Respiratory Disease Among Flavoring-exposed Workers in Food and Flavoring Manufacture

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Abstract: Fixed airways obstruction was found in workers producing microwave popcorn in relation to inhaling synthetic butter flavoring volatiles in 2000. Since then, an industry-wide hazard of clinical bronchiolitis obliterans was found in other microwave-popcorn plants, in flavoring manufacture, and in diacetyl (2,3-butanedione) manufacture. Recently, workers in 1 food production and 1 flavoring manufacturing facility have had excesses of spirometric restrictive abnormalities. Evidence of flavoring-related excessive declines in forced expiratory volume in 1 second (FEV_1) suggests that restriction in the latter flavoring plant is work-related. However, the pathologic and physiological correlates of restriction in flavoring-exposed workers remain uninvestigated. Diacetyl vapor causes respiratory epithelial necrosis in rodents, compatible with the pathologic mechanism for constrictive bronchiolitis, but exposures in flavoring manufacturing are more diverse than diacetyl. The diacetyl substitute, 2,3-pentanedione, has comparable toxicity to diacetyl, and other members of the α-diketone family have not been evaluated for respiratory toxicity. With the increasing spectrum of flavoring-related lung diseases and chemical exposures, pulmonologists caring for flavoring-exposed workers have novel challenges. These include examining excessive FEV_1 declines in serial spirometry and improving surveillance spirometry quality so that excessive declines can be detected at an earlier stage. The best means of preventing permanent impairment from irreversible occupational lung disease is to intervene for workers with excessive FEV_1 decline within the normal range and before diagnostic criteria for occupational lung disease can be met. Regulation of diacetyl and 2,3-pentanedione, which does not yet exist, may not prevent all occupational lung disease in flavoring-exposed workers.

Key Words: flavorings, bronchiolitis obliterans, 2,3-butanedione, spirometry surveillance

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A novel pattern of occupational bronchiolitis obliterans was recognized among microwave-popcorn manufacturing workers in 2000.[1] This pattern was the gradual development of fixed airways obstruction, often within months of first exposure, among workers exposed to butter flavoring volatiles without antecedent overexposure or spills. The pattern contrasted with that associated with silo-filler's disease (due to oxides of nitrogen), chemical warfare exposures (such as mustard gas), and other noxious gases (such as ammonia, chlorine, phosgene, and sulfur dioxide). These latter etiologies of occupational bronchiolitis obliterans were identified by acute lung injury due to overwhelming accidental exposure, followed by apparent resolution, and then delayed development of bronchiolitis obliterans several weeks later. Thus, the relation between bronchiolitis obliterans and prior exposure incident was surmised in individual cases rather than through epidemiologic investigation of exposed populations.

In contrast, the risk of bronchiolitis obliterans in microwave-popcorn workers was suggested by the recognition of an 8-person case cluster of severe lung disease among former workers of a single factory, including 4 on lung transplant lists.[2] Four of these sentinel cases had been mixers of synthetic butter flavorings in heated oil, and the estimated prevalence of bronchiolitis obliterans in mixers was 21 times that of other workers in microwave-popcorn production. None reported apparent overexposure in the workplace, and none had a work-related pattern of chest symptoms.[3] The cases had occurred insidiously over an 8-year period, and no known respiratory toxin was known to be present in the workplace. Indeed, exploration of the potential work-relatedness of the cases was triggered by the wife of a worker, who called a lawyer's attention to 4 cases. In turn, this lawyer referred the case list to a worker's compensation attorney who identified 4 additional cases and triggered medical record review.[4] The occupational physician recognized the importance of public health investigation and reported the cases to the state health department, which enlisted technical support from the National Institute for Occupational Safety and Health (NIOSH), a component of the Centers for Disease Control and Prevention with a mandate to investigate emerging occupational diseases. An earlier attempt to engage occupational health professionals by a local pulmonary physician who had seen many of the cases was unproductive. He had called the regulatory agency, the Occupational Safety and Health Administration, whose inspectors reported no regulated lung hazards in the plant. Enforcement of existing regulations regarding occupational exposures does not address emerging hazards, and the enforcement focus by those who measure workplace exposures is usually not informed by recognition of the health significance of disease clusters.

The ensuing public health investigation in the microwave-popcorn plant linked results of medical testing of current workers with both environmental characterization of workplace exposures and questionnaire interview data regarding demographics, symptom and diagnosis history, and job history.[1] With this epidemiologic approach to the current worker population, a 3.3-fold excess of spirometric airways obstruction was demonstrated in plant workers in comparison with the US general population: never-smokers in the current workforce had a 10.8-fold risk of airways obstruction in comparison with never-smokers in the US general population. When job tenure was linked with job-specific estimates of exposure to diacetyl, the principal volatile found in workplace

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The author declares that there is nothing to disclose.

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air, cumulative diacetyl exposures were associated with airways obstruction, with abnormal spirometry [airways obstruction or low forced vital capacity (FVC)], and with decreased percent predicted forced expiratory volume in 1 second (FEV_1). Five of the 6 workers in the quality control laboratory, who each popped about 100 bags of microwave popcorn per shift, had fixed obstructive abnormalities, despite having average diacetyl exposures about one quarter of the average of most microwave-popcorn workers on the lines who filled and packaged the microwave-popcorn bags with corn kernels and flavoring-containing oil. These quality control workers had higher exposures to other flavoring components when bags were microwaved and peak exposures when bags were opened to assess quality measures.

ADDITIONAL MICROWAVE-POPCORN PLANT INVESTIGATIONS

The new cross-sectional association between diacetyl and clinical bronchiolitis obliterans among current workers in the index microwave-popcorn plant triggered systematic investigation of 5 additional microwave-popcorn plants (Table 1).[5] Workers in these next 5 plants had lower average diacetyl exposures than workers in comparable jobs in the index microwave-popcorn plant, but 4 of these plants had cases of severe fixed airways obstruction that were consistent with bronchiolitis obliterans, demonstrating an industry-wide hazard of flavoring-related lung disease. Across the industry, mixers of flavoring in oil had excess risk of spirometric obstruction, and production line workers who worked in plants with isolated mixing areas had much less prevalence of airways obstruction than workers who worked in plants where mixing activities were conducted adjacent to the packaging lines. Mixers who had worked >12 months in mixing had greater prevalence of obstructive abnormalities than mixers with less work experience in mixing, consistent with an exposure-response relationship between diacetyl and airways obstruction.

In addition to these 5 microwave-popcorn investigations, NIOSH returned to the first sentinel plant to assist with the evaluation of recommended controls, intended to lower flavoring exposures for microwave-popcorn production workers.[6] The mixing room was isolated from the packaging lines, as was an area with heated holding tanks for flavorings mixed with oil. Microwave popping was isolated from the quality control worker laboratory and subject to exhaust ventilation. Despite adding additional ventilation to the new mixing room, all persons entering this area needed to wear air-line respirators that provided uncontaminated air for breathing. Engineering controls resulted in diacetyl measurements being below the limit of detection for the remainder of plant workers. Coincident with the lowering of average diacetyl concentrations, those workers who participated in all 8 cross-sectional spirometry surveys over nearly 3 years had their annualized FEV_1 decrements fall from 144 to 40 mL/y in the second year and then to 22 mL/year in the third year. This normalization of annual decline in FEV_1 constituted additional evidence that flavorings were a causal factor, as removal from exposure was accompanied by disappearance of a health effect. Similarly, workers hired after the initial cross-sectional survey with at least 3 serial spirometry measurements had a lower prevalence of excessive decline in lung function (defined as a 300 mL and/or 10% decline from first to last spirometry test) when compared with those workers who were present at the time of the historical higher exposures. These new hires had average FEV_1 measurements of 95.8% predicted at their last survey, in contrast to workers with historically higher exposures, whose last FEV_1 measurements averaged 85.7% predicted.

TABLE 1. Recent Reports (Since 2006) of Flavoring-exposed Worker Investigations of Airways Obstruction

References	Industry Type	Significance/Findings
Kanwal et al[5]	Microwave popcorn (6 plants)	Bronchiolitis obliterans cases in 5 of 6 plants demonstrated industry-wide risk, with proximity to mixing, including time as a mixer, conferring increased risk
Kanwal et al[6]	Microwave popcorn (index plant)	Lowering flavoring exposures interrupted excessive annual FEV_1 decline in workers tested serially and new workers remained healthy
Lockey et al[7]	Microwave popcorn (4 plants)	Mixers and higher exposure workers had more airways obstruction and excessive FEV_1 decline, even with respirators
van Rooy et al[8]	Diacetyl manufacture	4 of 102 process operators had bronchiolitis obliterans, previously misdiagnosed, with onset early in employment
van Rooy et al[9]	Diacetyl manufacture	Process operators had more chest symptoms and lower average FEV_1 with diacetyl being plausible causal exposure
Sahakian et al[10]	Popcorn popping	3 of 3 workers developed work-related asthma in adding flavors to popped corn, with aldehydes predominating
NIOSH[11]	Cooking	Grill cooks using butter-flavored oils had no excess obstruction
CDC[12]	Flavor manufacture	2 case reports of bronchiolitis obliterans in California triggered public health efforts across California industry
Hendrick[13]	Flavor manufacture	Bronchiolitis obliterans case report in worker manufacturing flavors for potato chips
NIOSH[14]	Flavor manufacture	Investigation of 18 production workers with 3 cases of severe fixed airways obstruction among those exposed to powders
NIOSH[15]	Flavor manufacture	2 of 14 production workers had fixed airways obstruction, including an incident case over a 4.5-month testing interval
Kim et al[16]	Flavor manufacture	Work-related risks of airways obstruction included greater company use of diacetyl, having a coworker with obstruction, production work, and work tenure
Israel et al[17]	Flavor manufacture	Case report of incident case of fixed airways obstruction
Kreiss et al[18]	Flavor manufacture	Excessive FEV_1 decline associated with greater company diacetyl use and occurred predominantly in workers with spirometry in the normal range

FEV_1 indicates forced expiratory volume in 1 second.

An industry-sponsored longitudinal study of a microwave-popcorn plant also documented increased hazard for mixers and those with higher exposure.[7] Before the advent of mandatory powered air-purifying respiratory protection for mixers of flavorings in oil, mixers had a statistically significant decrease in the FEV_1 percent predicted of 6.1 for non-Asian

males and 11.8 for Asian males, in comparison with employees with no mixing room or quality assurance employment. Among non-Asian males, work as a mixer before the implementation of respiratory protection was associated with an 8-fold increased risk of airways obstruction [95% confidence interval (CI), 2.26-29.25], and work as a mixer after the implementation of mandatory powered air-purifying respiratory use was associated with a 5.7-fold increased risk of airways obstruction (95% CI, 1.23-26.24). Thus, even introducing a stringent respiratory protection program did not sufficiently protect mixers from developing occupational airways abnormalities. Having a cumulative diacetyl exposure ≥ 0.8 ppm-years (exposures uncorrected for humidity and days to extraction and hence underestimations) was associated with airways obstruction (odds ratio, 9.2; 95% CI, 2.29-36.75) and with a decrease in the FEV_1 percent predicted of 10.3% for non-Asian and 12.7% for Asian males, compared with having a cumulative diacetyl exposure <0.8 ppm-years. Thus, longer and/or higher diacetyl exposure resulted in occupational effects on workers' airways.

DIACETYL MANUFACTURING WORKERS

Most synthetic butter flavorings are complex, with many chemicals present in addition to the historically predominant one, diacetyl. Dozens of other volatile chemicals were commonly present in the air of microwave-popcorn plants or in the headspace of flavoring samples. Diacetyl manufacture, in contrast, has only 3 feedstocks or contaminants: acetoin, acetaldehyde, and acetic acid. Dutch investigators constructed a retrospective cohort of workers at a diacetyl manufacturing facility that operated from 1960 through 2003, with 206 workers potentially exposed to diacetyl.[8] Medical testing of 175 members of this cohort identified 3 severe bronchiolitis obliterans cases among the 102 process operators, and a fourth case in a process operator was identified subsequently among the 10 living nonparticipants. Three of these cases had developed shortness of breath within 1 to 2 years of starting work at the plant and the fourth 14 years after starting work. All had received diagnoses of chronic obstructive pulmonary disease, despite 3 of them being nonsmokers, and the fourth, a smoker, also had received a diagnosis of asthma. The cross-sectional epidemiologic characterization of the cohort demonstrated excessive symptoms of continuous trouble with breathing, daily cough, and asthma attacks in comparison with the general population of the Netherlands.[9] The process operator group reported significantly more ever trouble with breathing and shortness of breath in the last year and an average 292 mL decrement in FEV_1 in comparison with a minimally exposed internal reference group.

OTHER FOOD PRODUCTION WORKERS

Food manufacturing workers have excessive obstructive lung disease in 3 population-based studies.[19] In a family business, all 3 workers developed work-related asthma while adding flavorings to corn they had popped without microwaves.[10] Although a case report exists of bronchiolitis obliterans in a cook from "overheated cooking oil fumes,"[20] no obstructive disease excess existed among cooks at 3 commercial kitchens who had previously used butter-flavored oil.[11]

FLAVORING WORKER INVESTIGATIONS

Recognition of bronchiolitis obliterans risk in butter flavoring-exposed, microwave-popcorn manufacturing workers prompted retrospective discovery of the same risk in flavoring manufacturing workers. The first known report was in a 1986 report of a NIOSH investigation at a plant that manufactured flavorings for the baking industry.[21] Two never-smoking workers aged 28 and 30 years, who prepared batches of flavorings, developed progressive exertional dyspnea and cough within 4 to 5 months of starting work and severe fixed obstructive lung disease within 5 to 7 months of employment. Two former mixers aged 36 and 38 years in the facility had asymptomatic airways obstruction, 1 moderately severe, which may have been related to flavoring exposure. Diacetyl was used frequently in production, as were many other chemicals. An occupational etiology was suspected, but no cause could be determined in the presence of so many exposures. Once the risk of flavoring-related occupational lung disease had been publicized, NIOSH became aware of biopsy-documented case reports of constrictive bronchiolitis obliterans in other flavoring manufacturing workers from New Jersey, Cincinnati,[22] and California,[12] and of granulomatous pneumonitis in Maryland. Lockey et al[22] reported a cluster of 5 workers in a flavoring plant with clinical findings consistent with bronchiolitis obliterans who had normal spirometry at the start of employment and developed moderate (60% to 69% predicted FEV_1) to severe (35% to 49% predicted FEV_1) obstruction. After cessation of exposure to flavoring chemicals, no further declines occurred over the next 4 to 5 years. Consultants for the Flavoring and Extract Manufacturers Association reported 4 cases in 3 flavoring manufacturing plants.[23] A case of bronchiolitis obliterans occurred in England in a worker manufacturing flavors for potato chips.[13] As flavoring manufacturing occurs in batches for many different flavors, quantitative exposure-response relations and specific chemical causation are difficult or impossible to determine.

Much of the work on fixed obstructive lung disease in flavoring manufacturing workers derives from surveillance efforts of the California Department of Public Health and the California Department of Industrial Relations (CalOSHA), with some assistance from NIOSH.[14,15] After physician reports of 2 case patients with bronchiolitis obliterans in 2 flavoring manufacturers,[12] the health department motivated voluntary reporting of spirometry, questionnaire results, and follow-up medical testing for workers in 20 flavoring manufacturing companies that received consultation from CalOSHA. California flavoring workers had a 2.7-fold (95% CI, 1.2-6.4) prevalence of severe and very severe airways obstruction compared with the US population.[16] In workers less than 40 years old, the prevalence ratio was 15 times higher (95% CI, 5.1-44.1) than the general population. Sixteen obstructed cases worked in 4 companies that used at least 800 lbs/y of diacetyl compared with 2 obstructed cases in companies using less diacetyl, for an odds ratio of 4.5 (95% CI, 1.03-19.9). The 17 workers with job history information had all worked in production or production support jobs, and those with moderate or worse airways obstruction had worked an average of 9.0 years compared with workers with mild airways obstruction who had worked an average of 1.5 years ($P=0.02$). Half of the 18 workers with airways obstruction reported no chest symptoms, particularly those with mild airways obstruction (5 of 6) and even moderate airways obstruction (4 of 7). Further medical testing was reported for only 13 workers, 12 of whom had fixed airways obstruction without bronchodilator response. Details of some of the clinical cases have been reported.[12,14,17]

The industry-wide surveillance of flavoring workers in California resulted in the report of serial spirometry test data for 416 workers administered from 2004 through March 2009, of whom 9.6% had abnormal FEV_1 decline (defined by

exceeding the relative longitudinal limit of decline appropriate to the within-person variation in the surveillance data set).[18] Workers at companies using ≥ 800 lbs/y of diacetyl had greater prevalence of abnormal FEV_1 decline than at companies using lesser amounts (7.3 vs. 3.0 per 1000 person-months of follow-up, $P = 0.01$). Using only high-quality spirometry data on a subset of 289 workers, only one of 21 with excessive FEV_1 decline had obstructive spirometry, and this worker lost 23.9% (−980 mL) of his baseline spirometry over 25 months. Thus, examination of excessive FEV_1 decline identified persons with occupational risk of lung disease in addition to and perhaps before they would develop abnormal obstructive spirometry. The mean FEV_1 change for workers using ≥ 800 lbs/y of diacetyl was −114.3 mL/y compared with −50.4 mL/y in companies using less diacetyl ($P = 0.06$).

RESTRICTIVE SPIROMETRY IN FLAVORING-EXPOSED WORKERS

In contrast to the fixed obstructive lung disease seen in California industry-wide surveillance and several workplace investigations,[14–16] 1 flavoring manufacturing worker population has had excesses of restrictive spirometry (FVC below lower limit of normal and normal FEV_1/FVC ratio) and work-related excessive declines of FEV_1 and FVC in a restrictive pattern.[24] Diacetyl was used nearly daily in this flavoring manufacturing facility, as well as many other flavoring chemicals. Among 106 production workers, 28% had restriction, and 4% had airways obstruction (FEV1 and FEV_1/FVC below the lower limits of normal set at the fifth percentile of the normal distribution), 1 with a very severe (< 35% percent predicted FEV_1) mixed obstructive and restrictive abnormality (FEV_1, FVC, and FEV_1/FVC all below the lower limits of normal). The excess of restrictive abnormalities was 3.8 times the expected prevalence in the US general population after adjustment for race, ethnicity, sex, age, smoking status, and body mass index. For 70 workers with serial spirometry tests, 19% had excessive FEV_1 decline compared with the relative longitudinal limit of decline appropriate to the within-person variation in the surveillance clinic's data set. Workers currently working in areas with higher potential for flavorings exposure had a 7.0-fold odds of excessive FEV_1 decline (95% CI, 1.3-38.2) in comparison with workers who were not currently working in areas with higher potential for exposure. The workers in these areas with higher potential for flavorings exposure had 2.8 times greater average annual declines in FEV_1 than workers in other areas, and 5 of 13 workers with excessive FEV_1 declines still had spirometry values within the normal range, suggesting that at-risk workers can be identified before they have impairment. Clinical evaluation to determine the nature of the excess disease in this worker population is not yet available, despite indications that occupational exposures are associated with spirometric deterioration.

Restrictive abnormalities or lung diseases have occurred in other diacetyl-exposed and flavoring-exposed worker populations (Table 2). One of the 8 former worker cases in the index plant had a predominantly restrictive pattern, and 2 of 3 obstructed cases with thoracoscopic lung biopsies had rare granulomas on biopsy.[3] Among current workers in the index microwave-popcorn plant, the 3.3-fold excess of airways obstruction in comparison with the US population was derived by combining the 11 workers with pure airways obstruction with 10 who had mixed airways obstruction and restriction (because air trapping can produce a restrictive picture).[1] However, combining those with pure restrictive spirometry with those with mixed airways obstruction and restriction would have resulted in a comparable restrictive excess. One worker with pure restrictive abnormalities had progressive disease over nearly 3 years of follow-up and had caseating granulomas on biopsy that, in the absence of infection, his physician attributed to his occupational flavoring exposure (unpublished NIOSH data).

In a small microwave-popcorn plant[25] with overall rates of obstructive or mixed obstructive and restrictive spirometric abnormalities similar to that in the index plant (20% vs. 18%, respectively), 2 of 35 workers had restriction, both of whom had low diffusing capacity (DLCO), low total lung capacity, and low body mass indices. One of the restricted workers had

TABLE 2. Reports of Spirometric Restriction or Restrictive Disease in Flavoring-exposed Workers

References	Study Type	Findings Pertinent to Restriction
NIOSH[24]	Cross-sectional, longitudinal	30/106 workers had low FVC alone; 1 had low FVC and airways obstruction; and 3 had airways obstruction. Excessive FEV_1 decline on serial spirometry, found in 13/70 workers, was associated with high potential for flavorings exposure
Akpinar-Elci et al[3]	Case series	1/9 cases had low FVC and airways obstruction with low RV, low TLC, and low DLCO with some reversibility postemployment
Kreiss et al[1]	Cross-sectional	10/116 had low FVC alone, of whom 7 had low TLC; 10/116 had low FVC and airways obstruction; 11/116 had pure airways obstruction. None had radiologic interstitial abnormalities
NIOSH[25]	Cross-sectional	2/35 had low FVC alone, both with low DLCO, low TLC, and low to normal BMI; 3/35 had low FVC and airways obstruction; 2/35 had pure airways obstruction
NIOSH[26]	Cross-sectional	3/39 ever with mixing experience had low FVC and low DLCO; 2 had low FVC and airways obstruction; 2 had pure obstruction; of 23 current mixers and quality control workers, 2 had low FVC (1 with low DLCO). 2 had low FVC and airways obstruction, and 1 had pure obstruction
NIOSH[27]	Cross-sectional	3/13 ever mixer current workers had low FVC alone and 2/13 had low FVC and airways obstruction. Of 5 mixer former workers, 1 had low FVC and airways obstruction
Day et al[28]	Cross-sectional	4/22 workers had low FVC alone
NIOSH[29]	Cross-sectional	2/15 flavoring production workers had restriction and 1 had restriction and fixed airways obstruction
NIOSH[14]	Cross-sectional, longitudinal	1/6 workers in liquid flavor production had low FVC alone
NIOSH[15]	Cross-sectional, longitudinal	1/15 workers in laboratory had low FVC alone
Alleman and Darcey[30]	Case report	Worker in snack food plant spraying spices and flavorings on potato chips had bronchiolitis obliterans/organizing pneumonia (restrictive) on biopsy

BMI indicates body mass index; DLCO, diffusing capacity of the lung to carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity.

possible basal bronchiectasis on high-resolution computed tomography scan. Three current workers had mixed restrictive and obstructive abnormalities, and 2 had pure airways obstruction. These proportions of types of spirometric abnormalities among the 7 with abnormal spirometry were similar to the proportions in the index plant. One obstructed worker in this plant had granulomas, and an additional worker with borderline airways obstruction (defined as an FEV_1/FVC ratio below the lower limit of normal but normal FEV_1) and low DLCO had biopsy-documented bronchiolitis obliterans.

In the 2 largest microwave-popcorn plants, several mixers had pure restriction and others had a mixed obstructive and restrictive picture. In one of these plants,[27] the proportions of those with restriction, mixed restriction and airways obstruction, and pure airways obstruction among the 7 (of 39) workers with current or former mixing experience were again similar to the index and small microwave-popcorn plant above: 3, 2, and 2. Among the 9 mixers with at least 1.5 years in the mixing slurry room, 1 had restriction and a low DLCO, 2 had restriction and airways obstruction, and 1 had pure airways obstruction. Similarly, among current quality control workers, 1 had restriction and normal DLCO, and 1 had pure airways obstruction. At the other large microwave-popcorn plant,[26] 3 of 5 current workers who had performed mixing tasks for ≥ 8 months had spirometric abnormalities, one of whom had restriction and 2 of whom had restriction and airways obstruction. Of 18 current and former workers who had been mixers, 3 had restriction, and 3 had restriction and obstruction; none had pure airways obstruction.

In a small plant manufacturing baking mixes including diacetyl, 18% of workers tested had restriction and none had airways obstruction, for a 2.9-fold excess prevalence (95% CI, 1.1-7.5) of spirometric restriction in comparison with the US population.[28] With the findings of excess restriction in this plant and the flavoring manufacturing plant,[24] the California industry-wide flavoring worker surveillance data[16] are of interest. Although the prevalence of pure restriction at 8.8% was much greater than any airways obstruction (3.9%) in California flavoring workers, office workers had a somewhat greater prevalence of restriction than production workers (13.6% vs. 6.4%, $P=0.11$).

In another small plant that manufactured starter distillate (containing 4.5% diacetyl), other flavorings, colors, and bacterial blends used as silage inoculants and probiotics, 2 of 15 flavoring production workers potentially exposed to diacetyl had restriction and 1 had both restriction and fixed airways obstruction.[29]

NIOSH has received unpublished case reports of a flavoring-exposed worker in Maryland with granulomatous bronchiolitis on biopsy, of restrictive interstitial lung disease in an employee who tested pumps by injecting butter-flavored oil into kettles for popping corn, and of pulmonary fibrosis in a candy operator who added flavorings to melted sugar.[19] A published case of a spice technician who may have been exposed to flavorings in potato chip manufacture had irreversible restrictive disease with pathologic findings of bronchiolitis obliterans and organizing pneumonia.[30] Whether restrictive physiology and diverse pathologies and diagnoses represent flavoring-related health outcomes requires more investigation. Certainly the common co-occurrence of pure restriction, mixed restriction and airways obstruction, and pure airways obstruction in most of the microwave-popcorn plants, along with the excessive restrictive abnormalities in 1 flavoring manufacturing plant and 1 food production plant, suggest that the spectrum of lung disease related to flavorings exposure does not fit neatly into the entity of constrictive bronchiolitis. Although rare granulomas are seen commonly in biopsied cases, classic hypersensitivity pneumonitis seems to be excluded by pathology, physiology, and absence of response to corticosteroid treatment.

ANIMAL TOXICOLOGY

Diacetyl is a reactive α-diketone that causes necrosis of the respiratory epithelium with sloughing of cells and damage below the basement membrane in both rats and mice.[31,32] Diacetyl is also a T-cell sensitizer in local lymph node assays after topical exposures in mice,[33] possibly mediated by formation of haptens because of its reactivity with arginine and lysine residues on proteins. Diacetyl's principal metabolism is to acetoin by dicarbonyl/L-xylulose reductase, which also catalyzes the reduction of several other dicarbonyl compounds including those that have been recently introduced as diacetyl substitutes (2,3-pentandione, 2,3-hexanedione, and 2,3-heptanedione). Butter flavorings commonly contain n-butyric acid, which inhibits dicarbonyl/L-xylulose reductase and is more efficiently taken up in the nasal mucosa, thereby leaving more diacetyl in the vapor stream being delivered to the lung.[34]

Unlike human beings, rodents are obligate nose breathers, and inhaled diacetyl causes respiratory epithelial injury in the nose and larynx far greater than in the intrathoracic airways and bronchioles where the predominant human lesion is located. To demonstrate intrathoracic injury, rat models require high inhaled doses, intratracheal instillation of diacetyl, oropharyngeal aspiration, or short-duration high exposures subchronically. With 15-minute exposures per day at 1200 ppm diacetyl, 5 d/wk for 2 weeks, mice develop lymphocytic inflammation around bronchi and preterminal bronchi.[32] With a single oropharyngeal aspiration, mice developed a fibrohistiocytic response at the bronchioloalveolar junction after 4 days. Evidence exists of dysregulation of airway sensory innervations and responses in rodents.[35,36] The differences in rat airway diameter, resistance, and mucosal absorption differ from those of humans. Hybrid computational fluid dynamic-physiologically based pharmacokinetic models have been developed to demonstrate the differing location of respiratory tract vapor absorption in rats and humans.[34,37] The differences in site of injury in humans and rodents reflect interspecies differences in diacetyl dosimetry within the respiratory tract. With low levels of exercise that could occur in the workplace, diacetyl dose to the bronchiolar epithelium of man may be >40-fold than the dose received by the bronchiolar epithelium of experimentally exposed rodents.[37]

Stimulated by CalOSHA's regulation of food production ingredients containing >1% diacetyl (promulgated in December 2010), flavor manufacturers introduced α-diketone substitutes for diacetyl in artificial butter flavorings, such as 2,3-pentanedione, 2,3-hexanedione, and 2,3,-heptanedione.[28] The limited toxicology spurred by finding these substitutes in a workplace indicates that 2,3-pentanedione has comparable toxicity with diacetyl.[38,39] This might be expected on the basis of structure-activity relationships, as these substitutes differ only in the carbon chain lengths of 4 for diacetyl through 7 for the 2,3-heptanedione. Inhalation toxicology does not yet exist for the higher order substitutes.

CLINICAL APPROACH TO FLAVORING-EXPOSED WORKERS

Pulmonologists seeing individual patients with a work history of flavoring exposure most commonly see persons with symptoms and/or objective abnormalities on lung function.

Before the association was made epidemiologically between flavoring exposure and clinical bronchiolitis obliterans, this diagnosis was missed by physicians, both in the United States and internationally.[40] Common misdiagnoses were asthma, emphysema, and bronchitis. Most pulmonologists were not aware that fixed obstructive lung disease consistent with bronchiolitis obliterans could develop gradually in the absence of an antecedent acute lung injury. Nonetheless, pulmonary functions with bronchodilator help to distinguish between asthma and bronchiolitis obliterans. Diffusing capacity and the natural history of smoking-related airways obstruction occurring in persons older than age 50 serve to guide differentiation of emphysema from bronchiolitis obliterans. The characteristics that commonly distinguish bronchiolitis obliterans in flavoring workers from other pulmonary diagnoses are youth, rapid evolution, absent improvement with bronchodilators and corticosteroid agents, and air trapping shown by lung volumes and by mosaic attenuation on paired inspiratory and expiratory high resolution computerized tomography scans. Unlike occupational asthma that can occur in young people with short employment histories, no work-related pattern of symptoms is evident, and even prolonged cessation of exposure does not result in improvement as bronchiolitis obliterans is an irreversible disease associated with bronchiolar scarring. Thus, clinical management is supportive with attention to absolute restriction from further flavoring exposure, pulmonary rehabilitation, immunization, and attention to supplemental oxygen if needed. Although some patients with flavoring-related bronchiolitis obliterans have undergone lung transplant before the association with occupational exposure was identified, most with severe disease have stabilized after cessation of exposure. The lack of progression of disease after exposure cessation, in contrast to the course of many other pulmonary diseases with similar impairment, has allowed many patients listed for lung transplant to avoid transplant, which itself induces bronchiolitis obliterans in a majority of recipients.

Pathologic confirmation of bronchiolitis obliterans has been insensitive, even in workers with severe airways obstruction and no other evident cause. Special serial sections of bronchioles are required, and the disease is patchy. Even experienced chest pathologists have missed the diagnosis on open-lung or thoracoscopic biopsies. Accordingly, there is little justification to proceed to open biopsy unless there is a competing treatable diagnosis.

The greater challenge to the pulmonologist is evaluation of the patient referred from workplace monitoring programs because of mild abnormalities or excessive decline in FEV_1 while still being within the normal range of FEV_1 (Table 3). In these instances, the patient is commonly asymptomatic, and the differential diagnosis of bronchiolitis obliterans is not aided by demonstrable air trapping. In such situations, the customary practice of making a diagnosis must be replaced by the precautionary principle of frequent follow-up to assess whether rapid decline or mild airways obstruction progresses, paired with follow back to the workplace to assess whether exposures can be lowered, whether other workers are affected, and whether respiratory protection can be enhanced. For an irreversible disease that may be developing, patient education is critical,[41] so that the patient can balance risk of impairment with work practices, relocation, or continued employment. The adversarial nature of the workers compensation system does not usually support the worker in following preventive counsel for the risk of this irreversible obstructive disease in its earliest or mild stages.

The recent recognition of pure restrictive pulmonary function abnormalities and excessive FEV_1 declines in fla-

TABLE 3. Clinical Pearls for Pulmonologists Seeing Patients With Flavoring Exposure

Pearls	Rationale and Tools/ References
Suspect occupational lung disease or risk in asymptomatic patients, those with mild abnormalities or excessive FEV_1 decline	Prevention of irreversible disease requires intervention in preclinical phase with lowering exposure, enhanced respiratory protection, and education. Give patient a copy of NIOSH Alert: Preventing Lung Disease in Workers Who Use or Make Flavorings[41]: http://www.cdc.gov/niosh/docs/2004-110/pdfs/2004-110.pdf.
Spectrum of flavoring-related lung disease is wide[40]	Fixed airways obstruction (bronchiolitis obliterans), asthma, bronchiolitis obliterans with organizing pneumonia, granulomatous pneumonitis, tracheomalacia and bronchiomalacia, fibrosis, systemic symptoms, and restriction.
Fixed airways obstruction with air trapping may be clinical bronchiolitis obliterans	Attribution of fixed airways obstruction to smoking in those less than 50 y old is not credible because smoking-related decrements in lung function are small in the subset of smokers who develop emphysema, in comparison with the excessive declines seen in flavoring-exposed workers. Smokers have less risk than never-smokers when flavoring-exposed.[1]
Assess excessive FEV_1 decline to identify susceptible persons	Choose criterion for excessive decline based on spirometry quality and duration of serial spirometry with SPIROLA[42] freeware available at http://www.cdc.gov/niosh/topics/spirometry/spirola-software.html.
Improve spirometry quality to be more health protective with smaller criterion for excessive decline	Post free NIOSH poster regarding common spirometry testing errors, available at: http://www.cdc.gov/niosh/docs/2011-135. Require $\geq$ 80% of tests to have A or B quality per most current ATS/ERS recommendations for test session acceptability and repeatability and give feedback to spirometry technicians to enable them to achieve higher quality tests.[43]
Healthy worker effect makes cluster identification difficult	Impaired workers leave employment, and healthy current workers remain. In index popcorn plant, no current mixers were affected although it was a high-risk group.[1] In a small microwave-popcorn plant,[25] none of 8 workers who had done mixing tasks had spirometric abnormalities. In the Netherlands diacetyl plant, affected workers could not have been identified in cross-sectional study.[8,40]

TABLE 3. (*continued*)

Pearls	Rationale and Tools/ References
Report concerns to public health agencies, not the OSHA	Public health agencies offer multidisciplinary expertise that can solve emerging issues, whereas regulators enforce existing regulations. In the index microwave-popcorn plant, a pulmonologist calling OSHA was told there were no lung hazards (known at the time). Call NIOSH at 1-800-232-2114 to talk to public health occupational lung disease specialists.
Regulation is not always protective, when it exists and is enforced	Regulations are constrained by economic feasibility and analytic limits of quantification. Diacetyl and 2,3-pentanedione have comparable toxicity, but diacetyl has a lower recommended exposure limit because the analytic method is more sensitive than the method for 2,3-pentanedione. No analytic method exists for diacetyl in powders. Chemicals are regulated one-by-one, and inhalation toxicology does not exist for most diacetyl substitutes.
Be alert for emerging occupational lung diseases	Thoughtful clinicians suspect new occupational risks and motivate public health agencies to pursue epidemiologic studies to identify risks in exposed populations. Many industries and occupations have elevations in obstructive disease, adjusted for smoking, without known cause.[40]

FEV_1 indicates forced expiratory volume in 1 second; OSHA, Occupational Safety and Health Administration.

voring-exposed workers calls for obtaining lung volumes, diffusing capacity, high resolution computerized tomography scan, and consideration of lung biopsy. The pathologic nature and clinical course of restrictive disease in flavoring workers is still not clear, and diagnostic evaluation will be of public health interest to staff at the Division of Respiratory Disease Studies at NIOSH (1-800-232-2114). The report of such cases will clarify the spectrum of flavoring-related disease so that clinicians will have better guidance in the future.

For the pulmonologist administering a medical monitoring program for a company with flavoring-exposed workers, regulations have been recommended with attention to credentials, components of medical screening and surveillance, spirometry quality and frequency, and need for examination of risk factors for preventive intervention.[43] Because severe flavoring-related lung disease can occur within a few months of employment and progress rapidly, serial spirometry at 6-month intervals is advisable and more frequently if cases of disease have occurred in coworkers with similar exposures. Determining excessive decline in FEV_1 at such short intervals is nearly unprecedented in occupational surveillance requirements, and few in the pulmonary community have much experience in evaluating serial FEV_1 declines for abnormality.

The criteria for excessive FEV_1 decline are dependent on spirometry quality. Many pulmonary function laboratories and occupational medicine spirometry providers have poor quality control oversight.[18] Recognizing the frequent poor quality of spirometry, the American Thoracic Society and the American College of Occupational and Environmental Medicine suggested that a 15% fall in FEV_1 over a year requires attention.[44] This corresponds to a 6% intraindividual variation and would trigger evaluation of a fall of 600 mL in a person with a preplacement FEV_1 of 4.0 L. With a 4% intraindividual variation in a provider's spirometry in a workforce monitoring program, a 10% decline over a year could be considered abnormal, for example, 400 mL in the person with a baseline FEV_1 of 4.0 L. NIOSH has developed free software to determine the criterion for excessive decline depending on quality and duration of follow-up (SPIROLA).[42] A statistically derived set of criteria in normal working populations also exists for excellent quality spirometry in workplace monitoring over 6 months and annually over 5 years[45,46]; this has been used in following serial lung functions in microwave-popcorn workers.[7,47] The better the spirometry quality, reflected in low intraindividual variation, the smaller the relative decline that can be identified as abnormal without misclassification.[47] Excessive FEV_1 decline can be more confidently identified after many years of serial spirometry, but flavoring-related obstructive disease sometimes arises too rapidly to benefit from a stable FEV_1 longitudinal slope.

To prevent impairment from an irreversible disease, the responsibility of the physician conducting worker monitoring is to identify "preclinical" presentations of workers who may be developing flavoring-related lung disease with excessive declines in FEV_1, which, if continued, will result in impairment from abnormal lung function. Neither physician nor asymptomatic worker may be accustomed to the need to take action from a preclinical signal. Indeed, with industry-wide surveillance of flavoring workers in California, most of those with mild and some with moderate obstructive abnormalities did not have diagnostic evaluations submitted to the California Department of Public Health.[16] In an individual flavoring worker with excessive FEV_1 decline or mild disease, worker education, rapid and frequent follow up, and motivation of enhanced personal protection are all potentially important.[41]

AREAS OF NEEDED AND ONGOING INQUIRY

The rapid evolution of knowledge about occupational lung disease risk for flavoring-exposed workers has resulted in stakeholder and governmental efforts at risk assessment. Risk assessment is the basis for recommendations to control flavoring exposures to a level that protects most workers from development of occupational lung disease in a lifetime of work exposure. On the basis of animal toxicologic experiments, Maier et al[48] suggested an exposure standard of 0.2 ppm diacetyl, but this was based on an assumption that there was a no-adverse-exposure level in animal experiments that had not been documented. On the basis of published human data in 2 plants and quantitative structure-activity relationships, Egilman et al[49] proposed an exposure limit of 0.001 ppm. Analyses of data from the serial cross-sectional studies at the index microwave-popcorn plant at NIOSH resulted in a draft Criteria Document for a Recommended Standard for Diacetyl and

2,3-Pentanedione with a recommended exposure limit of 0.005 ppm for diacetyl.[43] Although 2,3-pentanedione was described as having comparable toxicity, its recommended exposure limit was 0.0093, because no analytic technique was available to support a lower limit. In the event that the regulatory agency, the Occupational Safety and Health Administration, creates a permissible exposure limit, further constraints may exist, such as economic feasibility. Thus, exposure limits are not guaranteed to protect workers from occupational health effects, even when adopted and enforced. An uncertainty that remains at present is whether short-term exposure limits for 15-minute periods or whether a ceiling exposure limit that should never be exceeded can adequately protect flavoring workers, if enacted.

Despite considerable progress since a comprehensive review through 2006,[19] this summary documents many areas of needed inquiry. These include the underlying lung pathology of work-related restrictive spirometric abnormalities newly described in flavoring manufacturing and food preparation workers,[24,28] which is necessary to understand the spectrum of lung disease found in excess among flavoring workers. Issues of worker susceptibility have arisen in NIOSH risk assessment efforts, which may reflect genetic determinants of risk of rapidly progressive disease within months of employment in many workers. Protection of flavoring-exposed workers requires early detection of excessive lung function decline, but the means of improving spirometry quality for medical surveillance and clinical follow-up of workers who are still normal are unclear and would require profound changes in pulmonary practice to motivate intervention when a diagnosis cannot be made. Finally, flavoring workers will likely continue to be exposed to unregulated substitutes for which experimental toxicology will be unavailable or will lag years behind recommended or permissible exposure levels for diacetyl and 2,3-pentanedione. In the absence of toxicological information, workers and their downstream employers may not know the identity of substitutes introduced by flavoring manufacturers, as the hazard communication standard does not apply to undocumented hazards or to those that constitute <1% of a mixture. In conclusion, flavoring-related research continues, even as the clinical and epidemiologic observations from more than a decade ago have culminated in health-protective responses to control exposure to a new class of respiratory epithelial toxins. In turn, the diacetyl story is a humbling paradigm for keeping the limits of our knowledge in mind as we see patients with uncommon presentations in industries using materials that we have generally regarded as safe because they are safe to eat or because they have not been studied for safety by inhalation.

REFERENCES

1. Kreiss K, Gomaa A, Kullman G, et al. Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. *N Engl J Med.* 2002;347:330–338.
2. CDC. Fixed obstructive lung disease in workers at a microwave popcorn factory—Missouri, 2000-2002. *Morbid Mortal Weekly Rep.* 2002;51:345–347.
3. Akpinar-Elci M, Travis WD, Lynch DA, et al. Bronchiolitis obliterans syndrome in popcorn production plant workers. *Eur Respir J.* 2004;24:298–302.
4. Parmet AJ, Von Essen S. Rapidly progressive fixed airway obstructive disease in popcorn workers: a new occupational pulmonary illness? *J Occup Environ Med.* 2002;44:216–218.
5. Kanwal R, Kullman G, Piacitelli C, et al. Evaluation of flavorings-related lung disease risk at six microwave popcorn plants. *J Occup Environ Med.* 2006;48:149–157.
6. Kanwal R, Kullman G, Fedan K, et al. Occupational lung disease risk and exposures to butter flavoring chemicals after implementation of controls at a microwave popcorn plant. *Public Health Rep.* 2011;126:480–494.
7. Lockey JE, Hilbert TJ, Levin LP, et al. Airway obstruction related to diacetyl exposure at microwave popcorn production facilities. *Eur Respir J.* 2009;34:63–71.
8. van Rooy FG, Rooyackers JM, Prokop M, et al. Bronchiolitis obliterans syndrome in chemical workers producing diacetyl for food flavorings. *Am J Respir Crit Care Med.* 2007;176:498–504.
9. van Rooy FG, Smit LA, Houba R, et al. A cross-sectional study of lung function and respiratory symptoms among chemical workers producing diacetyl for food flavourings. *Occup Environ Med.* 2009;66:105–110.
10. Sahakian N, Kullman G, Lynch D, et al. Asthma arising in flavoring-exposed food production workers. *Int J Occup Med Environ Health.* 2008;21:173–177.
11. NIOSH. *Hazard Evaluation and Technical Assistance Report. Respiratory Symptoms in Workers at Three Commercial Kitchens. Aramark, New York, NY.* Morgantown, WV: U.S. Department of Health and Human Services (DHHS), CDC, NIOSH HETA Report No. 2008–0125–0126–0127–3093; 2009.
12. CDC. Fixed obstructive lung disease among workers in the flavor-manufacturing industry—California, 2004–2007. *Morbid Mortal Weekly Rep.* 2007;56:389–393.
13. Hendrick DJ. "Popcorn worker's lung" in Britain in a man making potato crisp flavouring. *Thorax.* 2008;63:267–268.
14. NIOSH. *Hazard Evaluation and Technical Assistance Report: Carmi Flavor and Fragrance Company, Inc., Commerce, CA.* Morgantown, WV: U.S. DHHS, CDC, NIOSH HETA Report No. 2006–0303–3043; 2007.
15. NIOSH. *Hazard Evaluation and Technical Assistance Report: Gold Coast Ingredients Inc., Commerce, CA.* Morgantown, WV: U.S. DHHS, CDC, NIOSH HETA Report No. 2007–0033–3074; 2008.
16. Kim T, Materna B, Prudhomme J, et al. Industry-wide medical surveillance of California flavoring manufacturing workers: cross-sectional results. *Am J Ind Med.* 2010;53:857–865.
17. Israel L, Kim T, Prudhomme J, et al. Workplace spirometry: early detection benefits individuals, worker groups and employers. ATS Clinical Cases. April 2009; American Thoracic Society. Available at: http://www.thoracic.org/clinical/ats-clinical-cases/index.php. Accessed September 3, 2011.
18. Kreiss K, Fedan K, Nasrullah M, et al. Longitudinal lung function decline among California flavoring manufacturing workers. *Am J Ind Med.* 2011. In press doi: 10.1002/ajim.21013.
19. Kreiss K. Flavoring-related bronchiolitis obliterans. *Curr Opin Allergy Clin Immunol.* 2007;7:162–167.
20. Simpson FG, Belfield PW, Cooke NJ. Chronic airflow limitation after inhalation of overheated cooking oil fumes. *Postgrad Med J.* 1985;61:1001–1002.
21. NIOSH. *Hazard Evaluation and Technical Assistance Report: International Bakers Services, Inc, South Bend, IN.* Cincinnati, OH: U.S. DHHS, CDC, NIOSH HETA Report No. 1985–0171–1710; 1985.
22. Lockey J, McKay R, Barth E, et al. Bronchiolitis obliterans in the food flavoring manufacturing industry. *Am J Respir Crit Care Med.* 2002;165(suppl):A461.
23. Flavor and Extract Manufacturers Association. *Respiratory Health and Safety in the Flavor Manufacturing Workplace.* Washington, DC: The Flavor and Extract Manufacturers Association of the United States; 2004.
24. NIOSH. *Hazard Evaluation and Technical Assistance Report: Lung Function (Spirometry) Testing in Employees at a Flavorings Manufacturing Plant—Indiana.* Morgantown, WV: U.S. DHHS, CDC, NIOSH HETA Report No. 2008–0155–3131; 2011.
25. NIOSH. *Hazard Evaluation and Technical Assistance Report: Agrilink Foods Popcorn Plant, Ridgway, IL.* Morgantown, WV: U.S. DDHS, CDC, NIOSH HETA Report No. 2002–0408–2915; 2003.
26. NIOSH. *Hazard Evaluation and Technical Assistance Report: ConAgra Snack Foods, Marion, OH.* Morgantown, WV: U.S. DHHS, CDC, NIOSH HETA Report No. 2003-0112-2949; 2004.

27. NIOSH. *Hazard Evaluation and Technical Assistance Report: American Pop Corn Company, Sioux City, IA.* Morgantown, WV: U.S. DHHS, CDC, NIOSH HETA Report No. 2001–0474–2943; 2004.
28. Day G, LeBouf R, Grote A, et al. Identification and measurement of diacetyl substitutes in dry bakery mix production. *J Occup Environ Hyg.* 2011;8:93–103.
29. NIOSH. *Hazard Evaluation and Technical Assistance Report: Chr. Hansen Inc., New Berlin, WI.* Morgantown, WV: U.S. DHHS, CDC, NIOSH HETA Report No. 2007–0327–3083; 2009.
30. Alleman T, Darcey DJ. Case report: bronchiolitis obliterans organizing pneumonia in a spice process technician. *J Occup Environ Med.* 2002;44:215–216.
31. Hubbs AF, Goldsmith WT, Kashon ML, et al. Respiratory toxicologic pathology of inhaled diacetyl in Sprague-Dawley rats. *Toxicol Pathol.* 2008;36:330–344.
32. Morgan DL, Flake GP, Kirby PJ, et al. Respiratory toxicity of diacetyl in C57Bl/6 mice. *Toxicol Sci.* 2008;103:169–180.
33. Anderson SE, Wells JR, Fedorowicz A, et al. Evaluation of the contact and respiratory sensitization potential of volatile organic compounds generated by simulated indoor air chemistry. *Toxicol Sci.* 2007;97:355–363.
34. Morris JB, Hubbs AF. Inhalation dosimetry of diacetyl and butyric acid, two components of butter flavoring vapors. *Toxicol Sci.* 2009;108:173–183.
35. Goravanahally MP, Hubbs AF, Fedan JS, et al. Diacetyl increases sensory innervation and substance P production in rat trachea. *Vet Pathol.* 2010;47:56S.
36. Larsen ST, Alarie Y, Hammer M, et al. Acute airway effects of diacetyl in mice. *Inhal Toxicol.* 2009;21:1123–1128.
37. Gloede E, Cichocki JA, Baldino JB, et al. A Validated hybrid computational fluid dynamics-physiologically based pharmacokinetic model for respiratory tract vapor absorption in the human and rat and its application to inhalation dosimetry of diacetyl. *Toxicol Sci.* 2011;123:231–246.
38. Hubbs AF, Cumpston AM, Goldsmith WT, et al. Respiratory and cytotoxicity of inhaled 2,3-pentanedione in Sprague-Dawley rats. *Am J Pathol.* 2012. (in press).
39. Morgan DL, Jokinen MP, Price HC, et al. Bronchial and bronchiolar fibrosis in rats exposed to 2,3-pentanedione vapors: implications for bronchiolitis obliterans in humans. *Toxicol Pathol.* 2012;40:448–465.
40. Kreiss K. Occupational bronchiolitis obliterans masquerading as COPD. *Am J Respir Crit Care Med.* 2007;176:427–429.
41. NIOSH. *NIOSH Alert: Preventing Lung Disease in Workers Who Use or Make Flavorings.* Cincinnati, OH: U.S. DHHS (NIOSH) Publication No. 2004-110; 2003.
42. NIOSH. Spirometry Longitudinal Analysis (SPIROLA) [computer program]. Version 3.0, updated November 2010. Available at: http://www.cdc.gov/niosh/topics/spirometry/spirola.html. Accessed May 20, 2011.
43. NIOSH. *Draft Criteria for a Recommended Standard: Occupational Exposure to Diacetyl and 2,3-Pentanedione.* Cincinnati, OH: U.S. DHHS (NIOSH) Publication No. 20XX-XXX, 2011. Available at http://www.cdc.gov/niosh/docket/archive/docket245.html. Accessed September 7, 2011.
44. Townsend M. Spirometry in the occupational health setting—2011 update. *J Occup Environ Med.* 2011;53:569–584.
45. Wang ML, Petsonk EL. Repeated measures of FEV1 over six to twelve months: what change is abnormal? *J Occup Environ Med.* 2004;46:591–595.
46. Wang ML, Avashia BH, Petsonk EL. Interpreting periodic lung function tests in individuals: the relationship between 1- to 5-year and long-term FEV1 changes. *Chest.* 2006;130:493–499.
47. Chaisson NF, Kreiss K, Hnizdo E, et al. Evaluation of methods to determine excessive decline of forced expiratory volume in one second in workers exposed to diacetyl-containing flavorings. *J Occup Environ Med.* 2010;52:1119–1123.
48. Maier A, Kohrman-Vincent M, Parker A, et al. Evaluation of concentration-response options for diacetyl in support of occupational risk assessment. *Regul Toxicol Pharmacol.* 2010;58:285–296.
49. Egilman DS, Schilling JH, Menendez L. A proposal for a safe exposure level for diacetyl. *Inter J Occup Environ Health.* 2011;17:122–134.