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Bronchiolitis in Popcorn-Factory Workers (Correspondence)
Ezrailson, Edward G.; Taubert, Dirk; Lazar, Andreas; Schomig, Edgar; Parmet, Allen J.; Kreiss, Kathleen; Hubbs, Ann; Kullman, Gregory; Schachter, E. Neil.
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TEXT

Letter 001

To the Editor: Kreiss et al. (Aug. 1 issue) (Ref. 1) report a high incidence of bronchiolitis obliterans at a microwave-popcorn factory. The chemical diacetyl (2,3-butanedione) was singled out as a possible causal agent of this deadly condition and other medical problems found in workers in this plant. As a chemist, biochemist, and toxicologist, I would like to point out that 2,3-butanedione is in chemical equilibrium with 1,3-butane-diene-2,3-diol (Figure 1. This phenomenon, which is well known in organic chemistry, is called keto-enol tautomerism. This isomer is expected to be very reactive with oxygen both at room temperature and on heating. Thus, 1,3-butane-diepoxide-2,3-diol would be expected as a product. Although the parent compound is known to be reactive with arginine, the diepoxide is of particular interest, since butadiene diepoxide is a known human carcinogen. The appropriate government agencies must investigate and evaluate whether diacetyl should be banned from food products.§*Figure 1.-Chemicals 2,3-Butanedione and 1,3-Butane-Diene-2,3-Diol, and Their Expected Product, 1,3-Butane-Diepoxide-2,3-Diol *.**FIGURE OMITTED**§Edward G. Ezrailson, Ph.D.2308 West Settler's WayThe Woodlands, TX 77380edez1@prodigy.net

Letter 002

To the Editor: Kreiss and colleagues report frequent cases of bronchiolitis obliterans among workers in a popcorn plant that were attributed to the inhalation of the volatile ingredient diacetyl in the butter flavoring. Although this conclusion is in keeping with the toxic effects of diacetyl on the respiratory epithelium in animals, and although a dose-response relation (a decreasing forced expiratory volume in one second associated with increasing exposure to diacetyl) was established, it may not be the only causative agent. The workers who were affected the most were also exposed to the highest concentrations of other volatile compounds and respirable dust. Maize bran, glumes, and stigmas contain considerable amounts of tannins, (Ref. 1) which are necessarily constituents of airborne particles. Inhaled tannins are considered to be an important causal factor in obstructive pulmonary diseases among workers exposed to dust of plant origin, such as those who work in cotton mills or grain elevators and those who work with herbal tea. (Ref. 2) Therefore, tannins may be one of the substances implicated in the development of popcorn worker's lung.'' This

hypothesis is supported by the finding that clinical symptoms that follow the occupational inhalation of tannins are similar to those reported among popcorn workers. In addition, the lack of improvement in the symptoms with (beta)(sub 2)-agonist bronchodilators is consistent with the inhibitory effect of tannin on adenylate cyclase in airway epithelial cells. (Ref. 3)§Dirk Taubert, M.D., Ph.D.Andreas Lazar, M.D.Edgar Schomig, M.D.Medical College of the University of Cologne50931 Cologne, Germanydirk.taubert@medizin.uni-koeln.de

Letter 003

To the Editor: In his editorial (Aug. 1 issue), (Ref. 1) Schachter comments on occupational airway diseases but leaves out what I think is an important finding described in the accompanying article by Kreiss et al. As the occupational physician involved in this case, I noted that not only was an epidemic of bronchiolitis obliterans present, but the number of tobacco smokers involved was unusually small. (Ref. 2) Only one of the initial eight patients was a smoker. Nonsmokers were overrepresented among patients as compared with the exposed population. In the study population described by Kreiss et al., the workers who never smoked had a rate of airway obstruction that was three times as high as that among the smokers, although all workers were affected. An understanding of the mechanism of this protection could lead to preventive interventions.§Allen J. Parmet, M.D., M.P.H.Midwest Occupational MedicineKansas City, MO 64108mommd@kc.rr.com

The authors and a colleague reply:§

Letter 004

To the Editor: We used diacetyl as an index of exposure to volatile organic chemicals in the popcorn plant because it was the predominant one found in plant air. However, identification of the causal agent or agents in the flavoring will rely on studies in animals in which individual constituents are tested; such studies are now under way. Diacetyl is a leading candidate for investigation of potential respiratory toxicity because alpha-dicarbonyl compounds react with functionally reactive arginine residues in proteins and with guanine and inhibit superoxide dismutase and glutathione reductase, which are involved in protection from oxidative stress. In addition to Dr. Ezrailson's concern about the properties of a derivative diepoxide, diacetyl itself has been nominated for studies by the National Toxicology Program (NTP) because of widespread human exposure, limited evidence of mutagenicity, and relations to carcinogens and mutagens in terms of structure and activity, as well as because diacetyl is representative of aliphatic alpha-diketones. (See the NTP Web site at http://ntp-server. niehs.nih.gov.)

We did not detect 1,3-butadiene-2,3-diol or 1,2;3,4-diepoxybutane-2,3-diol in any samples collected by thermal desorption tubes and analyzed with gas chromatography-mass spectrometry. However, we agree with Dr. Ezrailson that diacetyl would be present in equilibrium with its tautomers, as governed by the equilibrium constants for the conversions. Since diacetyl occurs naturally in butter and during the manufacture of alcoholic beverages, any proposed ban of diacetyl in food products raises issues of practicality.

As noted by Taubert and colleagues, other agents within the workplace may contribute to the clinical bronchiolitis obliterans seen in this workforce. Indeed, necrosis of the respiratory epithelium in the mainstem bronchus was more severe in rats exposed to butter-flavoring vapors than in

rats exposed to diacetyl alone at a similar diacetyl concentration (unpublished data). We did not measure tannins. Workers managing the grain bins, presumably with greater exposure to organic dust, were in the low-risk group; mixers, who had almost no active contact with corn or its dusts, had the highest historical risk of fixed airway obstruction. The role of respirable salt dust in the airway damage found in microwave-popcorn production workers remains unclear. However, our observation that the same syndrome occurs in flavoring-production workers without exposure to grains or salt makes these agents less likely to be causal contributors.§Kathleen Kreiss, M.D.Ann Hubbs, D.V.M., Ph.D.Gregory Kullman, Ph.D.National Institute for Occupational Safety and HealthMorgantown, WV 26505kkreiss@cdc.gov

The editorialist replies:§

Letter 005

To the Editor: Dr. Parmet points out an interesting but unexplained observation of his study and that by Kreiss et al. In his original study, nonsmoking workers accounted for the majority of index cases of bronchiolitis; among the workers studied by Kreiss et al., those who had never smoked had unusually high rates of airway obstruction. This latter finding is not particularly unusual, since a high prevalence of disease among nonsmokers is frequently used to confirm the presence of a true occupational or environmental effect. (Ref. 1) What Parmet focuses on is the fact that although the frequency of airway obstruction in smoking workers in this cohort is increased (prevalence ratio, 1.6), it is not increased to the same extent as that among nonsmoking workers (prevalence ratio, 10.8). In occupational airway disease, the effect of the pollutant tends to be more pronounced among smokers, because the injury is frequently additive. Possible explanations for the lack of such an additive effect in this setting include a healthy-worker effect, by which sicker smoking workers would leave the industry at an early date, before the onset of bronchiolitis, and the possibility that cigarette smoking alters the deposition of inhaled particles (Ref. 2) in such a way as to decrease the amount of other pollutants arriving in smaller airways. Further speculation is possible, but the primary public health message raised by these studies remains clear: injury to the airway in industries dealing with organic pollutants such as those associated with the manufacturing of microwave popcorn may be frequent, disabling, and occasionally life-threatening.§E. Neil Schachter, M.D.Mount Sinai School of MedicineNew York, NY 10029

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Popcorn Worker's Lung (Editorial)
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TEXT

Occupational airway diseases are common workplace injuries that include occupational asthma, bronchitis, reactive airways dysfunction syndrome, and byssinosis (an airway disease affecting textile workers). The population prevalence of these syndromes is not known with certainty, but some studies suggest that as many as 15 percent of adult patients with asthma have airway disease attributable to workplace conditions. (Ref. 1) Within different industries, the prevalence of these syndromes varies from sporadic to frequent (10 percent or greater). The mechanisms of these injuries may involve immune sensitization, but often the disease mechanisms are unknown and are presumed to involve nonallergic, irritant-mediated responses to inhaled agents. (Ref. 2) In such responses, the relations between the concentrations of agents to which workers are exposed and the severity of illness -- so-called dose-response relations -- can frequently be established.

Clinically, many of these illnesses are difficult to distinguish from their nonoccupational, sporadic counterparts. Often, epidemiologic investigations or specific challenge testing is required to establish an association between the workplace and the findings. In many industries, such as some of those that process textiles and food products, the prevalence of respiratory symptoms among employees is several times that in nonexposed populations, presumably because of the presence of subclinical disease. (Ref. 3,4) For some workers, such as those in the textile industry, early reversible symptoms have been linked to the gradual onset of nonreversible disease, such as chronic obstructive pulmonary disease similar to that found in some patients who smoke cigarettes. (Ref. 5)

Predominant involvement of the small airways, such as the bronchioles, is infrequently reported in occupational airway disease but may lead to serious consequences. Bronchiolitis obliterans is one disease with such involvement, initiated by damage to the epithelium of the small conducting airways and progressing to inflammation of these airways and frequently of the adjacent alveolar tissue; the clinical consequence of this injury and inflammation is irreversible airway obstruction. In the occupational setting, the clinical syndrome of bronchiolitis has been associated with the presence of irritant gases, notably oxides of nitrogen but also chlorine, phosgene, ozone, hydrogen sulfide, and sulfur dioxide as well as organic and inorganic dusts. Among silo workers, exposure to high concentrations of oxides of nitrogen (higher than 50 parts per million) is paradoxically well tolerated during the first few hours of exposure, with

relatively few symptoms. Unlike water-soluble irritant gases, which rapidly dissolve on the mucous membranes of the upper airway, oxides of nitrogen hydrolyze slowly into acids, which penetrate to the lower airways. Here, they produce an intense inflammatory reaction. Lower respiratory symptoms become apparent only 3 to 24 hours after the beginning of the exposure. The most common symptoms include cough, dyspnea, and fever. Occasionally, a worker who is exposed to very high levels of oxides of nitrogen may have acute respiratory failure as a result of noncardiogenic pulmonary edema and may die before resuscitation can be performed. For those who survive the acute illness, symptoms may recur in three to six weeks, with respiratory insufficiency developing slowly. Histologic examination reveals bronchiolitis obliterans with marked intraluminal proliferation of fibrous tissue. (Ref. 6)

A number of investigators have reported sporadic cases of bronchiolitis obliterans among workers in unrelated industries that have not previously been associated with this disease, including nylon-flock workers, (Ref. 7) workers who spray prints onto textiles (with polyamide-amine Acramin FWN, Bayer] dyes), (Ref. 8) battery workers (who are exposed to thionyl chloride fumes), (Ref. 9) and workers in the food-flavoring industry. (Ref. 10) Most of these cases have involved the identification of a few affected workers, followed in some instances by a concerted effort on the part of regional or national organizations to discover additional cases.

In this issue of the Journal, Kreiss et al. (Ref. 11) investigate the clustering of cases of bronchiolitis obliterans in a microwave-popcorn packaging plant. As reported earlier this year, (Ref. 12) in May 2000 a physician specializing in occupational medicine described fixed obstructive lung disease in eight former employees of this microwave-popcorn plant, all of whom had been employed there between 1992 and 2000. Symptoms in all eight were compatible with descriptions of bronchiolitis obliterans developing in workers in other industries. Four of the eight had worked in the mixing room, and the other four had worked in the microwave-popcorn packaging area. Of the 425 people who had been employed at the plant between 1992 and 2000, only 13 had worked in the mixing room, suggesting that the incidence of disease in this group was very high. Air sampling in the plant detected many volatile organic compounds, but diacetyl, a ketone with butter-flavor characteristics, was singled out as a likely cause of the disease, given its very high concentration in the mixing room. Subsequent toxicity studies in rats have supported this association. (Ref. 13) The current investigation was a cross-sectional evaluation of 117 current workers in the plant. Unlike previous studies of occupational bronchiolitis, (Ref. 7–10) this investigation concentrated on the frequency of subclinical findings in the plant. The authors found that the prevalence of respiratory symptoms and of findings of obstruction on spirometry among the current workers was about three times that in the general population. Moreover, there was a strong exposure-response relation between cumulative diacetyl exposure and the frequency and extent of airway obstruction.

The implications of these quantitative studies can best be understood in the context of the questions they answer and, perhaps more important, the questions they suggest. Clearly, work in the mixing room of this microwave-popcorn plant conferred a high risk of this rare, severe lung disease. In a more subtle finding, subclinical disease, corresponding to symptoms and lung-function abnormalities not of a degree sufficient to

cause respiratory impairment, was seen to be clearly associated with the gradient of the irritant presumed responsible for the overt bronchiolitis obliterans. If these symptoms represent subclinical, smoldering bronchiolitis obliterans, many more workers in this industry may be at risk, particularly for a slowly developing but progressive form of chronic obstructive pulmonary disease. Respiratory findings with similar prevalences have been widely reported in many dusty industries, none of which to date have been associated with bronchiolitis obliterans. (Ref. 3,4) If injuries of this nature are more common in industries that produce organic dust and fumes, then more widespread control measures are needed to prevent the possibility of chronic disease.

Certainly, for those at high risk in the microwave-popcorn industry, immediate controls are required. For workers with early respiratory symptoms and lung-function abnormalities, studies to characterize airway injury by bronchoalveolar lavage and possibly lung biopsy are warranted and would clarify the implications of the dose-response relations established in the current study. More generally, workers in other industries that produce similar irritant dusts, fumes, or gases need to be evaluated for small-airway disease that could result in serious impairment such as that seen in workers in the microwave-popcorn plant. As for the health effect of microwave-popcorn products in the general population, there are no findings to date to suggest that consumers are at any risk.§E. Neil Schachter, M.D.Mount Sinai School of MedicineNew York, NY 10029

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Clinical Bronchiolitis Obliterans in Workers at a Microwave-Popcorn Plant
(Original Articles)

Kreiss, Kathleen; Gomaa, Ahmed; Kullman, Greg; Fedan, Kathleen;
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CORPORATE SOURCE: From the Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, Morgantown, W.Va. (K.K., A.G., G.K., K.F., P.L.E.); and the Office of Epidemiology, Missouri Department of Health and Senior Services, Jefferson City (E.J.S.). Address reprint requests to Dr. Kreiss at NIOSH, H2800, 1095 Willowdale Rd., Morgantown, WV 26505, or at kkreiss@cdc.gov.

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.)

TEXT

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. (Ref. 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 degreesF (54 degreesC) 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 (Ref. 3) of bronchiolitis 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(sub 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(sub 1) in December 2001 was 0.61 liter (21 percent of the predicted value).

Medical Survey

Trained interviewers administered a standardized questionnaire, (Ref. 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). (Ref. 5) Experienced technicians followed standard guidelines for performing spirometry (Ref. 6) and measuring carbon monoxide diffusing capacity (Ref. 7,8) and used spirometric reference values and 95 percent normal confidence intervals generated from NHANES III data. (Ref. 9) We defined airway obstruction as a low ratio of FEV(sub 1) to FVC in the presence of a low FEV(sub 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(sub 1). (Ref. 10) Two National Institute for Occupational Safety and Health (NIOSH)-certified B readers (Ref. 11) independently classified full-size posteroanterior chest radiographs without knowledge of the participants' characteristics. (Ref. 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. (Ref. 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. (Ref. 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 (Ref. 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 that to which workers on the microwave-popcorn packaging lines were exposed (Table 2).§*Table 1.-Demographic and Employment Characteristics of 117 Microwave-Popcorn Plant Workers in November 2000 *.**TABLE OMITTED**§*Table 2.-Levels of Diacetyl and Respirable Dust According to Work Area in the Microwave-Popcorn Plant in November 2000 *.**TABLE OMITTED**

The majority of the participants (57 percent) reported having had
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 (Ref. 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.

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 (Figure 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.§*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 *.**TABLE OMITTED**§*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 (Ref. 5) and were adjusted for age and sex. The T bars represent standard errors *.**FIGURE OMITTED**

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

microwave-popcorn production areas than among those in the other areas.§*Table 4.-Prevalence of Symptoms According to Work Area within the Popcorn Plant, November 2000 *.**TABLE OMITTED**

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(sub 1) values (Figure 2). The average FEV(sub 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.§*Figure 2.-Mean Forced Expiratory Volume in One Second (FEV(sub 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 *.**FIGURE OMITTED**

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, emphysematous, 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, (Ref. 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 (Ref. 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(sub 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.'' (Ref. 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. (Ref. 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. (Ref. 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. (Ref. 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. (Ref. 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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