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# ASTHMA ARISING IN FLAVORING-EXPOSED FOOD PRODUCTION WORKERS

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**Abstract**
**Objectives:** While working for a small family-owned popcorn popping company, all of the three non-smoking workers developed a respiratory disease. Because of the newly identified associations between the flavoring chemicals and bronchiolitis obliterans, the specifics of these cases and their exposures were investigated to add to the body of knowledge of flavoring-related lung disease. **Materials and Methods:** We obtained data on work processes as well as full-shift personal and area air samples for diacetyl, acetoin, 2-nonanone, acetaldehyde, and total volatile organic compounds. Air samples were collected on thermal desorption tubes for analysis by gas chromatography mass spectrometry. We also reviewed medical records and conducted interview with the workers. **Results:** Air samples representative of the exposures that exacerbated asthma symptoms in two workers contained many different aldehydes. The data from interview and medical records and the high resolution computed tomograms of the chest indicated the presence of occupational asthma in all the three workers and possible bronchiolitis obliterans in two of them. This case series emphasizes a need for exposure reduction and medical surveillance among workers exposed to flavoring chemicals, and provides evidence for an increased risk of occupational asthma, as well as bronchiolitis obliterans, in flavoring-exposed workers.

**Key words:**
**Flavorings, Aldehydes, Occupational asthma, Bronchiolitis obliterans, Popcorn**

## INTRODUCTION

Several publications have documented the bronchiolitis obliterans syndrome among workers exposed to artificial flavoring. No cases of occupational asthma in this population have been reported in scientific literature. We report on a series of cases of probable occupational asthma in all of the three workers at a family-owned popcorn popping company that made plain and cheese- and jalapeno-flavored popcorn.

The normal 2–4 hour work shift occurred 1–2 days per week. Popcorn kernels and butter-flavored salt (Flavacol™) were dumped into a pre-heated popper. When the popcorn began popping, heated butter-flavored oil was added. Popped popcorn was manually screened to remove unpopped kernels. For cheese- and jalapeno-flavored popcorn, powdered flavorings were added to the popcorn during the screening process. Over 27 years of operation (1979-2006), the process changes included the use of different butter-flavored oils (Vo-Pop™, Gregg's Popcorn Oil™, Gregg's Ultrapop™); a change in Flavacol™ formulation (no longer contained diacetyl after 2002); an introduction of powdered flavorings (cheddar cheese in 1988, jalapeno in 1991, and white cheddar cheese in 2003), and moving to a larger building in 1999.

## MATERIAL AND METHODS

We interviewed two workers and the spouse of the third (deceased) worker, reviewed medical records of all the three, and reviewed high resolution computed tomography

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(HRCT) scans of the two living workers. In April 2006, we collected personal and work area air samples time-weighted over approximately 2- to 4-hour collection periods on two consecutive days. These samples were analyzed for diacetyl, acetoin, 2-nonanone, acetaldehyde, and total volatile organic compounds (VOCs) using NIOSH analytical methods (NMAM Methods 2557, 2558, 2538, and 1550) [1]. Limits of detection for diacetyl were 0.01 ppm for 4-hour samples and 0.02 ppm for 2-hour samples. Air samples collected on thermal desorption tubes were analyzed for VOCs using gas chromatography with mass spectrometry (NMAM Method 2549) [1] which yielded semi-quantitative measurements. We additionally measured diacetyl in workspace air using real-time Fourier transform infrared spectrometry (FTIR).

## RESULTS

### Medical Findings

Employee 1

A lifetime nonsmoker began working in the popcorn popping operation in 1979 and retired in 1994 due to respiratory problems. In 1990, he began experiencing intermittent shortness of breath, non-productive cough, and wheeze, which worsened when popping popcorn. The symptoms persisted for the remainder of the day after his work shift. He was treated for respiratory problems in the emergency department 23 times from 1991 to 1998. He was hospitalized for exacerbation of asthma or status asthmaticus in May 1992, April and September 1994, July 1995, and November 1998. He died during his last hospitalization at age 65, after a respiratory arrest outside the hospital.

**Table 1.** Spirometry test results using NHANES III prediction equations [2] for percentage of predicted and lower limit of normal values

| Date | BD | $FEV_1$ (L [% pred.]) | FVC (L [% pred.]) | $FEV_1$/FVC (%) | $FEV_1$ increase post-BD (% [ml]) | FVC increase post-BD (% [ml]) | BMI | Interpretation |
|---|---|---|---|---|---|---|---|---|
| Employee 1 | | | | | | | | Moderate airways obstruction; restrictive process possible; $FEF_{25–75}$ increased 14% post-BD; $FEV_1$ does not normalize post-bronchodilator |
| 5/26/92 | Pre | 2.15 [59]* | 3.57 [74]* | 60* | | | 29.1 | |
| | Post | 2.24 [61]* | 3.69 [76]* | 83 | 4 [90] | 3 [120] | | |
| 3/10/94 | Pre | 2.13 [60)]* | 2.58 [54]* | 61* | | | – | Mild obstruction; restrictive process possible |
| 7/6/95 | Pre† | 1.76 [49]* | 2.53 [53]* | 70 | 27 [–] | 26 [–] | – | Restrictive process possible; significant increase in $FEV_1$ and FVC post-BD |
| 12/15/95 | Pre | 2.33 [66]* | 3.45 [73]* | 68 | | | – | Restrictive process possible; significant reversibility of $FEV_1$ post-BD |
| | Post | 2.87 [81] | 3.82 [81] | 75 | 23 [540] | 11 [370] | | |
| 6/11/98 | Pre | 1.97 [57]* | 3.08 [66]* | 64* | | | 34.4 | Moderate airways obstruction; restrictive process possible; significant reversibility of $FEV_1$ post-BD; $FEV_1$ does not normalize post-BD |
| | Post | 2.27 [65]* | 3.31 [71]* | 69 | 15 [300] | 7 [230] | | |
| Employee 2 | | | | | | | | $FEF_{25–75}$ increased 19% post-BD |
| 8/25/04 | Pre | 2.67 [94%] | 3.52 [98%] | 76 | | | 36.9 | |
| | Post | 2.84 [100%] | 3.59 [100%] | 79 | 6 [170] | 2 [70] | | |
| Employee 3 | | | | | | | | Substantial increase in $FEV_1$ and 21% increase in $FEF_{25–75}$ post-BD |
| 3/29/06 | Pre | 4.35 [95%] | 5.92 [100%] | 74 | | | 26.6 | |
| | Post | 4.83 [106%] | 6.43 [109%] | 75 | 11 [480] | 8 [510] | | |

NHANES — National Health and Nutrition Examination Survey; BD — bronchodilator; $FEV_1$ — forced expiratory volume in one second; FVC — forced vital capacity; BMI — body mass index; pred. — predicted.

" – " information not in records.

* Below lower limit of normal; † Bronchodilator was administered but only pre-BD values were available.

**Table 2.** Plethysmographic lung volumes and diffusing capacity of the lungs for carbon monoxide

| Date | RV (L [% pred.]) | TLC (L [% pred.]) | RV/TLC (% [% pred.]) | DLCO (ml/min/mmHg [% pred.]) | DLCO corrected for hemoglobin, carboxyhemoglobin, and altitude (ml/min/mmHg [% pred.]) |
|---|---|---|---|---|---|
| Employee 1 | | | | | |
| 12/15/95 | 2.23 [118] | 6.21 [91] | 43 [129] | 24.3 [–] | – |
| 6/11/98 | 2.26 [97] | 5.34 [76]* | 42 [124] | 23.9 [71]* | 22.5 [67]* |
| Employee 2 | | | | | |
| 8/25/04 | 1.73 [98] | 5.25 [103] | 33 [97] | 24.0 [91] | 24.0 [91] |
| Employee 3 | | | | | |
| 3/29/06 | 3.51 [150] | 10.14 [127] | 35 [117] | 41.6 [100] | 41.6 [100] |

Percentage of predicted and lower limit of normal values obtained from the medical reports.
RV — residual volume; TLC — total lung capacity; DLCO — diffusing capacity of the lungs for carbon monoxide; pred. — predicted.
* Below the lower limit of normal per report.
" – " information not in records.

His first spirometry test in March 1990 was reported to be suggestive of reversible bronchospasm. Subsequent spirometry results demonstrated a mixed pattern of airways obstruction and restriction. Airways obstruction was responsive to bronchodilator; however, the forced expiratory volume in one second ($FEV_1$) did not normalize post-bronchodilator, indicating that some of his airways obstruction was fixed (Table 1). In June 1998, his diffusing capacity for carbon monoxide (DLCO) was below normal (Table 2). As early as May 1992, arterial blood gases indicated hypoxemia.

Inspiratory HRCT of the chest in June 1998 showed no evidence of interstitial lung disease. However, there was air trapping within the peripheral area of both segments of the middle lobe and the anterior segment of the upper lobe of the right lung (mosaic pattern) and bronchial wall thickening involving the bronchi of the right lung in both segments of the middle lobe and the superior segment of the lower lobe.

Employee 2

A lifetime nonsmoker worked in the popcorn popping operation from 1985 to September 2004. In 1994, she developed mild chest heaviness and cough on the days she was popping popcorn; the symptoms progressively worsened until she left this employment. Dyspnea and chest tightness began during the shift or shortly afterwards and persisted for 6–24 hours after the shift. Expiratory wheeze was documented on physical examination in July 2004. After the subject had left employment, the respiratory symptoms improved but she had daily coughing and wheezing and coughing with exposure to cold air and exercise. Two years later she had only cough.

In August 2004, at age 48, spirometry and plethysmography were normal (Tables 1 and 2). Airways resistance ($R_{aw}$) was 322% of predicted, suggesting airways obstruction, and forced expiratory flow over the middle 50% of the forced vital capacity ($FEF_{25–75}$) increased by 19% post-bronchodilator, suggesting reversibility. She was diagnosed with asthma by her pulmonologist, and respiratory symptoms improved with albuterol, which she no longer required in 2006.

HRCT of the chest with inspiratory and expiratory images, obtained in June 2006, showed moderate bronchial wall thickening, probable air trapping in the left lower lobe and a mosaic pattern in the same lobe.

Employee 3

A lifetime nonsmoker worked in the popcorn popping operation from 1990 to 2006. In 2000, he began experiencing mild chest tightness on the days he worked at the plant. By 2006, the symptoms persisted for several days after his work shift. One year after the subject had left employment, his respiratory symptoms had improved and consisted of occasional chest tightness and wheezing.

Spirometry and plethysmography obtained in March 2006, at age 51, suggested mild asthma with bronchodilator response, and an elevated RV/TLC (residual volume/ total lung capacity) ratio suggested air trapping (Tables 1 and 2). HRCT of the chest with inspiratory and expiratory images, obtained in June 2006, showed mild bronchial wall thickening and expiratory air trapping consistent with asthma.

**Environmental Findings**

In six air samples from work area, the air concentrations of total volatile organic compounds (VOCs) ranged from 0.47 $mg/m^3$ to 8.14 $mg/m^3$, with a mean of 2.90 $mg/m^3$. The predominant VOCs identified in three air samples collected on thermal desorption tube included many different aldehydes: valeraldehyde, furfural, dimethylfurfural, hexanal, 2-heptenal, methyl furfural, octanal, nonanal, 2-decenal, and 5-(hydroxymethyl) furfural. Other predominant VOCs included: seven-carbon aliphatic hydrocarbons (including heptane), propylene glycol, toluene, furfuryl alcohol, limonene, decamethylcyclopentasiloxane, t-butylcresol, alpha-terpineol, triacetin, levoglusan, and diethylphthalate. The concentrations of acetaldehyde in 8 air samples from work area ranged from less than 0.04 ppm to 0.15 ppm, with 7 of the samples being below the limit of detection. Diacetyl, acetoin, and 2-nonanone concentrations were below the detection limits in the 2 personal and 12 work area air samples that we collected. Diacetyl was not detected in workplace air when a direct-reading FTIR was used; however, diacetyl concentrations of approximately 0.14 ppm were detected near the surface of the heated, butter-flavored oil. Relative humidity readings on the two sampling days ranged from 19 to 35%.

## DISCUSSION

Medical records documented a strong physiological evidence of asthma in two employees (no. 1 and 3) and a weaker physiological evidence in another employee (no. 2). The variability of symptom severity in all the three employees, the improvement of symptoms with bronchodilator in Employees 1 and 2, and the exacerbation of symptoms with exposure to cold air in Employee 2 also support asthma diagnosis. An occupational etiology is supported by the post-hire onset of respiratory symptoms, the worsening of symptoms during or after work shift in all the three employees, and the improvement of symptoms after leaving employment in Employees 2 and 3.

The bronchiolitis obliterans syndrome may have additionally been present in Employees 1 and 2. Supportive evidence includes a fixed component of airways obstruction in one employee and a mosaic pattern on HRCT of the chest in both. In a retrospective blinded study of patients with severe asthma or bronchiolitis obliterans, the mosaic pattern was present on HRCT in 50% of cases with bronchiolitis obliterans compared to 3% of cases with severe asthma ($p = 0.0006$) [3]. Since Employee 2 did not have a severe asthma, her HRCT even more strongly suggests bronchiolitis obliterans.

Occupational asthma may have been caused by a number of different chemicals. Furfuryl alcohol, one of the predominant VOCs in plant air, is a recognized asthmagen [4]. Based on the chemical groups present, other chemicals may be asthmagenic as well. Twelve of the predominant VOCs in this plant [propylene glycol, toluene, furfural, furfuryl alcohol, 2-heptenal, methyl furfural, dimethylfurfural, limonene, 5-(hydroxymethyl) furfural, t-butylcresol, 2-decanal, and triacetin (glycerol triacetate)] have structural formulas that are associated with a greater risk for asthma [5].

Diacetyl may have caused the findings suggestive of bronchiolitis obliterans present in Employees 1 and 2. At the time of our survey, the diacetyl air levels were low; however, when Flavacol™ previously contained diacetyl, the air concentrations may have been higher. Respiratory injury has been demonstrated in animals exposed to diacetyl [6], and cumulative exposure to diacetyl was associated with increased rates of abnormal spirometry and decreased $FEV_1$ among microwave-popcorn workers [7]. Other possible agents include valeraldehyde and furfural, which were predominant VOCs in workplace air and which are considered to have a potential to cause respiratory injury [8].

A major limitation of this study is that the specific inhalation challenge, methacholine challenge, serial spirometry,

HRCT with inspiratory and expiratory images, and biopsy/autopsy were not performed on all of the affected employees. Nonetheless, the available clinical evidence clearly documents lung disease severe enough to have caused respiratory failure in Employee 1. Environmental measurements obtained in 2006 may not be representative of earlier exposures. Additionally, recent investigations have implied that the NIOSH Method 2557 may underestimate the actual concentrations of diacetyl, due to the interference from high humidity levels. However, the lower relative humidity at this worksite, and the absence of diacetyl in workplace air as indicated by the direct-reading instrument, suggest that diacetyl concentrations could be below the detectable limits.

Other flavoring chemicals may account for the broad spectrum of airways disease in the three exposed workers.

The present investigation demonstrates that the flavoring chemicals may be associated with work-related asthma. It is difficult to identify which flavoring agents or chemicals contributed to respiratory disease in these workers as several flavoring agents were used and product changes occurred during their work tenure.

Exposure to flavoring agents can be minimized through enclosure of work processes, use of lids on containers with flavoring agents (especially when heated), use of local exhaust ventilation, mandatory use of respirators, and eye and skin protection. We recommend the use of a NIOSH-certified full-facepiece negative-pressure respirator with combined organic vapor and particulate cartridges (or a higher level of respiratory protection) and a formal respiratory protection program. Pre-placement and biannual spirometry testing may help to identify new-onset reversible and fixed airways obstruction (including excessive fixed $FEV_1$ decrements [9]). If work-related or occupational asthma or bronchiolitis obliterans is diagnosed, we recommend avoidance of further exposure.

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