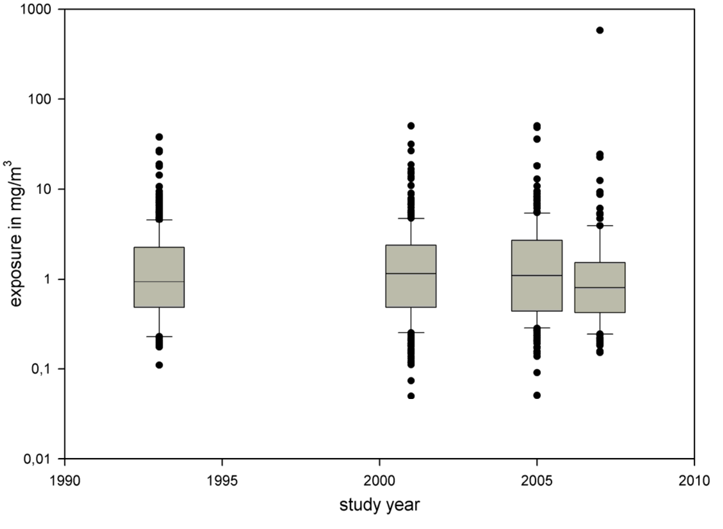

Figure 1a.Time trend in flour dust exposure for the total measured populations of bakery workers

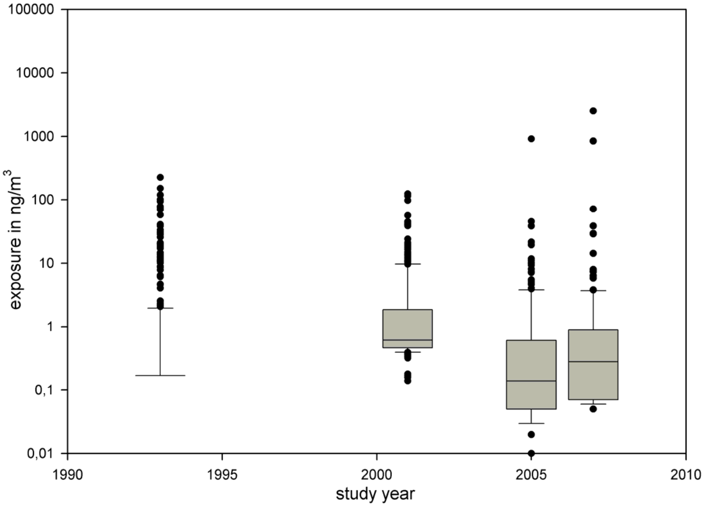

Figure 1b.Time trend in fungal α-amylase exposure for the total measured populations of bakery workers

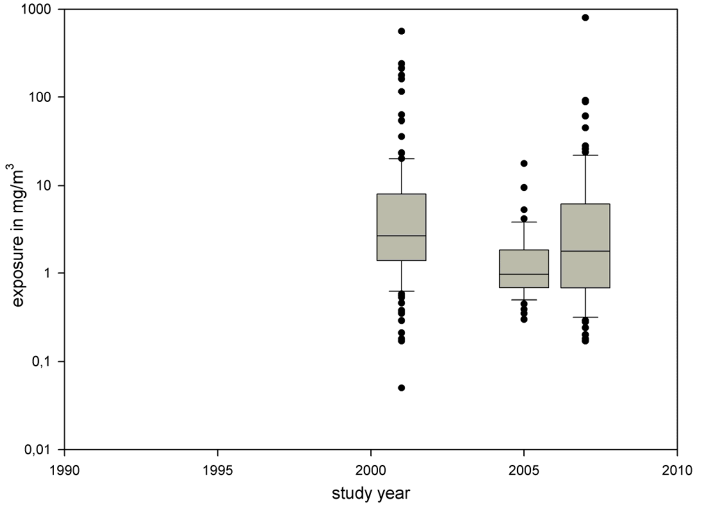

Figure 1c.Time trend in flour dust exposure for the total measured populations of flour mill workers

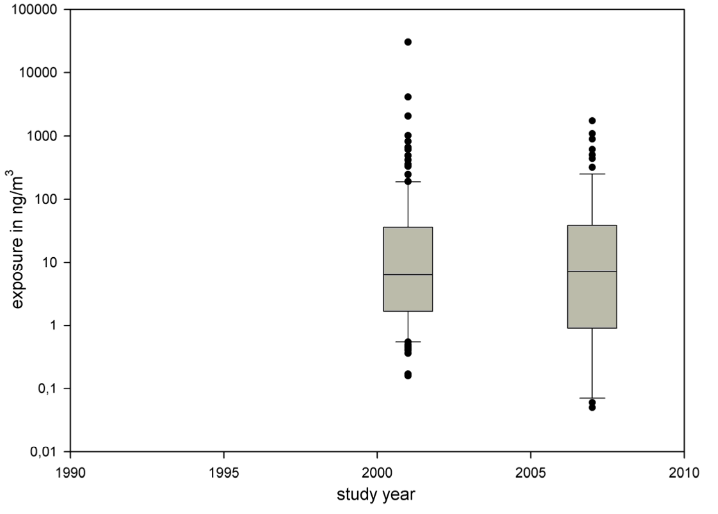

Figure 1d.Time trend in fungal α-amylase exposure for the total measured populations of flour mill workers

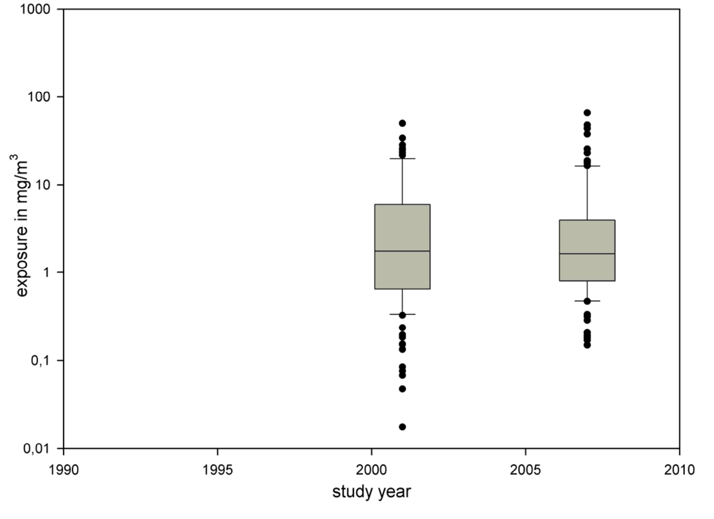

Figure 1e.Time trend in flour dust exposure for the total measured populations of ingredient production workers

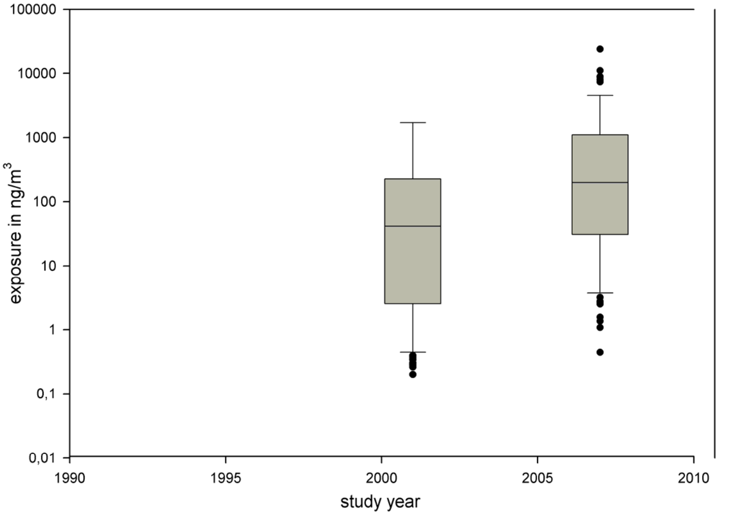

Figure 1f. Time trend in fungal α-amylase exposure for the total measured populations of ingredient production workers

In the overall models for each sector, job was included as a co-variable to account for possible selection effects in the various time periods. Sample time had a significant effect in only two job specific models, and was excluded from other analyses. For the sector specific analyses both worker and company random effects were statistically significant and were kept in the models. The company random effect was not significant in any of the job specific trend models, whereas the worker random effect was significant. Table 2 gives the overall yearly trends for all three sectors and the trends stratified by job title.

A significant yearly downward trend of approximately 2% was observed for flour dust and 8% for fungal α-amylase among the population of bakery workers. Trends varied substantially between job categories. Dough makers, general bakers, cleaners and maintenance workers showed a statistically significant downward trend for exposure to flour dust. No clear time trend was observed for the other jobs. For fungal α-amylase a statistically significant downward trend was observed for pastry bakers and cleaners. For general bakers a strong increasing trend in exposure to α-amylase was observed (>20% yearly), whereas trends were absent for bread bakers, dough makers, maintenance workers and low exposed jobs. Stratified analysis only looking at the data for the covenant period (i.e., 2001-2007) showed similar overall trend patterns.

In flour mills a strong decreasing exposure trend of 12% annually was observed for flour dust. This downward trend for flour dust was observed for almost all job categories (although not significant in most instances). Conversely, fungal α-amylase results indicate that an overall time trend was absent. On job levels a significant decreasing trend was only observed in maintenance workers.

Tabel 2. Yearly trends in flour dust and fungal α-amylase exposure between 1993 and 2007, stratified for sector. Results are based on mixed-effects regression models with time period and job as fixed effects and company and worker as random effects.

Sector	**Function**	**Dust**			**Fungal α-amylase**		
		N[1]	**Trend (%/year)**	**Significance (p-value)**	**N**[1]	**Trend (%/year)**	**Significance (p-value)**
Bakeries[4]		1259	**-1.9**	**0.08**	1149	**-8.2**	**0.00**
(1993-2007)	Bread bakers	305	0.8	0.57	281	3.0	0.23
	Dough makers[2]	233	**-4.0**	**0.00**	221	-0.0	0.90
	Pastry bakers	104	4.0	0.18	87	**-10.0**	**0.01**
	General baker[3]	122	**-3.6**	**0.00**	109	**20.4**	**0.00**
	Cleaners[5]	46	**-3.7**	**0.02**	43	**-4.8**	**0.08**
	Maintenance workers[5]	30	**-21.2**	**0.02**	29	-16.0	0.10
	Low exposed jobs	407	0.0	0.94	379	-1.3	0.29
Flour Mills [4]		291	**-11.9**	**0.01**	230	-3.3	0.81
(2001-2007)	Miller	39	-11.3	0.33	32	-14.4	0.45
	Baggers	22	-10.7	0.26	16	-1.9	0.93
	Cleaners	32	-11.5	0.27	25	14.3	0.47
	Storage workers	27	-16.0	0.23	-	-	-
	General operators	33	-7.2	0.44	19	-20.4	0.33
	Quality controllers	31	**-14.7**	**0.03**	26	-8.6	0.56
	Maintenance worker	47	**-10.6**	**0.01**	41	**-20.7**	**0.01**
	Chef	29	0.4	0.97	28	-13.6	0.33
Ingredient producers[4]		217	-6.1	0.42	202	28.5	0.16
(2001-2007)	Quality controllers	25	-9.9	0.25	22	31.8	0.15
	Chef	15	26.5	0.20	15	66.5	0.12
	Weigher/mixer	12	**-22.3**	**0.06**	11	**76.9**	**0.04**
	Bagger	38	4.2	0.63	37	**56.6**	**0.01**
	Storage worker	31	10.7	0.29	29	17.7	0.24
	General operator	30	0.8	0.93	15	16.5	0.38
	Dumper	31	-1.6	0.82	30	3.2	0.85

[1] number of samples used in the analysis
[2] only in industrial bakeries
[3] only in traditional bakeries
[4] only jobs with >5 samples in both measurement studies were evaluated
[5] corrected for sampling time

In flour mills a strong decreasing exposure trend of 12% annually was observed for flour dust. This downward trend for flour dust was observed for almost all job categories (although not significant in most instances). Conversely, fungal α-amylase results indicate that an overall time trend was absent. On job levels a significant decreasing trend was only observed in maintenance workers.

For workers in ingredient production an overall downward trend in flour dust exposure was not significant. Stratified analyses showed inconsistent results with non-significant increasing and decreasing exposure levels for various job titles. For fungal α-amylase there has been a strong increase in occupational exposure for all job titles. Overall a non-significant increasing exposure trend of almost 30% annually was observed for the covenant period.

Discussion

This study evaluated the impact of an intervention program implemented in several Dutch flour processing sectors, as part of a covenant. Moderate decreasing exposure trends were observed for flour dust and amylase in bakeries and for flour dust in flour mills. However, a significant trend was absent for amylase in flour mills and for both flour dust and amylase in ingredient producers. In bakeries the observed time related trends in exposure are strongest in workers involved in production and cleaning/maintenance activities. Attention focused on these activities during the covenant. In addition a recent study showed a substantial potential effect of a range of control measures, especially during production and processing of dough[21].

For flour mills, the observed trend in flour dust exposure is comparable with trends in inhalable dust exposure in several other industrial environments[19,22,23]. An important difference with bakeries was the strict implementation of the covenant in each individual flour mill. The number of production facilities is limited and implementation of the covenant was centralized, resulting in a higher percentage of workers being informed and a better implementation of control measures.

In the ingredient sector the reported trends fluctuated strongly between jobs. It seems that the (limited) additional measures taken in the covenant period had no significant effect on exposure to flour dust. For fungal α-amylase it is unclear how exposure could have increased. Information from the sector did not indicate an increased use and no obvious changes in the work practice occurred. In general for this sector the available data per job was limited and therefore trend estimates should be interpreted with caution.

Specific data quantifying the impact of control measures on exposure to fungal α-amylase is not available. It is likely that the observed changes in exposure for a large part can be attributed to the same control measures as for flour dust. The increased use of liquid enzyme containing bread improver instead of powder form may have further decreased exposure in bakeries. Finally, recent literature indicates that in some cases fungal α-amylase are replaced with other fungal enzymes[24,25]. The magnitude at which this occurs in the Dutch flour processing industries is unknown.

As this study shows, observed exposure trends may vary substantially between sectors and jobs and for different types of exposure. Therefore, if possible, analyses of exposure trends should be stratified for sectors and jobs and different compounds should be evaluated separately when dealing with exposure to mixtures in order to detect subtle effects. However associating these (subtle) changes in exposure with specific interventions or changes in work practice will generally remain difficult. An important reason for this is that a variety of changes in different exposure determinants is probably responsible for the relatively small changes in exposure. As a result it is also difficult to completely explain observed differences in exposure trends between jobs and sectors in light of this intervention program.

Although information on wheat allergens exposure was also available from the different measurement studies, this was not taken into account in the analyses. Most important reason for the exclusion is the large yearly variation in wheat protein levels in grains based upon exogenous factors like weather conditions, production soil, etc.[26,27]. To accurately perform trend analysis these exogenous factors should be taken into account and data to do so was not available

The questionnaire data obtained in the post-covenant study indicated a substantial increase in awareness of risk among workers. The familiarity with the dust control manual and respectively the implementation of good work practice remained fairly limited, especially in the bakery sector. Where changes were observed the overall impact on exposure levels seems limited and could generally not be directly associated with specific changes in the workplace.

This study shows that when evaluating the impact of complex intervention strategies the quality of the contextual data to a large extent determines the possibility to evaluate detailed association between control measures and changes in exposure. The power of an intervention study will benefit immensely from using a strict design that approaches a true scientific experiment, preferably a randomized controlled trial design[7,28,29]. However, in our study where a complete occupational population is subject of an intervention program, such a study will not be possible since a control population is not available. In these situations non-experimental longitudinal data as presented in this study, might be the next best choice, even though many factors will be beyond the influence of the researcher (e.g. drop out of companies/workers). Although we were able to match the majority of companies in the pre- and post-intervention study, we were only to a very limited extend able to trace the same workers in 2007. This is primarily caused by the relatively long follow up time (6-7 years) and the substantial turnover of workers in most branches. On the other hand a shorter follow up time would have strongly decreased the implementation of control measures, which would have prohibited a comprehensive evaluation as well.

Exposure trend analyses have been performed in recent years for a large range of occupational exposures and environments. Main conclusion from many of these trend analyses is that occupational exposure has been decreasing in the past decades[1,2,4]. Downward exposure trends of up to 12% annually are not uncommon, trends of between -5 to -8% annually were most commonly observed. It is likely that these changes in exposure do not occur gradually but in a step wise manner, either in relatively large steps associated with changes in legislation, elimination of exposure sources or other major changes in work characteristics, or in a combination of smaller steps associated with several relatively minor changes in the work characteristics[1,5,30]. In most cases specific data to underpin this pattern of exposure change is lacking as is data to determine the relation with specific changes in determinants of exposure[1,2]. Several studies that found downward trends in occupational exposure were to some extend able to identify determinants likely associated with exposure, but could generally not quantify their individual contribution to the observed exposure trends[31-35]. A study of Vermeulen and co-authors in 2000 in the rubber producing industry showed a decreasing trend in exposure to inhalable particles and dermal exposure to cyclohexane soluble matter (CSM) of 6-7% annually. They were able to relate different types of control measures and specific changes in work characteristics to changes in exposure over time[22].

An important reason for the absence of a substantial overall time related trend in exposure is the limited evidence base that underlies the content of the intervention program, especially the dust control manual. The design was primarily determined by the social partners of the covenant with only very limited input from research(ers). This resulted in an approach that focused on education and training. The actual implementation of control measures was largely left to the responsibility of the employers (individual companies). As a resulted, only a limited amount of companies actually introducing controls within the covenant period. There are likely two important reasons for this; first, a limited motivation to change work practices. This lack of motivation is likely associated with a still relatively low risk awareness related to occupational exposure among bakery workers, and the absence of exposure limits. The post-intervention study discloses that there remains a substantial group of workers that ignores the risks and continuous to work in a way that potentially leads to high (peak) exposure levels. Second, there is limited technological advancement observed in these sectors, especially in bakeries. Financial constraints in SMEs may have limited the introduction of more advanced (control) technologies. Especially in small bakeries the production processes still include a substantial amount of manual labour with many peak exposure moments[21]. This might also explain why, for example, the increased use of LEV only had a minor effect. LEV is only used in a limited part of the work activities and in these cases it should be used appropriately to benefit fully. Furthermore a substantial group of companies, especially in the small traditional bakeries, did not, or only to a limited extend, participate in the activities initiated by the covenant[12].

The fact that the intervention scheme implemented within the covenant period did not result in a more drastic overall exposure reduction is clearly disappointing. For bakeries this is specifically shown by the fact that the covenant did not result in a substantially larger change in exposure than what was observed in the period prior to the covenant (1993-2001). Earlier examples also show a limited effectiveness of large-scale intervention strategies among a broad worker population[6,7]. These results indicate that a much more rigorous approach is needed to effectively decrease exposures in complex worker environments, especially when dealing with small and medium sized enterprises. Although no design for such a rigorous approach is readily available, it is likely that tailored workplace interventions aimed at (individual) workers within an identified high risk population (e.g. high exposed workers) might prove to be more effective.

Results from this study provide insight into the trends of exposure resulting from an intervention program implemented in the recent Dutch covenant in the flour processing industry. Given the available dose-response information a limited reduction of the health risk is expected, with small differences between sectors[38,39]. More insight into the expected health impact of the observed changes in exposure will be provided by a recently performed health impact assessment using a recently developed dynamic population-based model. The results of this analysis may learn to what extend the observed (limited) decline in exposures will lead to an improvement of the health status in the population. This health impact assessment will also provide detailed information on exposure reductions that are required to arrive at a proportion of workers with health problems that is more acceptable to all parties involved.

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CHAPTER 6

A dynamic population-based model for the development of work related respiratory health effects amongst bakery workers.

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Submitted

Abstract

Objectives: This paper presents a dynamic population-based model for the development of sensitisation and respiratory symptoms in bakery workers. The model simulates a population of individual workers longitudinally and tracks the development of work-related sensitisation and respiratory symptoms in each worker.

Methods: The model has three components: a multi-stage disease model describing the development of sensitisation and respiratory symptoms in each worker over time; an exposure model describing occupational exposure to flour dust and allergens; and a basic population model describing the length of a worker's career in the bakery sector and the influx of new workers. Each worker's disease state is modelled independently using a discrete time Markov Chain, updated yearly using each individual's simulated exposure. A Bayesian analysis of data from a recent epidemiological study provided estimates of the yearly transition probabilities between disease states.

Results: For non-atopic/non-sensitised workers the estimated probabilities of developing moderate (upper respiratory) symptoms and progression to severe (lower respiratory) symptoms are 0.4% (95% C.I. 0.3%-0.5%) and 1.1% (95% C.I. 0.6%-1.9%) per mg/m^3/year flour dust respectively and approximately twice these for atopic workers. The model predicts that 36% (95% C.I. 26%-46%) of workers with severe symptoms are sensitised to wheat and 22% (95% C.I. 12%-37%) to amylase. The predicted mean latency period for respiratory symptoms was 10.3 years (95% C.I. 8.3-12.3).

Conclusions: Whilst the model provides a valuable population level representation of the mechanisms contributing to respiratory diseases in bakers, it was primarily developed for use in quantitative Health Impact Assessment. Future research will use the model to evaluate a range of workplace interventions, including achievable reductions in exposure and health surveillance. The general methodology is applicable to other diseases such as Chronic Obstructive Pulmonary Disease (COPD), Silicosis and Musculoskeletal Disorders and could be particularly valuable for forecasting changes in long latency diseases.

Introduction

Several studies have shown high rates of sensitisation and various (allergic) respiratory symptoms among workers exposed to flour dust[1-4]. Indeed, in the UK occupational exposure to flour dust is recognised as one of the main causes of occupational asthma[5]. These respiratory symptoms can, with continuing occupational exposure, lead to work disability[6]. Although reductions in occupational exposure are likely to reduce both the onset of new cases and the severity of symptoms in workers with existing conditions, supporting evidence is limited[7,8]. A recent study found no evidence of a downward trend in occupational exposure to flour dust, contrary to what has been observed in other sectors[9]. In an effort to decrease the prevalence of occupational respiratory diseases related to exposure to flour dust in the Netherlands, the Dutch Government, in association with labour and industry organisations, agreed to a covenant in 2001. The main goals of this covenant were the instalment of a health surveillance system focussed on screening workers for work-related sensitisation and respiratory symptoms and reducing occupational exposure through encouraging good working practice and use of control measures[10,11].

Health impact assessment provides a means to maximise the improvement in health through (prospectively) evaluating a range of possible intervention scenarios[12,13]. Although health impact assessment methodologies, including dynamic life table approaches, have been used to assess the impact of changes in the living environment on public health[14,15], the use of these techniques within the occupational health arena has been more limited[13]. One recent occupational example is a study by Wild *et al.*[16] who evaluated impact of a surveillance program for occupational asthma among workers exposed to (di-)isocyanates. However this study, as is also the case in many public health studies, does not explicitly take into account empirical information on exposure distributions and exposure-response relationships.

The dynamic population-based health model described in this paper enables prospective health impact assessment to be carried out for respiratory diseases in bakery workers occupationally exposed to flour dust. The model simulates a population of workers longitudinally through time and tracks the development of sensitisation and respiratory symptoms in each worker in response to their occupational exposure to flour dust. This approach allows the progression of the disease and transitions between different disease states over time to be studied, particularly in response to changes in the population's exposure distribution. Furthermore it enables more realistic modelling of the future disease burden related to alternative exposure population distributions. The proposed approach using a dynamic population-based model should therefore provide an important tool for health impact assessment enabling evaluation of the potential effects of interventions and the distribution of these effects within a population.

The model

General structure of the model

Our dynamic population-based model simulates a population of workers longitudinally through time and tracks the development of sensitisation and symptoms in each worker. The working population is dynamic with a continual process of workers leaving the workforce (possibly through ill-health) and being replaced with new recruits. There are 3 main components of the model:

1. a multi-stage disease model describing the development of work-related sensitisation to wheat and fungal α-amylase, severity of symptoms and disability;
2. an exposure model characterising variation in dust and fungal α-amylase exposures between workers and over time; and
3. a population model that describes migration of workers and population characteristics.

The main states in our model are work-related sensitisation to wheat and fungal α-amylase, moderate (upper respiratory) and severe (lower respiratory) symptoms and work-related disability. Different combinations of these give rise to 13 different diseases states as depicted in Figure 1 and listed in Table 1.

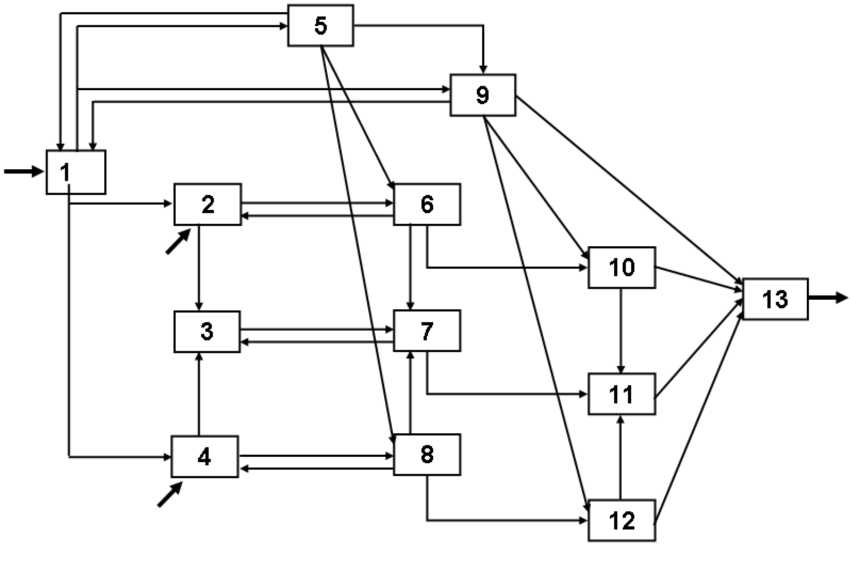

Figure 1. Causal diagram of population dynamic health model showing all possible health transitions within the population relating to the development of sensitisation and respiratory symptoms

Table 1. Summary of different health states within the model

State	Label
Non-sensitised & non-symptomatic	1
Sensitised to wheat & non-symptomatic	2
Sensitised to wheat & amylase & non-symptomatic	3
Sensitised to amylase & non-symptomatic	4
Non-sensitised & moderate symptoms	5
Sensitised to wheat & moderate symptoms	6
Sensitised to wheat & amylase & moderate symptoms	7
Sensitised to amylase & moderate symptoms	8
Non-sensitised & severe symptoms	9
Sensitised to wheat & severe symptoms	10
Sensitised to wheat & α-amylase & severe symptoms	11
Sensitised to α-amylase & severe symptoms	12
Work disabling asthmatic symptoms	13

The underlying structure and assumptions of the model have been based on recent mechanistic insights[17]. Work-related sensitisation to wheat flour and fungal α-amylase is assumed to be key a determinant, and pre-existing atopy (specific IgE response to common allergens) is assumed to modify the risk for development of sensitisation and respiratory symptoms[1,2,5,18,19]. Both are explicitly incorporated in the model. Furthermore, the model assumes that upper airway symptoms generally precede the development of lower respiratory symptoms, although not exclusively[16,20-22]. Eventually workers having severe lower respiratory symptoms may develop work disabling asthmatic symptoms and leave the work force[6,23,24]. Figure 1 depicts many of the transitions as being reversible, however due to inconsistent information on the relationship between exposure reduction (or cessation) on recovery and remission of symptoms[7,17,25], all recovery probabilities are currently set to zero. This could be relaxed in the future, if more detailed longitudinal observations become available.

Disease progression (i.e. development of sensitisation and symptoms) in an individual is modelled through a discrete time Markov chain that updates the disease state of each individual yearly on the basis of their exposure. In the current model only 'single change' yearly transitions are allowed i.e. development of sensitisation to wheat or fungal α-amylase or development of symptoms. However, if it is assumed that work-related sensitisation to amylase and wheat and the development of symptoms (conditional upon current sensitisation) are independent processes then more complex transitions might also be also possible, though much less likely. These rare two-change transitions e.g. development of sensitisation to both wheat and amylase in the same year are not currently modelled (see appendix for the matrix of transition probabilities).

Estimation of dose/exposure-response parameters

Transition probabilities are calculated using a number of dose-response models estimated from a study on symptoms and serological responses from 860 randomly selected workers. These data were collected in the context of the Health Surveillance System in the baking industry in The Netherlands, described elsewhere[4]. The probabilities assume a linear yearly dose-response dependent upon the current year's exposure with no threshold. The assumption of a linear yearly dose-response which, for low probabilities, approximates a lifetime risk proportional to cumulative exposure, is compatible with recent studies[4,26] which present a reasonable linear shape for the first part of the dose response-curve, flattening off at higher exposures (most likely caused by a healthy worker effect or development of tolerance).

Firstly, dose-response relationships for the development of work-related upper and lower airway symptoms in non-sensitised individuals were estimated using flour dust as the causal agent. Following this additional risk factors for developing work-related respiratory symptoms when sensitised to wheat or fungal α-amylase were estimated using logistic regression (with atopy and cumulative exposure to flour dust as additional covariates). These were integrated as multiplicative factors into the original dose-response models for non-sensitised individuals to obtain separate dose-response relationships for all sensitised groups. Finally, dose-response relationships for the development of sensitisation to wheat and fungal α-amylase were estimated using flour dust and exposure to fungal α-amylase as the respective causal agents. In all cases, separate dose-response relationships were determined for atopics and non-atopics. A detailed description of the Bayesian methodology used to estimate yearly dose-response probabilities for sensitisation and symptoms may be found in the Appendix.

Description of disease states

The different disease states and the estimated transition probabilities are discussed below with probabilities presented per unit exposure (mg/m^3 for flour dust and ng/m^3 for fungal α-amylase). The entire set of model parameters with accompanying confidence intervals are presented in Table 2.

<u>State 1: Healthy workers</u>

This state represents non-sensitised individuals without respiratory symptoms and is the entry state to the population for the majority of new workers.

<u>States 2,3,4: Sensitisation to wheat, fungal α-amylase or both</u>

The early states in our model are work-related sensitisation to wheat allergens, and/or fungal α-amylase without symptoms. The yearly probability for becoming sensitised to wheat allergens or fungal α-amylase is approximately 0.1% per unit exposure for non-atopic workers but considerably higher for atopic workers at approximately 4 times higher for fungal α-amylase and 8 times higher for wheat allergens (Table 2).

States 5,6,7,8: 'Moderate' (upper respiratory) symptoms

Moderate symptoms are defined as reporting at least two of the following three symptoms: sneezing, a runny nose, or itchy/teary eyes during work, but without lower respiratory symptoms (as defined below). Workers can develop upper respiratory symptoms through two routes: either the worker develops work-related sensitisation first and then develops allergic upper respiratory symptoms, or the worker develops upper respiratory symptoms without sensitisation (irritation route). The latter causal route is not completely understood but both upper and lower respiratory symptoms, as well as hyper-responsiveness, have been observed in bakery workers in the absence of sensitisation[17,27]. The probability of developing upper respiratory symptoms was estimated as approximately 0.4% per unit exposure per year for non-atopic/non-sensitised workers and approximately twice this for atopic workers (Table 2). Multiplicative risk factors for workers sensitised to wheat and fungal α-amylase were estimated as 3.2 and 2.2 respectively (Table 2).

States 9,10,11,12: 'Severe' (lower respiratory) symptoms

Severe symptoms are defined as reporting at least two of the following lower respiratory symptoms: asthma attacks, wheezing, shortness of breath or tightness of chest during work. Workers can develop symptoms either with or without first being sensitised. The probability of progressing to severe symptoms from moderate symptoms is 1.1% per unit exposure per year for non-atopic, non-sensitised workers and 1.7% for atopic non-sensitised workers (Table 2). These transition probabilities increases for sensitised individuals using the same multiplicative risk factors as those adopted for moderate (upper respiratory) symptoms.

State 13: Drop out due to lower respiratory symptoms

The final disease state of our model is work disability, defined as having work disabling asthmatic symptoms. In the current model only workers that develop severe respiratory symptoms can explicitly leave the workforce because of their symptoms i.e. through work disability. Although a large amount of literature is available describing hospitalisation and work-disability among workers with severe respiratory symptoms[6,8,17], the yearly probability of becoming disabled cannot easily be ascertained. To our knowledge there are only limited longitudinal data relating to the likelihood of becoming work disabled once respiratory symptoms have developed and any data that are available relate to diagnosed cases of asthma rather than our broader definition based upon self-reported symptoms. We have set the disability rate in the current model to a fixed rate of 5% per year irrespective of exposure. This is substantially lower than the value of 60% disabled after 4 years used by Wild *et al.*[16]; however (di-)isocyanate asthma has a worse prognosis for developing work disabling asthma then flour dust.

Table 2: Model parameters and literature sources

Population parameters	Notation	Value	Uncertainty	Data Source
Replacement probability	$P_{replace}$	1	-	Expert judgement
Mean working lifespan (years)	L	20	15-25[1]	4
Background prevalence of sensitisation wheat	B_w	0.03	0.02-0.04	18,28
Background prevalence of sensitisation α-amylase	B_a	0.01	0-0.02	19,28
Proportion atopic	A	0.30	0.25-0.35[2]	4
Exposure flour dust (mg m^{-3})				
Mean dust exposure (log scale)	μ	0.60	0.50-0.71[2]	4
Between-worker standard deviation (log scale)	σ_b	0.54	0.46-0.61[2]	4
Within-worker standard deviation (log scale)	σ_w	0.82	0.74-0.93[2]	10
Exposure fungal α-amylase (ng m^{-3})				
Mean amylase exposure (log scale)	μ	-0.01	-0.18- 0.16[2]	4
Between-worker standard deviation (log scale)	σ_b	0.69	0.48-0.85[2]	4
Within-worker standard deviation (log scale)	σ_w	1.52	1.36-1.71[2]	10
Dose-response probabilities ($mg^{-1}m^3y^{-1}$ or $ng^{-1}m^3y^{-1}$)				
Sensitisation to wheat | non atopic	$\alpha_w(1)$	0.0007	0.0003-0.0012[2]	4
Sensitisation to wheat | atopic	$\alpha_w(2)$	0.0064	0.0046-0.0083[2]	4
Sensitisation to amylase | non-atopic	$\alpha_a(1)$	0.0010	0.0006-0.0016[2]	4
Sensitisation to amylase | atopic	$\alpha_a(2)$	0.0038	0.0027-0.0053[2]	4
Moderate symptoms | non-sensitised & non-atopic	$\beta_{mod}(1)$	0.0041	0.0032-0.0051[2]	4
Moderate symptoms | non-sensitised & atopic	$\beta_{mod}(2)$	0.0091	0.0070-0.0116[2]	4
Severe symptoms | non-sensitised & non-atopic	$\beta_{sev}(1)$	0.0007	0.0004-0.0012[2]	4
Severe symptoms | non-sensitised & atopic	$\beta_{sev}(2)$	0.0010	0.0004-0.0020[2]	4
Moderate to severe symptoms | non-sensitised & non-atopic	$\beta_{prog}(1)$	0.0111	0.0063- 0.0187[2]	4
Moderate to severe symptoms | non-sensitised & atopic	$\beta_{prog}(2)$	0.0167	0.0094-0.0282[2]	4
Multiplicative risk factor symptoms given sensitisation to wheat	r_w	3.2	2.1 - 5..0[2]	4
Multiplicative risk factor for symptoms given sensitisation to fungal α-amylase	r_a	2.2	0.9 - 5.3[2]	40
Disability and remission				
Probability of recovery	P_{rec}	0	-	Expert judgement
Probability of developing disabling asthmatic symptoms	P_{dis}	0.05	0-0.1[1]	Expert judgement

[1] Expert judgment, lower and upper bounds **[2]** 95% confidence interval

Exposure

Separate exposures to flour dust and fungal α-amylase are modelled through a bivariate log-normal random effects model. That is:

$$\ln(\underline{E_{i,j}}) = \underline{\mu} + \underline{\delta_i} + \underline{\varepsilon_{i,j}} \tag{1}$$

where $\underline{E_{i,j}}$ is the dust and fungal α-amylase exposure of a random worker (*i*) on a random day *(j)* and the mean (log) exposure of the population is represented by $\underline{\mu}$. The random worker effect $\underline{\delta_i}$ and the residual variation $\underline{\varepsilon_{i,j}}$ have independent bivariate normal distributions with diagonal covariance matrices $\underline{\sigma_B}$ (between-worker variability) and $\underline{\sigma_W}$ (within-worker variability) respectively, implying independence of dust and α-amylase, consistent with the extremely low correlations reported elsewhere[10].

Upon entering the working population, each worker is assigned two standardised between-worker random effects that are scaled according to the between-worker variance components for dust and α-amylase. Subsequently, each individual's yearly mean exposures are calculated taking into account within-worker variability in the following manner:

$$\exp(\mu+\delta_i+0.5\,\sigma_W^2)$$

Temporal changes in the population exposure distribution may be modelled by altering $\underline{\mu}$ over time, whilst by assigning each worker a standardised random effect temporal changes in between-worker variability may be modelled (perhaps as a consequence of an intervention) whilst preserving each worker's relative position in the population exposure distribution. The baseline exposure parameters used in our model were derived from Jacobs et al.[4] and Meijster et al.[10] (Table 2).

Population characteristics

The population model determines all population characteristics and dynamics not related to exposure and/or symptoms. New individuals enter the population healthy but with a fixed probability of being atopic (30%) and a small likelihood of already being sensitised to either wheat or fungal α-amylase (2% and 1% respectively[18,19,28], Table 2). Each new worker is assigned a natural (i.e. un-impeded by asthma) working lifetime generated from a negative binomial distribution (mean 20 years, coefficient of variation =0.6, truncated at 1 and 50 years) chosen for consistency with cross-sectional data on length of working careers[4]. The proportion of atopic individuals in the population (30%) was based upon serological testing of workers in the Health Surveillance System database[4]. Subjects were classified atopic if they had at least one positive response to house dust mite allergens, cat or dog allergens, grass or birch pollen. An individual leaves the simulated working population when they either come to the end of their natural working life, or become disabled. In both cases, they are replaced with a new individual with a fixed probability (1 in the current model to maintain a constant population size).

Simulation of the model

The model is implemented in MATLAB[29] allowing efficient simulation using parallel calculations. An appropriate starting population, complete with exposure histories, sensitisation, and symptoms is created through running the model for a 'burn-in' period with an initial non-symptomatic population of workers who all start work simultaneously. By choosing a sufficiently long burn-in period, e.g. 100 years, the population achieves steady state by the first year of interest. Thereafter, temporal fluctuations in the number of individuals in each disease state reflect the genuine stochasticity of the population.

Each run of the model gives data on all the individuals ever present in the population including their yearly sequence of disease states, their yearly exposure history, and their atopic status. This data may then be interrogated to extract cross-sections of data for any given year and calculate the prevalence and incidence of disease states. Other population characteristics such as the cross-sectional distribution of current years worked or the proportion of atopic individuals in different states may also be determined. Baseline values were calculated as the average prevalence and incidence for each disease state over 100 simulations of a 50-year period for a population of size 10,000 (the approximate size of the population at risk in Dutch bakeries). This yields the expected prevalence and ignores stochastic year-to-year fluctuations. Confidence intervals for incidences and prevalences were obtained by running 1,000 model runs in the same way as for the baseline simulation but with (independent) random parameter values sampled from distributions corresponding to the confidence intervals presented in Table 2. A sensitivity analysis to provide insight into the dependencies between the model's behaviour and the input parameters was conducted using a local sensitivity ratio method. A detailed description of the sensitivity analysis and results can be found in the appendix.

Baseline model results

Table 3 presents the predicted prevalence and incidence (new cases per1000 workers per year) with their respective 95% confidence intervals for the major groupings of disease states for the simulated baseline situation (results for all thirteen disease states are presented in supplementary Table 3a in the online appendix). Our model predicts approximately 75% of workers will be neither sensitised nor symptomatic, around 12% will have moderate respiratory symptoms and a further 8% will have severe respiratory symptoms. The predicted prevalences of sensitisation to wheat and α-amylase are similar, both being around 10%. For work-disability the set up of the model (where disabled individuals leave immediately) is such that only incidence can logically be estimated at approximately 4 cases per thousand.

The proportion of workers who are atopic ranges from 40% in those with moderate symptoms to just over 60% in those sensitised to wheat but is only 20% in non-sensitised, non-symptomatic workers (the latter value not shown in Table 3). The proportion of symptomatic workers sensitised to wheat and amylase has also been determined: for those with moderate symptoms 15% (95% C.I. 11%-20%) are sensitised to wheat and 13% (8%-20%) to amylase rising to 36% (26%-46%) and 22% (12%-37%) respectively in workers with severe symptoms.

Table 3: Predicted annual prevalence, incidence (expressed as cases per 1000 workers) and proportion atopic for major groupings of disease states with accompanying 95% confidence intervals

State	Prevalence	Incidence	Atopic
Sensitised to wheat (states 2,3, 6, 7,10,11)	98 (73-130)	7 (5-9)	61% (47-74)
Sensitised to amylase (states 3,4, 7, 8, 11,12)	90 (55-139)	7 (4-10)	53 % (38-67)
Moderate symptoms (states 5, 6,7,8)	120 (95-150)	15 (12-18)	40 % (29-52)
Severe symptoms (states 9, 10,11,12)	77 (46-140)	9 (7-12)	52 % (40-64)
Work-disability (state 13)	-	4 (0 – 7)	52 % (40-64)

Figure 2 shows the distribution of the number of years to first onset of work-related sensitisation and work-related respiratory symptoms. Both sensitisation and moderate symptoms develop primarily within the first 10 years of employment with the majority in early years and considerably fewer cases thereafter. For severe symptoms, the peak of onset occurs later at around 10 years of employment and remains high for a considerable period afterwards. Taking respiratory symptoms as a whole, our model predicts a mean latency period of 10.3 years (95% C.I. 8.3-12.3).

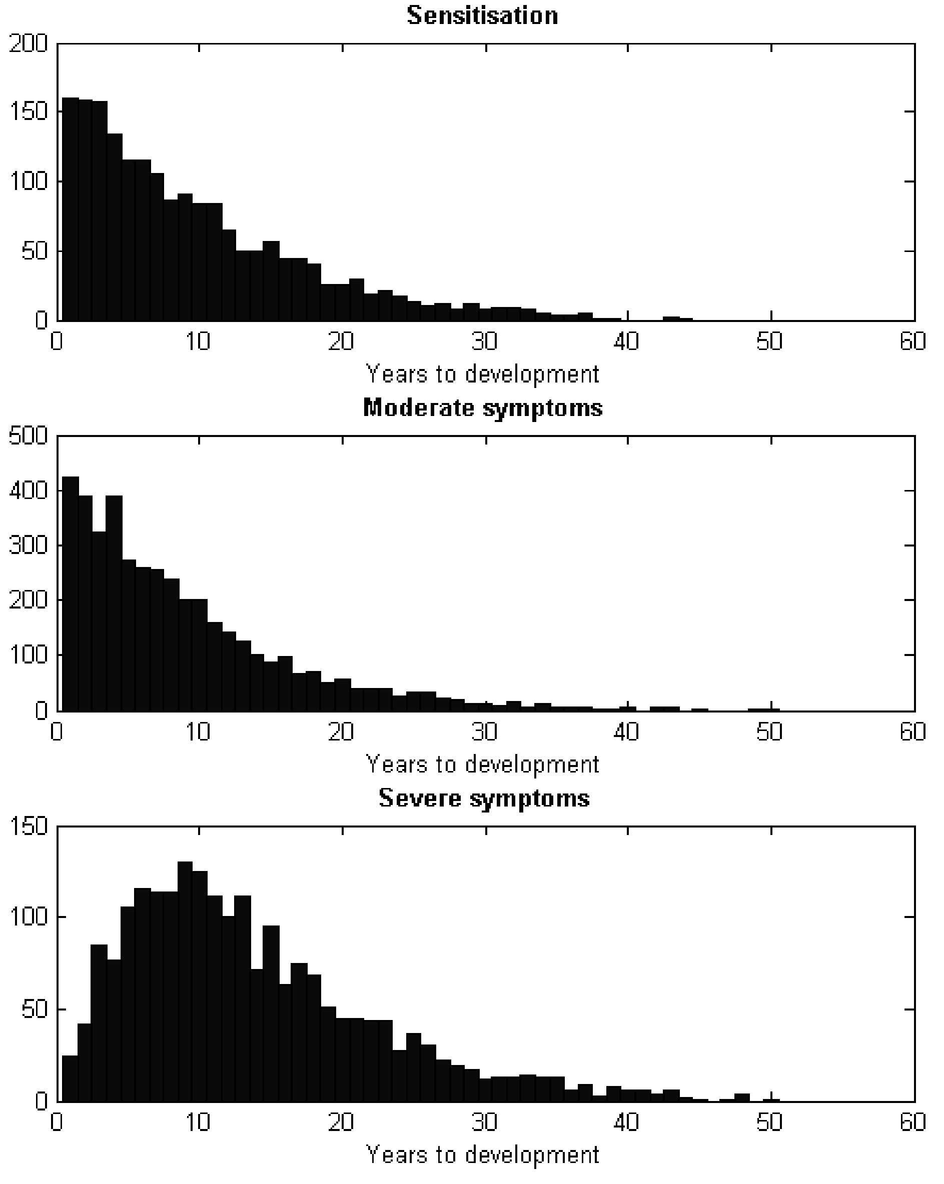

Figure 2: The distribution of the number of work years to first onset of sensitisation and symptoms

Discussion and Conclusions

To our knowledge, this paper presents one of the first attempts to develop a quantitative dynamic disease model in an occupational setting. It shows how epidemiological, exposure and population data obtained from different data sources can be integrated to develop a dynamic population-based model, that can be used for quantitative health impact assessment. In the future, this approach may provide an important contribution to the selection of cost-effective preventive policies at the workplace. However, it is clear that the value of model to health impact assessment is contingent upon it providing an adequate representation of the underlying processes and mechanisms

For respiratory symptoms our predictions are generally slightly lower than the prevalences reported in cross-sectional studies in the Netherlands[1], UK[30,31] and other countries[32,33]. However one German study[18] reported significantly higher prevalences for both sensitisation and respiratory symptoms than both our model and most other studies. According to the authors this was most likely caused by selection bias (unhealthy workers might have been more likely to participate), differences in symptom definitions and the analytical methodologies used. These are general issues surrounding comparisons of both longitudinal and cross-sectional studies looking at allergy and respiratory symptoms and makes clear-cut conclusions on observed differences difficult. In general, most input data for this study comes from cross-sectional studies and there is a need for more longitudinal observations to allow better estimation of the magnitude of the healthy worker effect and the transition from moderate to severe disease states.

Greater disparities are found between the incidence figures and published literature. For sensitisation the most likely cause is differences between the study populations. Since sensitisation is known to occur primarily in the first few years of exposure, this leads to higher incidences being reported in studies of new workers e.g. apprentices (which is the case in most longitudinal studies[2,19,22,34,35]) whereas our dynamic model simulates the total population of workers. For symptoms, whilst this might also play a role, it is likely to be less prominent due to the longer latency period. Instead the definition of symptoms is likely to be a more important cause of differences. A more fundamental reason for differences in both incidence and prevalence figures could be differences in exposure levels between studies. Unfortunately, of the longitudinal studies, only Cullinan *et al.*[2] presents quantitative exposure levels, which are approximately comparable to those used in our model.

We also compared time to development of symptoms with a longitudinal study of 90 bakery workers in the UK[36] which reported an average latency period of 7.3 years with 47% of symptoms within the first 4 years and 22% taking 10 or more years to develop. Our model shows considerable concordance predicting an average latency period of 10.3 years to first symptoms with 38% of cases taking 10 or more years to develop. The observed difference might result from a different exposure distribution (higher exposures might decrease the latency period) or a difference in population susceptibility (e.g. prevalence of atopy).

The model predictions for the proportion atopic and proportion sensitised by severity of symptoms also exhibit close agreement with cross-sectional studies in the Netherlands. For example, in the study of Jacobs *et al.* (2008) the proportion atopic using our definitions of moderate and severe symptoms was 46% and 54% respectively, compared with 40% and 52% in our model. Similar close agreement was obtained for the proportion sensitised. It must be recognised that these are favourable comparisons as this study was used in the estimation of the dose-response parameters for our model. Nevertheless, our model has not been fitted to this study in the conventional sense of optimising the input parameters to provide the closest alignment between the model predictions and the observational data.

Whilst considerable effort has been taken to ensure that all the model parameters are evidenced based, the estimation of some parameters could be improved. For example, the estimation of the dose-response parameters ignores the influence of workers becoming disabled and leaving employment in the bakery sector. This 'healthy worker effect' leads to negative bias in the estimates of the slopes of the dose-response relationships. A possible future application of our model would be to estimate the magnitude of this bias through estimating the dose-response parameters from simulated cross-sectional groups of workers and comparing the derived slope parameters to the input slopes. The multiplicative risk factors for the increased risk of symptoms given sensitisation to wheat and fungal α-amylase have been calculated from the cross-sectional health surveillance data using logistic regression. However, because workers only experience an increased risk of developing symptoms for the (unknown) fraction of their career for which they are sensitised, our logistic regression derived estimates of the multiplicative risks will under-estimate the true yearly multiplicative risks. This implies our model should underestimate the total number of symptomatic individuals, though comparison with observational studies suggests this underestimation is relatively modest.

Another important assumption in our model is that reversal of symptoms and sensitisation is not considered possible whilst still working in the bakery industry (all recovery probabilities in the model are currently set to zero). For respiratory, especially lower respiratory symptoms, this assumption is supported by several publications suggesting that once a worker develops occupational asthma the chances of recovering when still exposed are minimal[17,37]. This is less obvious for early states of disease processes such as sensitisation and upper airway symptoms. However, a recent study[25] shows strong remission for both work-related sensitisation and rhinoconjunctivitis symptoms in a cohort of workers exposed to high molecular weight allergens. Although information on the associated exposure in this study was limited, and the information was not specifically on bakery workers, the results indicate that further refinement of this aspect of the model might be necessary, if more detailed data were to become available.

The dose-response for sensitisation to wheat is based upon exposure to flour dust (which we also used for estimating the dose-responses for symptoms) rather than wheat exposure. However, as flour dust and wheat allergen exposure are highly correlated[10] comparable dose-response relationships for wheat sensitisation are obtained with either exposure metric. An obvious refinement of the exposure model would use separate strata for particular jobs within the traditional and industrial bakery sectors thereby allowing the modelling of individuals transferring between jobs or sectors. The authors hope to implement these changes in the future to allow more realistic modelling of health surveillance schemes.

Our model does not distinguish between lower respiratory symptoms with and without upper respiratory symptoms, both being classed as 'severe'. This decision was taken partly through an appreciation that many health surveillance schemes would regard both as equal priorities for intervention and partly due to the small number of workers with lower respiratory symptoms but without upper respiratory symptoms (<3% in the study of Jacobs *et al*.[4]). Furthermore, the model has been limited to sensitisation and respiratory symptoms since they are generally believed to be the most severe and disabling health effects in workers exposed to flour dust[38]. In the current model work disability is only associated explicitly with lower respiratory symptoms. Although asthma is generally acknowledged as the most severe and disabling state it is known that upper airway symptoms might also lead to workers leaving. In the future this could be incorporated as a separate route in the model if data would become available. The model could be easily extended to other disease outcomes (e.g. allergic dermal symptoms) or to include other exposure routes (e.g. rye exposure) if these were considered to play an important role, the mechanisms were sufficiently understood and provided suitable data were available. This makes the model flexible and easy to adapt to other, slightly different situations.

The results presented here only represent a part of the possible outputs from the model. The model may also be used to investigate the importance of different progression routes to a particular disease state, for example, the proportion of sensitised workers with lower respiratory symptoms that were sensitised first – something that is often assumed but cannot be verified in cross-sectional studies. The model might also be used to calculate lifetime risks or the probability of, for example, a sensitised individual developing severe symptoms within a certain period. However, although our model provides a valuable population level representation of the mechanisms contributing to respiratory diseases in bakers, it was primarily developed for use in health impact assessment. A future paper will describe the application of the model to the evaluation of a range of workplace interventions, including achievable levels of exposure reduction and health surveillance schemes. The results of this paper show the need for further longitudinal data to help develop and validate models, such as the one presented here, which can be used for prospective Health Impact Assessment. Therefore, epidemiological research agendas should be more focussed on longitudinal studies that can disclose information on disease progression mechanisms that cannot readily be obtained from cross-sectional studies.

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Appendix

Estimation of dose/exposure-responses

Under the assumptions set out in the disease model it is possible to derive expressions linking the yearly transition probabilities to the probability of observing sensitised or symptomatic individuals in a cross-sectional epidemiological study. The probability of an individual being sensitised to wheat after *Y* years may be written:

$$\mathrm{P(sensitised\ wheat)} = B_{\mathrm{w}} + (1 - B_w)\left\{1 - \prod_{i=1}^{Y}(1 - \alpha_w E_D^i)\right\} \tag{1}$$

where E_D^i is the worker's mean exposure to flour dust in year i, B_w is the background probability of sensitisation to wheat, and the dose-response slope parameter for wheat (α_w) differs according to the worker's atopic status. Assuming the same mean annual exposure for each working year gives:

$$\mathrm{P(sensitised\ wheat)} = B_w + (1 - B_w) \times \left\{1 - (1 - \alpha_w E_D)^Y\right\} \tag{2}$$

The probability of sensitisation to amylase is obtained in the same manner. In a similar fashion it is possible to derive expressions for the probability of having no symptoms conditional upon not being sensitised:

$$\mathrm{P(no\ symptoms)} = 1 - (1 - \beta_{\mathrm{mod}}\ E\ - \beta_{\mathrm{sev}}\ E)^Y \tag{3}$$

where β_{mod} is the dose-response slope for developing moderate symptoms and β_{sev} the dose-response slope for immediate development of severe symptoms (both again taking different values for atopic and non-atopic individuals). The probability of having moderate symptoms conditional upon being non-sensitised may be similarly derived, though it is necessary to condition upon the (unknown) year in which moderate symptoms first develop:

$$\mathrm{P(moderate\ symptoms)} = \sum_{i=1}^{Y}\left\{(1 - \beta_{\mathrm{mod}}E - \beta_{\mathrm{sev}}E)^{i-1}\beta_{\mathrm{mod}}E\,(1 - \beta_{\mathrm{prog}}E)^{Y-i}\right\} \tag{4}$$

Here β_{prog} is the dose-response slope for progression from moderate to severe symptoms. The probability of having severe symptoms, again conditional upon being non-sensitised, is obtained in a trivial fashion from equations 3 and 4:

$$\mathrm{P(severe\,symptoms)} = (1-\beta_{\mathrm{mod}}E-\beta_{\mathrm{sev}}E)^{Y} - \sum_{i=1}^{Y}\left\{(1-\beta_{\mathrm{mod}}E-\beta_{\mathrm{sev}}E)^{i-1}\beta_{\mathrm{mod}}E\,(1-\beta_{\mathrm{prog}}\,E)^{Y-i}\right\} \tag{5}$$

It is important to note that the derivation of equations 3-5 ignores the possibility of individuals leaving the population through disability following the development of severe symptoms.

The dose-response slope parameters have been estimated through fitting expressions 2-5 to the data set reported in Jacobs et al.[4] within a Bayesian framework using Markov Chain Monte Carlo (see for example Gilks et al.[41]). An adaptive Metropolis-Hastings algorithm (Winbugs[42]) was used with non-informative (uniform) prior distributions for the slope parameters and a chain length of 14000 iterations. Posterior parameter estimates were derived after checking for convergence and discarding the first 4000 values.

Multiplicative risk factors for the increased risk of symptoms given sensitisation to wheat or fungal α-amylase (denoted r_w and r_a respectively) were estimated using logistic regression with atopy and cumulative dust exposure as additional covariates. Applied to the data presented in Jacobs et al.[4] this analysis yielded a non-significant odds-ratio for α-amylase sensitisation, contrary to the general scientific consensus that fungal α-amylase sensitisation is a risk factor for rhinitis and baker's asthma[3,32,40]. Consequently, the risk factor for amylase was determined from the smaller data set previously examined by Houba et al.[40].

A more rigorous approach to the estimation of dose-response parameters would be to estimate all the model parameters simultaneously via 'fitting' the available epidemiological data directly to the dynamic population model. In principle, this could be achieved within a Bayesian framework using Markov Chain Monte Carlo methods and, if appropriate, using informative priors for model parameters with supplementary evidence. This methodology could be applied iteratively with posterior distributions for parameters obtained from one epidemiological study forming the priors for use with another, thereby integrating the evidence from a series of studies. However, it would appear that the only method of evaluating the likelihood function (required at each iteration of the MCMC algorithm) would be through numerical simulation i.e. running the dynamic population model at every iteration. Such an approach would clearly be highly computationally intensive. Nevertheless, the authors are currently investigating the feasibility of this approach.

Sensitivity analysis

A local sensitivity analysis was conducted using a sensitivity ratio method[43]. In this procedure each parameter was incremented by 20% above its baseline value whilst keeping all other parameters fixed and estimating the expected change in the outputs using Monte

Carlo simulation. The local sensitivity ratio was then calculated as ratio of the normalised change in the model output to the normalised change in the model parameter (effectively an estimate of the first-order partial derivative). Therefore a sensitivity ratio of one indicates a change in the output as large as the change in the input, in our case 20%, whilst sensitivity ratios less than one indicate smaller relative changes. The prevalence and incidence of each group of disease states were averaged over 100 runs of the model, each for a 50-year simulation period (as for the calculation of baseline values) in order to minimise the influence of stochastic variation. The reproducibility of these results was confirmed by comparing sensitivity ratios based upon the first 50 simulations with those based upon second 50. Sensitivity analyses have been performed for the prevalence and incidence of moderate symptoms (states 5, 6, 7 and 8 combined), severe symptoms (states 9, 10, 11 and 12 combined) and sensitisation to wheat or α-amylase (states 2, 3, 4, 6, 7, 8, 10, 11 and 12 combined).

In Figure 3, tornado plots show the impact of variation of the different model parameters on the prevalence and incidence of work related sensitisation, and work-related respiratory symptoms (both moderate and severe separately). As expected, the sensitivity analysis indicates substantial differences in the influence of model parameters between different disease states and between prevalence and incidence rates.

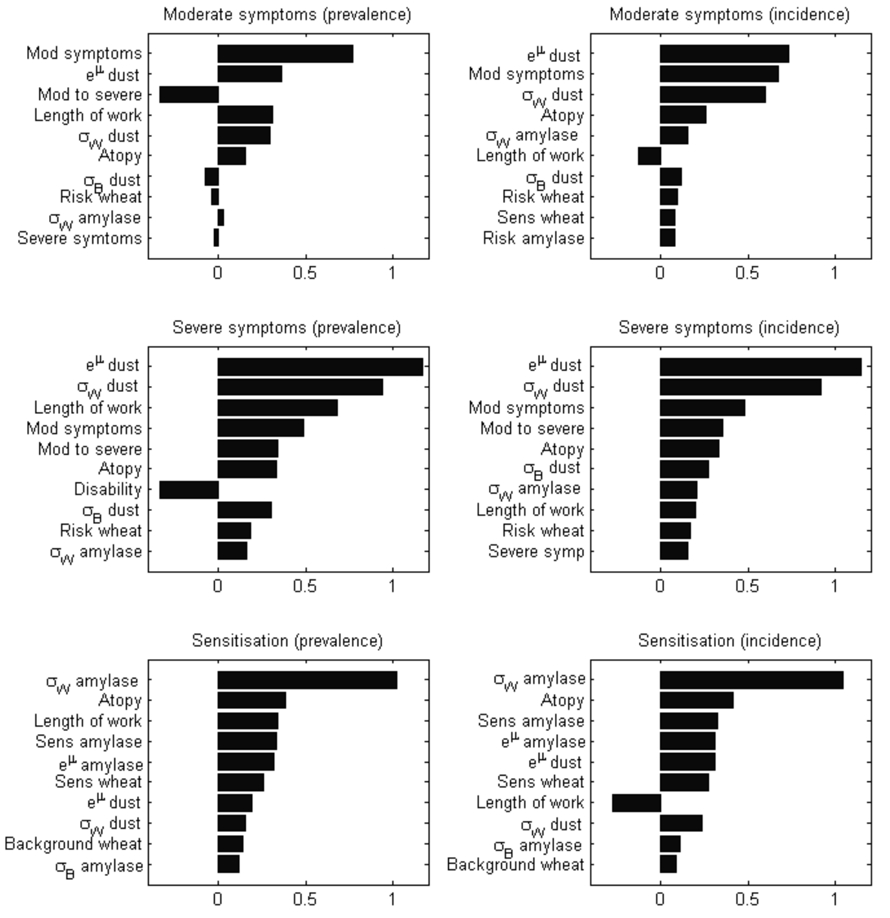

Figure 3. Sensitivity ratios for the prevalence and incidence of major groupings of disease states to model parameters

Moderate Symptoms

For the prevalence of moderate symptoms, the most influential parameters are the dose-response slopes for developing moderate symptoms. Median dust exposures, the dose-response slope for progression to severe symptoms (negative score), length of work and within-worker variation in dust all have a lesser influence with absolute sensitivity scores of between 0.3 and 0.4. For the incidence of moderate symptoms, the most influential parameters are exposure parameters that determine mean exposure levels - median dust exposure and within-worker variation in dust, and the dose-response slope(s) for developing moderate symptoms, these having sensitivity scores between 0.6 and 0.75. Between-worker variation in dust exposure has a much lower sensitivity score (approximately 0.1) as the effect of this parameter on mean dust exposures is less straightforward – increasing σ_B dust widens the range of individual mean exposures, simultaneously raising the risk of developing symptoms in some individuals whilst lowering it in others. Unlike the case for prevalence, the probability of progressing from moderate to severe symptoms has no impact on the incidence, whilst length of work has a negative sensitivity score. The latter reflects the reduction in population turnover with longer working careers and the consequent reduction in newly at risk healthy workers (a similar but stronger effect is seen for the incidence of sensitisation).

Severe symptoms
For severe symptoms, both the prevalence and the incidence are primarily influenced by changes to the distribution of exposure to flour dust, in particular the median dust exposure and within-worker variability, which have sensitivity scores of approximately 1 for both prevalence and incidence. Increasing the between-worker variance component has a much more limited impact. Other moderately influential parameters are the dose-response parameters for developing moderate symptoms and progression to severe symptoms, and atopy. In addition, for the prevalence of severe symptoms, length of work in the bakery sector and the probability of developing work-disability were influential (the latter having a negative sensitivity score). It is clear that probability of disability should only influence the latter part of a worker's career following the development of severe symptoms and should not alter their lifetime risk of developing severe symptoms. Very slight changes in the incidence rates of moderate symptoms and sensitisation were also discernable (not shown in Figure 3) and are most likely due to the increased turnover of workers created by an increase in the number of workers leaving the population due to disability.

Sensitisation
For sensitisation, the prevalence and the incidence are primarily affected by changes to the within-worker variance for amylase exposure, which as has a sensitivity score of approximately 1. The next most influential parameters on the prevalence of sensitisation are atopy, length of work, the dose-response slopes for amylase and wheat, length of work and median amylase exposure, all having sensitivity scores between 0.3 and 0.4. For incidence of sensitisation, the median dust exposure and within-worker variation in dust also appear to play a role. Background levels of sensitisation to wheat and α-amylase have little impact on any of the disease states reflecting pre-eminence of workplace exposure as the cause of sensitisation.

A limitation of this local sensitivity analysis is that different results will be obtained if the analysis is repeated in a different part of the model parameter space. Considering the exposure parameters, whereas increasing the median dust exposure by 20% always increases mean dust exposures (upon which the dose-response relationships are based) by 20%, the effect of changing the within-person variability component on mean exposure is dependent upon the baseline value. For example, increasing within-worker variation in dust (σ_W dust) by 20% from its baseline value (0.82) increases the mean dust exposure by 16%, making the sensitivity scores for median dust and σ_W dust on the incidence of severe symptoms consistent. In contrast, increasing within-worker variation in amylase (σ_W amylase) by 20% from its baseline value (1.52) increases mean amylase exposures by approximately 66%, explaining the high sensitivity score of σ_W amylase for sensitisation.

It is noteworthy that all the dose-response parameters have sensitivity ratios less than one despite the model using linear yearly dose-response relationships. However, whilst prevalence and incidence values may change by less than the model parameters, there may also be other associated changes, such as a shortening of time to onset of symptoms, increased lifetime risk of disability and a shortening of working lifetimes (leading to an increased rate of population turnover).

In summary, the sensitivity analysis has highlighted the complex and wide ranging effects of changing parameters in our dynamic population-based model, prompts further consideration of the underlying mechanisms and may provide useful insight when designing effective workplace interventions. Furthermore, the fact that the highest sensitivity scores are approximately 1, with many of the model parameters having sensitivity scores considerably less than this, provides reassurance that the model predictions are reasonably robust and are not extremely sensitive to small perturbations in the model inputs.

Table 3a: Predicted prevalence, incidence (expressed as cases per 1000 workers) and proportion atopics for all disease states with accompanying 95% confidence intervals

State	Prevalence	Incidence	Atopic
Non-sensitised & non-symptomatic	750 (680-820)	52 (41-64)	23% (18-27)
Sensitised to wheat & non-symptomatic	46 (34-60)	5 (4-7)	47% (33-60)
Sensitised to wheat & amylase & non-symptomatic	4 (2-9)	1 (1-1)	71% (48-89)
Sensitised to amylase & non-symptomatic	52 (33-81)	5 (3-8)	41% (28-54)
Non-sensitised & moderate symptoms	87 (67-107)	10 (8-12)	33% (24-44)
Sensitised to wheat & moderate symptoms	15 (10-25)	3 (2-5)	64% (44-80)
Sensitised to wheat & amylase & moderate symptoms	2 (1-6)	1 (0-1)	82% (59-96)
Sensitised to amylase & moderate symptoms	13 (8-23)	2 (1-4)	56% (39-78)
Non-sensitised & severe symptoms	40 (23 –66)	5 (4-7)	33% (21-46)
Sensitised to wheat & severe symptoms	19 (12-38)	3 (2-4)	73% (58-83)
Sensitised to wheat & α-amylase & severe symptoms	7 (3-16)	1 (0-2)	89% (74-95)
Sensitised to α-amylase & severe symptoms	10 (3-22)	1 (0-3)	61% (39-80)
Work disabling asthmatic symptoms	-	4 (0-7)	52% (40-64)

Table 4: Matrix of transition probabilities[1] for disease progression

	New disease state												
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
1	$1-p_1-p_2-p_4-p_5$	p_4	0	p_5	p_1	0	0	0	p_3	0	0	0	0
2	0	$1-p_5-r_w p_1$	p_5	0	0	$r_w p_1$	0	0	0	0	0	0	0
3	0	0	$1-r_w r_a p_1$	0	0	0	$r_w r_a p_1$	0	0	0	0	0	0
4	0	0	p_4	$1-p_4-r_a p_1$	0	0	0	$r_a p_1$	0	0	0	0	0
5	0	0	0	0	$1-p_2-p_4-p_5$	p_4	0	p_5	p_2	0	0	0	0
6	0	0	0	0	0	$1-p_5-r_w p_2$	p_5	0	0	$r_w p_2$	0	0	0
7	0	0	0	0	0	0	$1-r_w r_a p_2$	0	0	0	$r_w r_a p_2$	0	0
8	0	0	0	0	0	0	p_4	$1-p_4-r_a p_2$	0	0	0	$r_a p_2$	0
9	0	0	0	0	0	0	0	0	$1-p_4-p_5-P_{dis}$	p_4	0	p_5	P_{dis}
10	0	0	0	0	0	0	0	0	0	$1-p_5-P_{dis}$	p_5	0	P_{dis}
11	0	0	0	0	0	0	0	0	0	0	$1-P_{dis}$	0	P_{dis}
12	0	0	0	0	0	0	0	0	0	0	p_4	$1-p_4-P_{dis}$	P_{dis}
13	0	0	0	0	0	0	0	0	0	0	0	0	1

[1] Where $p_1 = \beta_{\mathrm{mod}} E_{Dust}$, $p_2 = \beta_{sev} E_{Dust}$, $p_3 = \beta_{prog} E_{Dust}$, $p_4 = \alpha_w E_{Dust}$, $p_5 = \alpha_a E_{Amylase}$

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Comparison of the effect of different intervention strategies for occupational asthma on the burden of disease in bakers.

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Submitted

Abstract

Rationale: In the Netherlands approximately 12.000 workers are potentially exposed to flour dust and at risk of developing (allergic) respiratory symptoms and occupational asthma. Improved insight into the effectiveness of intervention strategies will help realize a decrease in the occupational disease burden in this population.

Objective: To use a simulation model to assess the impact of different intervention strategies on the disease burden of the population over time

Methods: The dynamic population-based model describes development and progression of work related sensitisation and respiratory symptoms and diseases in a population of bakery workers in association to occupational allergen exposure. With this model the impact on disease burden resulting from intervention strategies was prospectively evaluated over a twenty year period. We distinguished interventions based on exposure reductions for wheat and fungal α-amylase allergens and health surveillance combined with reduction of exposure as well as pre-employment screening.

Main results: The impact on disease burden was limited, generally less then 50% for lower respiratory symptoms and work disabling asthma. Only the rigorous health surveillance intervention scenario identifying workers that are sensitized and/or report upper respiratory symptoms and decreasing their individual exposures with 90% resulted in a decrease of almost 60% in disease burden after 20 years.

Conclusions: This study clearly demonstrates that different intervention strategies lead to substantial differences in the impact on the burden of disease as well as affecting the speed with which changes occur. This information can assist policy makers in their choice of intervention and gives a guide to achievable reductions in disease burden.

Introduction

Occupational exposure accounts for approximately 10-15% of adult asthma cases, making it the most important respiratory occupational disease[1-3]. Workers exposed to flour dust, especially bakery workers, are among the high risk populations for developing occupational respiratory disease[4-6]. At present the burden of disease is considerable as has been described in various surveys[7-9]. In the Netherlands approximately 12.000 workers are potentially exposed to flour dust and thus at risk of developing (allergic) respiratory disease[7,10]. There is an urgent need for effective interventions to reduce the occupational disease burden related to flour dust exposure[11]. However, only limited information is available on the effectiveness of various intervention strategies and no robust rationale for choosing between specific strategies exists. Health surveillance and exposure reduction are the most prominent approaches but their relative effectiveness in reducing disease burden has not yet been established[12-17].

A recently conducted large scale dissemination and exposure reduction education program in the Dutch baking industry resulted in only a marginal reduction of exposure. The reduction of disease burden in the bakery population as a result of this exposure reduction is likely to be negligible[18]. This implies that more rigorous approaches for intervention are needed to significantly reduce the disease burden of occupational asthma. Since both the exposure level and the time till diagnosis (early identification) are of relevance to the prognosis of occupational asthma, both should be considered in designing an effective intervention strategy[19]. As a result, intervention scenarios might be complex and several intervention options may be considered and combined when dealing with (allergic) respiratory diseases[20-22].

Quantitative health impact assessment can be a powerful methodology to prospectively evaluate the impact of different intervention strategies thereby helping to provide the evidence base necessary to gain widespread stakeholder support for implementing health policies[23]. To perform quantitative health impact assessment related to occupational exposure and respiratory diseases in bakery workers, a dynamic population-based model was recently developed[24]. This model describes the onset and progression of work-related sensitisation into upper and lower respiratory symptoms as well as work disabling asthmatic symptoms, in relation to occupational allergen exposure levels over time.

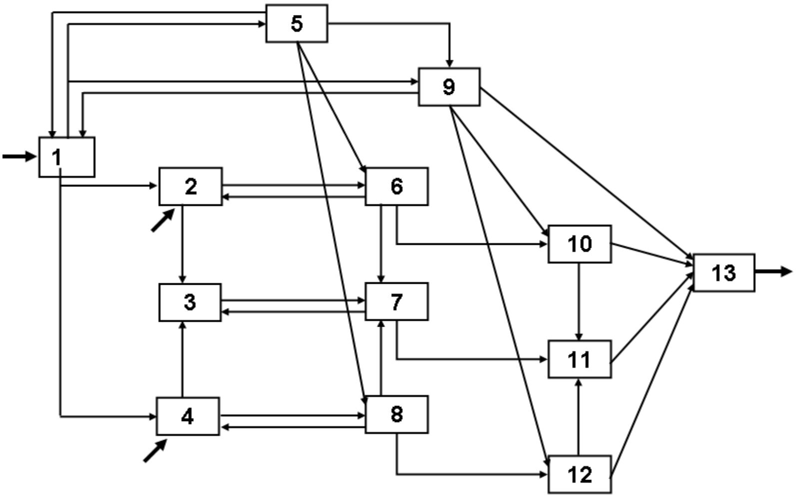
The main objective of this study was to evaluate the potential impact of different intervention strategies on the health of bakery workers. Three main strategies were included in the evaluation: 1) hygienic intervention, aimed at reducing exposure levels in the whole population, 2) health surveillance, identifying ‘high risk’ workers combined with tailored exposure control for these individuals, and 3) pre-employment screening for atopy. The results will inform policy makers on effective designs for reduction of (allergic) respiratory disease and will provide guidance for future actions.

Methodology

Disease model

The dynamic model simulates a population of workers longitudinally through time and tracks the development of work related symptoms in each individual worker related to their occupational exposure[24]. The model follows the classic disease model for development of occupational asthma[25]. Two mechanisms are taken into account: 1) Allergic sensitisation which precedes development of respiratory symptoms[26]. Sensitisation was defined as having a positive serological test against wheat flour or fungal α-amylase[7,27,28]. 2) A non-allergic route, where irritant mechanisms incites onset of nasal- and lower respiratory symptoms[25]. Work-related upper respiratory symptoms were defined as having at least two of the following symptoms: sneezing, a running nose or itchy/teary eyes during work. Work-related lower respiratory symptoms were defined as having at least two of the following symptoms: asthma attacks, wheezing, shortness of breath or tightness of chest during work[7]. We assumed that rhinitis symptoms generally precede development of lower respiratory symptoms, though not in every case[24,29,30]. Eventually some workers develop work disabling asthmatic symptoms[31-33].

Figure 1 gives the flow diagram of this multi-stage disease model with the boxes and the arrows representing the different disease stages and transition routes, respectively. Yearly transition probabilities were estimated from a recent survey among bakers comprising information on symptoms and exposure for a large number of individual workers[7]. A detailed description of the model is given by Warren et al.[24]. The model simulates a fixed worker population of 10.000 individuals. The worker population is dynamic with a continual process of workers leaving the workforce (possibly through ill-health) and being replaced with new recruits. Each new worker is assigned a working lifetime (average 20 years) and enters with a certain probability of being atopic (30%) and already sensitised to the occupational allergens (1% for amylase and 3% for wheat allergens) based on general population survey data [34]. An individual worker leaves the population when they come to the end of their natural working life, or become disabled.



State	Label
Non-sensitised & non-symptomatic	1
Sensitised to wheat and/or amylase & non-symptomatic	2,3,4
Non-sensitised & upper respiratory symptoms	5
Sensitised & upper respiratory symptoms	6,7,8
Non-sensitised & lower respiratory symptoms	9
Sensitised & lower respiratory symptoms	10,11,12
Work disabling asthmatic symptoms	13

Figure 1. Causal diagram of dynamic population-based health model showing all possible health transitions within the population relating to the development of sensitisation and respiratory symptoms

Table 1. Description of changes in input parameters in the dynamic population model to evaluate the impact of different intervention scenarios

Intervention scenario	Description of parameter change	Change in model input parameters: Flour dust exposure	Fungal α-amylase	Population parameters*
No Intervention	-	GM=1.19 GSD_{bw}= 2.29 GSD_{ww}= 2.27	GM=0.57 GSD_{bw}= 2.77 GSD_{ww}= 4.57	Prob_atopy=0.3
Covenant intervention	• First six years population GM exposure decreases with 2% annually for flour dust and 8% annually for amylase • After the six year level exposures stays constant • Variability is assumed to stay the same	*year t=1-6;* GM=GM(t-1) *0.98 *year t=7-20*; GM= 1.05 GSD_{bw}= 2.29 GSD_{ww}= 2.27	*year t=1-6;* GM=GM(t-1) *0.92 *year t=7-20*; GM= 0.35 GSD_{bw}= 2.77 GSD_{ww}= 4.57	Prob_atopy=0.3
Continuation of covenant	• Equal to the above described scenario. • Yet, the decrease of the GM values for both exposures is continued for the full 20 year period.	GM=GM(t-1) *0.98 GSD_{bw}= 2.29 GSD_{ww}= 2.27	GM=GM(t-1) *0.92 GSD_{bw}= 2.77 GSD_{ww}= 4.57	Prob_atopy=0.3
Hygiene intervention	• Individual exposure estimates from the baseline measurement dataset are recalculated, according to the reduction factors derived previously[34].	GM = 0.82 GSD_{bw}= 2.03 GSD_{ww}= 2.05	GM = 0.39 GSD_{bw}= 2.56 GSD_{ww}= 4.44	Prob_atopy=0.3
Health surveillance I	• Exposures of high risk individuals (sensitised workers) are reduced with 90% • Individual workers can only receive an intervention once. • The population variability of exposure is assumed to stay unchanged	*high risk individuals:* $GM_{post-int}$ = 0.1* $GM_{pre-int}$ *Others:* $GM_{post-int}$ = $GM_{pre-int}$ GSD_{bw}= 2.29 GSD_{ww}= 2.27	*high risk individuals:* $GM_{post-int}$ = 0.1* $GM_{pre-int}$ *Others:* $GM_{post-int}$ = $GM_{pre-int}$ GSD_{bw}= 2.77 GSD_{ww}= 4.57	Prob_atopy=0.3
Health surveillance II	• As above but now non-sensitized workers with rhinitis symptoms are also included in the definition of high risk workers	high risk individuals: $GM_{post-int}$ = 0.1* $GM_{pre-int}$ Others: $GM_{post-int}$ = $GM_{pre-int}$ GSD_{bw}= 2.29 GSD_{ww}= 2.27	high risk individuals: $GM_{post-int}$ = 0.1* $GM_{pre-int}$ Others: $GM_{post-int}$ = $GM_{pre-int}$ GSD_{bw}= 2.77 GSD_{ww}= 4.57	Prob_atopy=0.3
Pre-employment screening	• Exposure parameters are not affected. • The probability of atopy for new employees is set to 0 assuming no atopic enter the workforce.	GM= 1.19 GSD_{bw}= 2.29 GSD_{ww}= 2.27	GM=0.57 GSD_{bw}= 2.77 GSD_{ww}= 4.57	Prob_atopy=0

GM = geometric mean exposure level; GSDbw = the between worker or inter individual exposure variability; GSDww = the day to day or intra individual exposure variability; GMpre-int= individual exposure estimate before receiving an individual intervention; GMpost-int= individual exposure estimate after receiving an individual intervention; * Only the probability of being atopic is relevant for the evaluated intervention strategies

Simulation of interventions

All simulations were performed in Matlab (v7.5). The impact of the various interventions was evaluated over an equal period of 20 years. For each intervention scenario simulations were repeated forty times. The specific changes in model input parameters used to simulate health impact resulting from the intervention are presented in table 1. Prevalence and incidence ratios were extracted from the results matrix for the baseline year and year 20. Uncertainty was calculated as 2.5% upper and lower confidence intervals of the estimated prevalence and incidence values using a two-dimensional Monte Carlo simulation with 20 inner loops to correct for stochastic variability and 100 runs (outer loops) varying model parameters randomly according to input distributions chosen to represent parameter uncertainty[24].

The impact of the various simulated interventions was presented as the relative change in disease parameters for four aggregated disease states; 1) work related sensitisation, 2) upper respiratory symptoms, 3) lower respiratory symptoms, and 4) work disabling asthma. A trend plot of the prevalence over time was created to illustrate time effects of the impact.

Results

Intervention strategies

The baseline intervention scenario in this study corresponds to the intervention program implemented as part of the Dutch covenant program[18]. In this program sector wide training and education was performed to inform workers on the risk of occupational exposures and educate them with respect to a set of basic good exposure control practices. The intervention program was assumed to run for six years until the end of the covenant period. At the end of the covenant period a -12% decrease in flour dust exposure and a -39% decrease in fungal α-amylase exposure was observed.

The impact of this intervention scenario was compared with the impact of four other intervention strategies;

a) Continuation of the covenant intervention program for the full period of 20 years. This is predicted to result in a decrease of the population exposure levels with -33% for flour dust and -81% for fungal α-amylase after 20 years.

b) Hygiene intervention, implementing rigorous exposure control measures throughout the whole bakery sector as described by Meijster et al.[35]. This implies substantial investments in approximately 2500 small bakeries and 80 industrial bakeries. Implementation is assumed to be finished at the start of the simulation period. This is predicted to result in a decrease of population exposure levels with -32% for both flour dust and fungal α-amylase at the start of the simulation period as well as an approximately 20% decrease in exposure variability.

c) Health surveillance, high risk workers are identified and immediately after detection, the exposure is reduced by 90% for both flour dust and fungal α-amylase in these high risk workers. Health surveillance is performed every three years. We evaluated two scenarios; in the first scenario only workers with sensitisation are identified and labelled high risk. In the second scenario we included upper respiratory symptoms in the screening, so all workers with sensitisation or upper respiratory symptoms are labelled high risk.

d) Screening of new employees, workers are screened for their atopic status prior to employment and those who are atopic are not admitted to the worker population.

Simulation results

The baseline figures for prevalence of the different disease states are given in Table 2.

Table 2. Baseline disease figures for prevalence of the different disease states (per 1000 workers)

Disease state	**Prevalence (97.5% CI)**
Work related sensitisation	134 (106-163)
Upper respiratory symptoms	100 (80-123)
Lower respiratory symptoms	64 (41-110)
Work disabling asthmatic symptoms	3 (0.2-5)

Table 3 gives the impact of the different intervention strategies presented as the (relative) change in prevalence for the three aggregated disease states over the 20 year simulation period. For disability the change in onset of new cases was evaluated. The confidence intervals in Table 3 indicate that uncertainties around our estimates of the relative impact of interventions are fairly limited for both sensitisation and respiratory symptoms and somewhat larger for work disabling asthmatic symptoms. Figure 2 shows a plot with the trend lines for the change in prevalence for all simulated intervention scenarios for the full 20 year period.

Table 3. Change in prevalence of work related sensitisation, upper respiratory symptoms, lower respiratory symptoms and work disability for the different intervention scenarios

Scenario	Disease state	Prevalence Change[1]	Prevalence 97.5% upper and lower confidence intervals
Covenant intervention	Work related sensitisation	-13%	-17% – -10%
	Upper respiratory symptoms	-6%	-8% – -3%
	Lower respiratory symptoms	-13%	-16% – -10%
	Work disabling asthmatic symptoms[2]	-13%	-29% – +3%
Continuation covenant intervention	Work related sensitisation	-21%	-26% – -17%
	Upper respiratory symptoms	-14%	-17% – -10%
	Lower respiratory symptoms	-25%	-30% – -20%
	Work disabling asthmatic symptoms	-24%	-38% – -12%
Hygienic intervention	Work related sensitisation	-21%	-25% – -17%
	Upper respiratory symptoms	-21%	-26% – -16%
	Lower respiratory symptoms	-46%	-52% – -40%
	Work disabling asthmatic symptoms	-46%	-57% – -33%
Health surveillance intervention (I)	Work related sensitisation	3%	-1% – 8%
	Upper respiratory symptoms	-4%	-8% – 0%
	Lower respiratory symptoms	-31%	-40% – -22%
	Work disabling asthmatic symptoms	-30%	-45% – -15%
Health surveillance intervention (II)	Work related sensitisation	-2%	-6% – 2%
	Upper respiratory symptoms	18%	7% – 28%
	Lower respiratory symptoms	-58%	-66% – -50%
	Work disabling asthmatic symptoms	-59%	-71% – -45%
Screening intervention	Work related sensitisation	-21%	-31% – -13%
	Upper respiratory symptoms	-14%	-23% – -4%
	Lower respiratory symptoms	-18%	-26% – -6%
	Work disabling asthmatic symptoms	-16%	-35% – 4%

[1] Difference between pre- and post-intervention period over a 20 year period

[2] For work disabling asthma the figures reflect the change in onset of new cases, since disabled workers leave the workforce in the year they become disabled no prevalence figures can be estimated for this stage

The baseline scenario shows a modest change in the prevalence of the different disease states, generally less then -15%. With a continuation of the intervention program to the full period the health impact is substantially larger, especially for the respiratory symptoms. This intervention scenario requires continuous investment in training across the whole population over a 20 year period assuming this will have a constant decreasing effect on the population exposure levels.

The hygienic intervention reduces the disease burden by almost 50% for both severe symptoms and work disabling asthma. The impact levelled at the end of the 20 year period (Figure 2).

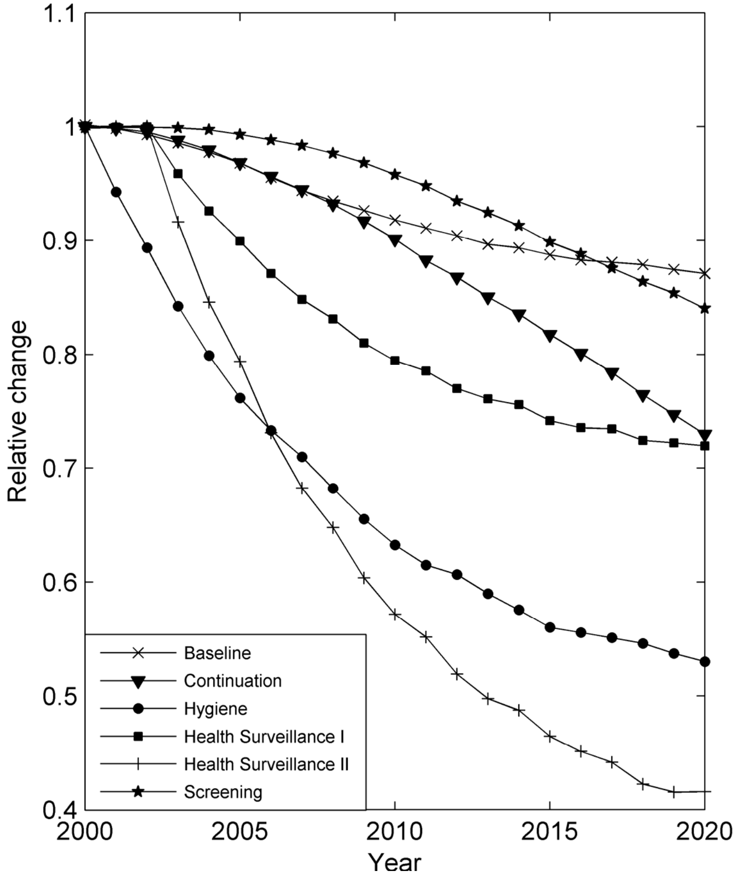


Figure 2. Trend plot of the change in the prevalence for lower respiratory symptoms for the 6 intervention scenarios for the 20 year simulation period

The two health surveillance scenarios exhibit substantial differences in terms of both their health impact and in number of individuals targeted. The reduction in lower respiratory symptoms and disabling asthma is approximately twice as high when upper respiratory symptoms are included in the screening. A consequence of the reduction in individuals progressing from upper respiratory symptoms to lower respiratory symptoms as a result of the individual interventions is an increased prevalence of upper respiratory symptoms. In the scenario based on screening for sensitisation, an initial 1100 individual interventions have to be performed at the start of the intervention program and an estimated 200-250 individual interventions after each following health surveillance cycle (every 3 years). When upper respiratory symptoms are also considered as risk factor, the number of interventions will increase substantially; i.e.1800 individual interventions at the start and around 400 interventions after each following health surveillance cycle. For both health surveillance scenarios the disease burden levels off after 20 years, implying that additional reductions in disease burden from these approaches will be limited.

Screening for atopy among new employees has a limited impact on work related disease burden, with prevalence for respiratory symptoms and work disabling asthma decreasing less than 20% after 20 years. The trend plot indicates that disease prevalence declines gradually and the effect does not seem to level off at the end of the simulation period.

No detailed data is presented here on changes in incidence for the different intervention scenarios. The magnitude of the change in incidence after a 20 year period for most scenarios is approximately similar to the decrease observed in disease prevalence. The only notable differences were observed for the scenario where the baseline intervention was assumed to continue, here the incidence figures showed a substantially larger reduction (up to 40% for lower airway symptoms). This observation is in line with the fact that the prevalence trend plot does not show a strong levelling of for this scenario. The other exemption is the upper airway symptoms for the health surveillance. The incidence does show a decrease over time of approximate 20 % for both scenarios, whereas the prevalence shows only a very limited decrease or even an increase. This is to be expected, given that in both scenarios, individuals that are sensitized receive an exposure reduction. This causes the occurrence of new cases for upper airway symptoms to drop. It also causes workers who have developed upper airway symptoms to stay in this disease state longer since their disease does not progress to more severe symptoms. As a result the prevalence does not show a similar decrease over time.

Discussion

This is one of the first quantitative health impact assessments for occupational respiratory symptoms that incorporates detailed information on occupational exposure and exposure-response relationships. It is also the first attempt to predict the effect of a range of different sector-wide intervention strategies on occupational disease burden. As the results show, the choice for a particular intervention might lead to substantial differences in the occurrence of new cases and overall change in disease burden. Also, the rates at which these changes occur differ substantially. This information can assist policy makers in their choice of intervention program and may also guide discussions on achievable reductions in disease burden related to occupational exposures especially where exposure limits are missing, as is the case for most sensitizing agents.

Complete cessation of exposure, often suggested as the only true effective measure for prevention of (occupational) asthma, is in many occupational settings not possible[12]. However, to decrease the disease burden from occupational respiratory diseases, especially occupational asthma, significant workplace exposure reductions are likely to play an important role[11,36]. Estimating the extent to which risks can be controlled through exposure reductions requires detailed quantitative information on both exposure levels and exposure-response relationships[37,38]. Unfortunately this information is often lacking[22]. The fact that such information is available for the bakery sector, and is explicitly taken into account in our model, enables the performance of quantitative impact assessment for a range of different intervention scenarios.

As this study shows, the impact of any intervention scenario will be modest for work related respiratory symptoms. Nevertheless, a reduction of almost 60% in the disease burden from lower respiratory symptoms and work disabling asthma, predicted for the extensive health surveillance program, is a substantial improvement compared to what was achieved with the most recent intervention in the covenant. The limited effect predicted for most scenarios is not surprising given the fact that recent epidemiological studies could not estimate a “no effect level” for work related allergy and respiratory symptoms related to flour dust exposure[39-41]. This implies that even (very) low exposures will lead to development of sensitisation and respiratory symptoms, although at a low rate. Elimination of the disease burden close to zero would require reduction of exposure levels in the overall population by more than 90%. This is clearly challenging and extremely expensive given the current state of intervention research and efficacy values for most control measures[42]. In order to achieve such goals more ambitious health policies and rigorous interventions are needed in the future.

Reduction of exposure might also have another effect; workers with moderate symptoms might stay in the workforce longer. In this case the number of healthy work years will increase even though the chance of getting diseased within the working life might stay approximately the same for an individual worker. This shows that it is important to take into account different aspects of disease burden (prevalence, time till occurrence, etc.) since the impact on each might differ substantially according to the characteristics of the disease(s) modelled (i.e. etiologic characteristics) and types of intervention.

The number of individual interventions (approximately 400 every 3 years) resulting from the more extensive health surveillance strategy seems feasible to implement. In contrast, the hygienic intervention would involve several thousands of companies within a short time period. This would introduce an almost impossible burden on Dutch occupational health services and large associated costs. Overall, a combination of health surveillance and substantial exposure reduction focussing on high risk workers seems to be the most (cost)effective choice of intervention. This approach should not only focus on sensitized workers, but also include those developing work related upper respiratory symptoms.

Besides the fact that pre-screening of workers only resulted in a limited decrease in disease burden, there also exist strong ethical reasons to oppose to such intervention measures. In general it is not believed to be ethical to exclude a substantial part of the (working) population because differences in susceptibility (atopy) when exposure interventions are possible and other risk factors exist as well. In the European Union regulations in most cases prohibit screening of new employees and excluding workers at high risk from entering a working population.

The intervention scenarios evaluated contain some assumptions that do not fully reflect the real life situation. For example, full implementation of state-of-the-art control measures is unlikely to be achieved in the near future, but the simulation does provide an illustrative insight in the possible impact given the current state of the art of controls. Screening of workers before they have developed symptoms in the health surveillance system will often prove to be difficult and costly, especially when based on serological evaluations. When using, for example, diagnostic questionnaires, the costs might be substantially cut, but using these methodologies will introduce more disease misclassification[43]. Furthermore they are generally based upon symptom related questions so only workers that already have developed certain (mild) symptoms will be identified. The simulations of both health surveillance and pre-employment screening assume the diagnostic tests used are 100% accurate. The misclassification is not easily estimated since a golden standard does not exist. All these assumptions have to be taken into account when making final decisions with respect to the preferred strategy. We emphasized the performance of quantitative health impact assessment to compare different intervention scenarios. Future work should include further refinement of intervention scenarios to better reflect real world situations. In addition, robustness of the results should be explored using comprehensive uncertainty analyses.

With respect to the dynamic model, sensitivity analysis performed in the development phase indicated that the approach is fairly robust to moderate changes and therefore uncertainty in input parameters[18]. Nevertheless, there is a need for longitudinal epidemiological studies, especially for work related (allergic) respiratory diseases. Data obtained from such studies will enable more thorough estimation of transition probabilities and improve our mechanistic insights. Epidemiological studies should also focus on getting more information on exposure-response relationships at low exposures. Currently, studies often focus on high exposed subjects and exposure-response relationships are extrapolated across the whole spectrum of exposure levels assuming, for example, a linear relationship[44]. Information on low exposed individuals will help to get better estimates of exposure-response relationships for these lower exposure ranges. In combination with longitudinal observations such data would lead to better insight in the potential of exposure reduction to reduce the onset of new cases and stop or delay the progression of disease in those already ill.

In conclusion this paper provides valuable information on changes of disease burden related to various intervention programs. Besides health impact, the final decision for a certain intervention strategy will generally be highly influenced by factors like the associated costs/benefit ratio, practical limitations, and support among employers and employees. Only after a careful weighing of all these factors can a definite decision on the preferred intervention design be made.

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CHAPTER 8

General discussion

Prevention and management of occupational diseases

Prevention and management of occupational diseases, including occupational respiratory diseases (i.e. occupational asthma), is complex. Effective design of interventions is a much discussed topic in scientific literature[1-4]. Recently, a variety of papers was published describing the need for a strong evidence base for occupational intervention and prevention programs. Some papers plea for a detailed review of the available scientific literature[5-7], but more generally an integration of data from different disciplines within occupational health research is presented as a condition to (prospectively) obtain quantitative evidence on effective intervention design. Especially the use of quantitative information on exposure levels and exposure-response relationships is presented as vital to quantify impact of primary preventive measures[8-14]. Examples that make use of such information and (prospectively) obtain insight into the quantitative impact of intervention strategies are scarce. An important reason for this is the limited availability of data and methodologies to perform quantitative health impact assessment[15].

Evaluating impact

A strong increase in burden of disease studies has been seen in the occupational health domain in recent years[16,17]. Several of these studies focused specifically on occupational asthma[18,19]. Most burden of disease studies assess the attributable fraction of a disease related to occupational exposure. These studies describe relationships between disease and exposure in a crude manner (yes/no exposed). The risk ratio together with information on exposure prevalence is used to calculate the attributable fraction. The approach generally does not take into account many influential factors like population dynamics, dose-response relationships, disease mechanisms (e.g. different disease states) and (shape of) exposure distributions in the population of interest. As a result of the generic nature of these assessments, they provide only a crude insight into health impact of different intervention strategies. They do not provide a possibility to associate subtle changes in population parameters (e.g. shape of the exposure distribution) with the development of the disease burden over time.

A recent study of Armstrong and Darnton[20] presents a methodology to take into account the shape of the exposure-response relationship and the exposure distribution. This allows a more detailed investigation of the impact of exposure reduction on disease burden. One of the few notable examples of a specific population dynamic model to prospectively evaluate the effectiveness of a health surveillance system is the study of Wild and co-authors[21]. A dynamic disease transition model was used to simulate development of asthma and work disability in a worker population exposed to isocyanates. They did take into account aspects of disease mechanisms (like latency time) and several population dynamics (like turnover of workers). As a result much more realistic assessment of changes in disease burden over time was modeled. Unfortunately, dose-response information on asthma and isocyanates exposure was not available at the time of this study. As a result a single yearly probability is used for disease transitions for exposed workers not related to their level of exposure. Therefore this approach can not be used to assess the disease impact as a result of changes in the shape of the population exposure distribution due to control strategies.

The above shows that several developments did take place in recent years and more emphasis has been paid to quantifying the occupational disease burden as well as providing approaches to evaluate impact of specific intervention strategies. Nevertheless, the applicability of these methodologies is a first step and results might in many cases still need substantial translation before policy makers can use them in their decision making process.

In this thesis some of the characteristics of the above described methods are integrated. The approach presented specifically incorporates some essential elements for quantitative health impact assessment as earlier mentioned;

- Disease mechanisms are modeled in a multi-stage disease model, simulating the transition between disease states over time;
- Population exposure distribution and the exposure-disease relationships are explicitly taken into account in the disease transitions of the multi-stage disease model;
- Population characteristics and dynamics are incorporated in the disease model, taking into account the normal in- and outflow (turnover) of workers, rates of atopy and background rates of sensitization in the worker population;
- Uncertainty of input parameters is explicitly incorporated in the simulation of the health impact.

The result is that the presented approach provides more flexibility and can evaluate health impact of a large diversity of intervention strategies influencing population characteristics (e.g., health surveillance and screening) and exposure distributions (e.g., occupational hygiene intervention). The information obtained from the model not only includes changes in disease burden but also provides information on trends in other population characteristics over time (i.e. duration of working life, change in number of healthy working years, etc.). Finally, the model can be used to evaluate implications for specific sub-populations; e.g. high risk workers or workers from a specific part of the exposure distribution (high exposed). As a result a more elaborate evaluation of the impact can be made and results will better assist final decision making on the appropriate intervention design and achievable goals.

Exposure assessment and exposure control

Detailed information on individual exposure levels as well as the population exposure distributions were part of the studies presented in this thesis. Exposure data are commonly used to assess effectiveness of control measures[2,22-24]. To our knowledge, the integrated use of exposure data to assess; 1) effectiveness of exposure control measures, 2) develop predictive exposure models for use in epidemiological analysis and 3) estimation of health impact of intervention strategies, is new.

We performed a probabilistic assessment of the impact of intervention on the population exposure distribution (see Appendix)[24]. This study showed the potential of using detailed exposure data in combination with probabilistic methodologies (Monte Carlo simulations) to show (subtle) shifts in the exposure distribution resulting from interventions. In our opinion, performing such a detailed analysis of impact on exposure will often proof to be the most challenging but also an important task within a quantitative health impact assessment.

This study shows the importance of having good quantitative and qualitative data if an evidence base for effective interventions is needed. This not only includes information on exposure and disease but especially also on effective exposure control measures. This will often be one of the major challenges and deserves continued attention within the occupational hygiene field. A good example of a literature review to disclose information on exposure control efficacy and make them available is a recently developed Exposure Control Efficacy Library (ECEL)[25]. In addition to measurement studies such initiatives might provide information where necessary.

There are several possibilities to further improve the value of the used exposure data in future quantitative health impact assessments. An important element that was not optimal in our study is the consistency between different studies in their design. Although this will often be beyond the influence of researchers, especially when using historical data, it would have increased the usability of the data, especially with respect to assessment of control effectiveness. On the other hand the use of the peak exposure measurements partially filled this gap.

The limited availability of exposure control efficacy information might often pose to be an important limitation to translate information on needed exposure reductions to a detailed plan for control. Even in the case of bakeries where large databases were available, the intervention scenario assuming 90% exposure reduction for intervention on individual workers can not be completely underpinned with an actual exposure control plan. In many cases this will have to be tailored interventions performed by a specialized occupational hygienist. In general, experience from the field suggests that such reduction will unlikely be reached without including the use of personal protective equipment during certain activities with peak exposures[26].

Conclusions for the bakery sector

The covenant in the bakery sector certainly represents one of the most extensive with respect to monitoring of occupational exposure and health. The evidence base with respect to occupational exposure determinants and exposure-response relationships is probably one of the strongest for Dutch occupational populations. In this respect the impact of the covenant on occupational exposure levels is clearly disappointing. The studies show that exposure processes are complex, especially in the small and medium sized enterprises, and therefore not easily reduced. Situations differ highly between the different sectors and within sectors between companies and individual workers. As a result policy makers have to shift to more rigorous intervention strategies to increase the effectiveness and truly establish a decrease in the observed disease burden.

This thesis indicates that most effects can be expected from a tailored intervention approach in first instance aimed at workers with high risk of developing severe symptoms. No readily available control strategies are available but the information from chapter 2, 3 and 5 do give an indication of possible control measures to implement and what issues to focus on with regard to workers education. Overall it is believe that the information presented in this thesis combined with the planned development of a methodology for cost-benefit analysis of the different intervention strategies provides a solid and detailed evidence base for further actions in the bakery sector and strong guidance for the other flour processing sectors.

The fact that the combination of identification of high risk individuals and individual exposure reductions seems to be the most effective intervention strategy does raise several issues. Such a tiered approach might imply denial of hygienic care for those individuals not selected and might also conflict with other principles in occupational health, like the ALARA principle (As Low As Reasonably Attainable). The design also means that workers will remain at high risk of becoming sensitized since only after being sensitized or symptomatic is someone labeled at high risk and thus included in the intervention program. Furthermore performing interventions on an individual worker might proof to be inefficient compared to performing these actions on a (small) company or department level once high risk workers are identified. This would prevent occupational hygienists from having to visit sites multiple times. The detailed discussion of these ethical and practical issues is beyond the scope of this thesis. Nevertheless it is an inextricable part of the final decision making process and plays a decisive role with respect to acceptability of an approach by policy makers.

Model limitations

Figure 1 in the introduction of this thesis presented the framework for performing quantitative health impact assessment. There are some limitations and possible improvements for several of the components of the presented methodology that will be discussed here. One of the major constraints especially for the development and validation of the dynamic population model is the limited availability of longitudinal data. This limits the possibility to obtain insight into population and disease mechanisms that are currently not in our dynamic population-based model. It also prevented us from directly estimating disease transition parameters and validating the model assumptions with a longitudinal dataset.

An important factor currently not taken into account in our model is remission from disease[27]. Very little information is available on remission from sensitization or asthmatic symptoms related to exposure reductions[28]. Where data is available it is primarily from follow up studies looking at (occupational) populations removed from an exposed environment[29] but some evidence exists that exposure reduction can also lead to substantial remission[30]. The fact that this element was not taken into account in our model could potentially lead to bias when evaluating interventions. Since longitudinal data is not available, alternatively the model itself could be used to study the potential effect in a similar way as was presented by Wild et al.[21]. Expert judgment could be used to produce estimated ranges for missing input parameters after which sensitivity analysis can provide insight in the importance of these parameters and the way in which they might influence our simulated outputs depending on the chosen input value(s).

The disease definitions in the model are currently based upon questionnaire information. Although using generally accepted symptom questionnaires[31], the use of self reported information has a higher potential for error, leading to bias in the predicted outcome of the model. An improvement would be to include more objective defined disease outcomes including measured parameters of ill health, like clinically diagnosed workers asthma. For work disability (or work disabling asthmatic symptoms) no data was available to underpin our estimates for the transition probabilities. Obtaining quantitative information on this, preferably related to exposure, would be a substantial improvement. We foresee that in the near future data obtained from the subpopulation of workers in the covenant that is currently referred to a lung clinic for more thorough medical evaluation could be used to update the model.

Future developments

Data rich vs data poor situations

Obviously, data to develop a model along the lines presented in this thesis will only be available in a limited number of occupational settings. Future research should investigate the usefulness of our methodology in less data rich situations where inputs will be more strongly determined by expert judgment and thus likely have higher levels of uncertainty. Insight into the performance of dynamic population-based models in such situations will determine how generic its usability will be. An explicit treatment of uncertainty in these situations will be a prerequisite.

Other applications

This thesis did not cover the potential of applying the model to other occupational populations exposed to flour dust. In theory there is no reason why this would not be possible given that information on the exposure distributions is available. A requirement is that the population characteristics are approximately similar. If, for example, the dose-response relationships differ substantially to the once used to develop the model the estimated probabilities for disease transition currently in the model might not be valid[31,32]. If specific data on exposure-response relationships are available, re-estimating the probabilities and adapting the model would be fairly straightforward.

The methodology presented seems to be especially useful in situations where occupational exposure can not be avoided. Furthermore, it provides a modeling approach for occupational diseases that have a long latency period and complex disease mechanism with various stages (e.g. allergic diseases). In situations where we deal with exposure-disease relationships for which an occupational exposure limit is not available, insight in impact on disease burden will be a requirement for any rational decision making with respect to required exposure reductions.

Several studies were recently performed looking at occupational causes of Chronic Obstructive Pulmonary Disease (COPD) and the associated disease burden[33-36]. These and other studies might provide a good starting point for exploring the possibility to assess health impact of (changes in) work related exposure on the COPD disease burden. Although in this case confounding factors, especially smoking, should be explicitly taken into account in any health impact model focusing on occupational exposures.

In recent years substantial work has been performed with respect to occupational iso-cyanate exposure and related occupational disease[37-39]. The available data might enable incorporation of explicit exposure-disease relationships that would provide a valuable addition to the earlier mentioned work of Wild et al.[21].

Cost-Benefit analysis

Some examples of studies are available that perform cost-effectiveness of general intervention scenarios based upon the global burden of disease studies[40-43]. The results of these studies can provide guidance to policy makers (e.g., national governments, UN WHO) on emerging issues and priorities in the global or national health programs. As was discussed earlier, the approach used in these studies has limited value with respect to evaluating different intervention scenarios with more subtle impact on population exposure levels.

The economic considerations in decision making in occupational health is getting increasing attention since available funds for the implementation of interventions is limited[44]. Insight into the costs and benefit ratio of different intervention strategies enables comparisons of the interventions from an economic point of view. To be able to perform detailed cost-benefit analysis for specific occupational diseases the results from our quantitative health impact assessment provide a good starting point for calculating the benefits. This can be done in a relatively generic approach pinning overall costs on disease cases. For example, a recent report from the Health and Safety Executive estimated the total lifetime cost to society in the UK to be between 121,000 and 176,000 GPB for a male worker with occupational asthma[45]. We propose a more detailed approach that will split up costs and benefits for employers, employees and society. The ability to perform such a differentiated cost-benefit analysis will improve transparency in discussions among policy makers. Comparing different strategies can then lead to a maximization of the cost-benefit-ratio given the available funds[40].

Conclusions

We succeeded in this thesis to integrate data from a variety of studies and used this to develop a methodology, the population dynamic model, which can be used for quantitative health impact assessment in occupational settings. The methodology presented in this thesis, although not perfect, provides an opportunity to policy makers and researchers to prospectively get insight into the health impact of different intervention scenarios. Compared to the classical more generic approaches currently used, this method provides more flexibility and detail to quantitatively evaluate different intervention designs.

The different studies in this thesis illustrate the importance and complexity of creating a good quantitative evidence base for occupational intervention. In many occasions, like in many of the Dutch covenants, the evidence base for effective interventions remains weak. We showed how the resulting intervention program, which focused mainly on educational tools and providing generic information on control measures, lacked structured support and facilitation of implementation of effective exposure controls. As a consequence the change in disease burden in the bakery population was very limited.

In chapter seven we evaluated a range of alternative intervention strategies and were able to show that a more rigorous design of the intervention strategy will likely result in a much more substantial reduction in disease burden. This implies that if this information would have been available at the start of the covenant other choices might have been made resulting in a much larger impact. Of course, the true effect of any long term intervention program will have to be established through monitoring programs. As a result of the progressing knowledge adaptations might constantly have to be made as factors change in the populations of interest continuously.

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APPENDIX 1

A probabilistic assessment of the impact of interventions on the exposure to antineoplastic agents of oncology nurses

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Abstract

Objective: The main goal was to investigate the potential of a probabilistic approach for exposure assessment and use this information to evaluate the impact of a complex of policy actions/interventions on dermal exposure to antineoplastic agents among oncology nurses. Central theme of this study was to make optimal use of existing data, supplemented only with limited additional information from a questionnaire survey.
Methods: A task-based exposure model was used to estimate dermal exposure of the hands among oncology nurses in non-academic hospitals in The Netherlands. Monte Carlo simulation was used to integrate information from available (exposure) studies and generate exposure distributions for the total population of oncology nurses in both pre- and post-intervention situation. Graphs and descriptive statistics of the simulated exposure distributions were used to evaluate trends in population exposure.
Results: The inventory showed that important intervention occurred in the preparation and administering of antineoplastic agents and in the handling of urine. Hardly any changes were identified in de nursing tasks. The use of gloves seemed to have decreased for a number of tasks. The results of the analysis show that the interventions did not affect the median exposure. However frequencies of occurrence of individuals with very high and very low total dermal exposures decreased substantially in the post-intervention situation. Analysis of the effect of pregnancy showed that pregnancy is very unlikely to influence exposure or any of the key input variables.
Discussion: The present study shows that the probabilistic approach adds valuable information to deterministic exposure assessment especially when extrapolating data on a subpopulation to populations of individuals at large.
The results presented in this paper show that the complex of identified changes in the past decade in Dutch non-academic hospitals resulted in changes in the exposure distribution of antineoplastic agents among oncology nurses.

Introduction

Trends in exposure have been observed in occupational settings at the level of sectors or entire industries for a substantial number of years now[1-6]. Except for a few cases[1] the general perception is that we are lacking in our knowledge of underlying factors that drive these trends[7,8]. When looking at small scale intervention studies, Goldenhar and Schulte, Zwerling et al. and more recent Roelofs et al. concluded that many of these studies showed methodological shortcomings resulting in an inability to perform, and evaluate the impact of specific interventions in a structured and effective manner[9-12]. Obviously, the evaluation of industry wide interventions involving a wide spectrum of control measures is even more an untouched topic in occupational health research. A rare example of such a study is the 'Minnesota Wood Dust Study'[13-15]. In this study effectiveness of different levels of intervention on wood dust exposure was studied using a group randomized trial looking at both quantitative and qualitative outcomes.

There is a need for understanding exposure trends in branches or industrial settings, if we want to effectively evaluate or predict the impact of interventions at population level. In the Netherlands this is stimulated by the introduction of covenants which are agreements between employers' organisations, trade unions and the government with the aim to improve working conditions in specific branches[16]. Covenants can comprise detailed agreements to reduce exposures, introduce exposure control measures or inform and educate workers. In the context of these covenants effectiveness of implemented control measures receives special attention.

Occupational exposure to antineoplastic drugs is a focal point of both the covenants for general and academic hospitals in the Netherlands. As a precursor to these covenants, several policy actions and research initiatives have taken place in order to reduce exposure to antineoplastic agents among hospital personnel. These research initiatives and policy actions presumably led to a strong increase in the awareness of the potential risk of occupational exposure to antineoplastic agents and the need for interventions to control exposure. The actual implementation of control measures and impact on the exposure levels in the population of nurses at large, has never been evaluated in a structured manner.

The main goal of this study was to investigate the potential of a probabilistic approach to assess exposure, and use this information to evaluate shifts in the population exposure distribution due to interventions in the past decade. Central theme of this study was to make optimal use of existing (exposure) data for both pre and post intervention periods, supplemented only with limited additional information from a questionnaire survey on present task frequency and glove use. A simple task based exposure model in combination with Monte Carlo (MC) simulations was used to integrate this information[17]. Exposure distributions were generated for the population of oncology nurses 'at large' for both the current situation and the situation one decade ago. In Monte Carlo simulations, distributions of output variables (in this case exposure to antineoplastic agents) are simulated by drawing random values from distributions of input variables, according to a given algorithm (in this case a task based exposure model) that describes that output variable. For logistical reasons academic hospitals did not participate in this study and results only directly apply to the population of oncology nurses working in non-academic (or general) hospitals.

Material & methods

The population of interest for this study are oncology nurses working in non-academic Dutch hospitals on departments with activities with antineoplastic agents or with patients receiving chemotherapy, and are at risk of exposure to antineoplastic agents. An overview was made of research and policy actions that occurred in relation to antineoplastic agents' exposure between 1990 and 2004. To get an overview of actual implementation of interventions resulting from the performed studies and policy actions we asked nurses to indicate specific changes in their work performance in the past decade related to antineoplastic agents. Additionally some key persons from hospitals and branch organisations were asked to indicate what changes they observed in general in work performance around antineoplastic agents. All this information was used to create an overview of the most important interventions that might have influenced exposure to antineoplastic agents and the period in which they took place. Information with respect to input data was obtained from existing exposure studies and an additional questionnaire survey among a random sample of nurses from our study population performed in this study[18-25]. In order to study the impact of policy initiatives taken the last decade, Monte Carlo simulation was used to generate population exposure distributions for pre- and post intervention situation.

Dermal exposure model

Equation 1 shows the model for dermal exposure of the hands to all antineoplastic agents. Since work pattern vary slightly between days within a week we used a cumulative exposure over a week to ensure a representative time frame for long-term exposure.

$$E = \sum_t (l_t \times e_t \times (1-(g_t \times p_t)) \times f_t) \qquad (1)$$

Where,

E = total dermal exposure of the hands (ng/week)
l_t = task performance (yes/no)
e_t = potential dermal contamination after performing task t (ng)
g_t = glove use during tasks t (yes/no)
p_t = glove protection at task t (%)
f_t = frequency of task t (times/week)

The tasks taken into account in the model are: preparation of antineoplastic agents, administering of chemotherapy, washing a patient, changing bedding, handling patient's urine and cleaning activities. A short description of each task is given in table 1.

Table 1. Description of tasks taken into account in the exposure model

Task	Description
Preparation	Incorporated activities like dissolving or diluting antineoplastic agents in vials and transferring the contents (high concentrated antineoplastic agents) between vials and syringes or IV bag. Exposure during these activities might occur through leakage or via contaminated objects
Administering	The tasks incorporates connection and disconnection of the IV system to the patients central IV system (if present) and other activities like unwrapping the IV system if packed and disposing it after administration. Exposure can occur through contact with contamination on the IV system.
Washing patient	Washing a patient that received chemotherapy within the past 48 hours with use of a bowl of water and washing towel. Patients sweat is known to be contaminated with antineoplastic agents.
Changing bedding	Changing of bed sheets from patients that have received chemotherapy within the past 48 hours. Bed sheets are contaminated through patients' sweat or other excreta.
Handling urine	Can incorporate transporting the pan/urinal emptying it in the washing machine or additional handlings like weighing the pot/urinal or transferring urine to a measuring cup. Exposure can occur through splashes or deposition of aerosols during handling or through contact with contaminated objects.
Cleaning	Includes cleaning of all known potentially contaminated object, these can be in the (bath)room of the patient or in the general cleaning room where e.g. pots and urinals are stored and cleaned.

Input data

A short description of all model parameters is given in table 2. Below a detailed description of the different studies and the extracted data is given as well as imputations and extrapolations that had to be performed for missing data.

Table 2. Description of model variables and data sources for input data

Input variable	Description	Distributions used in the simulation	Source	
			1990-1997	2003-2004
Task performance	Gives whether or not a certain task is performed for each iteration (scenario). Probability depends on the % of nurses performing the task in the study population (table 3)	Binomial ({1,0}; {#performed, #not-performed})	Peelen et al. 1999 [21]	Questionnaire survey conducted this study
Task frequency	For each iteration a value is generated (times/week) for each task from its respective input distribution	Lognormal (mean, standard deviation)	Peelen et al. 1999 [21]	Questionnaire survey conducted this study

Potential dermal contamination	The dermal contamination of the hands or gloves. At each iteration a value is drawn from the binomial to decide if exposure is above or below LOD (table 4). Secondly an exposure value is drawn from the respective distribution.	Binomial ({1, 2}; {#samples<LOD[1], #samples>LOD})
		1=Uniform (0,LOD)
		2=Lognormal ({mean, std}; truncated{LOD,})
			Fransman et al. 2005[2] [24]
			Peelen et al. 1999[3] [21]
				Fransman et al. 2005 [24]

Glove use	Gives whether or not gloves are either worn for each iteration (scenario). Probability depends on the % of nurses wearing gloves in the study populations (table 5).	Binomial ({1,0}; {# wear gloves, #no gloves})	Peelen et al. 1999 [21]	Questionnaire survey conducted this study
Glove protection	The protective effect of gloves is expressed as being between 0 – 100 % of potential exposure.	Triangular (min, mean, max)	Fransman et al. 2005 [24]	Fransman et al. 2005 [24]

[1] Limit of detection
[2] for tasks; washing patients, changing bedsheets, cleaning
[3] for tasks; preparation, urine handling, administering

Pre-intervention

Data on model parameters for the pre-intervention situation were obtained from a Dutch epidemiological study on reproductive effects among hospital personnel[21]. The dataset contained measurement data of the dermal exposure of the hands to cyclophosphamide, measured on gloves for three tasks; preparation, administering and handling urine. The measurements were performed in 1997 in seven different hospitals. For three tasks (washing patients, changing bed sheets, cleaning) no measurement data on dermal exposure were available. Data from the study of Fransman et al. used for the post-intervention (mentioned below) were extrapolated and also used for the pre-intervention period[24]. The results of our inventory on changes in work characteristics discussed later in this paper showed that no large changes occurred in these tasks suggesting no large difference in dermal exposure for these tasks.

A second dataset from the epidemiological study contained questionnaire information from a large sample of nurses (N=5546) with a response rate of 79% (n=4393)[21]. From this dataset nurses working in non-academic hospitals on departments where antineoplastic agents were used were selected. 507 Records of the questionnaire dataset contained sufficient information to be used for the analysis. From this population information was available on work performance characteristics, task frequency and glove use. The questionnaire information was related to activities with all antineoplastic agents. Each subject had provided this information for the first month of their most recent pregnancy or for the period they were trying to get pregnant. The majority of the population (n=345, 69%) provided information from a one-month period between 1995-1997. Since this questionnaire dataset only contained information from nurses who were pregnant or were trying to get pregnant, we evaluated the potential impact of pregnancy on exposure to antineoplastic agents. Because only the post intervention dataset contained data on both pregnant and non-pregnant women, these data were used to perform analysis with respect to the effect of pregnancy on the exposure to antineoplastic agents. The distribution for dermal exposure was simulated for the (sub) population of nurses being pregnant at the time of answering the questionnaire. This distribution was compared with the exposure distribution of the total population.

Post- intervention

For the post-intervention situation data on dermal task exposure of the hands was obtained from a dataset collected partially within a large European study RISKOFDERM described by Fransman et al.[24]. This dataset contains glove and hand wash samples, supplying data on both potential and actual exposure of the hands to cyclophosphamide for four tasks (washing patients, changing bedding, handling urine and cleaning). All samples were obtained from nurses during their normal working activities. Measurement data were not available for dermal exposure during administering. Dermal exposure estimates were imputed using data from surface wipes of IV infusion bags.[24] It was assumed that a 100% transfer occurs from the bags onto the hands, creating a worst-case scenario for the dermal contamination during administering.

Information on work performance, task frequency and glove use for the post-intervention situation was obtained through an additional questionnaire survey. A random sample of 33 hospitals was selected stratified for size and geographical location, of these 23 (70%) agreed to participate. In these hospitals 1863 nurses were selected for participation in the questionnaire survey. A total of 999 nurses completed and returned the questionnaire resulting in a 54% response rate.

Glove protection in our model was assumed to be equal for both time periods and was estimated using the dermal exposure data from Fransman et al[24]. The ratio of actual and potential exposure was calculated. This ratio was used as a measure of the protective effect of gloves (% of contamination 'blocked' by the gloves). No data were available for glove protection during administering. Protection was assumed to be in the same range as for preparation so a comparable distribution was imputed for protection during administering of antineoplastic agents. In our study cyclophosphamide was used as a marker; estimates of dermal exposure were assumed to be representative for antineoplastic agents in general during the performance of the measured tasks.

Input distributions

Distributions of input data for model parameters were determined using descriptive analysis performed in SAS v8.2 (SAS Institute) and the software package Best Fit (Palisade Corporation) and information from scientific literature. Dermal exposure, in the simulation, is for each task represented by three distributions to take into account the limit of detection in the measured data. A uniform distribution represents data points below the limit of detection (LOD) with zero as lower bound and the limit of detection as upper bound. Data points above LOD are represented by a lognormal distribution based on the geometric mean and the geometric standard deviation of the values above LOD in each dataset. A third, binomial distribution is used to simulate the probability of sampling a value below or above the LOD (based on the number of measurements above LOD in each dataset). Table 2 gives the distributions used for all input variables.

Data analysis and simulation

The model for total dermal exposure of the hands and input distributions for all model variables were programmed into an Excel (Microsoft Corporation) worksheet. The total exposure was simulated using @Risk 4.5 (Pallisade Corporation), an add-in for probabilistic modelling and simulation in Excel, using Monte Carlo simulations[26]. A stable output distribution for total exposure was obtained with 10000 iterations of the model. Correlations between input variables were studied using PROC CORR procedure in SAS v8.2. When correlation between input variables is observed @Risk offers the possibility to run MC simulations taking into account a correlation matrix. Population distributions of the actual dermal exposure to antineoplastic agents accumulated during a week were created for the pre- and post-intervention situation. Simulated data were then transported to Excel to create cumulative probability plots (on a log scale for exposure). Percentile values were generated to study shifts within the total range of the population dermal exposure distributions.

Uncertainty
A probabilistic uncertainty analysis was performed to obtain insight into effects of imprecise input parameters. Since datasets reflecting dermal exposure contained the smallest number of data points and incorporated the largest variability, the uncertainty analysis focussed on these input parameters. First, bootstrapping of the original data for dermal exposure was performed in SAS v8.2 (SAS Institute) for all datasets[27,28]. One hundred bootstraps were performed for each task, creating a hundred datasets of equal size compared to the original dataset. Secondly one hundred Monte Carlo simulation of total dermal exposure were performed using one set of bootstrapped input datasets for each simulation. This resulted in 100 different output distributions for total dermal exposure of the hands.

Scenario analysis
To explore the possibility of performing a scenario analysis we performed a prospective assessment of a fictive intervention scenario, in which we assumed that the use of gloves could be increased for all tasks to 90% of the population. The input distributions for glove use were changed and a Monte Carlo simulation of 10000 iterations was run. Data were then analysed as described above and output distribution plots were created to look at differences in the exposure distributions.

Results

Policy, research initiatives and interventions
Figure 1 shows the timeline with the most important studies and policy actions that occurred in the past fifteen years in the Netherlands. Antineoplastic agents first became a topic in occupational hygiene in the Netherlands with the introduction of the first guidelines (1992). Around this time focus was primarily on preparation of antineoplastic agents and the health risks of pharmacy personnel. From 1997 onwards the focus more and more shifted towards nursing staff and the patient as a possible source of exposure and work environment contamination. The results of the inventory on work characteristic and interventions from the questionnaire survey indicated that nurses experienced changes in several tasks. Preparation was largely eliminated from the wards and moved to the pharmacy. For administering of antineoplastic agents, most hospitals introduced the use of closed infusion systems to decreasing the chance of highly concentrated antineoplastic agents to enter the (work) environment during this task. When handling urine the use of different work protocol and technical equipment like automated urinal and pot washers was introduced in most of the hospitals. For the other tasks no obvious changes (e.g. control measures) were reported. Most of the changes occurred in the late 90’s after the results of the epidemiological study were published and again after the introduction of the guidelines in

2001[21]. The effect of the first guidelines primarily was the complete elimination of preparation of antineoplastic agents.

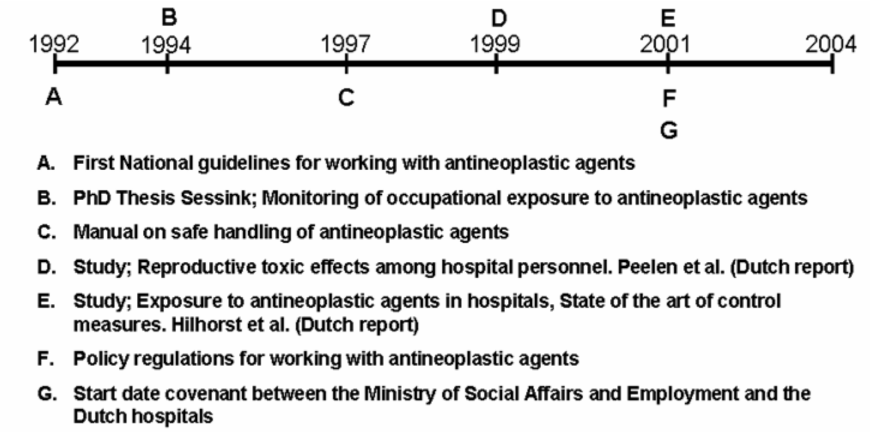

Figure 1. Timeline of activities between 1990 and 2004 related to nurses exposure to antineoplastic agents

Table 3. Input distribution data for task performance and task frequency

Variable	Task performance				Task frequency times/week			
	Pre-intervention		Post intervention		Pre-intervention		Post intervention	
Task	**Yes***	**No**	**Yes**	**No**	**GM†**	**GSD‡**	**GM†**	**GSD‡**
Preparation	6%	94%	0%	100%	2.17	3.11	-	-
Administering	52%	48%	76%	24%	2.26	3.18	3.62	2.71
Washing patients	54%	46%	53%	47%	2.32	2.82	1.88	2.29
Changing bed sheets	54%	46%	78%	22%	1.74	2.55	3.13	3.11
Handling urine	46%	54%	76%	24%	2.22	2.98	5.24	2.25
Cleaning	53%	47%	58%	42%	1.62	1.76	2.57	2.57

* Percentage of nurses in the study population performing this task
† Geometric mean of task frequency per week
‡ Geometric Standard deviation for task frequency per week

Input data

Table 3,4 and 5 give data of input distributions for all model variables. The bold values in the tables are the imputed values based on surrogate data and/or expert judgement as explained in the methods section. Table 3 shows the percentages of nurses in the study populations both pre- and post intervention that performed the six identified tasks. It also gives the geometric means and geometric standard deviations of the task frequency in times per week. The most important change is that preparation has completely disappeared from the work contents of oncology nurses. The frequency of other tasks except for washing patients increased. Correlation between input variables was only observed for task frequencies correlation coefficients being all below 0.6 for both pre- and post intervention data. Incorporation of a correlation matrix in the MC simulation for task frequency did not show large changes in the simulated output distributions.

Table 4 shows the values used to estimate the input distributions for the dermal exposure of each task. The geometric means and the geometric standard deviation are the parameters of the lognormal distribution based on the measurements above LOD from the respective input datasets of dermal exposure, as explained in the methods section. The column 'LOD' gives the respective Limits of Detection for each dataset, which was also set as the upper bound of the uniform distribution representing the measurements below LOD in our simulation. The last column in each section (pre- and post-intervention) indicates the percentage and number of samples above LOD and the total number of samples in each dataset. The mean values in Table 4 show that dermal contamination has decreased substantially for administering and urine handling. For administering the imputed data related to contamination of infusion bags also indicates a decrease in dermal exposure during this task.

Table 4. Input distribution data for dermal exposure, data on potential dermal exposure of the hands

	Pre-intervention exposure				**Post intervention exposure**			
Task	**GM†**	**GSD‡**	**LOD§**	**>LOD (total)¶**	**GM†**	**GSD‡**	**LOD§**	**>LOD (total)¶**
Preparation	52338	2.25	10	100% (8)	-	-	-	-
Administering	1078	3.99	10	52% (29)	**390**	**3.30**	16	**25% (20)**
Washing patients	**217***	**1.90**	**53**	**93% (28)**	217	1.90	53	93% (28)
Changing bed sheets	**82**	**1.80**	**53**	**61% (28)**	82	1.80	53	61% (28)
Handling urine	1030	3.06	10	64% (11)	70	1.75	53	54% (26)
Cleaning	**264**	**2.08**	**53**	**53% (19)**	264	2.09	53	53% (19)

* Bold values in the table indicate imputed data
† Geometric mean of potential dermal exposure of hands (in ng/ performance)
‡ Geometric standard deviation of potential dermal exposure of hands
§ Limit of detection in ng
¶ Number of samples above the limit of detection (total number of samples)

Table 5 shows that use of gloves has increased for cleaning and handling urine with respectively 24% and 8%, for administering there was a small decrease of glove use from 89% to 81%. A more substantial decrease of glove use was observed for the nursing tasks washing patients and changing bed sheets with more than 30% decrease of glove use.

Table 5. Input distribution data for glove use and glove protection

Variable	**Glove use**				**Glove protection**		
	Pre-intervention		**Post-intervention**				
Task	**Yes†**	**No**	**Yes**	**No**	**Mean‡**	**Min§**	**Max¶**
Preparation	84%	16%	-	-	0.93	0.74	0.99
Administering	89%	11%	81%	19%	**0.90***	**0.75**	**0.99**
Washing patients	67%	33%	30%	70%	0.83	0.40	0.97
Changing bed sheets	67%	33%	36%	64%	0.52	0.07	0.80
Handling urine	82%	18%	90%	10%	0.46	0.09	0.91
Cleaning	35%	65%	59%	41%	0.92	0.81	0.98

* Bold values in the table indicate imputed data
† Percentage of nurses in the study wearing gloves at this task
‡ Most likely value for glove protection in this case the mean was chosen
§ Minimum value for the protection of gloves
¶ Maximum value for the protection of gloves

Monte Carlo simulations of total dermal exposure of the hands
Figure 2 shows the cumulative probability plots of distributions of the simulated total dermal exposure of the hands on a weekly basis for the population of oncology nurses at large for both the pre- and post-intervention situation. The exposure is shown on the x-axis (log scale) in ng/ week. The plot shows that the median value of exposure has hardly changed being approximately 650 ng/week. Exposure to antineoplastic agents in the pre-intervention situation showed a larger variability than post intervention, where exposure seems to have converged towards the median exposure. In other words, the numbers of individuals with extreme 'high' - and 'low' values of total dermal exposures have decreased substantially. This is also shown by the 4-fold increase in the 10th percentile for the two distributions, from 31 to 124 ng/week and the 2.5 fold decrease of the 90th percentile from 8200 to 3200 ng/week. Comparison of cumulative probability plots for the (sub) population of pregnant nurses (not presented in this paper) and the total population of oncology nurses showed that the two graphs almost completely overlap. Hence pregnancy is very unlikely to influence exposure or any of the key input variables.

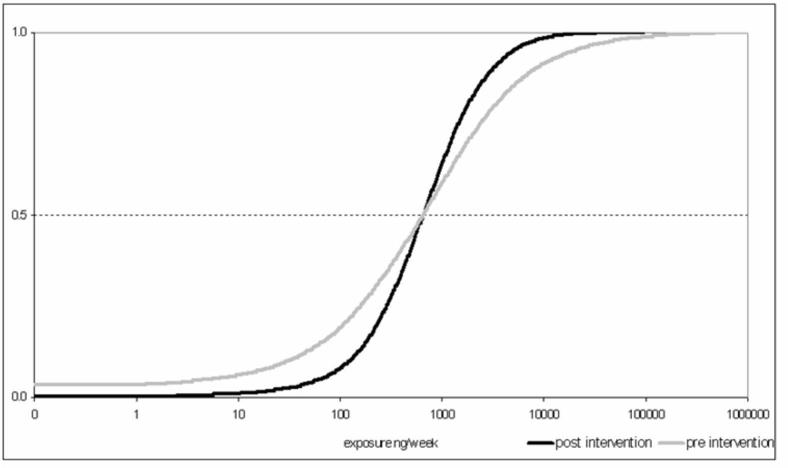

Figure 2. Distribution of dermal exposure for the total population pre- and post intervention

Uncertainty analyses

Figure 3 & 4 show the cumulative probability plots of the population distributions for the pre- and post intervention situation with their respective uncertainty bands caused by uncertainty in our dermal contamination data. When creating an overlay plot of both distributions (not presented), it shows that there is a large overlap between the uncertainty bands of both distributions. Nevertheless the tails of the post-intervention distribution falls outside the pre-intervention uncertainty area.

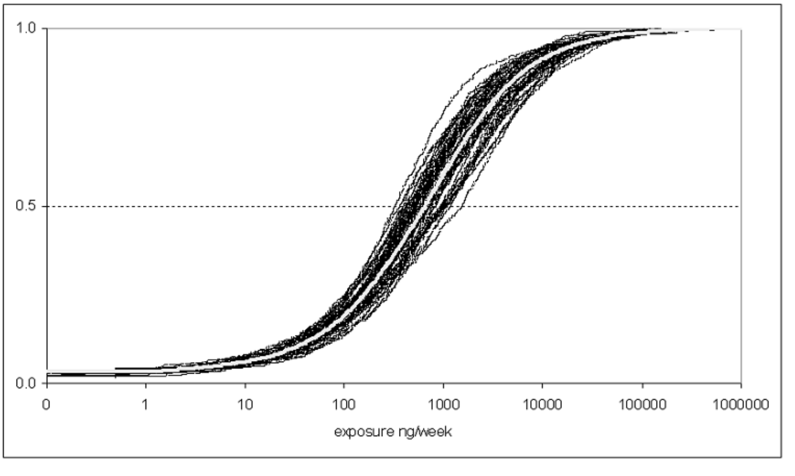

Figure 3. Uncertainty plot of the distribution of dermal exposure for pre-intervention situation

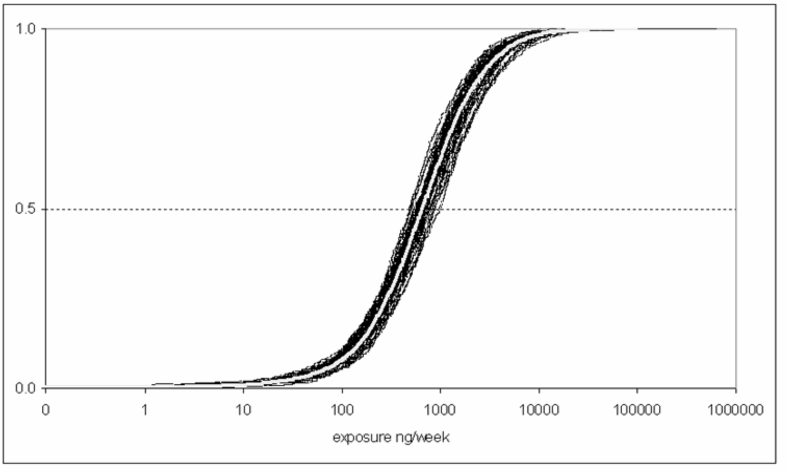

Figure 4. Uncertainty plot of the distribution of dermal exposure for the post-intervention population

Scenario analysis

The simulated scenario of increase of glove use to 90% during all six tasks results in a shift to the left of the exposure distribution. The median weekly dermal exposure of the hands decreases on average with approximately 30-percent from 650 to 432 ng/week. At the left tail of the distribution only a small decrease is observed as expected. The 90th percentile of exposure decreases almost two fold from 3200 to 1775 ng/week.

Discussion

The cumulative distributions of the population dermal exposure to antineoplastic agents indicate that a trend occurred over the past decade. The elimination of the highest exposure values is primarily associated with the complete disappearance of preparation from the work package. The strong decrease in dermal exposure when handling urine or administering antineoplastic agents, causes a further decrease of the number of oncology nurses with 'high' exposures. A shift towards fewer nurses with 'low' exposures seems to be associated with the centralisation of cancer treatments and patients on specialized oncology wards, which was indicated by many hospitals to have occurred over the past decade. The observed decrease in glove use, when washing patients and changing bedding, is contrary to what was expected in light of the suspected increase in awareness of potential exposure. No reason for this could be found. One may assume that these results will also apply to nurses performing the same tasks in academic hospitals. In general, work performance and characteristic do not vary substantially between academic and general hospitals in the Netherlands.

The use of a probabilistic approach enabled the integration of data from many different sources to simulate the exposure distribution for the population at large. This provided the opportunity to take into account the full range of potential exposure scenario's and exposure levels and study the trend in the population exposure distribution. Nevertheless, some issues have to be considered. When performing Monte Carlo simulations it is important that 'all' exposure scenarios based on possible combinations of input variables can be generated, especially when running a high number of iteration[29]. This means that extremely high exposures might be generated due to the combination of rare events and the choice could be made to restrict the model (e.g. by truncation of input distribution). In our case there were no reasons to restrict our model. Correlation between input variables also plays an important role in generating realistic exposure scenarios. In our analysis correlations were only observed in task frequencies. Incorporation of correlations matrix into our MC simulation did not show any large change in our simulated output distribution. Eventually the 'extreme' scenarios generated, although not very likely to occur, were not eliminated from the analysis.

The simulation could have been biased in several ways. First, six tasks were taken into account in our exposure model while exposure might also occur outside these tasks. Second we only assessed the dermal exposure of the hands. Nevertheless both national and international studies show that the six tasks considered are responsible for the majority of exposure. They also show that the primary route of exposure is via the skin with more than 90% of exposure found on the hands[18,22-24,30-32]. Another factor for potential bias was that all dermal exposure measurements focussed on exposure to cyclophosphamide. Since no information is available on exposure pattern for other antineoplastic drugs, the exposure pattern of cyclophosphamide was assumed to be a representative for dermal exposure of the hands to antineoplastic drugs. The results of the available measurements were used in our assessment to estimate dermal exposure of the hands to antineoplastic agents in general. A fourth important factor introducing uncertainty is the fact that we lack data for some variables of our model for one or both of our simulations. For our pre-intervention simulation, data were not available on dermal exposure during the tasks washing patients, changing bed sheets and cleaning. As mentioned earlier, the results of the questionnaire survey did not indicate important changes (control measures, technical) with respect to these tasks, therefore dermal exposure was assumed to be equal for pre-intervention and post-intervention situation.

For the post-intervention situation no data were available for dermal contamination when administering. Exposure through leakage of the intravenous infusion systems is generally believed to be very minimal after introduction of 'closed' infusion systems and strict work protocols. Therefore exposure during this task is believed to mainly occur through transfer from contaminated IV infusion bags. By assuming a 100% transfer we created a worst-case scenario overestimating the 'true' dermal exposure. A last source of uncertainty introduced by lack of data is the fact that no specific data were available on glove protection for the pre-intervention. It might have been that an increase in awareness did influence the protective effect in a positive way. Yet this could not be incorporated in our modelling approach.

Another important factor is the quality of the input data used in our simulation; i.e. number of samples available and representativeness of the data for the population at large. For the model variables task frequency, task performance and glove use we had questionnaire information from a large, random sample of our study population, probably resulting in low uncertainty in the input distributions for these variables. A source of uncertainty for the post-intervention data might have been a relatively low response (54%) in the questionnaire survey compared to the response for the pre-intervention data (79%). The dermal exposure datasets were significantly smaller (<30 data points) with in some cases a substantial number of values below LOD. Especially when the variability in these datasets was large this resulted in uncertainty in estimates of input distributions for dermal exposure. As our uncertainty analysis showed this was more the case for the pre-intervention assessment than for our post-intervention assessment.For glove protection data were too limited to fit any distribution and no a-priori information was available on a parametric distribution, therefore the triangular distribution was selected with an optimum (mean), minimum and maximum protection defined.

The analysis performed on the post-intervention data with regard to the influence of pregnancy on exposure, showed that pregnancy did not have an effect on the work characteristics and respectively the exposure distribution for this population. This is reassuring and indicates that the questionnaire survey used here is representative for the total population of oncology nurses subject to our evaluation. It also indicates that the expected raised awareness of the past decade around reproductive toxic effects associated with exposure to antineoplastic agents did not clearly result in a change in the work practice for pregnant nurses working on oncology departments. In general it can be stated that the data used was of good quality. Therefore the results of this probabilistic assessment are reliable and give a good insight in shifts of exposure to antineoplastic agents over the past decade. The man goal of the performed uncertainty analysis was to explore its potential in this type of assessments. Additional uncertainty and/or sensitivity analysis could have been conducted. Yet we believe this would not necessarily have added significant information to our impact assessment and was therefore considered beyond the scope of our study.

Probabilistic modelling is increasingly used as an approach to assess exposure for regulatory purposes[33,34]. The presented study shows that the probabilistic approach can also add valuable information to trend analysis, especially when extrapolating data on a subpopulation to populations of individuals at large. It enables researchers or policy makers to, prospectively or retrospectively, investigate and quantify the impact of policy and/or interventions on exposure in a population of workers. The important benefit is that probabilistic assessments enable the use of fragmented data available to researchers. The use of uncertainty and/or sensitivity analysis can subsequently give a good insight in the effect of the quality of the data on the estimated outcome distribution, enabling a transparent interpretation of the assessment results. Semple et al. also showed that MC simulation provides a tool to examine the influence of uncertainty on an exposure model[35].

Probabilistic evaluation like the one presented in this paper are to our opinion applicable, to a wide variety of prevention and/or intervention programs in the workplace. Obviously this increases the necessity of collecting and storing input data in a structured manner and make them available to researcher. This will increase the quality and level of information of future probabilistic evaluations of intervention programs.

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Summary

In the Netherlands a large study performed in the early nineties among bakery workers, created awareness of the potential disease burden related to occupational exposure to flour dust and related allergens. In 2000/2001 the possibilities for deriving exposure limits for occupational allergens from available data was explored. The results of this study indicated that sensitization and symptoms can occur even at very low exposure levels. This suggests the absence of a “no effect level” for high molecular weight allergens including wheat allergens and fungal α-amylase. At the same time a study was initiated in the major flour processing sectors to investigate exposure levels to flour dust and allergens, as well as, the prevalence and severity of associated occupational diseases. Furthermore, insight had to be obtained into the state of the art with respect to control measures. The results of these studies preceded the start of a covenant in 2001.

The covenant was an agreement between the major flour processing sectors (bakeries, flour mills and ingredient producers) and social partners with the main goal to decrease occupational exposures and diseases. Exposure surveys were performed to obtain more accurate insight in exposure levels to flour dust and allergens throughout the flour processing sectors and enable evaluation of the effect from covenant actions on exposure. The covenant also initiated the start of a health surveillance program to monitor the health status of the working population. To evaluate the impact of the potential exposure reductions on the population’s health status an assessment methodology was needed. Consequently, one of the main aims of this thesis was to develop a quantitative health impact assessment model. This model, the dynamic population-based model, was used to assess the effect of exposure (and other) interventions on the disease burden of work related respiratory symptoms in Dutch bakery workers.

The baseline exposure survey performed at the start of the covenant in all major flour processing sectors (bakeries, flour mills and ingredient producers) is described in Chapter 2 of this thesis. Combined with data from several other exposure surveys a dataset of 910 personal measurements was compiled containing information on exposure levels and potential determinants. Besides evaluation of (average) exposure levels the dataset was used to generate exposure models for all sectors and agents. Main determinants in these models were job, tasks and company size, taking into account worker and company as random effect components. Use of control measures and, where possible, their effectiveness were evaluated. The results indicated that, as expected, flour dust and enzyme exposures vary strongly between sectors. The job performed and specific tasks were identified as important determinants of exposure. The number of identified control measures during walk-through surveys, and their effectiveness in reducing dust exposure was generally limited. The exposure models explained significant exposure variability between companies and workers but performed poorly in explaining day to day differences in exposure. The dataset from this study served as a baseline estimate and was compared with the post covenant survey in chapter 5. The predictive exposure models provided a relevant measure of average personal exposure that was used both in the health

surveillance system and the epidemiological study presented in chapter 4.This study also provided detailed information on main determinants of exposure and a limited evaluation of control measures.

Additionally to the time weighted average (TWA) exposure measurements described in chapter 2, a substantial dataset of real time exposure measurements was also obtained from several surveys. In chapter 3 this dataset was used to get more detailed insight in the role of peak exposures. Furthermore, to effectively decrease occupational exposure to flour dust and related allergens, detailed information on exposure determinants and effectiveness of control measures is essential. The personal real time exposure measurements were used to get more insight into the relationship between specific work characteristics, including the use of control measures, and (peak) exposure to flour dust. The dataset that was studied contained 82 real time exposure measurements in combination with detailed contextual information from observations on tasks and activities performed and other determinants, especially control measures. Descriptive statistics of peak exposure on job level were generated as well as information on contribution of task specific peak exposures to TWA exposure levels. Finally the efficacy of a variety of control measures on task exposure was evaluated by comparing exposure levels of groups of workers with and without controls. In workers included in this study more then 75% of TWA exposure is directly associated with peak exposures during a limited set of well defined tasks/activities. The impact of a single task on population TWA exposure is generally limited (less then 40%). In general, reductions of task specific peak exposures were above 50% (between 22-100%) for most identified control measures, except for partial substitution of sprinkling flour with oil where no reduction on task level was observed. Most effective control measures (with respect to percentage reduction) in bakeries were; no shaking of cotton hose attached to flour silo, no flour dusting, perform only wet cleaning. For ingredient production sector the elimination of use of pressured air, installation of local exhaust ventilation (LEV) when bagging and not shaking bags when dumping ingredients were most effective control measures. These findings show that worker behavior is an important determinant in effective exposure control for many tasks. Data from real time measurements provided important detailed information with respect to exposure determinants and control measures, not obtainable from conventional measurement studies focusing on TWA exposure. This information is essential to perform prospective impact assessments of intervention strategies focused on the populations' exposure.

Besides detailed exposure assessment, the covenant also initiated health monitoring of the worker population and the development of a diagnostic tool. This was used to identify workers with a high probability of being sensitized to occupational allergens and thus at higher risk of developing work related diseases. As part of the health surveillance system a validation study was performed among Dutch bakers for validation of the diagnostic model. In this study serology and questionnaire data on a subgroup of 860 bakers was gathered. The exposure models from chapter 2 were used to predict average and cumulative personal

exposure to wheat allergens for individual workers. These data were used in chapter 4 to study the association between exposure to wheat allergen and sensitization, work-related upper and lower respiratory symptoms and asthma, in bakery workers. Results indicated that the prevalence of wheat sensitization and symptoms increased till average wheat exposure levels of approximately 25-30 µg/m3, leveled off, and decreased at higher exposure concentrations. Exposure-response curves showed a stronger pronounced bell-shape with cumulative exposure. Associations were strongest for asthma and work-related lower respiratory symptoms (PR~2 and PR~3.5-4.5 for respective average and cumulative exposure). Associations were only found in atopics. Wheat sensitization was an important factor in the prevalence of respiratory symptoms. In accordance with earlier studies, the present study showed a bell-shaped exposure-response relationship especially for cumulative wheat allergen exposure with sensitization, allergic respiratory symptoms and asthma. The healthy worker effect may be the possible explanation for the bell-shaped relationship. Mechanistic insight from this study was used in the development of the health impact model.

Chapter 6 describes the development of the quantitative health impact assessment methodology: i.e., the dynamic population-based model. Information from the studies described in the earlier chapters as well as information from additional studies was used to generate input parameters for this model. The model simulates a population of individual workers longitudinally and tracks the development of work-related sensitisation, respiratory symptoms and work disability in each worker. The model has three components: a multi-stage disease model describing the development of sensitisation and respiratory symptoms in each worker over time; an exposure model describing the population variation in occupational exposure to flour dust and allergens; and a basic population model describing the length of a worker's career in the bakery sector and the influx of new workers. Each worker's disease state is modelled independently using a discrete time Markov Chain, updated yearly using each individual's simulated exposure. A Bayesian analysis of the data from the epidemiological study presented in chapter 4 is used to estimate the yearly transition probabilities between disease states. Separate probabilities were estimated for atopic and non-atopic workers. For non-atopic/non-sensitised workers the estimated probabilities of developing moderate (upper respiratory) symptoms and progression to severe (lower respiratory) symptoms are 0.4% (95% C.I. 0.3%-0.5%) and 1.1% (95% C.I. 0.6%-1.9%) per mg/m^3/year flour dust respectively and approximately twice these for atopic workers. The model predicts that 36% (95% C.I. 26%-46%) of workers with severe symptoms are sensitised to wheat and 22% (95% C.I. 12%-37%) to amylase. The predicted mean latency period for respiratory symptoms was 10.3 years (95% C.I. 8.3-12.3). The model provides a valuable population level representation of the mechanisms contributing to respiratory diseases in bakers, and can be used for quantitative health impact assessment.

This is demonstrated in chapter 7 where the impact of different intervention strategies on the disease burden of the population over time was assessed. Different interventions based on

exposure reductions for wheat and fungal α-amylase allergens and health surveillance combined with reduction of exposure as well as pre-employment screening were evaluated. The impact of the interventions was compared with the baseline intervention program performed as part of the covenant. The result of the latter intervention program was discussed in detail in chapter 5. In short, the intervention program of the covenant, that focussed on risk education and providing information on good work practices, was limited with respect to reductions in occupational exposure levels. At the end of the covenant period a -12% decrease in flour dust exposure and a -39% decrease in fungal α-amylase exposure was observed. This resulted in a modest change in the prevalence of the different disease states, generally less then -15%. The impact of most of the other intervention strategies evaluated was higher, but still generally less then -50% for lower respiratory symptoms and work disabling asthma. Only the rigorous health surveillance intervention scenario, identifying workers that are sensitized and/or report upper respiratory symptoms and decreasing their individual exposures with 90%, resulted in a decrease of almost 60% in disease burden after 20 years. This study clearly demonstrated that different intervention strategies lead to substantial differences in the impact on the burden of disease and pace with which changes occur in the population. The comparisons of these results give an indication of the most effective design for decreasing the occupational respiratory disease burden in bakery workers and may provide more generic lessons for intervention research. This information can assist policy makers in their choice of intervention and gives an indication of achievable reductions in disease burden over time.

The different studies in this thesis illustrate the importance and complexity of creating a good quantitative evidence base for occupational intervention. In many occasions, like in many of the Dutch covenants, the evidence base for effective interventions remains weak. We showed how the resulting intervention program, which focused mainly on educational tools and providing generic information on control measures, lacked structured empirical support with respect to feasibility of implementation and effectiveness of exposure controls. As a consequence the change in disease burden in the bakery population was predicted to be limited. In chapter seven we evaluated a range of alternative intervention strategies and were able to show that a more rigorous design of the intervention strategy will likely result in a much more substantial reduction in disease burden. This implies that if this information would have been available at the start of the covenant other choices might have been made resulting in a much larger impact. Of course, the true effect of any long term intervention program will have to be established through monitoring programs.

Samenvatting

Begin jaren negentig kwam er in Nederland aandacht voor de gezondheidsrisico's van werkgerelateerde blootstelling aan meelstof in het bijzonder bij bakkerijmedewerkers. Dit werd vooral veroorzaakt doordat resultaten van een groot onderzoek beschikbaar kwamen. Deze resultaten lieten zien dat er een duidelijk verband is tussen blootstelling aan meelstof en enzymen in het meel en allergie en luchtwegklachten[1] bij medewerkers. Om medewerkers te kunnen beschermen is het van belang dat er grenswaarden beschikbaar zijn voor de blootstellingen op de werkplek. In 2000 bleek uit onderzoek dat sensibilisatie (overgevoeligheid) en symptomen zelfs bij zeer lage blootstellingen voor kunnen komen. Dit suggereert dat er geen veilige blootstellingniveaus voor o.a. tarweallergenen en schimmel α-amylase (enzym in meelstof) bestaat waaronder sensibilisatie niet optreedt. Parallel aan deze studie werd een nieuwe grote studie gestart om de blootstellingniveaus aan meelstof en allergenen te onderzoeken in de grote meelverwerkende sectoren (bakkerijen, meelmaalderijen, grondstofproducenten). Daarnaast werd in deze studie in detail gekeken naar het voorkomen en de ernst van werkgerelateerde ziekten. Als laatste moest in deze studie inzicht worden verkregen in de stand der techniek van beheersmaatregelen voor blootstelling. De resultaten van deze studies initieerde de start van een arboconvenant in 2001. Dit convenant was een overeenkomst tussen werkgevers (grote meelverwerkende sectoren), werknemers en sociale partners met als doel werkgerelateerde blootstelling en ziektelast in de meelverwerkende sectoren te verlagen. Blootstellingstudies werden uitgevoerd om gedetailleerd inzicht te krijgen in de blootstellingniveaus aan meelstof en allergenen. Daarnaast dienden deze studies als een nulmeting om uiteindelijk de impact van het convenant op de blootstelling te kunnen evalueren. Het convenant initieerde ook de start van een monitoringsprogramma voor de gezondheid van de werknemers.

Binnen het convenant werd getailleerde informatie verzameld over zowel blootstellingniveaus als over de relatie tussen blootstelling en werkgerelateerde allergie en luchtwegaandoeningen. Hieruit was echter niet direct af te leiden welk effect veranderingen in de blootstelling uiteindelijk zullen hebben op de ziektelast (aantal zieke werknemers en duur van de ziekte). Om deze impact van (potentiële) blootstellingverlagingen op de gezondheid van de werknemerspopulatie te voorspellen en/of te evalueren moest een geschikt model ontwikkeld worden. Dit leidde tot de ontwikkeling van het "dynamische populatie model" een kwantitatief simulatie model voor het schatten van het effect van interventies op de ziektelast (health impact assessment) over de tijd. Dit model is uiteindelijk gebruikt om het effect van verschillende interventiescenario's te schatten op luchtwegaandoeningen in de Nederlandse bakkerspopulatie.

[1] Er wordt onderscheid gemaakt in hoge en lage luchtwegklachten in dit proefschrift. Onder hoge luchtwegklachten verstaan we voornamelijk rhinitis klachten, geïrriteerde of ontstoken neus gepaard met klachten als loopneus, niezen en geïrriteerde oren en/of ogen. Onder lage luchtwegklachten verstaan we astmatische klachten zoals kortademigheid en benauwdheid, piepen op de borst.

De blootstellingstudie die is uitgevoerd bij de start van het convenant wordt in combinatie met enkele kleinere studies beschreven in hoofdstuk 2 van dit proefschrift. De uiteindelijke dataset bevat 910 individuele blootstellingmetingen met zowel informatie over individuele blootstellingniveaus als belangrijke determinanten van de blootstelling. Deze dataset is gebruikt om blootstellingmodellen te genereren op basis van belangrijke factoren als iemands beroep, de taken die worden uitgevoerd en de omvang van het bedrijf. Aanvullend is gekeken naar het gebruik van beheersmaatregelen voor de blootstelling en waar mogelijk naar de effectiviteit van deze maatregelen. De resultaten laten zien dat er tussen de verschillende sectoren aanzienlijke verschillen zijn in de blootstellingniveaus aan meelstof en enzymen. Het blootstellingniveau wordt voor een groot deel bepaald door het beroep van de medewerker en specifieke taken die worden uitgevoerd. Het aantal geïdentificeerde beheersmaatregelen was beperkt net als de effectiviteit van de aangetroffen maatregelen. De blootstellingmodellen verklaren redelijk waardoor verschillen tussen bedrijven en werknemers ontstaan, maar niet waardoor verschillen van dag tot dag ontstaan (bijvoorbeeld voor een werknemer). De modellen uit deze studie zijn in hoofdstuk 4 gebruikt om blootstelling van individuele medewerkers te voorspellen aan de hand van gegevens over hun beroep en werkzaamheden. Daarnaast zijn de gegevens uit deze studie in hoofdstuk 5 gebruikt om het effect van het convenant op de blootstellingniveaus aan meelstof te evalueren.

Naast de conventionele blootstellingmetingen, die zijn beschreven in hoofdstuk 2, zijn er in verschillende studies ook metingen uitgevoerd met behulp van direct registrerende meetapparatuur. Hierbij werd de blootstelling constant gemeten en opgeslagen in een datalogger (elke 3 seconde). Deze direct registrerende metingen of piekmetingen zijn beschreven in hoofdstuk 3. Deze metingen geven informatie over het belang van piekblootstellingen en bij welke activiteiten ze optreden. De gegenereerde dataset bevatte naast de informatie van de metingen ook informatie uit observaties uitgevoerd tijdens de werkzaamheden. Met behulp van deze gegevens is in detail gekeken naar het effect van allerlei factoren, met name beheersmaatregelen, op de (piek)blootstelling van werknemers. Uiteindelijk zijn groepen werknemers met en zonder specifieke beheersmaatregelen voor blootstelling vergeleken. Op die manier is bekeken hoeveel een specifieke maatregel de blootstelling gemiddeld zou kunnen verlagen. Uit de metingen bleek dat over het algemeen meer dan 75 procent van de totale blootstelling wordt bepaald door piekblootstellingen. Ook bleek dat de blootstelling wordt veroorzaakt door heel veel verschillende blootstellingmomenten en dat een individuele taak zelden meer dan 40% van de blootstelling veroorzaakt. De meeste beheersmaatregelen die in deze studie zijn bekeken hadden een aanzienlijk effect op de piekblootstelling tijdens een taak, meestal meer dan 50% verlaging. Meest effectieve manieren om de blootstelling te verlagen in bakkerijen zijn volgens deze studie: niet schudden met de katoenen hoes van een meelsilo, niet gebruiken van meel om te strooien en het nat reinigen van de werkplek. In de overige sectoren werd ook een groot effect gezien van het gebruik van afzuiging en het niet gebruiken van hoge druk lucht bij schoonmaken. Ook het “niet uitschudden van zakken” bij het storten van meelproducten zorgde voor een verlaging van de blootstelling aan meelstof. Er kan geconcludeerd worden dat de gegevens van deze studie een gedetailleerd inzicht geven in de factoren die blootstelling veroorzaken en in de potentiële effectiviteit van beheersmaatregelen. Deze informatie is van groot belang om het effect van interventie strategieën van tevoren te kunnen schatten.

Naast het meten van de blootstelling is er tijdens het convenant ook een monitoringsprogramma gestart rond de gezondheid van werknemers. In dit programma is onder werknemers een vragenlijst verspreid om te inventariseren welke gezondheidsklachten men heeft. Daarnaast is een diagnostisch model ontwikkeld om aan de hand van de informatie uit de vragenlijsten werknemers met een hoog risico op sensibilisatie te identificeren. Om te kijken of deze methode betrouwbaar is, is een validatiestudie uitgevoerd onder bakkerijmedewerkers. In deze studie is, naast het invullen van de vragenlijst, bloed geprikt om te kijken of de werknemer gesensibiliseerd was tegen tarweallergenen en/of schimmel α-amylase. In hoofdstuk 4 is een studie beschreven die de gegevens uit deze validatiestudie gebruikt om de relatie tussen blootstelling aan tarweallergenen en werkgerelateerde allergie en luchtwegklachten te onderzoeken. Met behulp van de vragenlijstinformatie en de modellen uit hoofdstuk 2 is vervolgens voor individuele medewerkers de blootstelling geschat. In combinatie met de informatie over sensibilisatie (bloedonderzoek) en gezondheidsklachten (vragenlijst) is vervolgens de relatie tussen de bloostelling en de gezondheidseffecten onderzocht. Hieruit blijkt dat er meer werknemers ziek zijn bij een toenemende blootstelling. Echter, vanaf een blootstelling van 25-30 $\mu g/m^3$ neemt het percentage zieke werknemers ineens af. Dit lijkt te wijzen op een “healthy worker” effect. Dit betekent dat zieke werknemers bij hoge(re) blootstelling de werkerpopulatie verlaten (meestal vanwege toenemende klachten) en er daardoor dus minder zieken geregistreerd worden. De sterkste relatie werd gevonden tussen de blootstelling aan tarweallergenen en astma- of lage luchtwegklachten. Deze relatie werd alleen gevonden bij mensen die atopisch[2] waren. Sensibilisatie voor tarwe was een belangrijke factor voor het ontwikkelen van luchtwegklachten. Inzichten uit deze studie over luchtwegklachten en de relatie met blootstelling zijn gebruikt bij het ontwikkelen van het “dynamische populatie model”.

Hoofdstuk 6 van dit proefschrift beschrijft de ontwikkeling van de kwantitatieve “health impact assessment” methode; het zogenaamde dynamische populatie model. Het model simuleert de ontwikkeling van ziekte (allergie en luchtwegklachten) in een populatie werknemers over de tijd. Het model bestaat uit drie onderdelen: 1) een ziektemodel dat de ontwikkeling van de verschillende ziektestadia beschrijft, 2) een model dat de variatie in blootstelling aan meelstof en schimmel α-amylase in de populatie werkers beschrijft en 3) een populatiemodel dat de populatiekarakteristieken zoals het aantal werkjaren en de

[2] Atopisch betekent dat je al allergisch bent voor bijvoorbeeld katten, grassen of huisstof. Hierdoor is de kans dat je allergisch wordt voor allergenen op de werkplek groter.

instroom van nieuwe werknemers beschrijft. Informatie van de hierboven beschreven studies, aangevuld met informatie uit andere studies, is gebruikt om alle benodigde gegevens voor het model te genereren. De ontwikkeling van ziekte is gemodelleerd voor elke werknemer in de populatie en wordt elk jaar geüpdate afhankelijk van de blootstelling. Voor elke transitie tussen de verschillende ziektestadia (zie figuur 1 in hoofdstuk 6) is een jaarlijkse kans berekend per eenheid blootstelling. Deze kans bepaalt dus het aantal werknemers dat, gegeven de blootstelling in de populatie, de ziekte zal ontwikkelen. De berekende kansen zijn groter voor werknemers die atopisch zijn dan voor niet atopische werknemers. Een voorbeeld is dat de kans om hoge luchtwegklachten te ontwikkelen voor iemand die niet atopisch en niet allergisch is voor meelstof allergenen 0.4% per mg blootstelling per jaar. De kans dat eenzelfde persoon, nadat hij hoge luchtwegklachten heeft gekregen, vervolgens lage luchtwegklachten krijgt is geschat op 1.1% per mg blootstelling per jaar. Op deze manier zijn voor alle ziekteovergangen kansen per mg per jaar geschat zodat de ontwikkeling van ziekte over de tijd gesimuleerd kan worden. Het model voorspelt verder dat van de werknemers die lage luchtwegklachten ontwikkelen ongeveer 36% allergisch is voor tarweallergenen en ongeveer 22% voor schimmel α-amylase. Daarnaast voorspelt het model bijvoorbeeld ook dat het gemiddeld 10.3 jaar kost voordat iemand met lage luchtwegklachten deze ontwikkeld. Het model laat duidelijk zien hoe ziekte zich ontwikkelt in de populatie bakkerijmedewerkers en wat de rol is van verschillende factoren zoals blootstelling. Het model kan gebruikt worden voor kwantitatieve "health impact assessment" van interventiestrategieën.

In hoofdstuk 7 wordt de impact van verschillende interventies op de ziektelast in de populatie geschat met behulp van het dynamisch populatie model. De interventiescenario's zijn gebaseerd op verlaging van de blootstelling aan meelstof en/of schimmel α-amylase. Daarnaast zijn scenario's geëvalueerd die gezondheidsmonitoring en blootstellingverlaging combineren. Evenals een scenario waarbij nieuwe medewerkers gescreend worden op atopy. De impact van deze interventiescenario's is vergeleken met het effect dat het interventieprogramma van het convenant heeft gehad. Dit programma is in detail beschreven in hoofdstuk 5 waar ook een evaluatie is uitgevoerd van het effect van dit programma op de blootstelling aan meelstof en schimmel α-amylase. Het convenant heeft bij bakkers uiteindelijk geleid tot een 12% verlaging in meelstof blootstelling en een 39% verlaging in blootstelling aan schimmel α-amylase. Op basis van deze gegevens kon met het populatie dynamisch model geschat worden dat dit over een periode van 20 jaar zou leiden tot een daling van minder dan 15% in ziektelast voor de verschillende ziektestadia. Het voorspelde effect van de geëvalueerde scenario's was over het algemeen groter, maar de verlaging in ziektelast was over het algemeen lager dan 50%. Alleen het scenario waarbij werknemers met werkgerelateerde sensibilisatie en hoge luchtwegklachten werden geïdentificeerd vervolgens en een substantiële blootstellingverlaging kregen (-90%), reduceerde de ziektelast met bijna 60% na 20 jaar.

Deze studie laat duidelijk zien dat er grote verschillen zijn tussen de impact die verschillende interventies hebben op de gezondheid van de populatie en ook de snelheid waarmee veranderingen plaats vinden. Met behulp van het hier ontwikkelde model kan inzicht worden verkregen in de meest effectieve invulling van een interventieprogramma om de ziektelast bij bakkerijmedewerkers te verlagen. Daarnaast geeft het algemene inzichten voor verder interventieonderzoek. Deze informatie kan beleidsmakers helpen in hun keuze voor een interventiestrategie en daarnaast inzicht geven in haalbare reducties in ziektelast binnen een bepaalde termijn.

De verschillende studies in dit proefschrift laten zien hoe belangrijk en tegelijk complex het is om een goede kwantitatieve kennis basis te creëren voor werkgerelateerde interventies. In veel situaties, onder andere bij een groot deel van de convenanten, is er weinig informatie beschikbaar over de effectiviteit van interventies. In dit proefschrift wordt aangetoond dat het interventieprogramma bij de bakkers, uitgevoerd tijdens het convenant, te weinig ondersteuning bood voor daadwerkelijke invoering van beheersmaatregelen in de bakkerijen. Als gevolg hiervan werden relatief weinig veranderingen doorgevoerd op de werkplek en was de impact op de ziektelast dus beperkt. De evaluatie in hoofdstuk 7 laat zien dat alternatieve programma's met daadwerkelijke blootstellingverlaging, vooral wanneer deze gericht is op werknemers met een hoog risico op ontwikkeling van astma, zeer waarschijnlijk een aanzienlijk grotere impact zal hebben op de ziektelast. Dit betekent dat beschikbaarheid van deze informatie aan het begin van het convenant mogelijk zou hebben geleid tot andere keuzes voor invulling van het interventieprogramma. Natuurlijk zal het daadwerkelijke effect van elk lange termijn interventieprogramma vastgesteld moeten worden door middel van monitoringsprogramma's.

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Curriculum Vitae

Curriculum Vitae

Tim Meijster werd geboren op 11 November 1976 in Arnhem. Na in 1995 zijn VWO diploma gehaald te hebben op de Gemeentelijke Scholengemeenschap Doetinchem (GSGD) ging hij milieuhygiëne studeren in Wageningen. Hier koos hij, na het behalen van de propedeuse, voor de specialisatie milieu, arbeid en gezondheid met een focus op de Arbeidshygiëne. Na twee afstudeeropdrachten, één naar blootstelling aan cytostatica bij verpleegkundigen en één naar blootstelling aan chemische mengsels bij een nieuw productieproces voor composieten, liep hij in 2001 stage bij de Universiteit van Kaapstad. Hier werkte hij mee aan een onderzoek naar blootstelling aan pesticiden bij druivenboeren. In 2002 studeerde hij af bij de Universiteit Wageningen. Direct na zijn afstuderen kwam hij in dienst bij het Institute for Risk Assessment Sciences (IRAS) aan de Universiteit Utrecht waar hij meewerkte aan verschillende blootstellingonderzoeken. In 2003 begon hij aan zijn promotieonderzoek beschreven in dit proefschrift wat een gezamenlijk project was tussen het IRAS en TNO Kwaliteit van Leven. Tussen 2002 en 2008 werkte hij geregeld in Zuid Afrika, aan de universiteit van Kaapstad, aan verschillende onderzoeksprojecten en verzorgde onderwijs binnen verschillende programma's. Sinds juli 2008 is hij in dienst bij TNO Kwaliteit van Leven als onderzoeker. Hier houdt hij zich voornamelijk bezig met onderzoek op het gebied van blootstellingmodellering en "health impact assessment"