ORIGINAL ARTICLE

Respiratory symptoms and lung function abnormalities related to work at a flavouring manufacturing facility

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ABSTRACT

Objectives To better understand respiratory symptoms and lung function in flavouring manufacturing workers.
Methods We offered a questionnaire and lung function testing to the current workforce of a flavouring manufacturing facility that had transitioned away from diacetyl and towards substitutes in recent years. We examined symptoms, spirometric parameters and diffusing capacity measurements by exposure variables, including facility tenure and time spent daily in production areas. We used linear and logistic regression to develop final models adjusted for age and smoking status.
Results A total of 367 (93%) current workers participated. Shortness of breath was twice as common in those with tenure ≥7 years (OR 2.0, 95% CI 1.1 to 3.6). Other chest symptoms were associated with time spent daily in production. Participants who spent ≥1 h daily in production areas had twice the odds of any spirometric abnormality (OR 2.3; 95% CI 1.1 to 5.3) and three times the odds of low diffusing capacity (OR 2.8; 95% CI 0.9 to 9.4) than other participants. Mean spirometric parameters were significantly lower in those with tenure ≥7 years and those who spent ≥1 h daily in production. Mean diffusing capacity parameters were significantly lower in those with tenure ≥7 years. Differences in symptoms and lung function could not be explained by age, smoking status or employment at another flavouring plant.
Conclusions Symptoms and lung function findings were consistent with undiagnosed or subclinical obliterative bronchiolitis and associated with workplace exposures. Further efforts to lower exposures to flavouring chemicals, including diacetyl substitutes, are warranted.

What this paper adds

- Flavouring manufacturing workers may be exposed to the butter flavouring chemical diacetyl, which causes obliterative bronchiolitis, and hundreds of other chemicals of unknown respiratory toxicity.
- In a facility transitioning away from diacetyl to substitutes such as 2,3-pentanedione, workers with higher flavouring chemical exposures from more time spent daily in production areas and/or longer facility tenure had more respiratory symptoms, more lung function abnormalities and lower mean lung function parameters.
- Efforts to address adverse respiratory effects of flavouring manufacture that focus solely on diacetyl exposure reduction are unlikely to be successful. Until the safety of other flavouring chemicals is established, exposure reduction (such as through enhanced ventilation and use of respiratory protection) and medical surveillance are prudent.

INTRODUCTION

Occupational exposure to the butter flavouring chemical diacetyl has been associated with obliterative bronchiolitis (also known as bronchiolitis obliterans) in the microwave popcorn, diacetyl manufacture and coffee processing industries.[1–3] Laboratory animal models have confirmed the respiratory toxicity of diacetyl and its substitute, 2,3-pentanedione.[4–6] A decade of investigation led to the formal proposal in 2011 of recommended exposure limits for diacetyl and 2,3-pentanedione in the USA.[7]

Far less is known about the respiratory toxicity of other diacetyl substitutes or the multitude of other flavouring chemicals currently in use. Two cases of obliterative bronchiolitis in California flavouring manufacturing workers[8] prompted industry-wide state surveillance that identified other probable cases and abnormal declines in the forced expiratory volume in 1 s (FEV_1) on longitudinal spirometry.[9 10] An investigation at an Indiana flavouring manufacturing facility found an excess of spirometric restriction cross-sectionally and flavouring-related abnormal declines in FEV_1 longitudinally.[11] The finding of spirometric restriction could be consistent with obliterative bronchiolitis from diacetyl[12] or it could represent distinct pathological effects of other exposures.

To better understand the spectrum of respiratory health in flavouring manufacturing workers, we conducted a cross-sectional study at a large flavouring manufacturing facility where obliterative bronchiolitis reportedly had been diagnosed in two former workers. Since the facility opened in 1998, the use of diacetyl reportedly had declined and the use of substitutes had increased. Neither air sampling conducted by consultants to the facility in 2008 nor our own air sampling in 2011 detected

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diacetyl, although we did detect 2,3-pentanedione.[13] Thus, results of recent industrial hygiene evaluations were consistent with a transition away from diacetyl and towards substitutes in the years prior to our study.

METHODS

Study design

The study was conducted in accordance with the NIOSH Institutional Review Board's requirements for health hazard evaluations. We invited all current workers at the facility to give written informed consent for an interviewer-administered questionnaire, spirometry and measurement of diffusing capacity. The questionnaire addressed respiratory symptoms and diagnoses, smoking history, work history and practices, and demographic information.[13] The respiratory questions were adapted from validated survey instruments.[14–16]

We conducted and interpreted spirometry testing according to published guidelines using a dry rolling-seal spirometer.[17–19] We defined obstruction as FEV_1 and ratio of FEV_1 to forced vital capacity (FVC) below their respective lower limits of normal (5th centiles) with a normal FVC. We defined restrictive pattern as a normal FEV_1/FVC ratio with FVC below the lower limit of normal. We classified participants with both FEV_1/FVC ratio and FVC below the lower limit of normal as having mixed obstructive and restrictive abnormalities. We considered participants to have any spirometric abnormality if they met the definition of obstruction, restrictive pattern or mixed pattern.

Participants with any spirometric abnormality who did not have medical contraindications were administered a bronchodilator to determine reversibility using four puffs of a β-agonist (albuterol). We defined reversibility as an increase in FEV_1 of at least 12% and 200 mL after bronchodilator administration.[19]

We measured and interpreted the diffusing capacity of the lung for carbon monoxide (DL_{CO}) using the single breath technique with helium as the tracer gas following published guidelines.[20 21] We defined low diffusing capacity as DL_{CO} below the lower limit of normal and low total lung capacity as alveolar volume below the lower limit of normal.

Following the survey, we mailed reports to each participant at his or her home address. The reports explained individual lung function test results and provided recommendations for follow-up of abnormalities.

Statistical methods

We defined asthma-like symptoms as current use of asthma medicine and/or one or more of the following symptoms in the last 12 months: wheezing or whistling in the chest, awakening with a feeling of chest tightness or attack of asthma.[16] We defined work-related symptoms as those that were reported to be better away from the facility. Of note, this definition of 'work-related' is most consistent with symptoms of reversible pathologies related to occupational exposures, such as irritant and allergic effects; irreversible pathologies related to occupational exposures, such as obliterative bronchiolitis, may not demonstrate a temporal relationship to the workplace.

We calculated prevalence ratios and 95% CIs of symptoms, diagnoses and lung function abnormalities through comparisons with data obtained from the US adult population from NHANES III[15] using indirect standardisation for race (white or black), sex, age (17–39 or ≥40 years) and cigarette smoking status (ever/never).

To explore potential associations between health outcomes and work, we examined questionnaire responses and lung function test results by exposure variables using contingency tables

and analysis of variance to compare means. When these analyses revealed significant associations, we developed multivariable models using linear and logistic regression, adjusting for current/former/never smoking status (for all health outcomes) and age (for health outcomes based on questionnaire responses). Most of the health outcomes based on lung function test results involve predicted values that account for age (as well as sex, height and, for spirometry, race). For analyses of the FEV_1/FVC ratio, which is calculated from raw (not predicted) values, we examined the effect of age in adjusted models. For final adjusted models, we report ORs (for categorical outcomes) or least squares means (for continuous outcomes), with corresponding 95% CI.

Exposure variables were defined on the basis of participants' self-reported work histories and categorised as follows: facility tenure (≥7 vs <7 years), average amount of time spent daily in production areas (≥1 vs <1 h); use of flavouring ingredients; use of cleaning products; and history of work at another flavouring plant (including another facility owned by the same employer).

In this paper, we present comparisons of current/non-current categories. We also examined comparisons of current/never, ever/never and former/never categories, which had similar estimates.

Statistical analyses were conducted using SAS software V.9.3 and JMP software V.10.0.1 (SAS Institute, Inc, Cary, North Carolina, USA). We considered two-sided p≤0.05 to be statistically significant. We used likelihood ratio tests to determine significance.

RESULTS

A total of 367 (93%) of 393 current workers participated. All participants completed the questionnaire, and most had spirometry testing (n=357) and measurement of diffusing capacity (n=347). All spirometry tests and 325 (94%) of the diffusing capacity tests were interpretable and included in our analyses.

The majority of participants were male (n=231; 63%) and white (n=334; 91%). Median facility tenure was 7 years (mean 8; range <1–14). Median time spent daily in production areas was 0 h (mean 2; range 0–10); 138 (38%) reported spending ≥1 h daily in production areas. A total of 165 (45%) participants reported using flavouring ingredients and 211 (57%) reported using cleaning products. Eighty-two (22%) had worked at another flavouring plant.

Table 1 displays age and smoking status by time spent daily in production areas and tenure. Age was not associated with time spent daily in production areas. Participants who spent ≥1 h daily in production areas were more likely than other participants to be current smokers. Participants with tenure ≥7 years were older than other participants and less likely to be current smokers.

The first column of table 1 also displays participants' responses to questions on symptoms and diagnoses. In addition, 10 participants (3%) reported a diagnosis of chronic bronchitis and 2 reported a diagnosis of chronic obstructive pulmonary disease. One participant reported a diagnosis of bronchiolitis obliterans, but medical records were not available for review. No participant reported a diagnosis of emphysema, hypersensitivity pneumonitis or chemical pneumonitis.

Thirty (8%) participants who had spirometry testing had an abnormal result (table 2, first column). Bronchodilator was administered to 24 (80%) of those with abnormal spirometry. The majority (n=8; 67%) of participants with obstruction or a mixed pattern (which may represent obstruction) had a fixed

Table 1 Demographics, symptoms and self-reported diagnoses of participants overall and by exposure categories

	All participants	Time spent daily in production areas		Facility tenure	
		<1 h	≥1 h	<7 years	≥7 years
N	367	229	138	189	178
Demographic					
Age, years, mean (range)	42 (20–71)	42 (22–71)	42 (20–65)	**37 (20–66)**	**47 (27–71)**
Smoking status					
Current, n (%)	70 (19)	**28 (12)**	**42 (30)**	**43 (23)**	**27 (15)**
Former, n (%)	91 (25)	**56 (24)**	**35 (25)**	**36 (19)**	**55 (31)**
Never, n (%)	206 (56)	**145 (63)**	**61 (44)**	**110 (58)**	**96 (54)**
Symptom* or diagnosis					
Sinusitis, n (%)	174 (47)	100 (44)	74 (54)	87 (46)	87 (49)
WR sinusitis, n (%)	43 (12)	**17 (7)**	**26 (19)**	20 (11)	23 (13)
Nasal symptoms, n (%)	164 (45)	96 (42)	68 (49)	85 (45)	79 (44)
WR nasal symptoms, n (%)	55 (15)	**26 (11)**	**29 (21)**	31 (16)	24 (13)
Asthma-like symptoms†, n (%)	101 (28)	**52 (23)**	**49 (36)**	55 (29)	46 (26)
Shortness of breath‡, n (%)	81 (22)	51 (22)	30 (22)	**29 (15)**	**52 (29)**
Wheeze, n (%)	82 (22)	45 (20)	37 (27)	41 (22)	41 (23)
WR wheeze, n (%)	20 (5)	**8 (3)**	**12 (9)**	11 (6)	9 (5)
Breathing trouble, n (%)	75 (20)	42 (18)	33 (24)	40 (21)	35 (20)
WR breathing trouble, n (%)	25 (7)	**8 (3)**	**17 (12)**	15 (8)	10 (6)
Usual phlegm, n (%)	56 (15)	**23 (10)**	**33 (24)**	29 (15)	27 (15)
Usual cough, n (%)	45 (12)	**19 (8)**	**26 (19)**	25 (13)	20 (11)
WR usual cough, n (%)	12 (3)	**4 (2)**	**8 (6)**	6 (3)	6 (3)
Ever asthma, n (%)	44 (12)	28 (12)	16 (12)	25 (13)	19 (11)
Current asthma, n (%)	28 (8)	20 (9)	8 (6)	17 (9)	11 (6)

Statistically significant differences (p≤0.05) are in bold.
*All symptoms were reported for the last 12 months, with the exception of shortness of breath, cough and phlegm. Work-related symptoms were defined as symptoms that improved away from the facility.
†Asthma-like symptoms were defined as current use of asthma medicine and/or one or more of the following symptoms in the last 12 months: wheezing or whistling in the chest, awakening with a feeling of chest tightness or attack of asthma.
‡Shortness of breath when hurrying on level ground or walking up a slight hill.
WR, work related.

abnormality; two of those with a fixed abnormality reported a past history of asthma and two reported current asthma. In total, 15 (5%) tested participants had low diffusing capacity and 24 (7%) had low total lung capacity. Most (73%) participants with low diffusing capacity had normal spirometry; one had obstruction, two had a restrictive pattern and one had a mixed pattern. Most (67%) participants with low total lung capacity had normal spirometry; 8 (33%) had a restrictive pattern.

Table 2 Pulmonary function test results of participants overall and by exposure categories

	All participants	Time spent daily in production areas		Facility tenure	
		<1 h	≥1 h	<7 years	≥7 years
Spirometry, N	357	220	137	184	173
Obstruction, n (%)	13 (4)	5 (2)	8 (6)	6 (3)	7 (4)
Restrictive pattern, n (%)	15 (4)	7 (3)	8 (6)	5 (3)	10 (6)
Mixed pattern, n (%)	2 (1)	0	2 (1)	0	2 (1)
Any abnormality, n (%)*	30 (8)	**12 (5)**	**18 (13)**	11 (6)	19 (11)
FEV₁% predicted, mean	99.5	**101.3**	**96.6**	**101.5**	**97.4**
FVC % predicted, mean	101.2	**102.6**	**98.9**	**102.5**	**99.8**
FEV₁/FVC %, mean	78.9	**79.5**	**77.9**	**80.3**	**77.3**
Diffusing capacity, N	325	201	124	170	155
Low diffusing capacity, n (%)	15 (5)	**5 (2)**	**10 (8)**	5 (3)	10 (6)
Low total lung capacity, n (%)	24 (7)	13 (6)	11 (9)	12 (7)	12 (8)
Diffusing capacity % predicted, mean	95.1	94.9	95.5	**97.0**	**93.0**
Total lung capacity % predicted, mean	92.0	92.2	91.8	**93.5**	**90.5**

Statistically significant differences (p≤0.05) are in bold.
*Defined as obstruction, restrictive pattern or mixed pattern.
FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 3 Adjusted* comparisons of symptoms, self-reported diagnoses and spirometric abnormalities among participants to US adult population

	Observed (n)	Expected (n)	PR	95% CI
Symptom or diagnosis				
N=365				
Sinusitis	172	136.0	**1.3**	**1.1 to 1.5**
Nasal symptoms	163	207.3	**0.8**	**0.7 to 0.9**
Shortness of breath	81	65.9	1.2	1.0 to 1.5
Wheeze	82	58.1	**1.4**	**1.1 to 1.8**
Usual phlegm	56	25.5	**2.2**	**1.7 to 2.8**
Usual cough	26	28.1	0.9	0.6 to 1.4
Asthma, ever	44	28.4	**1.5**	**1.2 to 2.1**
Asthma, current	28	17.7	**1.6**	**1.1 to 2.3**
Chronic bronchitis, ever	10	18.4	0.5	0.3 to 1.0
Spirometric abnormality				
N=355				
Obstruction	13	12.6	1.0	0.6 to 1.8
Restrictive pattern	15	25.4	**0.6**	**0.4 to 1.0**
Obstruction and mixed pattern	15	18.7	0.8	0.5 to 1.3

Statistically significant prevalence ratios and CIs are in bold.
*Adjusted for race, sex, age and smoking status.
PR, prevalence ratio.

Results of adjusted comparisons with the US adult population are shown in table 3. Participants had higher than expected prevalence of sinusitis, wheeze, usual phlegm and asthma. Nasal symptoms and restrictive pattern on spirometry were less common than expected.

Tables 1 and 2 also display health outcomes by time spent daily in production areas and tenure. Participants who spent ≥1 h daily in production areas had significantly higher prevalence of most symptoms, any spirometric abnormality and low diffusing capacity, as well as significantly lower mean spirometric parameters. Participants with ≥7-year tenure had nearly twice the prevalence of shortness of breath of participants with shorter tenure and significantly lower mean spirometric and diffusing capacity parameters. Some symptoms were more common in participants who reported use of flavouring ingredients or use of cleaning products (data not shown). There were no associations between symptoms and history of work at another flavouring plant. Furthermore, there were no significant associations between lung function abnormalities or mean lung function parameters and other exposure variables.

Associations between categorical health outcomes and exposure variables seen in simple analyses were evident in adjusted regression models (table 4). Participants who spent ≥1 h daily in production areas had significantly higher odds of work-related breathing trouble, usual phlegm and any spirometric abnormality. These participants also had higher odds of asthma-like symptoms, usual cough and low diffusing capacity, although these associations did not reach statistical significance. Participants with tenure ≥7 years had significantly higher odds of shortness of breath. Use of flavouring ingredients was significantly associated with work-related nasal symptoms, work-related breathing trouble and work-related usual cough. Use of cleaning products was significantly associated with work-related sinusitis and work-related nasal symptoms.

Most associations between mean pulmonary function test parameters and exposure variables noted in simple analyses were significant in regression models adjusted for smoking

Table 4 Results of adjusted models of relationship between symptoms and lung function abnormalities and exposure variables*

Health outcome	Exposure variables	OR (95% CI)
Symptom		
Sinusitis	Use flavourings ingredients	1.5 (1.0 to 2.4)
	Use cleaning products	1.3 (0.8 to 2.1)
WR sinusitis	Time in production areas	1.7 (0.8 to 3.5)
	Use flavourings ingredients	1.9 (0.9 to 4.2)
	Use cleaning products	**3.0 (1.3 to 8.0)**
Nasal symptoms	Use flavourings ingredients	1.4 (0.9 to 2.2)
	Use cleaning products	1.5 (0.9 to 2.4)
WR nasal symptoms	Time in production areas	1.2 (0.6 to 2.3)
	Use flavourings ingredients	**2.2 (1.1 to 4.5)**
	Use cleaning products	**2.1 (1.0 to 4.6)**
Asthma-like symptoms	Time in production areas	1.5 (0.9 to 2.4)
Shortness of breath	Tenure	**2.0 (1.1 to 3.6)**
WR wheeze	Time in production areas	1.8 (0.7 to 5.0)
	Use flavourings ingredients	2.1 (0.7 to 6.7)
	Use cleaning products	2.0 (0.6 to 7.7)
WR breathing trouble	Time in production areas	**2.7 (1.1 to 7.1)**
	Use flavourings ingredients	**2.8 (1.1 to 7.7)**
Usual phlegm	Time in production areas	**2.2 (1.2 to 4.0)**
	Use flavourings ingredients	1.4 (0.7 to 2.8)
	Use cleaning products	1.5 (0.7 to 3.0)
Usual cough	Time in production areas	1.9 (1.0 to 3.7)
WR usual cough	Time in production areas	1.8 (0.5 to 7.6)
	Use flavourings ingredients	**4.7 (1.1 to 33)**
Lung function abnormality		
Any spirometric abnormality	Time in production areas	**2.3 (1.1 to 5.3)**
Low diffusing capacity	Time in production areas	2.8 (0.9 to 9.4)

Statistically significant associations are shown in bold.
*Each model includes the exposure variables associated with the health outcome in univariate analyses. Wheeze and breathing trouble were not included in this table as they were not associated with the exposure variables in univariate analyses. Models of symptoms are adjusted for age and smoking status. Models of lung function abnormalities are adjusted for smoking status.
WR, work related.

(table 5). Both time spent daily in production areas and tenure were significantly associated with mean per cent predicted FEV_1 and FVC. Tenure was significantly associated with lower mean diffusing capacity parameters. The associations with FEV_1/FVC ratio were not significant after adjustment for smoking status and age.

DISCUSSION
In a flavouring manufacturing workforce without excess lung function abnormalities overall, we found consistent associations of symptoms and lung function parameters with exposure. Shortness of breath, a hallmark of chronic respiratory impairment, was significantly associated with facility tenure. The prevalence of other chest symptoms varied with time spent in production areas, and work-related cough was more common in those who used flavouring ingredients. Upper respiratory symptoms that improved away from work were associated with use of cleaning products. Lung function derangements, including spirometric abnormalities and low diffusing capacity, were more common among participants spending more time in production areas. Furthermore, mean lung function values were inversely associated with both facility tenure and time spent in production areas. Associations could not be explained by age, smoking status or employment at another flavouring plant.

Our findings of exposure-related chest symptoms, spirometric abnormalities, diffusing capacity defects and total lung capacity

Table 5 Results of adjusted models of relationship between mean lung function parameters and exposure variables*

Health outcome	Exposure variables	Mean (95% CI)
Spirometry (n=357)		
FEV₁% predicted	Time in production areas	
	<1 h	**100.4 (98.4 to 102.3)**
	≥1 h	**96.4 (94.2 to 98.7)**
	Tenure	
	<7 years	**100.6 (98.6 to 102.7)**
	≥7 years	**96.2 (94.1 to 98.3)**
FVC % predicted	Time in production areas	
	<1 h	**102.8 (101.0 to 104.6)**
	≥1 h	**99.0 (96.9 to 101.1)**
	Tenure	
	<7 years	**102.3 (100.4 to 104.2)**
	≥7 years	**99.5 (97.6 to 101.4)**
Diffusing capacity (n=325)		
Diffusing capacity % predicted	Time in production areas	
	<1 h	94.0 (91.8 to 96.2)
	≥1 h	95.4 (92.9 to 97.9)
	Tenure	
	<7 years	**97.0 (94.7 to 99.2)**
	≥7 years	**92.5 (90.1 to 94.8)**
Total lung capacity % predicted	Time in production areas	
	<1 h	92.6 (91.2 to 94.1)
	≥1 h	91.9 (90.2 to 93.5)
	Tenure	
	<7 years	**93.8 (92.3 to 95.3)**
	≥7 years	**90.7 (89.1 to 92.3)**

Statistically significant differences are shown in bold.
*Each health outcome model includes the exposure variable(s) associated with the lung function parameter in univariable analyses. Time spent in production areas was not associated with diffusing capacity parameters in univariable models, but is included in the final adjusted models for comparison with the spirometry models. Means are least squares means adjusted for the other exposure variable and smoking status.
FEV1, forced exploratory volume in 1s; FVC, forced vital capacity.

observed in the association between exposure and health across a variety of metrics is reassuring. Finally, we were made aware of two former workers who left employment due to lung disease, and it is possible that others may have left employment due to respiratory illness. Thus, the current workforce included in the survey may have been healthier than the entire cohort of people who had been employed at this facility.[24] The absence of former workers in our survey may have obscured relationships between exposure and health outcomes that an evaluation of both current and former workers would have found. Nonetheless, even among relatively healthy current workers, the impact of exposure on health was evident.

NIOSH has proposed a recommended exposure level for diacetyl of 5 ppb,[7] which is hundreds to thousands of times lower than what was measured during prior evaluations at other flavouring manufacturing facilities.[25–27] In contrast, this facility did not have documented high diacetyl exposures. However, the facility reported using amounts of diacetyl substitutes that put it in the same potential higher health risk category as California flavouring manufacturing facilities that used larger amounts of diacetyl annually.[10] Our detection of 2,3-pentanedione at a concentration of 47 ppb in a short-term sample[13] is notable as the proposed short-term (15 min) exposure limit is 31 ppb.[7] Similarly, a longer-term sample that resulted in a concentration of 26 ppb[13] is concerning as the proposed time-weighted average exposure limit for 2,3-pentanedione is 9.3 ppb. Our measurements, although limited, highlight what appears to be an ongoing shift in the flavouring manufacturing industry away from diacetyl and towards chemically related substitutes that may have comparable toxicity.[5 6 28] Until the safety of diacetyl substitutes has been established, these flavouring chemicals should be considered to be respiratory toxins and handled using the same controls in place for diacetyl.

Little is known about the respiratory toxicity of the many flavouring chemicals other than diacetyl and 2,3-pentanedione used at the facility. It is certainly possible that we detected not only a spectrum of physiological findings of one flavouring-related disease, obliterative bronchiolitis, but also a spectrum of flavouring-related lung diseases. In addition to obliterative bronchiolitis, our findings could indicate risk of emphysema (obstruction and low diffusing capacity) and/or interstitial lung disease (restriction and low diffusing capacity). Despite predominantly fixed obstruction, the reported work-related pattern of some symptoms also raises the possibility of occupational or work-exacerbated asthma.[16 29 30] Ultimately, distinguishing among these diagnoses would require additional evaluation, including chest imaging, bronchoprovocation testing, cardiopulmonary exercise testing and lung biopsy. Yet the possible occurrence of more than one exposure-related lung disease in this workforce and uncertainty about the chemical cause should not serve as barriers to prevention. Given that decline in lung function can occur rapidly and early in employment in flavouring-related obliterative bronchiolitis,[3 31–33] frequent medical surveillance of exposed workers that includes high-quality spirometry and close attention to declines (even within the normal range) is warranted.[7] Furthermore, in the absence of additional toxicological information, an emphasis on exposure reduction through enhanced ventilation and use of respiratory protection is prudent.

CONCLUSION

Among current flavouring manufacturing workers, some symptoms and diagnoses were more common than expected, while spirometric abnormalities were not in excess. Symptoms, lung function abnormalities and average lung function values differed

reductions indicate risk of occupational lung disease in this facility. Given the reported cases of obliterative bronchiolitis in two former workers, the recognised toxicity of diacetyl[1–4] and the evolving understanding of lung function in obliterative bronchiolitis,[22] these observations are most consistent with undiagnosed or subclinical obliterative bronchiolitis in the current workforce. Indeed, earlier reports of obliterative bronchiolitis in flavouring-exposed workers that emphasised fixed obstruction on spirometry and normal diffusing capacity[1 2 23] have given way to a more nuanced picture that includes a range of spirometric and diffusing capacity results.[12 22] In one recent case series of biopsy-proven obliterative bronchiolitis unrelated to flavourings, a minority (5%) had obstruction and 60% had diffusing capacity defects.[12]

There are several limitations to address. First, because our evaluation was cross-sectional, it was not possible to demonstrate patterns of lung function change over time. To estimate exposure, we used exposure surrogates rather than quantitative measurements, which may have allowed us to make more definitive conclusions about particular flavouring chemicals and cleaning products. It is possible that differences between participants and non-participants introduced bias, but the high participation rate (93%) suggests our findings are representative. As we relied on participants' reports for exposure surrogates and some health outcomes, our results could be affected by reporting biases. However, systematic bias in self-report of hire date (used to calculate tenure) seems unlikely, and lung function test results are not subject to reporting bias. As such, the consistency we

by exposure. These differences could not be explained by age, smoking status or employment at another flavouring plant, suggesting that they reflect outcomes of occupational exposures at the facility. These findings are most consistent with undiagnosed or subclinical obliterative bronchiolitis in this workforce and indicate that further efforts to lower exposures to flavouring chemicals, including diacetyl substitutes, are warranted.

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