

Work-Related Spirometric Restriction in Flavoring Manufacturing Workers

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Background *Flavoring-exposed workers are at risk for occupational lung disease.*

Methods *We examined serial spirometries from corporate medical surveillance of flavoring production workers to assess abnormality compared to the U.S. population; mean decline in forced expiratory volume in one second (FEV1) and forced vital capacity (FVC); and excessive declines in FEV1.*

Results *Of 106 workers, 30 had spirometric restriction, 3 had obstruction, 1 had both, and 13 (of 70, 19%) had excessive declines in FEV1. The adjusted prevalence of restriction was 3.7 times expected. Employees with higher potential for flavorings exposure had 3.0 times and 2.4 times greater average annual declines in FEV1 and FVC respectively, and had 5.8 times higher odds of having excessive FEV1 declines than employees with lower potential for exposure.*

Conclusion *Exposure-related spirometric abnormalities consistent with a restrictive process evolved during employment, suggesting that exposures in flavoring production are associated with a range of pathophysiology.* Am. J. Ind. Med. 57:129–137, 2014. Published 2013. This article is a U.S. Government work and is in the public domain in the USA.

KEY WORDS: *flavorings; diacetyl; hydrogen sulfide; spirometry; spirometric restriction; excessive decline*

INTRODUCTION

Cases of biopsy-confirmed constrictive bronchiolitis have occurred throughout the microwave popcorn and flavoring manufacturing industries [NIOSH, 2011b]. Recently, constrictive bronchiolitis clusters have been reported in other food production, such as cookie dough manufacture and coffee roasting and flavoring [Cavalcanti et al., 2012; CDC, 2013]. Such cases have been sentinels of risk of occupational lung disease among co-workers that have often had excesses of abnormal spirometry [Kreiss et al., 2002]. In the microwave popcorn industry, abnormal spirometry was associated with exposure to inhaled diacetyl (2,3-butane-

dione), a main ingredient of artificial butter flavorings [Kreiss et al., 2002]. Because sentinel cases were recognized as having clinical or biopsy-confirmed constrictive bronchiolitis, investigators concentrated on fixed airways obstruction, but restrictive spirometry abnormalities and mixed restriction and obstruction also commonly occurred in these plants [Kreiss, 2012]. The full spectrum of occupational lung disease associated with diacetyl or other flavoring exposures is still under investigation.

In 2008, the National Institute for Occupational Safety and Health (NIOSH) received a request for an evaluation of respiratory health risks at a flavoring manufacturing facility [NIOSH, 2011a]. This facility used batch processes to produce a variety of flavor formulations in liquid, paste, and powder form. Flavors produced included butter, buttermilk, cheese, sour cream, coffee, orange, blueberry, raspberry, grape, beef, chicken, and fish, among many others. Diacetyl was used in producing butter, cheese, nut, and berry flavors. The facility used many chemicals on the 2004 list of priority potential respiratory hazards generated by the Flavor and Extract Manufacturers Association (FEMA) (Table I) [FEMA, 2004]. A subsequent compliance investigation by

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TABLE I. Chemicals (Including Those on the 2004 FEMA High Priority List for Respiratory Hazards) Used at the Flavoring Manufacturing Facility by Frequency of Use in June 2008

Near daily use	Frequent use	Less Frequent use	Rare use
Acetaldehyde	Furfural	Formic acid	Ammonium sulfide
Acetic acid	Limonene ^a	Isobutyraldehyde	Ethyl acrylate
Acetoin	Propionic acid	Isobutyric acid	Hydrogen sulfide
Benzaldehyde	Starter distillate ^a	Methyl mercaptan	2-pentenal
Butyric acid		Propionaldehyde	Phenol
Diacetyl		Trimethylamine	Piperidine
Phosphoric acid		Valeraldehyde	Pyridine
			Pyrrolidine

^aNot on 2004 Flavoring and Extract Manufacturers Association priority list as potential respiratory hazards.

the Indiana Occupational Safety and Health Administration (IOSHA) found additional chemicals, such as dimethyl sulfide, ethanol, 6-methylcoumarin, and hydrogen sulfide, the last at concentrations immediately dangerous to life and health [IOSHA, 2012].

The NIOSH health hazard evaluation documented an impressive increased cross-sectional prevalence of abnormal restrictive spirometry compared to the general U.S. population. This finding suggestive of restrictive lung disease contrasted with the excess of obstructive spirometric abnormalities seen in many other flavoring-exposed workforces [NIOSH, 2011a]. This paper derives from the NIOSH evaluation, supplemented by later environmental information and recoding of smoking status information, which was incomplete in the previous report. The objective of this study was to examine routine medical surveillance data collected by the company to determine whether the excess abnormalities were associated with indices of exposure reflected in workers' job histories and areas of production work. Since the company surveillance data was longitudinal in nature, we had the opportunity to look at declines of lung function during employment in production workers as individuals and in subgroups by job title and area. We hypothesized that statistically different distributions of spirometric abnormalities, including abnormal declines in lung function over time, within the production workforce existed. Such work-related differences would likely implicate work exposures as responsible for excess abnormalities.

Exposure Background

Industrial hygiene measurements of diacetyl conducted for the company between 2004 and 2007 were limited to 14 area and 10 personal samples taken when diacetyl-containing products were being prepared in six areas. The NIOSH 2557 method used for diacetyl measurement was subsequently shown to result in underestimation in relation to absolute humidity and days to extraction of the samples in the

laboratory [NIOSH, 2011a]. The maximum 8-hr time-weighted average (TWA) concentration of diacetyl was 10.17 parts per million (ppm) in an area sample in liquid compounding; a personal breathing zone sample in X-Oil (process flavors, adjacent to liquid compounding) was as high as 3 ppm, but insufficient data regarding sampling volume and time were available to calculate a TWA. For comparison, NIOSH has proposed a recommended diacetyl exposure limit of 0.005 ppm, with a 15-min short-term exposure limit (STEL) of 0.025 ppm [NIOSH, 2011b]. Other sampled analytes included acetaldehyde, acetic acid, benzyl alcohol, butyric acid, ethyl acetate, ethyl alcohol, phosphoric acid, respirable dust, and total dust, all of which were found at levels below occupational guideline limits, when available. In 2008–2009, 71 area samples in 10 locations and 45 personal breathing zone measurements in 8 areas were conducted for the company using updated sampling/analytical methods for diacetyl that are not affected by humidity. All areas sampled (including laboratory, packaging, and warehouse) had detectable levels of diacetyl, at 8-hr TWA concentrations up to 2.9 ppm for area samples and 1.9 ppm for personal samples [NIOSH, 2011a].

In 2011–2012, IOSHA measured diacetyl concentrations in the factory when diacetyl was suspected to be present, with 28 results based on measurements from 9 to 92 min in duration that exceeded the American Conference of Governmental Industrial Hygienists' (ACGIH) guidance not to exceed 0.02 ppm as a 15-min STEL or 0.01 ppm as an 8-hr TWA diacetyl concentration [IOSHA, 2012]. Calculated diacetyl concentrations, adjusted assuming zero exposure for the balance of the time not sampled, ranged up to 9.19 ppm short-term (based on 13 min of sampling) and 0.52 ppm for an 8-hr average (based on 55 min of sampling). Concentrations were higher during the actual sampled periods (10.66 and 4.56 ppm, respectively). These diacetyl concentrations occurred on 5 days over 2 months and were in the X-Oil and packaging areas. The settlement of the compliance citations in January 2013 eliminated four of the

28 excessive diacetyl measurements after comparison to a 2009 OSHA proposed Permissible Exposure Limit (PEL) of 0.2 ppm as a STEL and 0.05 ppm as an 8-hr TWA (including two packaging worker measurements) and eliminated an additional six excessive diacetyl measurements from an acetoin pour which was deemed not to be a source of diacetyl [IOSHA, 2012].

An unexpected finding in the IOSHA compliance investigation was hydrogen sulfide concentrations that were above the ceiling permissible exposure limit of 20 ppm and above the 100 ppm value immediately dangerous to life or health. Appropriate personal respiratory protection was not provided, nor was evacuation required when hydrogen sulfide exposure monitors alarmed. These exposures, measured at 125, 172, 200, and 200 ppm, occurred for compounders in a reactions/savory area where employees described emanation of hydrogen sulfide when ammonium sulfide was added to sulfur-containing amino acids in making beef, chicken, and crab flavors. IOSHA measured acetic acid in the liquid compounding area at levels of 28.5 and 54.7 ppm as 15-min time-weighted averages, both exceeding the ACGIH STEL of 15.0 ppm [IOSHA, 2012].

METHODS

Population

The population was a retrospective cohort study of 112 production workers who had participated in spirometric medical surveillance arranged by the flavoring company during the 2004–2009 interval for the purpose of medical clearance for respirator use. The company had approximately 115 production employees and 100 office workers in 2008, and the retrospective cohort study of those with spirometry measurements included at least 4 former workers at that time. We abstracted age, height, weight, and smoking status (when available) as non-smoker, former smoker or current smoker, from all spirometry records supplied by the company's medical contractor for employees who participated in the production worker medical surveillance program. In conducting a public health investigation, NIOSH investigators had authority to receive personally identifiable information subject to the Health Insurance Portability and Accountability Act, which permits medical providers to disclose protected health information without a patient's written authorization to public health authorities [U.S. Code of Federal Regulations, 2002]. From these records, we classified employees as having been an ever-smoker if they had been a current or former smoker at any testing session.

We obtained work history information from company personnel records that indicated job title and area with start dates for each job title and date of termination, if the worker was no longer employed. We calculated tenure at work from these employment records. The company identified 12 areas:

administration, dry blend, extract and distillation, liquid compounding, maintenance, packaging, process flavors, sample ordering, spray dry, warehouse, quality control, and research and development. We combined the last two areas into one category for analyses because of the small numbers in these two areas and the likely similar levels of exposure to flavoring chemicals. Based on information about where liquid and dry flavorings were produced from a site visit in 2008, we a priori assigned employees in the following areas to a category of higher potential for exposure to flavoring chemicals: dry blend, extract and distillation, liquid compounding, process flavors, and spray dry. Workers who did not work in these areas, including packaging, were assigned to the lower category of flavorings exposure. We categorized the work history information in four different ways: (1) currently working in an area; (2) ever worked in an area; (3) currently working in areas with higher potential for exposure; and (4) ever worked in areas with higher potential for exposure.

Spirometry Records Evaluation

We evaluated the quality of 369 spirometry records from 112 employees with test sessions dating from July 6, 1998 to August 25, 2009, including examination of curves for all efforts in a test session. Two-thirds of the spirometry tests were performed using an EasyOne™ spirometer (ndd Medical Technologies, Andover, MA); most test sessions included a quality grade. When reports did not include a quality grade (as was the case for 29 tests performed using an EasyOne spirometer and for 119 tests performed with another type of spirometer), we graded spirometry using the EasyOne Spirometry EasyGuide criteria from the version 4.0 manual. Spirometry tests graded A or B had at least three acceptable expiratory efforts, and measurements of forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) matched within 200 ml or less. Spirometry tests graded C had at least two acceptable efforts, and measurements for FEV1 and FVC matched within 250 ml or less. Spirometry tests graded D had only one acceptable effort, or the two best acceptable measurements did not meet the 250 ml criterion for repeatability. Spirometry graded F had no acceptable efforts. There were four tests performed with a different model spirometer that did not have enough information about each individual expiratory effort to allow for a quality grade to be assigned, and these data were not used. Where recorded heights differed for individuals with more than one spirometry report, we used the most frequently recorded height value (mode) to interpret spirometry results; when there was no modal height value, we used the mean of the reported heights.

We interpreted spirometry results with A, B, or C quality grade as normal or abnormal in relation to U.S. population reference equations [Hankinson et al., 1999]. If a test had a D quality grade but documented normal ventilatory function,

we interpreted it as normal; if abnormal or F quality, the test was uninterpretable. We defined obstructive spirometric abnormalities as having FEV1 and FEV1/FVC below the lower limits of normal; restrictive abnormalities as having FVC below the lower limit of normal; and mixed obstructive and restrictive as having FEV1, FVC, and FEV1/FVC all below the lower limits of normal. We further categorized such abnormalities as mild, moderate, moderately severe, severe, or very severe [Pellegrino et al., 2005].

We compared the prevalence of an abnormal restrictive pattern of spirometry with the prevalence that would be expected in the U.S. general population with the same distributions of age (less than 40 years and 40 or older), sex, race, ethnicity, ever smoking (yes, no), and body mass index (less than 25, 25 to less than 30, and 30 or greater kg/m²). The U.S. population prevalences were based on the third National Health and Nutrition Examination Survey [National Center for Health Statistics, 1996]. We used SAS[®] (version 9.2, SAS Institute, Inc., Cary, NC) statistical software to analyze the data and chose a probability (*P*) less than or equal to 0.05 as a criterion of statistical significance and $0.05 < P < 0.1$ as showing a trend with marginal statistical significance.

Changes in lung function over time

For each employee having spirometry on more than one occasion, we estimated change in serial lung function using multivariate linear regression of both all FEV1 and all FVC measurements of A, B, or C quality. As a first approach, we estimated population average changes in FEV1 and FVC as ml/year. As a second approach, we identified individuals with excessive changes in FEV1 over time using SPIROLA software [Hnizdo et al., 2010]. SPIROLA analyses of longitudinal change in FEV1 are appropriate for both patterns leading to restrictive or obstructive spirometry because FEV1 decreases in both patterns. For individuals with less than 8 years of follow-up, this program compares FEV1 values to the limit of longitudinal decline (LLD). The LLD is a threshold value used to determine whether the lung function decline between the first FEV1 value (or a mean of the first two observations, if the first FEV1 value is lower than the second one) and each follow-up FEV1 value is excessive. Observations that fall below the LLD warrant concern as having less than a 5% chance of being normal. Beginning with 8 years of follow-up, SPIROLA bases the interpretation of excessive decline on an individual's regression slope and the lower 95% confidence limit around the regression line.

The SPIROLA software adjusts its determination of LLD for spirometry quality, as reflected by mean pair-wise within-person variation, in addition to considering what would be normal declines in healthy persons. High quality spirometry monitoring programs, often carried out for research purposes, can achieve a within-person variation of approximately 3%

[Wang and Petsonk, 2004] or 4% [Wang et al., 2006]. We determined that the employees' spirometry data of A, B, and C quality had a within-person variation of 5%. We used SPIROLA to identify an LLD of 12.4% longitudinal decline based on the relative within-person variation of 5% and a referential rate of FEV1 decline of 30 ml/year [Hnizdo et al., 2010]. Supplemental on-line information for this paper shows an illustrative example of SPIROLA plots.

Associations between Work History and Lung Function

Using logistic regression, we modeled the categorical outcomes of restrictive abnormalities on the most recent spirometry test and having excessive FEV1 decline against work area. We used multivariate linear regression models to investigate the association of changes in FEV1 and FVC as continuous variables with work area variables. For these models, the outcome was the change in lung function in ml/year that had been estimated for each individual. For both types of models, we adjusted for body mass index of 30 or more kg/m² at the last test, change in weight over the spirometry testing period for each employee (as pounds per year), age at last test, ever-smoking as a yes or no categorical variable, and tenure in years. For the models using ever worked in any specific area with higher potential for flavoring exposure, we used those who never worked in the areas with higher potential for exposure to flavoring chemicals as the comparison group. Similarly, we compared current employees in any specific area with higher potential for exposure to the employees not currently working in areas with higher potential for exposure.

RESULTS

Demographics

The demographic characteristics of the 112 employees with spirometry records are given in Table II. Those 97 employees with work history data showed that 42 currently

TABLE II. Demographic Characteristics for 112 flavorings manufacturing facility production employees at date of most recent spirometry test

Male gender, n (%)	96 (85.7)
Race, n (%)	
White	86 (76.8)
Black	23 (20.5)
Hispanic	3 (2.7)
Ever smoker, n (% of 108 employees)	42 (38.9)
Age in years, mean (range)	45.5 (21–67)
Tenure in years, mean (range for 95 employees)	16.2 (0.64–36.1)
Body mass index ≥ 30 kg/m ² , n (%)	33 (29.5)

TABLE III. Numbers of Employees With Spirometry and Work History Data by Work Area in Flavorings Manufacturing Plant

Work area	Number of current employees	Number of employees ever ^a
Administration	0	6
Dry blend ^b	7	20
Extract and distillation ^b	0	1
Liquid compounding ^b	22	47
Maintenance	7	16
Packaging	19	49
Process flavors ^b	9	16
QC and R&D ^c	12	20
Sample order	3	3
Spray dry ^b	4	8
Warehouse	14	27
Total	97	

^aIncludes current employees in addition to employees who had a previous assignment in the area during their work tenure.

^bIn our analyses, an area defined as having higher potential for flavoring exposure in comparison to other work areas.

^cQuality Control and Research and Development.

worked in areas having higher potential for flavoring exposure (Table III), and 63 had ever worked in such areas. Few spirometry measurements were made prior to 2004 (17 of 369), and the proportion of test sessions with A, B, or C quality was 81.8%. The range of spirometry follow-up time was 0 to 11 years; 28 employees had only one spirometry test. Seventy of 84 had more than one spirometry test of A, B, or C quality, of whom 63 had work history information that included tenure. Of these 63, the group of 43 employees who had ever worked in areas of higher potential for flavoring exposures had an average follow-up of 5.5 years, in comparison to 3.6 years follow-up for the group of 20 employees always in areas with lower exposure potential. The 28 employees who were currently working in areas of higher potential for flavoring exposure had an average of 5.6 years of follow-up, compared to 4.4 years of follow-up for the 35 employees with lower current potential for exposure.

Interpretation of Most Recent Spirometry Tests

The most recent test was performed in 2009 for 96 employees, in 2008 for 12 employees, and between 2004 and 2006 for four employees. Forty-eight percent of the most recent spirometry tests for each individual had A quality, 14% had B quality, 18% had C quality, 18% had D quality, and 2% had F quality. We interpreted 106 of the 112 tests (90 of A–C quality and 16 of D quality with a normal interpretation). We identified 34/106 (32%) employees as having abnormal spirometry results. We found a restrictive pattern in 30/106

(28%) employees (22 mild abnormality, six moderate abnormality, one moderately severe abnormality, and one severe abnormality). Additionally, we identified two employees with mild obstruction, one employee with moderate obstruction, and one with a very severe mixed pattern. Employees with interpretable spirometry measurements and smoking histories had 3.7 times the prevalence of abnormal restriction compared to the U.S. population adjusted for age, gender, race, ever smoking, and body mass index (95% confidence interval [CI] 2.6–5.3).

Changes in lung function over time

For non-smokers ($n = 38$), the mean decline in FEV1 was 81.3 (standard error [SE] 13.2) ml/year, and the mean decline in FVC was 94.8 (SE 16.9) ml/year. For ever smokers ($n = 30$), these values were 94.5 (SE 25.3) ml/year for FEV1 and 125.1 (SE 32.8) ml/year for FVC. Results for percent predicted FEV1 and FVC (which adjust for age) for the 18 employees tested for all four years from 2006 to 2009 showed parallel declines in average percent predicted FEV1 and FVC over time with relatively stable FEV1/FVC ratio (Fig. 1), consistent with a tendency toward restriction.

Of 70 employees with two or more spirometry tests of A, B, or C quality used in the SPIROLA analyses of abnormal declines in FEV1, 13 (19%) were identified as having excessive FEV1 declines using the 12.4% longitudinal decline criterion. The employee with abnormal decline and the shortest period of follow-up (1.9 years) lost 499 ml/year, for a total of 900 ml in FEV1. The others with abnormal declines in FEV1 had abnormal declines over 4.3–10.7 years with annualized declines of 92–188 ml/year. Of these 13 employees that had experienced abnormal rates of decline, five continued to have FEV1 values in the normal range at their most recent spirometry test. Eight (32%) of 25

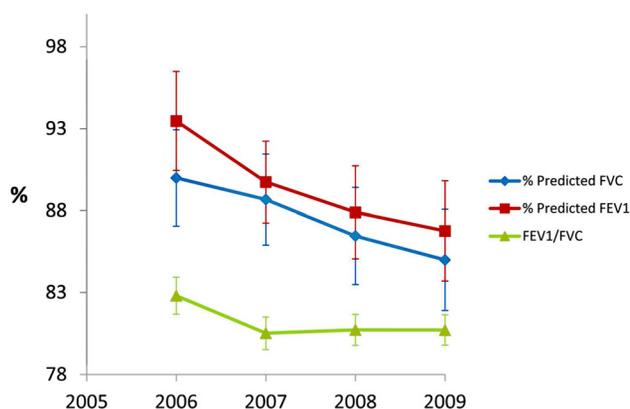


FIGURE 1. Group means of percent predicted forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) and FEV1/FVC ratio (expressed as percent) by year of test for all A–C quality spirometry tests for 18 employees tested 2006–2009. If there was more than one test per worker in a year, the last test of the year was used.

TABLE IV. Logistic Regression and Multiple Linear Regression Models of Spirometric Outcomes in Relation to Areas Reflecting Different Potential Flavoring Exposures

Work area	Logistic models ^a				Multiple linear regression models ^a	
	Restrictive abnormality		Excessive FEV1 decline		FEV1 ml/yr decline	FVC ml/yr decline
	OR	95% CI	OR	95% CI	Adjusted mean	Adjusted mean
Worked in areas with higher potential for exposure						
Ever vs. never	1.1	0.34–3.43	7.0*	0.93–52.6	–115 vs. –38**	–134 vs. –56*
Currently vs. not currently	0.58	0.19–1.76	5.8**	1.2–28.8	–110 vs. –76	–119 vs. 101
Worked in liquid compounding						
Ever vs. never in areas of higher potential for exposure	1.1	0.31–3.70	3.6	0.51–26.02	–109 vs. –40**	–128 vs. –62
Currently vs. not currently in areas of higher potential for exposure	0.82	0.23–3.0	3.2	0.56–18.23	–104 vs. –75	–113 vs. –100

OR, odds ratio; CI, confidence interval; vs., versus; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; ml, milliliters; yr, year.

^aModels adjusted for body mass index of 30 or more kilograms/meter², change in weight over the spirometry testing period for each employee (as pounds per year), age at last test, ever-smoking as a yes or no categorical variable, and tenure in years.

*0.05 < *P* ≤ 0.1.

***P* ≤ 0.05.

employees with both abnormal restrictive spirometry and serial measurements had excessive decline in FEV₁, suggesting that the abnormality was progressing.

Associations between Work History and Lung Function

Restriction on last spirometry showed no significant associations with work area (Table IV). Changes in FEV₁ in ml/year were significantly associated with ever having worked in areas with higher potential for exposure to flavorings. The adjusted means for change in FEV₁ for those ever having worked in higher potential exposure areas versus those never having worked in these areas were –115 ml/year compared to –38 ml/year (*P* = 0.015). Changes in FVC were also higher in those ever working in higher potential for exposure areas (adjusted means of –134 ml/year vs. –56 ml/year; *P* = 0.057). Within the category of higher potential for exposure, ever having worked in liquid compounding, as compared to never having worked in areas with higher potential for exposure, was associated with a larger decline in FEV₁ (adjusted means of –109 ml/year vs. –40 ml/year; *P* = 0.024). Excessive decline in FEV₁ was associated with currently working in higher potential for exposure areas (odds ratio = 5.8; 95% CI = 1.2–28.8, *P* = 0.032) and with ever working in higher potential for exposure areas (odds ratio = 7.0; 95% confidence interval = 0.93–52.6, *P* = 0.059).

DISCUSSION

Burden of Occupational Lung Disease

Of production employees in the medical surveillance program of this flavoring manufacturing company, 37% had

either abnormal spirometry or abnormal declines in spirometry or both, with the predominant abnormality being a restrictive pattern. Restriction was about 3^{1/2} times more common than expected compared to the general United States population, after adjusting for potential contributing factors such as smoking, overweight and obesity. Abnormal loss in lung function during employment raises the possibility of an employment-related cause of progressive decline. The statistical associations that we have documented between abnormal declines in lung function and persons in jobs with higher potential for flavorings exposures are consistent with employment conditions causing deterioration in lung health.

The evidence in favor of work-relatedness is three-fold. First, employees with higher potential for flavorings exposure in their work areas had 3.0 times greater annualized decline in FEV₁ than employees in jobs with lower potential for exposure; 2.4 times greater annualized decline in FVC; and the average yearly FEV₁ decline was 3.8 times greater than is normal in the general population (115 vs. 30 ml/year). Second, employees with current higher potential for flavorings exposure had 5.8 times the odds of abnormal decline in FEV₁ compared to employees with lower potential for exposure. Because employees often relocate to other jobs if they suspect health effects related to their work (“healthy worker effect”), we evaluated whether employees that had ever worked in areas with higher potential for flavorings exposure had higher risk of excessive decline compared to employees that had never worked in such areas and found a trend to even higher odds (7.0-fold) than was associated with current employment in higher potential exposure jobs. Third, within the higher potential for flavorings exposure work areas, we identified a single job group (those ever working in liquid compounding) that had a statistically increased annual FEV₁ decline in comparison to employees that never worked

in areas with higher potential flavorings exposures. The liquid compounding subgroup of employees was the largest among those employees working in the five areas with higher potential for flavorings exposure, which conferred adequate power to demonstrate an association with greater FEV1 decline in comparison to employees in areas with lower potential for exposure.

Although excessive decline in lung function was strongly associated with current work areas with higher potential for flavorings exposure, we found no statistical association between restrictive abnormality and such work areas. The 3.7-fold excess of restriction in the employee population undergoing surveillance compared to the general population was broadly distributed among all work areas. The employees referred for spirometric testing were all thought to have potential for flavorings exposure. Indeed, IOSHA testing in 2012 documented two high levels of diacetyl exposure in packaging, which we had previously classified in the lower potential for flavorings exposure category [IOSHA, 2012]. The calculated concentrations were 0.05 ppm for a STEL, based on 13 min of sampling and 0.01 ppm for a TWA, based on 92 min of sampling (actual measurements were 0.06 and 0.07 ppm, respectively). In addition, company diacetyl sampling in 2009 documented that measurable diacetyl exposure was broadly distributed across all work areas sampled, including the warehouse, packaging, and laboratory, although geometric mean diacetyl measurements, where available, were higher in areas that we had previously classified as having higher potential for flavorings exposure [NIOSH, 2011a]. With batch operations of many different flavorings, representative sampling is unlikely in any small flavoring manufacturing data set. The maximum diacetyl exposures documented in some of the employees working in lower potential for exposure areas were in the range associated with lung disease in microwave popcorn plant employees [Kanwal et al., 2006]. Thus, our classification into areas with higher and lower potential for flavorings exposure did not preclude exposures that could have resulted in spirometric abnormality, even if excessive decline in spirometry was not evident in recent serial measurements.

With our analytic exclusion of body mass index, weight gain, and spirometry quality as explanations for work-related restrictive abnormalities, we suspect inflammatory or scarring interstitial lung or bronchiolar disease in a substantial fraction of company employees with abnormal spirometry. In case series of biopsy-documented constrictive bronchiolitis, cases frequently have normal spirometry; when abnormal, spirometry can be restrictive, obstructive, or mixed restrictive and obstructive in pattern [Markopoulou et al., 2002; Ghanei et al., 2008; King et al., 2011]. In epidemiologic work to date in microwave popcorn, other food production, and flavoring manufacturing industries, restrictive abnormalities have been common in employees exposed to diacetyl among other flavoring chemicals [Kreiss, 2012]. Inhalation toxicology

documents epithelial necrosis in rodents exposed to diacetyl or 2,3-pentanedione, consistent with the mechanism of constrictive bronchiolitis in humans [Palmer et al., 2011; Hubbs et al., 2012]. Inhalation toxicology does not exist for many of the priority respiratory hazards of flavoring ingredients. Altogether, the risks of occupational lung disease in this plant are considerable, and the ongoing employee health burden is clear, particularly among employees with higher potential for flavoring exposures. To date, we do not know the pathophysiology underlying the excess restriction among these employees, which could be interstitial, bronchiolar, or alveolar in location.

The literature on nonfatal and subacute hydrogen sulfide exposures documents exertional dyspnea and both obstructive and restrictive effects, including organizing pneumonia with a mixed pattern of obstructive and restrictive abnormalities [Arnold et al., 1985; Parra et al., 1991; Richardson, 1995; Hessel et al., 1997; Doujaiji and Al-Tawfiq, 2010]. IOSHA measured high levels of hydrogen sulfide in the reactions area, which was adjacent to the packaging area in 2008, but we are not certain how workers in this area would have been classified among the 12 areas identified by the company.

Potential Causal Exposures

Work-relatedness of the spirometric abnormalities does not imply that diacetyl is the sole or primary cause. Flavoring companies have hundreds of chemical exposures other than diacetyl and its alpha-diketone substitutes. In the complex exposure setting of batch operations of many different flavor formulations, each lasting a short time, teasing out single causes of respiratory impairment may be impossible. Fortunately, identifying the causative agent(s) is not required to put preventive measures in place in flavoring manufacture. These include medical surveillance for respiratory complaints, excessive interval pulmonary function declines, and abnormal spirometry regardless of measured concentrations of chemicals, only a few of which have exposure level guidance.

Limitations

The company spirometric surveillance data had several limitations. First, 19% of the spirometry records provided by the company's medical provider had D or F quality, and an additional 18% had C quality, indicating marginal repeatability of measurements within a test session. Our evaluation of serial spirometry records may have underestimated abnormal declines because we excluded poor quality spirometry, and only 70 (63%) employees had serial tests with A, B, or C quality. Thus, the 39 (37%) employees with either abnormal spirometry (30 restricted, 3 obstructed, and 1 mixed), an

isolated excessive decline in FEV1 (5), or both (8) may be an underestimate of the number of employees with spirometric findings suggestive of lung disease. The effect of comparison of highest FEV1 and FVC for company employees with U.S. population spirometry data that may have been of higher quality is not knowable because quality scores post-dated the NHANES III public dataset.

The work history information provided by the company was incomplete and lacked details concerning tasks associated with job titles or areas of production. Few exposure measurements were available initially to support our classification of some areas as having higher potential for flavoring exposures than the remainder of jobs and areas. These two data limitations may have resulted in misclassification of exposures and health outcomes, either of which would lower our ability to detect possible work-related associations. For example, we did not include laboratory, maintenance, research and development and quality control, and packaging employees in the group with higher potential for exposure, although this classification would be appropriate in some other flavoring or food production plants. Those with spirometry data certainly were not an unexposed control group, and exposures in all areas may have been sufficient to cause restrictive abnormalities. The company air sampling data from 2009 provided some evidence that the areas that we considered to have higher potential for flavoring exposures had higher diacetyl measurements [NIOSH, 2011a]. But subsequent OSHA measurements documented notable diacetyl exposures in packaging, which we had classified in the lower potential exposure category. We don't know whether reactions area workers with high hydrogen sulfide exposures were in the higher or lower potential for flavorings exposure group.

Finally, small numbers of employees in many production categories limited statistical power to determine differences among subgroups. We were able to demonstrate that employees that ever worked in liquid compounding had significantly greater declines in FEV1 compared to employees that had never worked in areas with higher potential for exposures to flavorings. This statistical finding does not imply that employees in other areas within the group of higher potential exposure areas had no risk, nor does it mean that employees in areas with lower potential for exposure had no risk. Indeed, diacetyl has been measured by the company in all production areas; all employees participating in medical surveillance were thought to have potential flavoring exposure; and approximately two-thirds of the employees with spirometry for whom we had work history information had at some time worked in areas classified as having higher potential for flavorings exposure. Together, these limitations may explain why we did not find an association between higher potential for exposure areas and abnormal restrictive spirometry, despite finding higher risk for excessive decline in recent spirometry measures in relation to current exposure category.

Conclusions

Our finding that abnormal loss of lung function was not uniformly distributed among company employees and was concentrated among employees with higher potential for flavoring exposures is consistent with a work-related cause. With the insensitivity of spirometry and lung volumes in detecting both constrictive bronchiolitis [Markopoulou et al., 2002; Ghanei et al., 2008; King et al., 2011] and clinical restrictive disease [Boros et al., 2004], the burden of occupational lung disease among these employees may be far greater. Further medical testing of those with symptoms or abnormalities in spirometry is of interest to define any lung diseases resulting in restrictive spirometric abnormality in this workplace. Frequent spirometric follow-up of the workforce and those with excessive FEV1 decline may assist in documenting whether workplace interventions to lower flavoring exposure are effective in preventing work-associated declines in lung function. In the meantime, those responsible for medical surveillance, diagnosis, and clinical management of flavoring-exposed workers need to take account of the widening spectrum of occupational lung disease presentation in both the food production and flavoring manufacturing industries.

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