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ABSTRACT

Objectives: Four diacetyl workers were found to have bronchiolitis obliterans syndrome. The aim of this study was to investigate exposures, respiratory symptoms, lung function and exposure-response relationships.

Methods: The study was conducted among 175 of a cohort of 196 workers from a plant which produced diacetyl between 1960 and 2003. All available historical exposure data were used to model diacetyl exposure. Lung function and questionnaire data on respiratory symptoms were compared to a general population sample and respiratory symptoms to an internal reference group.

Results: Workers were potentially exposed to acetoin, diacetyl, acetaldehyde, and acetic acid. Historic diacetyl exposure in the working environments ranged from 1.8 to 351 mg/m³ and for specific tasks from 3 to 396 mg/m³. Diacetyl workers reported significantly more respiratory symptoms compared to the general population sample (continuous trouble with breathing prevalence ratio (PR=2.6; 95% CI 1.3-5.1); daily cough (PR=1.5; 95% CI 1.1-2.1); asthma attack (ever) (PR=2.0; 95% CI 1.2-3.4); doctor diagnosed asthma (PR=2.2; 95% CI 1.3-3.8); asthma attack in the last year (PR=4.7; 95% CI 1.9-11.4)). Lung function did not differ between the groups. A positive relationship between exposure and FEV₁ was found. Operators reported significantly more respiratory symptoms compared to a minimally exposed internal reference group (ever trouble with breathing prevalence ratio (PR=2.8; 95% CI 1.1-7.0); work-related shortness of breath in the last year (PR=7.5; 95% CI 1.1-52.9)).

Conclusion: The excess of respiratory symptoms in this retrospective cohort supports the occupational hazard in diacetyl production demonstrated earlier in the case cluster. A job title-related excess of symptoms existed in operators with the highest exposures compared to an internal reference population. Limited historical exposure data did not support a quantitative individual diacetyl exposure-response relation, but our findings suggest that preventive measures are prudent.

INTRODUCTION

Fixed airway obstruction consistent with bronchiolitis obliterans syndrome (“Popcorn workers lung”) was first reported among workers in microwave popcorn production in relation to inhalatory exposure to airborne butter-flavouring chemicals.¹

Within the spectrum of butter flavouring vapours, diacetyl, a predominant chemical in butter flavouring, is suggested to play a prominent role.¹⁻⁴

In the index plant an exposure-response relationship was reported between cumulative exposure to diacetyl (using quartiles of increasing exposure) and the proportion of workers with abnormal spirometric lung function results including airway obstruction.¹ Analyses of aggregated data in the microwave popcorn industry of current workforces indicated a wide spread risk for occupational lung disease from exposure to butter-flavouring chemicals.

Mixers of oil and butter flavourings had medical findings consistent with bronchiolitis obliterans syndrome (BOS), and mixers with more than 12 months mixing experience had a higher prevalence of respiratory symptoms and airways obstruction and lower mean percent predicted FEV₁ compared with workers who did this task during less than 12 months indicating a relationship with exposure.⁴

Elsewhere, we reported earlier four cases of BOS in a chemical plant producing diacetyl that were previously not detected or suspected. Exposure to an agent during diacetyl production appeared responsible for causing BOS in chemical process operators.⁵

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

This investigation was conducted in the same plant that was addressed earlier and the epidemiologic description of the cohort in this study is complementary to the case reports of BOS.⁵

METHODS

STUDY POPULATION

We performed a cross sectional study in 2005 in a cohort of former workers in a chemical plant producing diacetyl in The Netherlands in the period 1960-2003. The plant was closed in 2003. The Human Resources department identified 206 workers who potentially had been exposed to diacetyl in that period of whom 10 had died. We traced the remaining 196 and obtained written, informed consent from 175 (89%).⁵

The questionnaire is based on one with items described in NIOSH Health Hazard Evaluation Reports and some of the questionnaire items were taken from the European Community Respiratory Health Survey (ECRHS).⁵

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

Experienced technicians obtained spirometric lung function variables in all participants according to European Respiratory Society standards⁶ by using a pneumotachograph with specific software (Pneumotachograph and 4.66 software, Jaeger; Wurzburg, Germany). Age- and standing height-adjusted spirometric reference values of the European Community for Steel and Coal were used.⁶

Reversibility was measured after bronchodilation with 400 micrograms salbutamol (metered dose inhaler) and defined as $\geq 9\%$ increase in FEV₁.⁷

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

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

EXPOSURE ESTIMATES

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

The working schedule varied considerably among workers; some worked at the diacetyl plant for five successive days, whereas others were scheduled to work in the diacetyl plant for one day per week. Company representatives thought that all process operators worked on average an equal number of days per year at the diacetyl plant, but some individual differences may have existed among workers.

We used three different exposure proxies to study diacetyl exposure-response relationships: (1) the number of years in the diacetyl plant, (2) the number of years in the diacetyl plant before 1995, and (3) an exposure estimate in which both the duration and the level of diacetyl was taken into account. For two of these estimates, there are three crucial moments in time. First, in the mid-1980s, diacetyl production was changed from batch production into a continuous production process. Second, in 1995, several hand-operated processes were automated and, as a result, operators only had to be present in the diacetyl plant for 2 hours per day instead of 8 hours. Third, in 2001, exposure to diacetyl and other relevant chemical agents was considerably reduced by enclosure of the installation (Table 1). We translated these process changes into exposure multipliers resulting in a relative cumulative exposure

estimate for each worker, using the most recent time episode as the reference period. We estimated exposure between 1995-2000 to be about 4 times higher compared to 2001-2003, based on the arithmetic mean of environmental area sampling results. We estimated exposure between 1986-1994 to be about 4 times higher compared to 1995-2000, based on the time present in the plant (8 versus 2 hours). We estimated exposure between 1960-1985 to be about half compared to 1986-1994, based on the change in production volume. Thus, the relative cumulative diacetyl exposure for each worker was calculated as: $8 \times (\text{years between 1960-1985}) + 16 \times (\text{years between 1986-1994}) + 4 \times (\text{years between 1995-2000}) + (\text{years between 2001-2003})$. The period with highest diacetyl exposure was before 1995.

STATISTICAL ANALYSIS

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

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

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

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

RESULTS

CHARACTERISTICS OF THE WORKERS

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

RECONSTRUCTION OF THE EXPOSURE PROFILE

Limited routine exposure monitoring was done by company representatives using cartridges containing silica gel coated with dinitrophenylhydrazine (DNPH-cartridges), and each sample was analyzed externally for both diacetyl and acetaldehyde using gas chromatography.

Between 1995 and 2003, 26 area samples (mean sampling duration 120 minutes; range 82-219 minutes) and 4 personal task-based samples (mean 65 minutes; range 33-90 minutes) could be traced (Table 1). All area samples had been taken in locations in the plant where operator activities were performed. Control measures taken in 2001 with the aim to enclose the process, led to a reduced exposure for both diacetyl (geometric mean (GM) change from 10.0 to 5.8 mg/m³) and acetaldehyde (GM change from 7.6 to 0.7 mg/m³).

During production, process operators were potentially exposed to diacetyl during several tasks (quality checking, discharging to buffer vessel, checking process parameters in the plant, charging batch column, discharging in 50 kg and in 2.5 l containers, and cleaning activities). According to the company representatives, discharge of diacetyl in containers had the highest exposure potential, and for this reason, task based samples were available for this specific activity. Although exposure to diacetyl was mainly relevant for process operators, workers with several other occupational titles were also potentially exposed to diacetyl. Maintenance workers were likely to be exposed but exposure was highly variable. Laboratory workers were potentially exposed but no further qualitative or quantitative information was available. 'Other jobs' (transport, health and safety, and management and research and development personnel) had low exposure potential for diacetyl and, if they had exposure, it was always of short duration.⁵

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

	N	AM	GM	GSD	Range
Diacetyl (mg/m³)*					
All samples	26	27.9	8.1	3.9	1.8-351
Samples 1995 to 2001	16	38.7	10.0	4.5	1.9-351
Samples after 2001	10	10.6	5.8	2.9	1.8-51
Acetaldehyde (mg/m³) †					
All samples	26	6.2	3.1	3.8	0.4-29
Samples 1995 to 2001	16	9.6	7.6	2.1	1.6-29
Samples after 2001	10	0.9	0.7	1.7	0.4-2.3

Personal task-based sampling results during tapping containers of diacetyl.

	N	AM	GM	GSD	Range
Diacetyl (mg/m³)*					
All samples	4	122.0	38.4	7.5	3-396
Samples 1995 to 2001	3	152.0	40.8	11.7	3-396
Samples after 2001	1	32	32	-	-
Acetaldehyde (mg/m³) †					
All samples	4	3.8	0.9	7.4	0.2-14
Samples 1995 to 2001	3	4.8	0.8	11.6	0.2-14
Samples after 2001	1	1.0	1.0	-	-

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

* 1 mg/m³ = 0.21 ppm

† 1 mg/m³ = 0.56 ppm

QUESTIONNAIRE AND SPIROMETRY

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

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

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

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

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

Definition of abbreviation: NA = Not available.

* Men only, age between 30 and 70.

† All only male Caucasians (n = 159).

‡ p < 0.05, § p < 0.10; adjusted for age and smoking habits (categorical: never-, ex-, or current smoker)

- (-) prohibited to calculate due to nihil subjects in the reference group.

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

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

	<i>Diacetyl plant workers*</i>	<i>General population†</i>
Age – yr, mean (sd)	51 (7.7)	50 (11.4)
Smoking status (%)		
Current smoker	29	41
Former smoker	42	40
Never smoked	30	19
FEV ₁ % pred (sd)	105.4 (18.0)	104.9 (18.1)
FVC % pred (sd)	108.9 (15.9)	108.4 (15.0)
FEV ₁ /FVC % (sd)	77.5 (7.1)	77.9 (8.6)
[‡] Reversibility (%)	10 (6.7)	NA
Body Mass Index in kg/m ² (sd)	26.5 (3.9)	25.7 (3.2)

Definition of abbreviations: yr = year; sd = standard deviation; FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity; FEV₁/FVC = forced expiration ratio; NA= not available.

% pred = percentage of the predicted value.

* n = 149, Caucasian males only, age between 30 and 70.

† n = 1084, Caucasian males only, age between 30 and 70.

[‡] Reversibility = increase in FEV₁ ≥ 9% pred.

EXPOSURE-RESPONSE RELATIONSHIP

There was no clear association between FEV₁ (% predicted) and exposure to diacetyl (Figure 1). Multiple linear regression analysis of pulmonary function variables on exposure in process operators (Table 4) showed a significant increase in actual FEV₁ of 28 ml per year working in the diacetyl plant before 1995 (95% CI 3 - 53) and a significant increase in FEV₁ of 2 ml per cumulative weighted number of years in the diacetyl plant (95% CI 0 – 4).

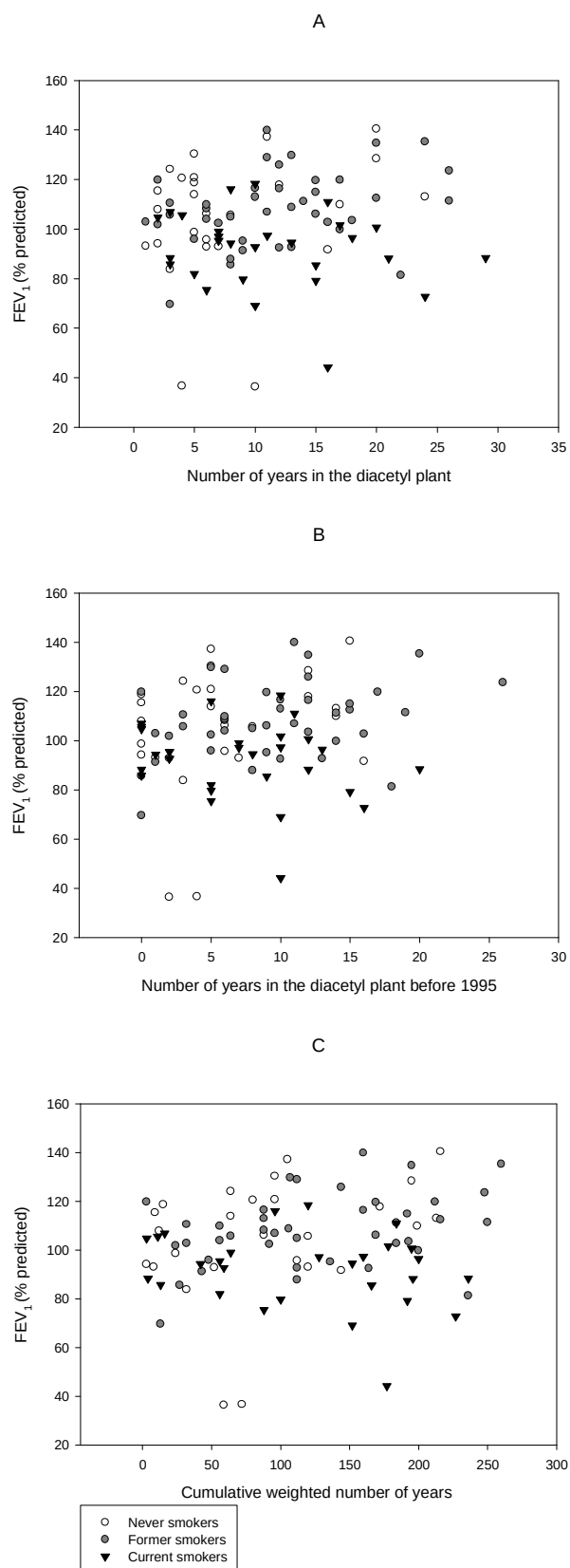
Figure 1

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

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

* n = 95, only male Caucasians

Definition of abbreviation: SE = standard error.

† adjusted for age, height, and smoking habits

‡p<0.05; § p<0.10.

DISCUSSION

EXPOSURE

During production of diacetyl, process operators were potentially exposed to acetoin, diacetyl, acetaldehyde and acetic acid. Diacetyl levels ranged from 1.8 - 351 mg/m³ and acetaldehyde levels from 0.4 - 29 mg/m³. Diacetyl exposure levels could not be evaluated in relation to an occupational standard as no Dutch occupational exposure limit ("MAC value") or international equivalent is available. Average levels of acetaldehyde were low compared to the previous Dutch MAC-value of 180 mg/m³ and the new Dutch health standard value of 37 mg/m³ as of 2007.¹¹ A detailed comparison could not be made because sampling times were relatively short, and the MAC value is based on an eight hour time weighted average (TWA). Although exposure data were limited, available data suggest that diacetyl exposure before 2001 in the production plant was as high as in the index microwave popcorn plant where the first cases of BOS were described.¹ In this index plant, mixers had a mean area exposure of 180 mg/m³ diacetyl, with a range to 467 mg/m³, as determined by full-shift area sampling.³ In the microwave popcorn industry, diacetyl was the predominant chemical among many in air sampling of volatiles and was used as a proxy for flavouring exposure.³ The spectre of potential causative agents in this production plant is much smaller than in the index microwave popcorn plant.³ After several control measures were implemented in the diacetyl plant to enclose the process, diacetyl levels were lower but still in the range found in microwave popcorn plants where cases of BOS were found.⁴ This supports the conclusion that the diacetyl concentration in our study was high enough to be potentially associated with cases of BOS.

RESPIRATORY SYMPTOMS AND SPIROMETRY

Workers at the diacetyl production plant reported significantly more respiratory symptoms and self reported asthma compared to the Dutch ECRHS population, and process operators reported significantly more respiratory symptoms compared to an internal reference group. There were no significant differences in spirometric abnormalities compared to the Dutch ECRHS.

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

The general population data were obtained with the same procedure and device, with same age and distribution, but not restricted to a working subpopulation. The general population

sample also included non-active workers who were not fit enough to be active in the workforce; therefore the differences in respiratory status between exposed workers and the general population are likely to be underestimated.

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

The finding of significantly more respiratory symptoms among workers compared to a general population sample is consistent with the findings at the micro-wave popcorn plant.¹ Persistence of symptoms despite plant closure that differ among groups is consistent with permanent injury. The marginally significant finding, such as work-related wheezing in the last year in operators is compatible with asthma, and many have high adjusted prevalence ratios despite low power to detect differences. With asthma as a possible outcome, as shown in a NIOSH health hazard evaluation report of a popcorn plant, one would not necessarily expect pulmonary function abnormalities.¹²

Three robust findings support the occupational hazard of diacetyl: 1) The highest exposed group, the process operators, had significantly more respiratory symptoms than other occupational groups, and the plant population as a whole had excess symptoms compared to the general population. 2) A previously published spirometric analysis internal to the cohort showed that process operators had a job title-related decrement in FEV₁ (-292 ml).⁵ 3) All severe BOS cases occurred in process operators. In addition to these robust findings, our analyses supply supporting information from (marginally) significant excesses of respiratory symptoms (from Table 2).

EXPOSURE-RESPONSE RELATIONSHIPS

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

These findings seem inconsistent with the results of the study of Kreiss et al. where the estimated cumulative exposure to diacetyl was correlated with chronic effects on lung function, in terms of both the rate of abnormalities on spirometry and the average decreases in FEV₁ in quartiles of increasing cumulative exposure.¹

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

The finding that pulmonary function increased with increasing exposure proxies might be due to a healthy worker effect (HWE) bias. In cross-sectional studies the healthy worker effect is a common type of bias which can obscure exposure-response effects.¹³ Despite our retrospective survey which is less sensitive to a potential HWE survivor bias by including

inactive and active workers, affected workers may have migrated to lesser exposed jobs over time. This bias is difficult to assess quantitatively because of a lack of exposure data for all jobs involved. We had neither symptoms onset times nor past exposures which would have allowed a historical cohort design, and thus correct for selection bias.

Alternatively, no cumulative exposure-response relationship may exist, and peak exposures could play a role. Operators reported significantly more exposure incidents compared to the internal reference group and had (marginally) significantly more respiratory symptoms. However there was no association between symptoms and ever having experienced an exposure incident, which may be a result of recall bias.

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

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

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

In conclusion, this epidemiological study supports the respiratory hazard in the production of diacetyl where four cases of severe BOS were found and indicates a process associated risk. A cumulative diacetyl exposure-response relationship couldn't be demonstrated or did not exist. The job title-related risk suggests further attention to peak exposures, and host factors among the susceptible in high-risk jobs are also of interest. The research on diacetyl-exposed populations to date supports the prudence of taking preventive measures.

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COMPETING INTERESTS

All authors declare none conflict of interests.

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Legend figure 1: Percent predicted FEV₁ value of process operators (n=95), and: A) the total number of years that process operators had tasks in the diacetyl plant; B) the number of years before 1995 that process operators had tasks in the diacetyl plant (if the number of years is 0, then process operators started after 1995); and C) cumulative weighted number of years that process operators had tasks in the diacetyl plant.

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MAIN MESSAGES

1. This study supports the occupational hazard of diacetyl in a production setting with few other exposures.
2. Physicians should be aware of occupational lung diseases as a result of exposures to diacetyl and other food flavouring components.
3. Clinical case finding is indispensable for detecting occupational lung disease, in addition to epidemiological research.

POLICY IMPLICATIONS

Effective preventive measures should minimize worker exposure to diacetyl on the basis of job title-related risk.

STATEMENT

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