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A cross-sectional study of lung function and respiratory symptoms among chemical workers producing diacetyl for food flavourings

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ABSTRACT

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

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

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

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

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

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

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

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

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

METHODS

Study population

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

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

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

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

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

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

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

Exposure estimates

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

The working schedule varied considerably among workers as some worked in the diacetyl plant for five successive days, whereas others were scheduled to work in the diacetyl plant for only 1 day per week. Company representatives thought that all process operators worked on average an equal number of days per year in the diacetyl plant, but some individual differences may have existed among workers.

We used three different exposure proxies to study diacetyl exposure–response relationships: (1) the number of years in the diacetyl plant, (2) the number of years in the diacetyl plant before 1995, and (3) an exposure estimate in which both the duration of exposure and the level of diacetyl were taken into account. Three crucial changes must be noted. First, in the mid-1980s, diacetyl production was changed from batch production to a continuous production process. Second, in 1995, several hand-operated processes were automated and, as a result, operators only had to be present in the diacetyl plant for 2 h per day instead of 8 h. Third, in 2001, exposure to diacetyl and other relevant chemical agents was considerably reduced when the installation was enclosed (table 1). We translated these process changes into exposure multipliers resulting in a relative cumulative exposure estimate for each worker, using the most recent time episode as the reference period. We estimated exposure between 1995 and 2000 to be about four times higher compared to 2001–2003, based on the arithmetic mean of environmental area sampling results. We estimated exposure between 1986 and 1994 to be about four times higher compared to 1995–2000, based on the time present in the plant (8 vs 2 h). We estimated exposure between 1960 and 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×(years between 1960 and 1985)+16×(years between 1986 and 1994)+4×(years between 1995 and 2000)+(years between 2001 and 2003). The period before 1995 had the highest diacetyl exposure.

Statistical analysis

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

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

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

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

RESULTS

Characteristics of the workers

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

Reconstruction of the exposure profile

Limited routine exposure monitoring was carried out by company representatives using cartridges containing silica gel

Table 1 Sampling results

	n	AM	GM	GSD	Range
Environmental area sampling results in the diacetyl production plant by historic period					
Diacetyl (mg/m³)*					
All samples	26	27.9	8.1	3.9	1.8–351
Samples 1995–2001	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 1995–2001	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 when tapping diacetyl containers					
Diacetyl (mg/m³)*					
All samples	4	122.0	38.4	7.5	3–396
Samples 1995–2001	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 1995–2001	3	4.8	0.8	11.6	0.2–14
Samples after 2001	1	1.0	1.0	–	–

*1 mg/m³ = 0.21 ppm; †1 mg/m³ = 0.56 ppm.
AM, arithmetic mean; GM, geometric mean; GSD, geometric standard deviation; n, number of samples; Range, lowest and highest sampling results.

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coated with dinitrophenylhydrazine (DNPH cartridges), and each sample was analysed externally for both diacetyl and acetaldehyde using gas chromatography. Twenty six area samples (mean sampling duration 120 min; range 82–219 min) and four personal task-based samples (mean 65 min; range 33–90 min) for the period 1995–2003 could be traced (table 1). All area samples had been taken in locations in the plant where operator activities were performed. Control measures taken in 2001 to enclose the process led to a reduced exposure for both diacetyl (geometric mean (GM) change from 10.0 to 5.8 mg/m^3) and acetaldehyde (GM change from 7.6 to 0.7 mg/m^3).

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

Questionnaire and spirometry

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

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

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

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 2 Prevalence (%) and adjusted prevalence ratios (PR) with 95% confidence intervals (CI) for respiratory symptoms in diacetyl plant workers and a general Dutch population sample of the European Community Respiratory Health Survey and adjusted PR with 95% CI of jobs compared with an internal reference group ("Other jobs")

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

†Men only, aged between 30 and 70; ‡male Caucasians only (n = 159).
*p<0.05, **p<0.10; adjusted for age and smoking habits (categorical: never-, ex- or current smoker).
NA, not available; SOB, shortness of breath; – (–) unable to calculate as no subjects in the reference group.

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

	Diacetyl plant workers*	General population†
Age, years, 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, kg/m^2 (SD)	26.5 (3.9)	25.7 (3.2)

*n = 149, Caucasian males only, aged between 30 and 70; †n = 1084, Caucasian males only, aged between 30 and 70; ‡reversibility defined as ≥9% increase in FEV_1 predicted.
FEV_1, forced expiratory volume in 1 s; FEV_1/FVC, forced expiration ratio; FVC, forced vital capacity; NA, not available; SD, standard deviation; % pred, percentage of the predicted value.

Exposure-response relationship

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

DISCUSSION

Exposure

During production of diacetyl, process operators were potentially exposed to acetoin, diacetyl, acetaldehyde and acetic acid. Diacetyl levels ranged from 1.8 to 351 mg/m^3 and acetaldehyde levels from 0.4 to 29 mg/m^3. Diacetyl exposure levels could not be evaluated in relation to an occupational standard as no Dutch occupational exposure limit ("MAC value") or international equivalent is available. Average levels of acetaldehyde were low compared to the previous Dutch MAC value of 180 mg/m^3 and the new Dutch 2007 health standard value of 37 mg/m^3.[11] A detailed comparison could not be made because sampling times were relatively short, and the MAC value is based on an 8 h time weighted average (TWA).

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

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

Respiratory symptoms and spirometry

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

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

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

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

In addition, data in the general population sample were obtained earlier (1991–1992) and so socio-economic characteristics may be different. We did not correct for socio-economic status and educational 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 microwave popcorn plant.[1]

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

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

Exposure-response relationships

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

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

Several explanations may account for our findings and all related to possible misclassification of biologically-relevant

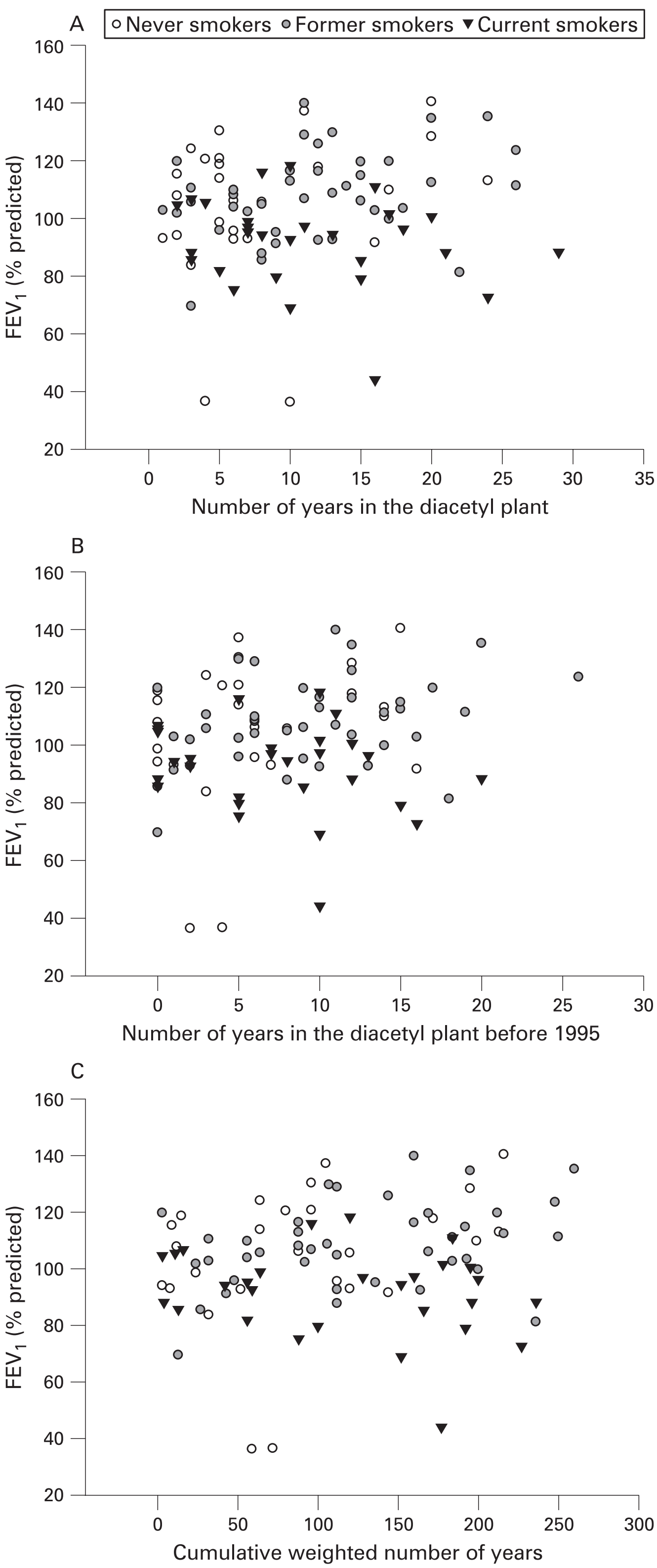

Figure 1 Per cent predicted FEV_1 value of process operators (n = 95). (A) Total number of years that process operators had tasks in the diacetyl plant; (B) number of years before 1995 that process operators had tasks in the diacetyl plant (if the number of years is 0, then process operators started after 1995); (C) cumulative weighted number of years that process operators had tasks in the diacetyl plant. FEV_1, forced expiratory volume in 1 s.

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

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

†n = 95, only male Caucasians; ‡adjusted for age, height and smoking habits.
*$p<0.05$; **$p<0.10$.
Coeff, coefficient; FEV_1, forced expiratory volume in 1 s; FEV_1/FVC, forced expiration ratio; FVC, forced vital capacity; SE, standard error.

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

The finding that pulmonary function increased with increasing exposure proxies might be due to a healthy worker effect (HWE) bias. In cross-sectional studies the HWE is a common type of bias which can obscure exposure–response effects.[13] Although our retrospective survey is less sensitive to a potential HWE survivor bias as it includes inactive and active workers, affected workers may have migrated to lesser exposed jobs over time. This bias is difficult to assess quantitatively because of a lack of exposure data for all jobs involved. We had no data on either symptoms onset times or past exposures which would have allowed a historical cohort design and thus would have corrected for selection bias.

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

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

Exposed workers in our study developed BOS following 0−14 years' exposure to diacetyl, an observation which is consistent with the findings of Akpinar-Elci *et al* who showed that workers first exhibited symptoms between 5 months and 9 years after starting work in the plant.[16] Thus, incident cases occur with a short exposure period or a low cumulative exposure. Such cases might be explained by specific exposure patterns involving short high peaks during spills or specific tasks. Thus far, the possible importance of short-term, peak exposures or host factors which may play a role in the

Main messages

- This study supports previous finding that diacetyl in a production setting with few other exposures is an occupational hazard.
- Physicians should be aware of occupational lung diseases as a result of exposures to diacetyl and other food flavouring components.
- Clinical case findings are indispensable for detecting occupational lung disease in addition to epidemiological research.

Policy implications

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

development of BOS related to diacetyl exposure have not been studied.

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

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

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REFERENCES

1. **Kreiss K,** Gomaa A, Kullman G, *et al*. Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. *N Engl J Med* 2002;**347**:330–8.
2. **Hubbs AF,** Goldsmith WT, Kashon ML, *et al*. Respiratory toxicologic pathology of inhaled diacetyl in Sprague-Dawley rats. *Toxicol Pathol* 2008;**36**:330–44.
3. **Kullman G,** Boylstein R, Jones W, *et al*. Characterization of respiratory exposures at a microwave popcorn plant with cases of bronchiolitis obliterans. *J Occup Environ Hyg* 2005;**2**:169–78.
4. **Kanwal R,** Kullman G, Piacitelli C, *et al*. Evaluation of flavourings-related lung disease risk at six microwave popcorn plants. *J Occup Environ Med* 2006;**48**:149–57.
5. **van Rooy FGBGJ,** Rooyackers JM, Prokop M, *et al*. Bronchiolitis obliterans syndrome in chemical workers producing diacetyl for food flavorings. *Am J Respir Crit Care Med* 2007;**176**:498–504.
6. **Quanjer PH,** Tammeling GJ, Cotes JE, *et al*. Lung volumes and forced ventilatory flows. Official statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;**16**:5–40.
7. **Celli BR,** MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;**23**:932–46.
8. **Rijcken B,** Kerkhof M, de Graaf A, *et al*. *Europees luchtweg onderzoek Nederland*. Groningen: Stichting Drukkerij C Regenboog, 1996.
9. **Thompson ML,** Myers JE, Kriebel D. Prevalence odds ratio or prevalence ratio in the analysis of cross sectional data: what is to be done? *Occup Environ Med* 1998;**55**:272–7.
10. **Deddens JA,** Petersen MR. Approaches for estimating prevalence ratios. *Occup Environ Med* 2008;**65**:501–6.
11. **Staatscourant**. Wijziging Arbeidsomstandighedenregeling. *Staatscourant* 28 December 2006; no 252:1–23.
12. **NIOSH**. *Health Hazard Evaluation Report: 2006-0195-3044, Yatsko's Popcorn Sand Coulee, Montana*. Washington, DC: National Institute for Occupational Safety and Health.
13. **Le Moual N,** Kauffmann F, Eisen EA, *et al*. The healthy worker effect in asthma: work may cause asthma, but asthma may also influence work. *Am J Respir Crit Care Med* 2008;**177**:4–10.
14. **Hendrick DJ.** ''Popcorn worker's lung'' in Britain in a man making potato crisp flavouring. *Thorax* 2008;**63**:267–8.
15. **Hansell DM.** Small airways diseases: detection and insights with computed tomography. *Eur Respir J* 2001;**17**:1294–1313.
16. **Akpinar-Elci M,** Travis WD, Lynch DA, *et al*. Bronchiolitis obliterans syndrome in popcorn production plant workers. *Eur Respir J* 2004;**24**:298–302.