CLINICAL BRONCHIOLITIS OBLITERANS IN WORKERS AT A MICROWAVE-POPCORN PLANT

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ABSTRACT

Background In May 2000, eight persons who had formerly worked at a microwave-popcorn production plant were reported to have severe bronchiolitis obliterans. No recognized cause was identified in the plant. Therefore, we medically evaluated current employees and assessed their occupational exposures.

Methods Questionnaire responses and spirometric findings in participating workers were compared with data from the third National Health and Nutrition Examination Survey, after adjustment for age and smoking status. We evaluated the relation between exposures and health-related outcomes by analyzing the rates of symptoms and abnormalities according to current and cumulative exposure to diacetyl, the predominant ketone in artificial butter flavoring and in the air at the plant.

Results Of the 135 current workers at the plant, 117 (87 percent) completed the questionnaire. These 117 workers had 2.6 times the expected rates of chronic cough and shortness of breath, according to comparisons with the national data, and twice the expected rates of physician-diagnosed asthma and chronic bronchitis. Overall, the workers had 3.3 times the expected rate of airway obstruction; those who had never smoked had 10.8 times the expected rate. Workers directly involved in the production of microwave popcorn had higher rates of shortness of breath on exertion and skin problems that had developed since they started work than workers in other parts of the plant. There was a strong relation between the quartile of estimated cumulative exposure to diacetyl and the frequency and extent of airway obstruction.

Conclusions The excess rates of lung disease and lung-function abnormalities and the relation between exposure and outcomes in this working population indicate that they probably had occupational bronchiolitis obliterans caused by the inhalation of volatile butter-flavoring ingredients. (N Engl J Med 2002; 347:330-8.)

IN May 2000, eight persons who had formerly worked at a plant that produces microwave popcorn were reported to the Missouri Department of Health to have bronchiolitis obliterans.[1,2] These workers had become ill during the period from 1993 to 2000, while employed at the popcorn plant, and none had reported an incident of presumed overexposure that preceded their symptoms. Four had worked in the room where microwave-popcorn flavoring agents were mixed, and four had worked only in the microwave-popcorn packaging areas. On the basis of these cases, we conducted medical examinations and environmental surveys of workers employed at the plant in November 2000 to determine whether any of them had signs or symptoms of this illness and whether exposures at the plant contributed to the disease.

The production area of the microwave-popcorn plant encompassed a flavor-mixing room, a quality-control room for popping sample product, a maintenance shop, and packaging lines where microwavable bags were filled with popcorn and flavorings, packaged, and boxed. The ingredients of the flavorings included soybean oil, salt, butter flavoring, and coloring agents. In the mixing room, one worker per shift opened the lid of an oil tank that was heated to approximately 130°F (54°C) and added flavorings in batch operations. The flavoring mixture was then pumped into heated holding tanks above the microwave-popcorn packaging lines. On the packaging lines, the kernel popcorn and flavoring mixture were added to the microwavable bags by a machine operator; the bags were then sealed, labeled, and boxed; and the boxes were stacked on pallets. The following areas of the plant were physically separate from the microwave-popcorn production area: the warehouse, the bag-printing area, outdoors, the line where unflavored kernel popcorn was packaged (in polyethylene bags), and the offices where management and clerical activities were performed.

Analysis of air samples from the mixing room identified more than 100 volatile organic compounds. There were no known occupational causes[3] of bron-

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chiolitis obliterans identified among these compounds or in the plant at large. Diacetyl (2,3-butanedione), a ketone with butter-flavor characteristics, was the predominant compound isolated from air samples.

METHODS

Index Patient

A housewife began her first job in October 1993, at the age of 40, on the microwave-popcorn packaging line at the plant. She had no chest symptoms, had never smoked, and was accustomed to walking three to five miles (5 to 8 km) daily. In March 1994, she started coughing about three hours after the start of her evening shift, without any changes in her work environment or her usual seated job activities and without any improvement in this symptom while she was away from work. Two to three weeks later, myalgias, night sweats, and exercise-induced exacerbation of the cough developed. Gradually, exertional dyspnea developed and prevented her from taking her accustomed walks and from lifting 25-lb (11-kg) boxes at work. In April, her dry cough became productive; she consulted an allergist because of right-sided chest pain, and the allergist diagnosed bronchitis, hay fever, and asthma. Use of a bronchodilator did not result in an improvement in symptoms. In June, she consulted a pulmonologist, who documented a forced expiratory volume in one second (FEV_1) of 0.86 liter (30 percent of the predicted value), a forced vital capacity (FVC) of 2.27 liters (66 percent of the predicted value), and a normal diffusing capacity for carbon monoxide. The patient stopped working in mid-June; she had lost 8 lb (3.6 kg) over the course of her employment. Her dyspnea subsequently increased, but her cough slowly improved.

In October 1994, the patient's FEV_1 was 0.73 liter (24 percent of the predicted value), with no response to a bronchodilator; the total lung capacity was 6.1 liters (120 percent of the predicted value); the residual volume was 3.1 liters (251 percent of the predicted value); and the airway resistance was 441 percent of the predicted value. The carbon monoxide diffusing capacity was 85 percent of the predicted value, but she had a decrease in oxygen saturation, from 95 percent to 88 percent during a three-minute walk and to 87 percent during a six-minute walk. High-resolution computed tomography showed minimal, diffuse bronchial-wall thickening; air trapping; and a right-upper-lobe granuloma. Thoracoscopic lung biopsy revealed scattered, non-necrotizing granulomas; focal bronchiolar fibrosis; fibroblast proliferation compressing one bronchiolar lumen; and no interstitial pneumonia. The patient had no response to high-dose prednisone and only a symptomatic response to a three-month course of cyclophosphamide (100 mg per day). She was placed on a waiting list for a lung transplant in November 1995 but has not received a transplant. Her FEV_1 in December 2001 was 0.61 liter (21 percent of the predicted value).

Medical Survey

Trained interviewers administered a standardized questionnaire,[4] supplemented with questions about respiratory, mucous-membrane, and constitutional symptoms and work history, to employees of the popcorn plant. Written informed consent was obtained from all participating employees. We compared the responses with data from identical questions on the third National Health and Nutrition Examination Survey (NHANES III).[5] Experienced technicians followed standard guidelines for performing spirometry[6] and measuring carbon monoxide diffusing capacity[7,8] and used spirometric reference values and 95 percent normal confidence intervals generated from NHANES III data.[9] We defined airway obstruction as a low ratio of FEV_1 to FVC in the presence of a low FEV_1 value, and we assessed the reversibility of the obstruction with a bronchodilator, with improvement defined as 12 percent and 200-ml increases in FEV_1.[10] Two National Institute for Occupational Safety and Health (NIOSH)–certified B readers[11] independently classified full-size posteroanterior chest radiographs without knowledge of the participants' characteristics.[12]

Assessment of Exposure

We characterized job-specific exposure to diacetyl, a marker of organic-chemical exposure, by testing air samples from various areas in the plant with the use of sorbent tubes (Anasorb, SKC), a sampling rate of 0.03 liter per minute, and gas chromatography according to method 2557 of NIOSH.[13] To examine respirable dust samples from employees' breathing zone and various areas in the plant, we used cyclones (BGI) with 37-mm filters, a flow rate of 4.2 liters per minute, and gravimetric analysis according to NIOSH method 500.[13] A detailed description of sampling methods and the results for other analytes (nitrogen oxides, endotoxins, viable fungi and bacteria, total dust, particles according to size, volatile organic compounds, acetoin, nonanone, methyl ethyl ketone, acetaldehyde, and acetic acid) are available from the National Auxiliary Publications Service (NAPS).* We estimated the cumulative exposure for each participant by summing the products of the time spent at each job and the mean exposure in that job area. Participants were placed in four groups of equal numbers (quartiles) according to rank order of increasing cumulative exposure to diacetyl.

Statistical Analysis

We used SAS software[14] to conduct the statistical analyses. Chi-square and Fisher's exact tests were used to analyze categorical data, and Student's t-test and Pearson's correlation were used to analyze continuous data. We applied the Cochran–Armitage test for trend. Logistic regression was used to analyze airway obstruction, with forward entry of data on exposure or symptom indexes, smoking status, and age. We considered two-sided P values of 0.05 or less to represent associations unlikely to be due to chance, except for tests of trend, in which we used one-sided, alternative hypotheses.

RESULTS

Characteristics of the Workers

Of the approximately 135 employees at the popcorn plant in late October 2000, 117 completed a questionnaire (87 percent) (Table 1). Ninety-seven of the respondents (83 percent) worked in the microwave-popcorn production area of the plant. Of these workers, six (including four who had worked in the mixing room or who had trained to work there) reported having changed job assignments at the plant because of breathing difficulties. We considered the 20 participants who did not work in this production area to constitute a minimally exposed, internal reference group; these employees worked on the plain-popcorn packaging line (where polyethylene bags were used), the bag-printing areas, the warehouse, the offices, or outdoor areas. Analysis of average levels of diacetyl according to work area indicated that mixing-room employees were exposed to roughly 800 times the level to which workers in the internal reference group were exposed, 55 times that to which the quality-control and maintenance workers were exposed, and 15 times

*See NAPS document no. 05608 for 10 pages of supplementary material. To order, contact NAPS, c/o Microfiche Publications, 248 Hempstead Tpke., West Hempstead, NY 11552.

that to which workers on the microwave-popcorn packaging lines were exposed (Table 2).

The majority of the participants (57 percent) reported having had exposures outside the popcorn plant to other possible causes of occupational lung disease; the leading sources of exposure were farming (40 percent), grain dust (32 percent), irritant gases (14 percent), and nitrogen oxides (8 percent). More workers in the internal reference group than in the microwave-popcorn production group reported at least one outside exposure (80 percent vs. 53 percent, $P=0.02$). Quartiles of increasing cumulative exposure to diacetyl had decreasing rates of farming exposures ($P=0.02$ for trend).

Medical Tests

Of the 116 participating employees who underwent spirometric testing, 31 had abnormal results on spirometry: 10 had low FVC values alone, 11 had airway obstruction alone, and another 10 had airway obstruction and low FVC values. Of the 21 employees with airway obstruction, 3 had FEV_1 values below 40 percent of the predicted value, and 2 had a significant response to an inhaled bronchodilator. Of the 10 employees with a low FVC value alone, 8 had minimal abnormalities; 7 had a low total lung capacity, indicating the presence of volume restriction; and 3 reported that their respiratory symptoms had preceded their employment in the popcorn plant. Of the 103 participants with interpretable results on diffusing-capacity tests, 7 had abnormal values (ranging from 60 percent to 76 percent of the predicted value). All the patients with abnormal results on diffusing-capacity tests were current or former smokers; only one had airway obstruction.

Chest radiographs obtained from 115 participants showed neither small (1/0 profusion criterion of the International Labour Organization[12]) nor large opacities consistent with the presence of pneumoconiosis, no other types of interstitial disease, and no cor pulmonale. Two radiographs showed emphysema (one of which involved bullae); one radiograph showed saber-sheath tracheal narrowing, attributable to chronic obstructive pulmonary disease or tracheal stenosis; and one radiograph showed focal upper-zone scarring and atelectasis at the left lung base.

TABLE 1. DEMOGRAPHIC AND EMPLOYMENT CHARACTERISTICS OF 117 MICROWAVE-POPCORN PLANT WORKERS IN NOVEMBER 2000.

CHARACTERISTIC	VALUE
Age — yr	
Median	36
Range	18–67
Female sex — no. (%)	61 (52)
Race or ethnic group — no. (%)	
White	107 (91)
Hispanic	5 (4)
Other	5 (4)
Smoking status — no. (%)*	
Current smoker	47 (40)
Former smoker	17 (15)
Never smoked	52 (44)
Time since start of employment — yr	
Median	3.4
Range	0.1–17.6
Length of workweek — hr	
Median	40
Range	36–50

*Data on smoking status were not available for one worker.

Prevalence of Health-Related Outcomes

We calculated the ratio of the observed to expected prevalence of health-related outcomes, with expected rates based on rates from NHANES III, after adjustment for age and smoking status. The current workers reported 2.6 times the prevalence of chronic cough that was reported in NHANES III; 2.6 times the prevalence of exertional shortness of breath (shortness of breath when hurrying on level ground or walking up a slight hill); and 3.0 times the prevalence of wheezing (other than wheezing due to colds) (Table 3). The prevalence ratios were higher among workers who had never smoked than among current or former smokers and were higher among younger workers (those 17 to 39 years old) than among older workers (those 40 to 69 years old). The prevalences of self-reported, physician-diagnosed asthma and chronic bronchitis among the current workers were 1.8 and 2.1 times the expected rates, respectively, but there was no evidence of a disproportionate prevalence of hay fever (data not shown). Overall, current employees had 3.3 times the expected rate of airway obstruction. The prevalence of airway obstruction increased with increasing age in both current and former smokers at the plant and especially in workers who had never smoked (Fig. 1): the prevalence ratios in this subgroup were 11.4 among workers 40 years old or older and 8.3 among those younger than 40.

Relation between Exposures and Health-Related Outcomes

The excess prevalence of respiratory symptoms was not distributed uniformly within the plant (Table 4). Workers in the microwave-popcorn production areas (including quality-control and maintenance workers) had significantly higher rates of exertional shortness of breath, regular trouble with breathing, a combination of two or more respiratory symptoms, unusual fatigue, and any systemic symptoms than minimally exposed workers in other areas of the plant. The rate of rashes or other skin problems since the date of hire was also significantly higher among workers in the mi-

TABLE 2. LEVELS OF DIACETYL AND RESPIRABLE DUST ACCORDING TO WORK AREA IN THE MICROWAVE-POPCORN PLANT IN NOVEMBER 2000.*

WORK AREA	DIACETYL		RESPIRABLE DUST†	
	NO. OF SAMPLES	LEVEL	NO. OF SAMPLES	LEVEL
		ppm		mg/m³
Plain-popcorn packaging line, bag-printing areas, warehouse, offices, or outside	14	0.04 (≤0.25)‡	33	0.05 (0.008–0.12)
Quality control or maintenance	5	0.56 (0.33–0.89)	15	0.11 (≤0.29)‡
Microwave-popcorn packaging lines	22	1.88 (0.26–6.80)	72	0.12 (0.01–0.18)
Mixing room	12	32.27 (1.34–97.94)	18	0.34 (0.12–0.78)

*Levels of analytes are expressed as means, with ranges given in parentheses.

†Measurements of respirable dust included both 54 area samples and 84 personal samples.

‡At its minimum, the analyte was undetectable (diacetyl, less than approximately 0.01 ppm; respirable dust, less than 0.005 mg per cubic meter).

crowave-popcorn production areas than among those in the other areas.

The prevalence of airway obstruction increased with increasing cumulative exposure to diacetyl. The rates of airway obstruction, according to quartiles of increasing exposure, were 10.3 percent, 10.3 percent, 24.1 percent, and 27.6 percent (P for trend=0.03). The proportion of workers with abnormal results on spirometry (airway obstruction or a low FVC value) also increased with increasing cumulative exposure, to 13.8 percent, 24.1 percent, 31.0 percent, and 37.9 percent in successive quartiles (P for trend=0.02). Workers in each quartile of increasing cumulative exposure to diacetyl had decreasing average FEV_1 values (Fig. 2). The average FEV_1 was 4.5 percent, 8.9 percent, and 12.5 percent lower than the predicted value in the second, third, and fourth quartiles of diacetyl exposure, respectively, than in the first quartile.

Of other indexes of exposure, working in the quality-control room at the plant was significantly associated with airway obstruction in a logistic-regression analysis, after adjustment for age and smoking status: five of six persons were affected (odds ratio for the comparison with all the other workers, 41.7; 95 percent confidence interval, 3.5 to 494).

Associations among Outcome Variables

Workers with cough, phlegm, chest tightness on awakening, exertional shortness of breath, or wheezing (other than wheezing due to colds) were significantly more likely than workers without each of these chest symptoms to have airway obstruction, with odds ratios ranging from 4.2 (95 percent confidence interval, 1.1 to 15.6) to 10.5 (95 percent confidence interval, 2.7 to 40.1), after adjustment for age and smoking status. In contrast, about one in four people with airway obstruction reported no respiratory symptoms. Workers with airway obstruction did not have a significantly higher prevalence of systemic symptoms, skin problems that began after the date of hire, or mucous-membrane irritation than those without airway obstruction. The 21 participants with airway obstruction on spirometry were significantly more likely than those without airway obstruction to have reported a physician's diagnosis of acute or chronic bronchitis ($P<0.001$ for both comparisons), asthma ($P=0.001$), pneumonia ($P<0.001$), or emphysema ($P=0.005$) since starting work at the plant (data not shown). Among those with physician-diagnosed acute bronchitis, the number of attacks ranged up to 22 (median, 4). Only 13 of the 21 (62 percent) reported having been given a diagnosis by a physician that would account for the obstructive impairment (asthma, emphysema, or chronic bronchitis).

DISCUSSION

The respiratory symptoms and physician-diagnosed conditions identified in both popcorn-plant workers who were current or former smokers and those who had never smoked and corroborated by objective findings of spirometric abnormalities are not specific for any single type of lung disease. Although the physicians who saw the workers with symptoms often told them that they had asthma or chronic bronchitis, the medical findings of this cross-sectional study make these diagnoses unlikely. We found most cases of airway obstruction to be unresponsive to the administration of a bronchodilator, making asthma an unlikely possibility. Chronic bronchitis probably does not explain exertional shortness of breath. Abnormalities in the diffusing capacity for carbon monoxide or on the chest radiograph were rare, ruling out interstitial, em-

TABLE 3. PREVALENCE RATIOS OF RESPIRATORY CONDITIONS ACCORDING TO SMOKING STATUS AND AGE GROUP AMONG THE POPCORN-PLANT WORKERS, AS DERIVED FROM EXPECTED RATES FROM NHANES III.*

SYMPTOM OR CONDITION†	AGE GROUP	CURRENT OR FORMER SMOKERS				NEVER SMOKED				ALL PARTICIPANTS			
		NO.	EXPECTED NO.	OBSERVED NO.	PREVALENCE RATIO	NO.	EXPECTED NO.	OBSERVED NO.	PREVALENCE RATIO	NO.	EXPECTED NO.	OBSERVED NO.	PREVALENCE RATIO
	yr												
Chronic cough	17–39	40	5.2	15	2.9	26	0.6	3	5.0	66	5.0	18	3.6
	40–69	25	3.6	6	1.7	26	1.6	4	2.5	51	5.7	10	1.8
	Total	65	8.9	21	2.4	52	2.0	7	3.5	117	10.8	28	2.6
Shortness of breath	17–39	38	8.6	23	2.7	26	2.3	11	4.8	64	10.0	34	3.4
	40–69	24	7.3	13	1.8	24	4.9	14	2.9	48	12.7	27	2.1
	Total	62	16.4	36	2.2	50	6.8	25	3.7	112	23.1	61	2.6
Wheezing	17–39	40	6.5	18	2.8	26	1.6	6	3.8	66	7.4	24	3.2
	40–69	25	4.2	11	2.6	26	2.0	7	3.5	51	6.7	18	2.7
	Total	65	10.7	29	2.7	52	3.5	13	3.7	117	14.0	42	3.0
Asthma	17–39	40	3.6	6	1.7	26	1.7	2	1.2	66	5.1	8	1.6
	40–69	25	2.1	4	1.9	26	1.9	5	2.6	51	4.1	9	2.2
	Total	65	5.7	10	1.8	52	3.6	7	1.9	117	9.2	17	1.8
Chronic bronchitis	17–39	40	2.8	5	1.8	26	0.6	3	5.0	66	3.0	8	2.7
	40–69	25	2.2	3	1.4	26	1.3	3	2.3	51	3.7	6	1.6
	Total	65	5.1	8	1.6	52	1.8	6	3.3	117	6.8	14	2.1
Airway obstruction	17–39	39	1.5	0	0	26	0.6	5	8.3	65	2.0	5	2.5
	40–69	25	3.0	8	2.7	26	0.7	8	11.4	51	4.3	16	3.7
	Total	64	5.1	8	1.6	52	1.2	13	10.8	116	6.4	21	3.3

*The expected numbers were obtained from the third National Health and Nutrition Examination Survey (NHANES III).[5]

†The questions corresponding to the self-reported symptoms or physicians' diagnoses were obtained from the American Thoracic Society–Division of Lung Disease standardized questionnaire[4] and are as follows: chronic cough, question 7E; shortness of breath (when hurrying on level ground or walking up a slight hill), question 13A; wheezing (other than wheezing due to colds), question 10A2; asthma, question 20C; and chronic bronchitis, question 18C. Airway obstruction was assessed by spirometry.

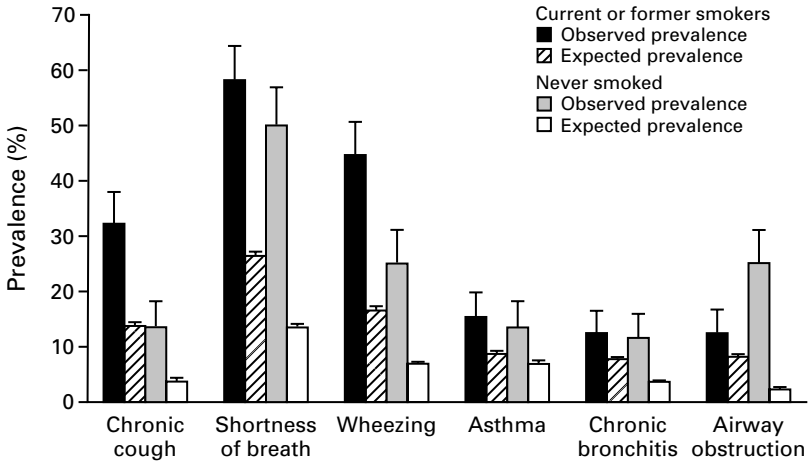

Figure 1. Observed and Expected Prevalence of Respiratory Conditions among Workers in the Popcorn Plant, According to Smoking Status, in November 2000.

The expected prevalence rates were calculated from data in the third National Health and Nutrition Examination Survey[5] and were adjusted for age and sex. The T bars represent standard errors.

TABLE 4. PREVALENCE OF SYMPTOMS ACCORDING TO WORK AREA WITHIN THE POPCORN PLANT, NOVEMBER 2000.

SYMPTOM	PLAIN-POPCORN PACKAGING, BAG-PRINTING, WAREHOUSE, OFFICES, OR OUTSIDE (N=20)	QUALITY CONTROL, MAINTENANCE, MICROWAVE-POPCORN PACKAGING, OR MIXING (N=97)	P VALUE
	no. of workers (%)		
Respiratory*			
Chronic cough	3 (15)	25 (26)	0.40
Phlegm	3 (15)	18 (19)	1.00
Wheezing	5 (25)	37 (38)	0.31
Attacks of wheezing	2 (10)	23 (24)	0.24
Chest tightness	3 (15)	29 (30)	0.27
Exertional shortness of breath	1 (5)	30 (33)†	0.01
Regular trouble with breathing	1 (5)	36 (37)	0.004
Two or more of the above respiratory symptoms	3 (15)	44 (45)	0.01
Systemic			
Fever	0	1 (1)	1.00
Chills	0	3 (3)	1.00
Night sweats	0	10 (10)	0.21
Influenza-like achiness	0	8 (8)	0.35
Unusual fatigue	1 (5)	37 (38)	0.003
One or more of the above systemic symptoms	1 (5)	42 (43)	<0.001
Other			
Mucous-membrane irritation‡	10 (50)	66 (70)§	0.12
Skin irritation	1 (5)	33 (34)	<0.004

*Wheezing was defined as wheezing other than that due to colds; attacks of wheezing as at least two such attacks accompanied by shortness of breath; chest tightness as that occurring on awakening during the previous 12 months; exertional shortness of breath as shortness of breath when walking with persons of similar age on level ground.

†Data were available for 92 participants.

‡Mucous-membrane irritation was defined as irritation of the eyes, nose, or throat.

§Data were available for 94 participants.

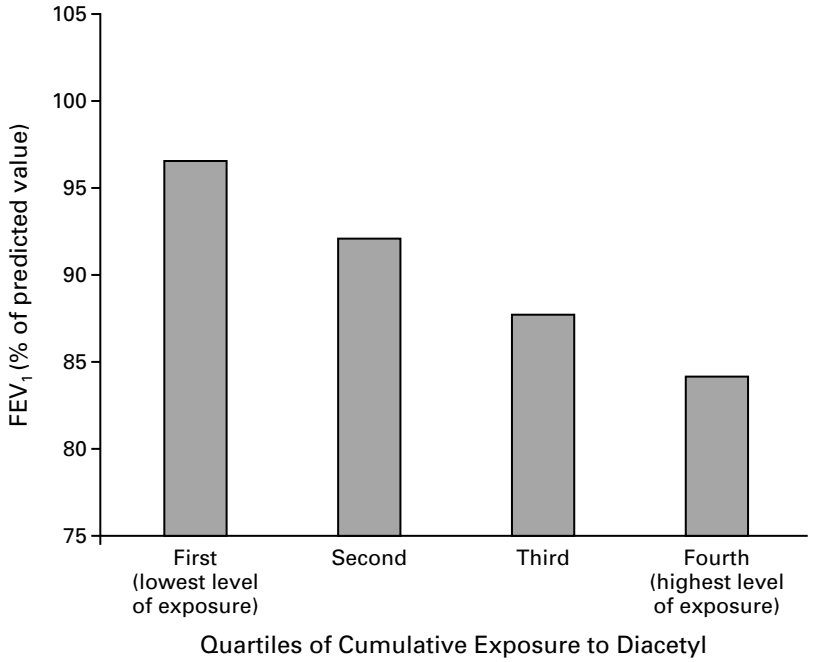

Figure 2. Mean Forced Expiratory Volume in One Second (FEV_1) Value, According to Cumulative Exposure to Diacetyl in the Popcorn Plant in November 2000.

Cumulative exposure to diacetyl ranged from 0 to 126 ppm-year. The cutoff points for the four quartiles of cumulative exposure were 0.65, 4.5, and 11 ppm-yr.

physematous, or alveolar disease as explanations of the excess rates of lung disease in these workers. The combination of fixed airway obstruction with normal findings on chest radiography is best explained by bronchiolitis obliterans, which had been recognized in eight former workers. However, in contrast to most examples of occupational constrictive bronchiolitis obliterans,[3] neither the former workers nor the current workers reported a distinct episode of overexposure that preceded the onset of symptoms. Unlike occupational asthma, no temporal relation existed between working at the plant and the severity of symptoms over the course of the workday or workweek. Thus, the association of this endemic disease with exposures in the workplace was largely unsuspected by the workers, their physicians, and plant managers.

The distribution of health-related conditions among the workers and over time provides clues to the identity of the previously unsuspected agent that caused bronchiolitis obliterans in the former workers and the excess prevalence of respiratory disease in the current workers. Since the onset of illness in the earliest index case occurred in 1993, the causative agent was present in the plant over a long period; that respiratory illness was endemic in this plant suggests that the hazard was frequently and perhaps continually present. The persons who worked in the mixing room had the highest risk, as reflected in their high level of representation among the index patients[15] and among the workers who changed jobs because of respiratory symptoms. Severe symptoms and high rates of symptoms were found in the overall group of participants who worked in the microwave-popcorn production area, as compared with those who worked on the plain-popcorn packaging line, in the bag-printing areas, in the warehouse, in the offices, or outdoors. Among the microwave-popcorn production workers, quality-control workers also had substantial risk. Current exposures to ketones, other volatile organic compounds, and respirable dust were all highest among those who worked in the microwave-popcorn production area and were particularly high among those who worked in the mixing room. 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. The relation between cumulative diacetyl exposure and changes in pulmonary function suggests that diacetyl may be a cause of respiratory disease or a marker of the causative exposures in this population.

This study had several limitations. Despite the high

rate of participation, the numbers of participants who were minimally exposed or highly exposed were small, limiting statistical power in comparisons and multivariate modeling. Nonetheless, there was no evidence of confounding, either by smoking status or by the presence or absence of other occupational exposures. In a cross-sectional design, measured exposures may not reflect historical exposures. The average diacetyl levels used in our assessments of exposure in various areas of the plant may misclassify individual exposures to the causative agents. Certainly, our analyses of exposure do not address the possible importance of short-term, peak exposures among workers in the mixing room when they lifted the lids of the heated tanks containing flavorings. Quality-control workers may have been exposed to volatile flavoring ingredients that were qualitatively different from those to which the other workers were exposed, because of the high temperatures generated by popping the microwave popcorn; however, their exposures exceed those likely to occur in the household by orders of magnitude.

Cross-sectional surveys of occupational hazards underestimate health-related outcomes because of the "healthy-worker effect."[16] In this plant, eight former workers were known to have left their jobs because of lung disease, thus leaving a healthier workforce that did not carry the entire burden of disease. Workers who changed assignments because of respiratory problems were included in our analyses of current exposures as having these problems in their current assignments, an assumption that may be inaccurate. Our analyses of cumulative exposure in relation to indexes of airway obstruction partially correct for this limitation.

In inhalation studies, butter-flavoring vapors producing diacetyl levels of 352 ppm damaged respiratory epithelium in the airways of rats.[17] NIOSH scientists chose this exposure level as one similar to that of possible peak levels in the space above the heated oil within the mixing or holding tanks in the popcorn plant. A peak diacetyl level of 1230 ppm was later measured in this space in a tank holding the same butter flavoring tested in the animal studies. Damage in the rats extended below the basement membrane of sloughed respiratory epithelium, suggesting that repair would probably involve airway fibrosis. These preliminary findings in animals suggest that a volatile ingredient in the butter flavoring is a biologically plausible cause of the respiratory effects seen in the workers in the popcorn plant. Support for this hypothesis comes from the findings of a health-hazard investigation at a company that mixed flavorings in cornstarch for the baking industry.[18] At that company, two young workers in the mixing facility, neither of whom had ever smoked, had bronchiolitis obliterans within five months after beginning work; one of them reported that he suspected the "cinnabutter" flavoring to be a cause. Two other suspected cases of bronchiolitis obliterans occurred in smokers who worked in the mixing facility. Another cluster of cases of bronchiolitis obliterans occurred in workers in a flavoring-manufacturing plant.[19] An additional case of fixed airway obstruction in a person who had never smoked was reported at another microwave-popcorn packaging plant; this worker had mixed butter flavorings from a different manufacturer with oil.[1]

Our findings of excess rates of lung disease and associations between indexes of exposure to volatile organic chemicals and obstructive lung disease support the conclusion that an agent in butter flavoring caused occupational bronchiolitis obliterans in exposed workers at this popcorn plant. Although many questions remain about the specific agents involved and about safe and unsafe levels of exposure, prevention is possible on the basis of the current findings. We recommended the use of air-purifying respirators with cartridges that filter organic vapors and particulates to decrease exposures to flavorings and isolation of ventilation in the mixing room from that in other areas of the plant. We have advised workers with symptoms or obstructive abnormalities to seek medical counsel regarding diagnosis, smoking cessation, immunization, and the advisability of continued exposure in the workplace, with or without respiratory protection.

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