Bronchiolitis Obliterans Syndrome in Chemical Workers Producing Diacetyl for Food Flavorings

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

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

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

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

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

Keywords: popcorn; bronchiolitis; exposure; occupation; diacetyl

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

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

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

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

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

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Bronchiolitis obliterans syndrome is an occupational lung disease called "popcorn worker's lung" in workers exposed to flavorings in the food processing industries. The etiology has not previously been clarified.

What This Study Adds to the Field

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

METHODS

Study Design and Population

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

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

Exposure Assessment

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

The plant produced diacetyl by oxidation of 2,3-butylene glycol into acetyl-methyl-carbinol (AMC; acetoin), which was further partly oxidized

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into diacetyl (2,3-butanedione). Acetaldehyde and acetic acid were side products of the two primary reaction products, AMC and diacetyl. Diacetyl production took place in a completely closed system in a reactor vessel at an elevated process temperature (~360°C). Exposure for process operators only existed at the end of the production process and they did not have exposures to heated product.

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

Spirometry

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

Clinical Evaluation

Referred workers underwent medical history taking and physical examination. We used medical files of the Occupational Health Service to reconstruct case histories and collected additional information on pulmonary function, including static lung volumes by body plethysmography and single-breath carbon monoxide diffusing capacity (D_{LCO}). We performed a high-resolution computed tomography (HRCT) scan of the lungs in all workers with fixed airway obstruction using a volumetric acquisition with 16×0.75 or 64×0.625 mm collimation during inspiration and dynamic expiration.

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

Epidemiologic and Statistical Analysis

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

RESULTS

Characteristics of the Study Population

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

Exposure Assessment

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

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

TABLE 1. CHARACTERISTICS OF DIACETYL PLANT WORKERS*

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

* n = 175.

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

Clinical Investigation

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

TABLE 2. MULTIPLE LINEAR REGRESSION ANALYSIS OF PULMONARY FUNCTION VARIABLES ON AGE, STANDING HEIGHT, SMOKING, AND JOB IN A POPULATION OF DIACETYL PLANT WORKERS*

Determinant	FEV_1 (*ml*)		FVC (*ml*)		FEV_1/FVC (%)		MEF_{50} (*L/s*)	
	β	SE	β	SE	β	SE	β	SE
Intercept	21	1,601	−4,502†	1,817	146†	17	6.91‡	3,62
Age	−34†	6	−29†	7	−0.28†	0.07	−0.06†	0.01
Height	3,275†	810	6,208†	919	−29†	9	0.45	1.83
Smoking status, %§								
Current smoker	−284†	138	−288‡	156	−0.77	1.49	−0.34	0.31
Former smoker	259†	130	271‡	148	1.61	1.41	0.53‡	0.29
Jobs‖								
Process operator	−292†	144	−182	164	−3.08‡	1.56	−0.51	0.33
Quality control lab	−247	203	−200	231	−1.69	2.19	−0.76‡	0.46
Technical service	−260	197	−100	223	−2.89	2.13	−0.82‡	0.44
Adjusted R^2, %	37		41		12		13	

Definition of abbreviation: MEF_{50} = mean expiratory flow at 50% of FVC.
* n = 159, only white males.
† $p < 0.05$.
‡ $p < 0.10$.
§ Never smoked as reference group.
‖ The job title "other jobs" as reference group.

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

TABLE 3. CHARACTERISTICS OF CASES WITH RADIOLOGIC SIGNS OF BRONCHIOLITIS OBLITERANS

	Case 1	Case 2	Case 3
Age at time of diagnosis, yr	55	72	59
Age at symptom onset, yr	45	52	39
Sex	M	M	M
Smoking pack-years	0	0	14
Process operator	+	+	+
Year started at the diacetyl plant	1993	1971	1985
Year of symptom onset*	1994	1985	1985
Year stopped at the diacetyl plant	2003	1987	2001
Wheeze	+	−	+
Fever	+	−	−
Fatigue	+	+	−
Night sweats	−	−	+
Eye irritation	+	−	+
Nasal irritation	−	−	+
Skin irritation	+	−	−
Crackles on chest examination	−	−	−
Initial diagnosis	COPD	COPD	Asthma, COPD
Lung function at time of examination			
FEV_1% pred†	35.1	37.4	42.3
FVC % pred†	65.2	65.0	57.7
FEV_1/FVC %†	42.9	43.8	57.8
Reversibility‡	−	−	−
TLC % pred	110	94	99
RV % pred	157	132	140
RV/TLC % pred	131	125	130
D_{LCO} % pred	85	70	61
K_{CO} % pred	108	117	76

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; D_{LCO} = diffusing capacity for carbon monoxide; K_{CO} = transfer coefficient for carbon monoxide; M = male; RV = residual volume; TLC = total lung capacity.
* Based on medical history.
† Post-bronchodilator.
‡ Reversibility defined as ⩾ 9% increases in FEV_1 after bronchodilation.
+ Yes/present.
− No/not present.

All three subjects had previously been diagnosed by chest physicians as having chronic obstructive pulmonary disease (COPD) or asthma, for which they were treated by inhaled β-agonists and corticosteroids. Case 1 used a long-acting anticholinergic agent; none received maintenance oral corticosteroid therapy.

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

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

Lung Function

All three cases showed a fixed airway obstruction. An increased residual volume (RV) as well as an increased RV to TLC (total lung capacity) ratio, together with a decreased FVC indicated hyperinflation in all cases. D_{LCO} was below the normal range in two cases, and the K_{CO} in one case was below normal.

Radiology

Multislice HRCT showed slight inhomogeneity of the lung attenuation during inspiration; on expiratory scans, air trapping was visible in all three cases. None of the cases demonstrated major centrilobular or paraseptal emphysema compatible with COPD as seen in smokers (Figure 2). In case 1, HRCT showed a mosaic pattern with air trapping compatible with bronchiolitis obliterans (Figure 2). In case 2, air trapping was less geographic and mainly localized in the lower lobes and the posterior portions of the upper lobe. There was mild bronchial wall thickening and

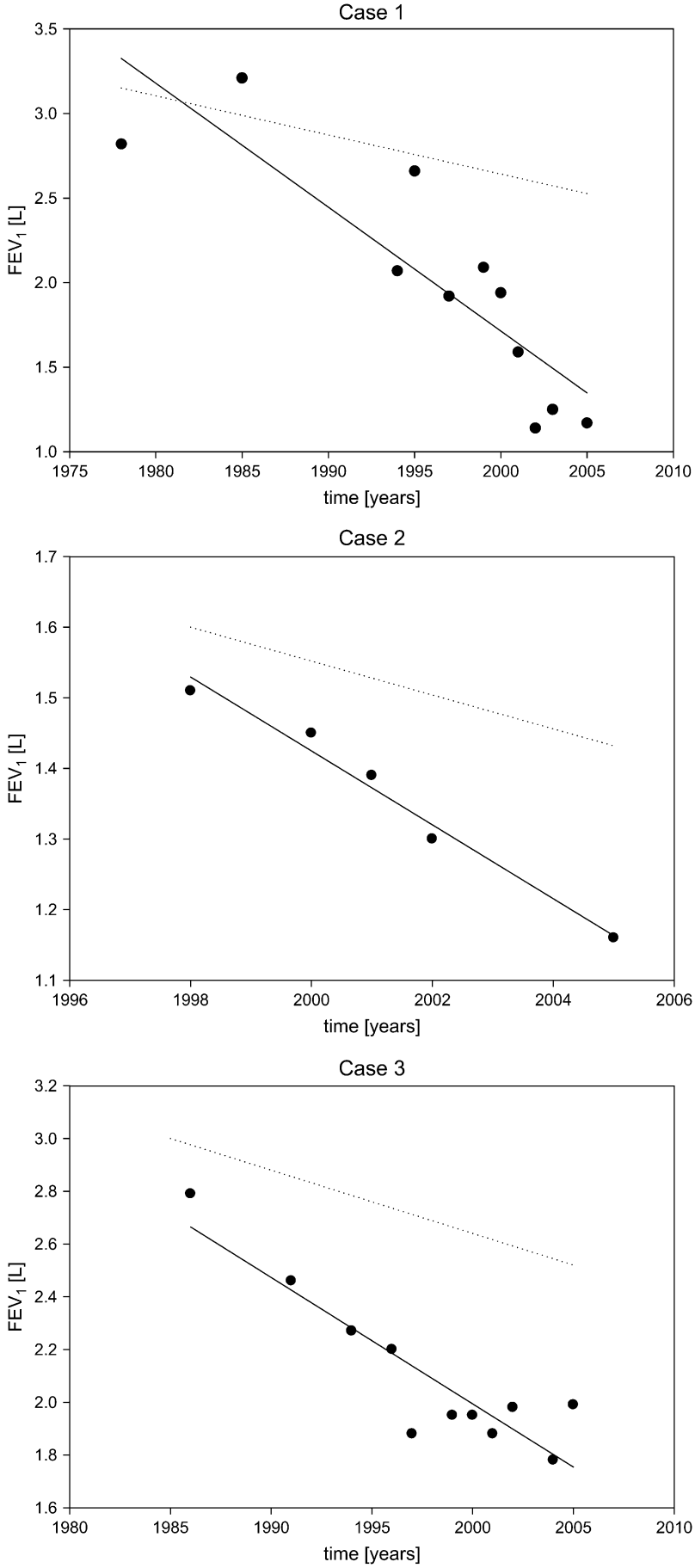

Figure 1. FEV_1 as a function of time for cases with bronchiolitis obliterans syndrome in comparison with expected decline. FEV_1 values as shown were available from occupational health records before 1995 and from hospital records since 1995. Expected decline, *dotted lines*; FEV_1 data points, *solid circles*; observed decline, *solid lines*.

focal accentuation of centrilobular structures. In case 3, the inhomogeneity of the lung parenchyma accentuated on the expiratory scan with air trapping, especially in central and ventral portions of the lung. The lung periphery, lung apex, and the basal lungs showed a normal increase in lung density during expiration. This effect was combined with an almost complete collapse of the central bronchi (main and lobar bronchi) during expiration. Modest bronchial wall thickening was present.

Thoracic Lung Biopsy

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

DISCUSSION

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

Lung biopsies obtained in one case showed nonspecific small airway disease. The main histologic finding in bronchiolitis obliterans is a constrictive bronchiolitis as seen in patients with connective tissue disease and in bone marrow and (heart–)lung transplants. Because lesions are often patchy or may present as centrilobular emphysema, the diagnosis may be missed (18). When pathology is lacking, the term "obliterative bronchiolitis" may more accurately describe the clinical syndrome—that is, airway obstruction due to bronchiolitis.

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

Population at Risk

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

The decline of FEV_1 value of cases was higher than expected in periods in which they worked at the diacetyl plant. Typically, FEV_1 shows average declines of 24 ml/year in nonsmokers and

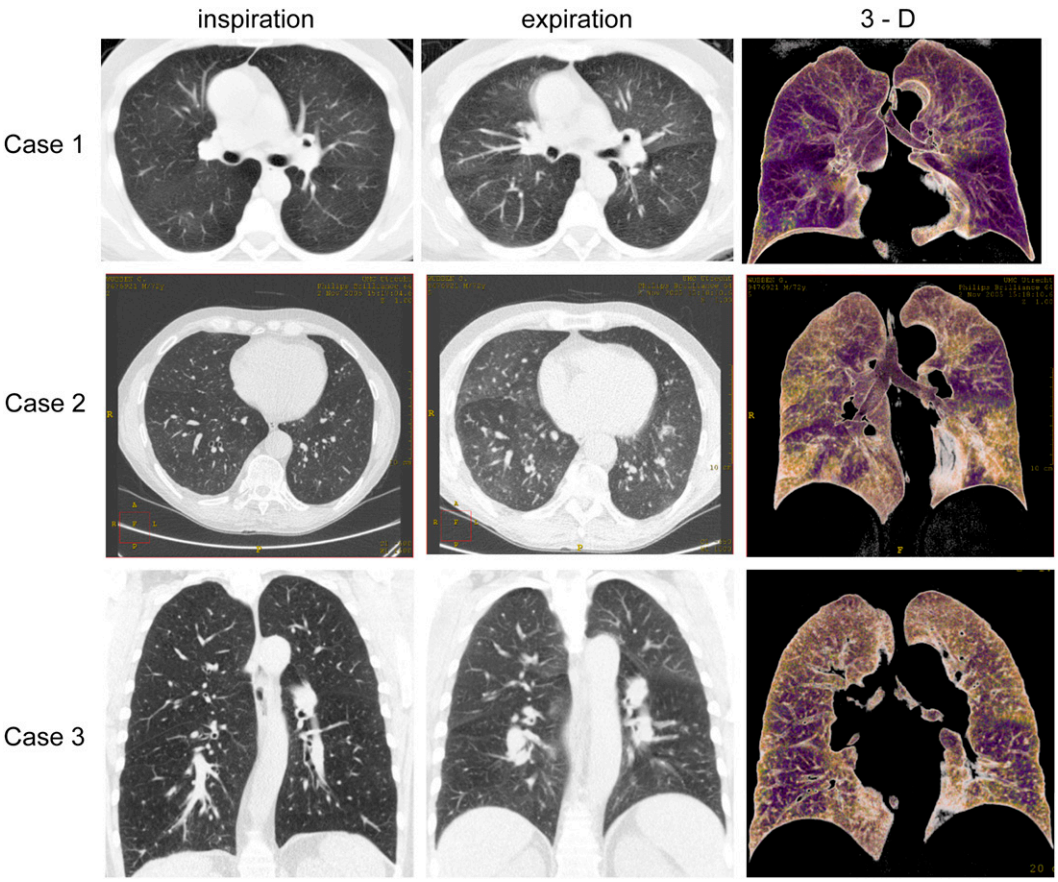

Figure 2. Multislice high-resolution computed tomography scans of the lungs during inspiration (*leftmost column*) show inhomogeneity of the lung attenuation during inspiration. In Case 1 (*top row*), a slight mosaic pattern of the lung parenchyma is already present during inspiration. During expiration (*middle column*), a mosaic pattern is visible in all three cases. Note that areas in which lung density remains virtually unchanged are indicative of substantial air trapping. In expiratory three-dimensional color rendering of coronal 3-cm-thick sections of the lungs (*rightmost column*) inhomogeneity is even more pronounced with purple areas due to air trapping. Findings are compatible with bronchiolitis obliterans.

28 ml/year in smokers in longitudinal studies (19). The excess declines may have been affected by spirometry measured in different settings with different devices and technicians, but each of the cases had quite consistent declines despite different data sources.

Exposure

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

Causal Relationship between BOS and Diacetyl Exposure

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

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

Study Limitations

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

Moreover, our analyses of exposure have not addressed the potential importance of short-term or peak exposures among workers because such information was lacking. By not pursuing decedents and not obtaining clinical evaluation of one case of fixed airway obstruction, we may have underestimated the number of BOS cases. Indeed, an additional case was found after the study among the 10 nonparticipants among the former workers at the plant. This post-study case was a 63-year-old nonsmoking process operator who worked from 1968 to 1970 and stopped working in 1970 when he became symptomatic and was diagnosed with severe COPD (FEV_1, 31% predicted; FEV_1/FVC, 37%). The 2006 HRCT scan of the lungs was compatible with a diagnosis of bronchiolitis obliterans. Thus, at least four cases of clinical bronchiolitis obliterans arose in 206 workers employed in this diacetyl manufacturing plant.

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

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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