

Bronchiolitis obliterans in workers exposed to flavoring chemicals

Richard Kanwal

National Institute for Occupational Safety and Health,
Centers for Disease Control and Prevention,
Morgantown, West Virginia, USA

Correspondence to Richard Kanwal, MD, MPH,
National Institute for Occupational Safety and Health,
1095 Willowdale Road, MS H-2800, Morgantown,
WV 26505, USA
Tel: +1 304 285 5932; fax: +1 304 285 5820;
e-mail: rkanwal@cdc.gov

Current Opinion in Pulmonary Medicine 2008,
14:141–146

Purpose of review

Medical and environmental surveys at microwave popcorn plants and flavoring production plants have revealed a risk for bronchiolitis obliterans in workers exposed to flavoring chemicals. Workers in other food industries may also be at risk. This review summarizes the available information on disease characteristics and natural history and provides information on workplace characteristics associated with disease development.

Recent findings

Investigations carried out in flavoring plants in California have identified severely affected current and former workers in four plants. Affected former workers have also been identified at a plant in the Netherlands that manufactured diacetyl, a predominant chemical in butter flavorings which has been implicated as a causal agent for lung disease in microwave popcorn workers.

Summary

Workers who manufacture or use flavorings can be subjected to repeated intense exposures to flavoring chemicals. Affected workers can progress to severe fixed airways obstruction in as little as 7 months. Since medical treatment is generally ineffective, early identification of affected workers and removal from further exposure, along with control of exposures to protect coworkers, are essential to minimize this hazard.

Keywords

bronchiolitis obliterans, diacetyl, flavorings, occupational lung disease

Curr Opin Pulm Med 14:141–146
© 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins
1070-5287

Introduction

Medical and environmental surveys at microwave popcorn plants and flavoring plants have established that workers with inhalation exposures to butter flavoring chemicals can develop bronchiolitis obliterans. The magnitude of risk to workers exposed to butter flavorings in the production of other food products, such as snack cakes, cookies, pretzels, candy, and dairy products, is currently unknown. This review provides detailed information on the nature and natural history of flavoring-related lung disease and on the workplace characteristics that can contribute to risk. Hopefully, this information will lead to earlier diagnosis and exposure cessation for affected workers, and preventive measures for coworkers.

Evidence of risk

In May 2000, an occupational medicine physician notified public health authorities of a cluster of cases of severe fixed airways obstruction and other findings consistent with bronchiolitis obliterans among former workers of a microwave popcorn production plant (sentinel plant)

[1,2]. These employees had worked in the room where butter flavoring was mixed into heated soybean oil (mixing room) and on packaging lines in the adjacent microwave popcorn packaging-area. A National Institute for Occupational Safety and Health (NIOSH) study showed that the prevalence of airways obstruction on spirometry tests of plant employees was 3.3 times higher than expected when compared with national data; the prevalence of obstruction in never smokers was 10.8 times higher than expected. Nineteen of 21 workers with obstruction had fixed obstruction (unresponsive to bronchodilators), and most chest radiographs and diffusing capacity tests were normal [3]. These findings suggested that a number of current workers may also have bronchiolitis obliterans. Five of six quality control workers who repeatedly popped bags of product in microwave ovens (approximately 100 bags per worker per work shift) in a poorly ventilated room had airways obstruction [4**]. A strong exposure–response relationship was demonstrated between quartiles of estimated cumulative exposure to diacetyl (a volatile butter flavoring chemical contaminating the air in the plant) and

the frequency of airways obstruction on spirometry tests [3].

Including the sentinel plant, five of six microwave popcorn plants evaluated by NIOSH had affected workers [5^{••}]. Analyses of aggregated data from medical surveys at these plants showed that mixers had excess respiratory symptoms and lower mean percentage predicted forced expiratory volume in the first second of exhalation (FEV₁) compared with workers who had never worked as mixers. Mixers who had done this job for more than 12 months had excess respiratory symptoms and lower mean percentage predicted FEV₁ compared with workers who had only worked as mixers for 12 months or less time. The prevalence of airways obstruction in mixers who had spent more than 12 months in this job was 19.2%, compared with 4.4% in mixers with 12 months or less time in this job. Packaging line workers in plants where tanks of heated soybean oil and butter flavorings were located near the lines had higher prevalences of respiratory symptoms and airways obstruction compared with packaging line workers in plants where the tanks were isolated in a separate room with the door closed. These findings were mostly unchanged when the data were stratified by smoking history [5^{••}].

Since 1985, 16 workers with bronchiolitis obliterans have been identified at a total of eight flavoring production plants in the United States. Evaluations carried out recently by NIOSH and by public health and occupational safety and health agencies in California identified seven affected workers in four flavoring plants [6^{••},7^{••}]. Previous investigations [8,9] and communications by physicians to NIOSH had identified nine affected workers at four other flavoring plants in other states. Four of these eight plants had more than one affected worker; all affected workers were nonsmokers. At least three workers became symptomatic and were identified as having severe fixed airways obstruction within 7 months of starting work in flavoring production [6^{••},8]. With the exception of one large plant, the approximate number of production workers at each plant ranged from five to 20. In the US general population under age 50 (smokers and nonsmokers), the prevalence of severe airways obstruction (with a FEV₁ less than 40% predicted) is one in 1000 (0.1%) [10]. Given this low background prevalence, the identification of severe fixed airways obstruction among small numbers of flavoring production workers at several plants is a striking finding which emphasizes the high risk for occupational lung disease in this industry.

A recently published study of workers at a chemical manufacturing plant in the Netherlands [11^{••}] has revealed evidence of risk to workers involved in the production of diacetyl. Out of 206 workers with potential

exposure to diacetyl from 1960 to 2003, four production workers were identified as having severe fixed airways obstruction and findings consistent with constrictive bronchiolitis obliterans on high-resolution computerized tomography (HRCT) scans. All four had been previously diagnosed with asthma or chronic obstructive pulmonary disease (COPD). Three of these four were lifelong nonsmokers and the fourth only had a 14 pack-year smoking history.

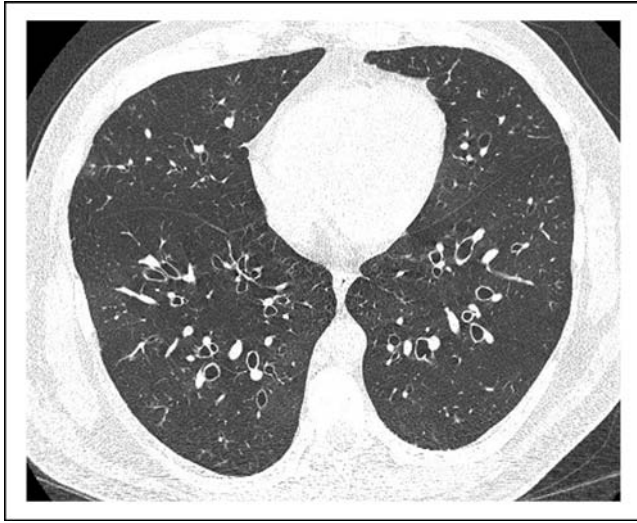
The results of recent toxicology studies support the evidence of flavoring-related lung disease risk obtained from studies in the workplace. In animal inhalation exposure studies conducted at NIOSH, rats developed severe injury to their respiratory epithelium after a 6 h exposure to vapors from a butter flavoring used at the sentinel microwave popcorn plant [12]. In other experiments, diacetyl alone produced similar (although less extensive) effects [13,14], which suggests that the toxicity of butter flavoring may be due to diacetyl in combination with other chemicals in the mixture. Additional information on diacetyl respiratory toxicology can be found in a recently published review [15^{••}].

Clinical findings

The main symptoms include progressive shortness of breath on exertion, chronic cough (usually nonproductive), and wheezing [1,6^{••},7^{••},8,11^{••},16–18]. The most striking clinical finding in affected workers has been the presence of severe airways obstruction on spirometry that is not responsive to bronchodilator administration. In the case series of affected workers at the sentinel microwave popcorn plant, seven of nine workers had FEV₁ measurements less than 40% of predicted (less than 20% predicted in two of nine) [16]. In the report of workers affected at California flavoring plants, FEV₁ measurements ranged from 17% to 44% of predicted in seven affected workers [7^{••}]. In the four affected workers at the plant that produced diacetyl in the Netherlands, FEV₁ measurements ranged from 31% to 42% of predicted [11^{••}]. Lung volume measurements have shown normal to slightly elevated total lung capacity and markedly increased residual volume [8,16]. Diffusing capacity for carbon monoxide (DLCO) has usually been normal; in some workers it has been mildly decreased [6^{••},8,16]. Chest radiographs have been normal or shown lung hyperinflation [8,16]. HRCT scans with expiratory views have shown mosaic attenuation and air trapping, bronchial wall thickening, cylindrical bronchiectasis, and scattered ground glass opacities (Figs 1 and 2) [1,7^{••},11^{••},16].

Historically, there has been much confusion and revision regarding the various names applied to the bronchiolar syndromes [19,20]. Publications describing workers

Figure 1 Inspiratory computed tomography scan in a flavor worker shows diffuse cylindrical bronchial dilation and mosaic attenuation



Courtesy of David Lynch MD.

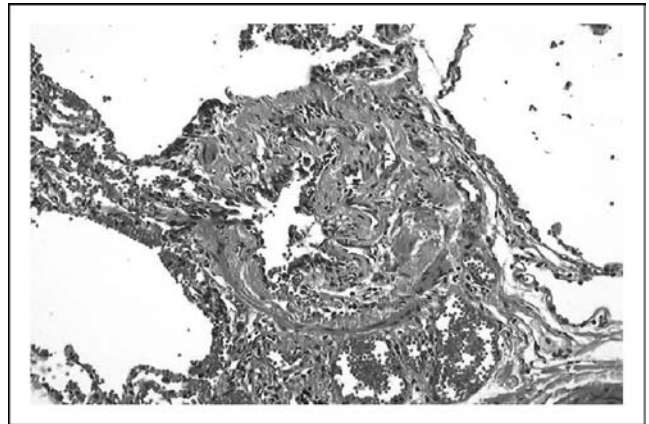
affected by flavoring exposures have used the terms 'bronchiolitis obliterans', 'clinical bronchiolitis obliterans', and 'bronchiolitis obliterans syndrome'. Of the few surgical lung biopsies that have been performed in affected workers, some have been interpreted as showing evidence of 'constrictive bronchiolitis' or 'obliterative bronchiolitis'

Figure 2 High-resolution computerized tomography scan in a flavor worker shows scattered areas of subtle ground glass opacification



Courtesy of Arthur Gelb MD.

Figure 3 Thoracoscopic lung biopsy sample revealing constrictive bronchiolitis



The bronchiole shows marked submucosal fibrosis causing severe narrowing of the airway lumen. Reproduced with permission from [16].

(Fig. 3). All of these terms are referring to the same key characteristic of the disease process: inflammation and fibrosis primarily involving the bronchioles, leading to airflow limitation. In general, constrictive or obliterative bronchiolitis is a difficult process to diagnose pathologically because it is patchy in distribution. In one case series study of pathologic and physiologic correlations in 19 cases of obliterative bronchiolitis (cases not known to be flavoring related), inflammation involved only half of the bronchioles, and subepithelial fibrosis was present in only one-third of the bronchioles examined [19]. Due to the patchy nature of the pathology, identification of the lesion may require step-sectioning and special staining [20], processes which are not routinely used by many pathologists. Granulomas have been noted in some biopsies of affected flavoring-exposed workers [7^{••},16], leading to pathologist interpretations of granulomatous bronchiolitis or hypersensitivity pneumonitis. For the most part, affected workers have not demonstrated other findings which would more strongly favor hypersensitivity pneumonitis, such as restriction on spirometry, diffuse ground glass opacification on CT scans, decreased DLCO, progression to diffuse fibrotic lung disease apart from the airways, or significant improvement of the disease with cessation of exposure or treatment with steroid medications.

Natural history of disease

Affected workers have ranged in age from their early 20s to early 50s at symptom onset [1,6^{••},7^{••},8,11^{••},16–18]. Symptom onset has usually been gradual, with progressive shortness of breath over months or years with continued exposure. Some workers have reported an acute onset of symptoms, sometimes followed by a slight improvement although not completely back to normal, and then

progressive worsening. Many affected workers were initially diagnosed by physicians as having asthma, bronchitis, COPD, or pneumonia [6^{••},11^{••},16]. The possibility that workplace exposures were causing or contributing to the workers' respiratory problems was usually not considered initially by the workers or their physicians. In part, this may have been due to the fact that workers did not experience any significant improvement in their symptoms on days off from work or on vacations.

Some affected workers can experience very rapid progression of their disease, with symptom onset and identification of severe fixed airways obstruction on spirometry testing occurring less than 1 year after starting work in microwave popcorn production or flavoring manufacture [6^{••},8,16]. In a case summary of nine workers affected at the sentinel microwave popcorn plant, the median length of employment prior to symptom onset was 1.5 years [16]. The median duration of employment was 2 years. Another worker at this plant experienced a decline in FEV₁ of 1.3 l over 9 months [4^{••}]. At this plant and others where workers developed flavoring-related disease, an affected worker would often train his replacement once he or she was no longer able to lift or carry heavy loads (e.g. 50–100 lb) due to extreme shortness of breath or fatigue. In several instances the new worker subsequently also developed lung disease [8].

After exposure cessation, affected workers have generally experienced stabilization of their disease, although some workers continued to have lung function declines up to 2 years after they were no longer exposed [4^{••},16]. Affected workers have noted their coughs to subside, with persistence of severe shortness of breath on exertion. Treatment with oral corticosteroids and bronchodilators has generally not led to any significant improvement in airways obstruction [8,16]. The same is true of treatment with cyclophosphamide in two affected workers [16]. One microwave popcorn worker with mild airways obstruction did return to normal after treatment with oral corticosteroids and cessation of exposure to flavoring chemicals [1], but lung function again declined after he returned to work. Of the nine sentinel microwave plant workers summarized in a case series, five were placed on lung transplant lists due to the severity of their disease [16]. None of these workers has gone on to receive a transplant. Recent communications to NIOSH indicate that a flavoring worker, and a worker at a plant that intermittently packaged microwave popcorn, underwent lung transplantation in the early 1990s before flavoring-related occupational lung disease risk had been recognized.

Workplace risk factors

Approximately 2000 different chemicals are used in varying combinations to produce mixtures that impart

specific flavor characteristics [21]. In general, flavoring chemicals are very volatile, so they evaporate into the air from their liquid or solid form and can be easily inhaled. They can also be inhaled in the form of a powder if airborne dust is created in the production process. Many of these chemicals are highly irritating to the eyes, respiratory tract, and skin. They are generally assessed for safety to consume in small amounts in food; for the majority of these chemicals, little is known about their potential to cause lung disease if inhaled by workers [22]. A recent investigation has revealed a possible association between workplace exposures to flavoring chemicals and new-onset asthma [23[•]]. Exposures to highly irritating flavoring chemicals may also exacerbate stable preexisting asthma.

At flavoring and microwave popcorn production plants where workers developed severe lung disease, workers routinely handled or were exposed to large open quantities of flavorings or their chemical ingredients. In a sense, such plants are large kitchens in which workers mix several ingredients in large open pots or other containers to produce various products. The application of heat in the production process can increase the volatilization of flavoring chemicals. Production facilities vary in their implementation of exposure controls (e.g. isolation of mixing processes; ventilation). Local exhaust ventilation to minimize intense exposures to chemicals during mixing and pouring of ingredients is often not available or is ineffective due to poor design. There is concern that the same workplace characteristics and processes that put workers at risk in flavoring and microwave popcorn plants may also be present in other plants that use butter flavorings (or related flavorings) to make other food products.

Respirators are often used in an attempt to minimize worker exposures. This approach often fails to protect workers for several reasons, including the incorrect selection of respirators and filters, inadequate respirator fit, respirator malfunction, or failure of the worker to use the respirator at all times when he or she is exposed. Respirators can be very uncomfortable to wear and difficult to work with for long periods of time. Respirators should be considered a last resort and should only be used as part of a respiratory protection program that complies with all parts of the Occupational Safety and Health Administration (OSHA) respiratory protection standard. Such a program must include medical evaluation, fit testing, and education, and must be overseen by an individual who has sufficient knowledge and expertise to ensure correct implementation of all parts of the program.

Implications

Physicians should consider the possibility of work-related lung disease in flavoring-exposed workers who present

with respiratory symptoms. This is especially important in smokers; respiratory symptoms and airways obstruction in these individuals are often assumed to be smoking related even without evidence of emphysema on medical tests. The majority of smokers do not develop COPD, and when it does occur, disease onset is usually in the fifth decade of life or later and after a significant smoking history (e.g. more than 20 pack-years) [24]. Airways obstruction on spirometry should be considered as possibly flavoring-related in exposed workers unless another etiology is apparent or is identified in the course of medical workup. New-onset asthma or exacerbation of preexisting asthma may also occur in flavoring-exposed workers. The physician and the worker with possible flavoring-related lung disease should discuss the issue of communication with plant management, and with public health and occupational safety and health agencies, to ensure that appropriate prevention strategies are implemented at the workplace.

Conclusion

The findings from studies at flavoring plants, microwave popcorn plants, a diacetyl production plant, and from animal studies strongly indicate that workers are at risk for rapid progression to severe obstructive lung disease from exposures to diacetyl and possibly other flavoring chemicals. Since medical treatment has so far been ineffective, early identification of affected workers and removal from further exposure, along with control of exposures to protect coworkers, are essential to minimize this hazard.

Acknowledgements

Arthur Gelb, Philip Harber, David Lynch, and Muge Akpinar-Elci provided assistance with the radiographic and biopsy images. Kristin Cummings and Kathleen Kreiss reviewed the draft manuscript and provided thoughtful comments and suggestions. This work was supported by the National Institute for Occupational Safety and Health. The findings and conclusions in this report are those of the author and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 150).

- 1 Parmet A, 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.
- 2 Centers for Disease Control and Prevention. Fixed obstructive lung disease in workers at a microwave popcorn factory: Missouri, 2000–2002. *MMWR Morb Mortal Wkly Rep* 2002; 51:345–347.
- 3 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.
- 4 NIOSH. Hazard evaluation and technical assistance report: Gilster-Mary Lee Corporation, Jasper, Missouri. Cincinnati, Ohio: US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health; 2006. DHHS (NIOSH) Publication No. 2000-0401-2991.
- Summary of eight serial cross-sectional studies at an index popcorn plant, including evaluation of intervention effectiveness; more accessible publication likely to follow.
- 5 Kanwal R, Kullman G, Piacitelli C, *et al.* Evaluation of flavorings-related lung disease at risk at six microwave popcorn plants. *J Occup Environ Med* 2006; 48:149–157.
- Combined analyses of industry-wide epidemiologic and exposure assessment which demonstrate risk at apparently low diacetyl exposure levels.
- 6 NIOSH. Hazard evaluation and technical assistance report: Carmi Flavor and Fragrance Company, Inc., Commerce, California. Cincinnati, Ohio: US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health; 2007. DHHS (NIOSH) Publication No. 2006-0303-3043.
- Medical and environmental survey reveals association between severe fixed airways obstruction and work in the production and packaging of powdered flavorings.
- 7 Centers for Disease Control and Prevention. Fixed obstructive lung disease among workers in the flavor manufacturing industry: California, 2004–2007. *MMWR Morb Mortal Wkly Rep* 2007; 56:389–393.
- Article contains case reports and description of findings and prevention efforts of California public health and occupational safety and health agencies.
- 8 Hazard evaluation and technical assistance report: International Bakers Services, Inc., South Bend, Indiana. Cincinnati: National Institute for Occupational Safety and Health; 1986. DHHS (NIOSH) Publication No. 85-171-1710.
- 9 Lockey J, McKay R, Barth E, *et al.* Bronchiolitis obliterans in the food flavoring manufacturing industry [abstract]. *Am J Respir Crit Care Med* 2002; 165 (Suppl):A461.
- 10 CDC. Third National Health and Nutrition Examination Survey, 1988–1994, NHANES III Examination Data File [CD-ROM]. Hyattsville, Maryland: US Department of Health and Human Services, Public Health Service, CDC; 1996. Public use data file Documentation No. 76300.
- 11 Van Rooy F, Rooyackers J, 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.
- First report of bronchiolitis obliterans in workers who produced diacetyl at a European chemical plant.
- 12 Hubbs A, Battelli L, Goldsmith W, *et al.* Necrosis of nasal and airway epithelium in rats inhaling vapors of artificial butter flavoring. *Toxicol Appl Pharmacol* 2002; 185:128–135.
- 13 Hubbs A, Battelli L, Mercer R, *et al.* Inhalation toxicity of the flavoring agent, diacetyl (2,3-butanedione), in the upper respiratory tract of rats. *Toxicol Sci* 2004; 78 (S1):438–439.
- 14 Morgan DL, Flake G, Kirby PJ, *et al.* Respiratory tract toxicity of diacetyl in C57BL/6 mice. In: Program and Abstracts of the Society of Toxicology (SOT) Annual Meeting; 5–9 March 2006; San Diego, California. p. 1029.
- 15 Harber P, Saechao K, Boomus C. Diacetyl-induced lung disease. *Toxicol Rev* 2006; 25:261–272.
- A review of diacetyl toxicology data and discussion of health surveillance considerations for exposed workers.
- 16 Akpinar-Elci M, Travis W, Lynch D, Kreiss K. Bronchiolitis obliterans syndrome in popcorn plant workers. *Eur Resp J* 2004; 24:298–302.
- 17 NIOSH. Hazard evaluation and technical assistance report: American Pop Corn Company, Sioux City, Iowa. Cincinnati, Ohio: US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health; 2004. DHHS (NIOSH) Publication No. 2001-0474-2943.
- 18 NIOSH. Hazard evaluation and technical assistance report: ConAgra Snack Foods, Marion, Ohio. Cincinnati, Ohio: US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health; 2004. DHHS (NIOSH) Publication No. 2003-0112-2949.
- 19 Markopoulou K, Cool C, Elliot T, *et al.* Obliterative bronchiolitis: varying presentations and clinicopathologic correlation. *Eur Respir J* 2002; 19: 20–30.
- 20 King T. Bronchiolitis. In: Schwartz M, King T, editors. *Interstitial lung disease*, 4th ed. Hamilton, Ontario: BC Decker, Inc.; 2003. pp. 787–789.
- 21 FEMA. *Respiratory health and safety in the flavor manufacturing workplace*. Washington, DC: The Flavor and Extract Manufacturers Association of the United States; 2004.

- 22** NIOSH Alert. Preventing lung disease in workers that use or make flavorings. Cincinnati, Ohio: National Institute for Occupational Safety and Health; 2004. DHHS (NIOSH) Publication No. 2004-110.
- 23** NIOSH. Hazard evaluation and technical assistance report: Yatsko's Popcorn, Sand Coulee, Montana. Cincinnati, Ohio: US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health; 2007. DHHS (NIOSH) Publication No. 2006-0195-3044.
- Workers at a plant where popcorn was popped, flavored, and bagged had findings suggestive of bronchiolitis obliterans and asthma.
- 24** American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; 152:S77–S120.