Flavoring-related bronchiolitis obliterans

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Purpose of review

In 2000, inhalation of butter flavoring vapors was first associated with clinical bronchiolitis obliterans among workers in microwave popcorn production. Toxicologic and epidemiologic studies in the succeeding 5 years have intervention and research implications.

Recent findings

Irreversible obstructive disease exists in workers throughout the microwave popcorn industry, in flavoring manufacture, and in the chemical synthesis of diacetyl, a predominant chemical in butter flavoring. Biologic plausibility of the role of diacetyl and other components of butter flavoring in causing bronchiolitis obliterans exists in rodent experiments which demonstrate respiratory epithelial necrosis. Some risky jobs were associated with short-term peak flavoring exposures, and average 8-h diacetyl exposures as low as 0.02 parts per million were measured in a work area where disease occurred in workers mixing butter flavorings with heated oil.

Summary

Until safe levels of flavoring chemicals are determined, prevention requires substitution, engineering controls, improved work practices, and personal protective equipment to lower exposure, in conjunction with medical surveillance for accelerated declines in pulmonary function. An epidemiologic approach to longitudinal medical surveillance and flavoring chemical exposures, paired with inhalation toxicology studies of flavoring components, will lay the basis for determining health-protective exposure limits for various flavoring chemicals.

Keywords

bronchiolitis obliterans, diacetyl, flavorings, occupational lung disease

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Abbreviations

COPD	chronic obstructive pulmonary disease
FEV_1	forced expiratory volume in one second
NIOSH	National Institute for Occupational Safety and Health

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Introduction

This review encompasses the publications and reports available on flavoring chemical-related bronchiolitis obliterans and fixed airways obstruction from initial recognition of this occupational lung disease in late 2000 through October 2006. Surveillance of flavoring manufacturing workers, in progress by both industry consultants and public health agencies, will likely enrich the information available pertinent to prevention. In the meantime, this review synthesizes available knowledge, outlines questions for further research, and places this story into a context of evolving implications for science and prevention of occupational and environmental lung disease.

Case recognition

Bronchiolitis obliterans is a rarely recognized disease, the etiology of which is apparent in classical occupational cases because of the severity of acute reaction to noxious chemicals; after apparent recovery over several weeks, affected workers developed fixed airways obstruction. Cases of flavorings-related bronchiolitis obliterans develop insidiously without a history of overexposure. Thus, recognition of this new cause of a rare disease required the occurrence of clusters of cases in occupational groups.

The difficulty of such recognition is manifest by the first cases reported in flavoring manufacture in 1986, for which the cause was not determined [1]. In a company which mixed flavorings in corn starch and flour for use in the baking industry, two never-smoking men in their 20s in the same mixing job successively developed progressive dyspnea due to severe bronchiolitis obliterans in their fifth month of employment. Of four other men who had held the mixing job, two additional cases of airways obstruction were documented among ex-smokers, aged 36 and 38 years. In view of their respective smoking histories of 22 and 10–15 pack-years, lack of symptoms, and ages, it seems unlikely that the latter two cases are attributable to smoking or flour exposure. Thus, four of six mixers appear to have developed the disease. The

flavoring chemical exposures were diverse in this work setting, but the report mentions that one of the cases attributed his early symptoms to 'cinnabutter'; a principal component of butter flavoring, diacetyl, was listed as a common ingredient. Because the cause was unrecognized, preventive measures and respiratory protection in this plant were directed solely against particulates and not against volatile organic compounds.

Recognition of a lung disease cluster whose investigation implicated a flavoring etiology occurred in 2000 [2] after a workers' compensation lawyer compiled medical records of eight former workers of a rural microwave popcorn manufacturing plant. After these cases were reported, the Missouri Department of Health and Senior Services sought technical assistance from the National Institute for Occupational Safety and Health (NIOSH) [3]. Concurrently, a staff person in the lawyer's office was in touch with a symptomatic relative who worked at a microwave popcorn plant in Nebraska. Thus, the case cluster in the Missouri plant allowed recognition of an occupational cause in an individual worker in another microwave popcorn packaging plant [2]. Although the published case report indicated that the Nebraska case had improved substantially after treatment with corticosteroids, the subsequent clinical course showed return to the initial degree of fixed airways obstruction [4]. Clinical details of the eight cases in the sentinel Missouri microwave popcorn plant are tabulated in a publication that addresses latency since first employment, degree of impairment, clinical course, and insensitivity of thoracoscopic lung biopsy in establishing the diagnosis [5].

Attribution of the microwave popcorn plant case cluster to flavoring exposure led to identification of individual bronchiolitis obliterans cases in several other work settings. In flavoring manufacture, biopsy-documented cases from New Jersey, Maryland (post-dimethylphenol spill), and California were reported to NIOSH investigators. In California, cases were recognized in two plants among mixers of liquid flavorings with powder [6]. Five cases of bronchiolitis obliterans were reported from a flavoring plant which conducted serial pulmonary function screening; one case was attributed to acetaldehyde [7], and affected workers had been exposed to diacetyl as well. Industry consultants reported four cases of fixed airways obstruction compatible with bronchiolitis obliterans in three flavoring manufacturing plants [8]. Exposures in these three plants included lactones, low concentrations of acetic and lactic acids, and diacetyl in one plant; butter-type flavorings in the second plant; and many types of flavoring in the third plant.

Food production and other manufacturing operations which share the application of heat to flavorings, as in the microwave popcorn industry, may have a risk for flavoring-related lung disease. In snack food manufacture, a case of bronchiolitis obliterans/organizing pneumonia was recognized in a 51-year-old who sprayed flavorings on potato chips [9]. Three cases of lung disease including reversible airflow limitation arose in a family whose business was to pop corn in kettles and coat it with powdered flavorings while hot [10]; diacetyl was not detected in plant air, but acetoin and several aldehydes were measured. NIOSH has received a case report of restrictive interstitial lung disease in an employee who tested pumps by injecting butter-flavored oil into kettles for popping corn and a case report of pulmonary fibrosis in a candy operator who added flavorings to melted sugar (A.J. Parmet, e-mail communication, 29 May 2006). The diverse physiology and diagnoses reported in these cases require further investigation. Finally, a case report of bronchiolitis obliterans in a worker exposed to overheated cooking oil [11] may have had a flavoring cause, although this case differs from most other cases by an acute onset which made the occupational cause evident.

In contrast to diverse chemical exposures in flavor manufacture and downstream flavor use, the number of chemical exposures in the manufacture of diacetyl is limited to diacetyl and low concentrations of acetoin, acetic acid, and acetaldehyde. Thus, the occurrence of three clinical bronchiolitis obliterans cases among 206 former workers of a chemical plant manufacturing diacetyl is of particular importance in narrowing potential chemical etiologies for this lung disease [12•].

Epidemiology of risk factors

The sentinel cluster of eight cases of clinical bronchiolitis obliterans among former workers in the Missouri microwave popcorn plant pointed to a disproportionate risk to mixers of flavorings into heated soybean oil [3]. Other risk factors for flavoring-related clinical bronchiolitis obliterans were documented in six cross-sectional epidemiologic studies of current workforces in the microwave popcorn industry [13,14••,15,16,17••,18]. In the sentinel plant, age, sex and duration of employment were not associated with airways obstruction. Smokers and non-smokers both had excess airways obstruction, and the prevalence ratios for non-smokers were particularly striking, being 10.8-fold greater than national rates [13]. Five of six quality control workers had airway obstruction, despite having low average exposures to diacetyl (0.6 parts per million) in comparison to packaging (1.9 ppm) and mixing workers (32.3 ppm). Peak exposures in mixing and quality control areas may have contributed to excess risk. Quartiles of cumulative diacetyl exposure were associated with increasing risk of abnormal spirometry and decreasing mean forced expiratory volume in one second (FEV_1).

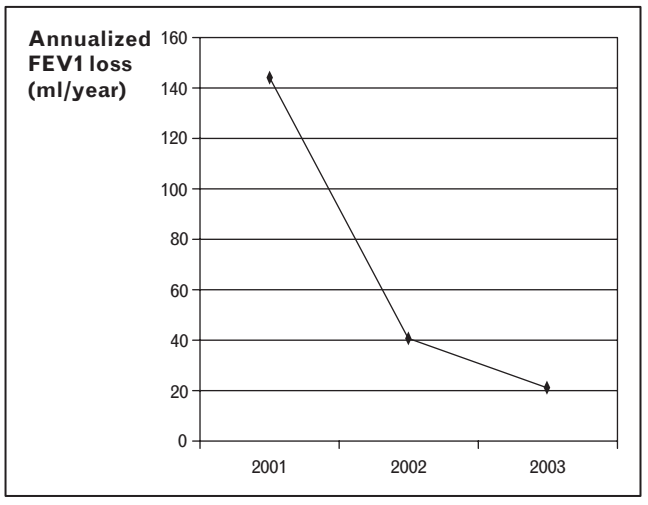
In aggregated data from all six plants [14••], packaging area workers adjacent to heated tanks of oil and flavorings

had elevated rates of chest symptoms and obstruction when compared to packaging area workers from plants where tanks were isolated. The corollary of this observation is that the proportion of employees at risk can be minimized by isolating flavoring exposure from packaging production. Across the six plants, ever-mixers had excess chest symptoms and lower mean percent predicted FEV_1 when compared to the remainder of employees. Ever-mixers with more than 12 months of mixing area experience had significantly lower mean percent predicted FEV_1 and exertional dyspnea when compared to ever-mixers with less mixing work tenure.

Intervention effectiveness

In the sentinel plant, isolation of mixing activities and heated tanks containing flavorings from the packaging area appeared to protect most workers in longitudinal follow-up [17••]. The 27 workers who participated in all eight cross-sectional surveys between 2000 and 2003 had a normalization of their mean annualized FEV_1 decline (Fig. 1). Of nine mixers, four had 300 ml/year or greater longitudinal declines of FEV_1 between 2000 and 2003; those with such declines had worked 34 months on average as mixers, whereas the mixers without such declines had worked an average of 8 months. The excessive declines in mixing area workers following introduction of respiratory protection and exhaust ventilation of tank headspaces suggest inadequacy of these control measures or delayed evolution of pulmonary effects from earlier higher exposures. Thus, protection of mixing area workers likely requires reengineering to closed systems or better exhaust ventilation, including prevention of peak exposures during tank monitoring and cleaning operations.

Figure 1 Mean annualized loss in forced expiratory volume in one second for 27 workers who participated in all eight cross-sectional spirometry surveys in the sentinel Missouri plant by year, 2000–2003



FEV_1, forced expiratory volume in one second.

Biomarkers of flavoring health effects

Detecting excessive pulmonary function decrements in serial spirometry tests is one means of identifying workers who may have early evidence of flavoring-related health effects, as implemented in the sentinel plant [17••].

Exhaled nitric oxide and induced sputum parameters were assessed as potential biomarkers of susceptibility or early effect in the sentinel plant approximately 1 year after the initial cross-sectional study and after some control measures were taken [19•,20•]. Popcorn workers had sputum neutrophilia in comparison to healthy unexposed controls, and those with high neutrophil counts (above median) were 3.8-fold more likely to be microwave popcorn production workers than less-exposed workers in the plant. As expected, median sputum IL-8 and eosinophil cationic protein measurements were also higher in production workers than less-exposed workers. As explained in the induced sputum paper [20•], eosinophil cationic protein correlates with neutrophilic inflammation. The only statistically significant correlation between other health outcomes and these potential biomarkers was between sputum IL-8 and history of phlegm and frequent fever; no correlations existed with airways obstruction or other respiratory symptoms.

Exhaled nitric oxide was significantly lower in the microwave popcorn production workers than in less-exposed workers in the plant or in healthy external controls. In contrast with poorly controlled asthma cases (who have increases in exhaled nitric oxide), the lower nitric oxide levels in these exposed workers are in the same direction as the changes found in cigarette smokers. Workers reporting chest tightness had lower exhaled nitric oxide levels than workers without this symptom, taking smoking status and age into account. As with induced sputum parameters, however, no association existed between exhaled nitric oxide and airways obstruction or respiratory symptoms of bronchiolitis obliterans. Those with systemic symptoms, particularly night sweats, had lower mean levels of exhaled nitric oxide, similar to the finding of association between sputum IL-8 and frequent fever.

These biomarker findings associated with exposure (but not with airways obstruction) raise the possibility that some flavoring-exposed workers are susceptible to bronchiolitis obliterans, whereas others develop systemic symptoms without obstruction, as was apparent in the initial cross-sectional study [13]. In the microwave popcorn plants with the highest prevalence of abnormal pulmonary functions [13,15], many workers with

seemingly comparable exposure were spared pulmonary impairment. Even among the highest risk jobs in the mixing area, maintenance, and quality control workers in the index plant, only 30% had airways obstruction [17••]. Across all six microwave popcorn plants, 19% of mixers with more than 12 months employment had obstruction [14••]. These observations prompt continued exploration of biomarkers, including genetic markers of susceptibility, for flavoring-related airways disease.

Exposure assessment

In the microwave popcorn industry, diacetyl was the predominant chemical in air sampling of volatiles and was used as a proxy for flavoring exposure [21•,22]. In cross-sectional studies, 8-h time-weighted average diacetyl exposures varied by orders of magnitude in process areas associated with affected workers within the sentinel Missouri plant [13,21•] and among plants [14••]. In the sentinel plant, mixers had a mean area exposure of 37.8 ppm diacetyl, with a range to 98 ppm. The highest prevalence of airways obstruction was in the quality control room, which had a mean area exposure of 0.6 ppm diacetyl, with a range to 0.9 ppm. Among plants with clinical bronchiolitis obliterans in mixers, the lowest mean mixing room personal time-weighted average measurement was 0.02 ppm diacetyl.

Less information is available regarding peak exposures in areas associated with clinical bronchiolitis obliterans cases. In the sentinel plant, mixers may have had brief exposures as high as 1230 ppm when opening the lid of a tank of heated flavoring prior to mixing it with heated oil [17••]. Measurements in the head space of the heated flavored oil tanks were up to 184 ppm. Airborne concentrations of diacetyl in a mixing area when powdered butter flavoring was used were below the detection limit of 0.001 ppm, in comparison to 0.6 ppm in the same plant on a day when liquid and paste flavorings were used [23•]. In experimental pouring of different powdered flavorings, an oiled powdered flavoring generated the lowest amount of respirable dust [23•].

In flavoring manufacture, characterization of chemical exposures is just beginning, and reports and publications are not yet available. In a California company with clinical bronchiolitis obliterans cases, peak diacetyl levels exceeded 100 ppm at blender machines in which liquids were plated onto powders (G. Kullman, unpublished observations in 11 October 2006 letter to the company). An industry consultant reported somewhat lower peak diacetyl measurements in two California flavoring plants during a 2 August 2006 workshop sponsored by the National Jewish Medical and Research Center. In diacetyl manufacture, historical area measurements ranged from 1.8 to 351 mg/m^3 (0.38 to 73.7 ppm) in a plant with at least three clinical bronchiolitis obliterans cases; in personal task-based sampling during tapping of diacetyl containers, concentrations as high as 396 mg/m^3 (83 ppm) were measured (G.B.G.Y. van Rooy, unpublished observations).

Toxicology

Recognition of bronchiolitis obliterans in the microwave popcorn industry motivated toxicology studies of one of the butter flavorings used in the sentinel plant in 6-h exposures of rats, with necropsy the next day [24]. Butter flavoring vapors containing 285–371 ppm diacetyl caused multifocal, necrotizing bronchitis and necrosuppurative rhinitis, without affecting alveoli. Additional rat studies with diacetyl alone at 184 ppm resulted in significant necrosis of nasal epithelium with associated neutrophilic inflammation. At 294 ppm, diacetyl additionally caused tracheal epithelial necrosis [25]. At the National Institute for Environmental Health Sciences, subchronic diacetyl exposure studies are underway in mice, with additional experiments planned in rats. To reduce nasal toxicity, inhalation exposures were reduced to 1 h per day, 5 days per week, and investigators reported chronic bronchitis, laryngitis, and rhinitis after 2 and 4-week exposures. With oropharyngeal aspiration of 100, 200, and 400 mg/kg, foci of fibrosis without inflammation were present at the junction of the terminal bronchiole and alveolar duct in all mice that survived to day 4 after treatment at the highest dose and in one of five mice treated at the intermediate dose [26]. In an isolated perfused guinea pig trachea model, diacetyl exerted a direct toxic effect on airway epithelium, which led to degradation of its protective barrier function and tracheal hyperreactivity [27•].

Public health response

The emerging etiology of lung disease in flavoring manufacture and downstream food production workers stimulated dissemination of a NIOSH Alert to inform company health and safety personnel and exposed workers [28]. The Flavoring and Extract Manufacturers Association (FEMA) disseminated a list of 34 high priority chemicals and 49 low priority chemicals (among the 2200 individual chemically defined flavoring substances), which should prompt development of workplace respiratory health and safety programs [8].

NIOSH conducted evaluation of effectiveness of interventions to progressively limit flavorings exposure in the sentinel microwave popcorn plant by serial cross-sectional medical and industrial hygiene surveys [17••]. No other evaluations of interventions exist. One large microwave popcorn company, however, has instituted medical and environmental surveillance paired with exhaust ventilation for sources of flavoring exposures, which will enable an evaluation of the new engineering controls (W. Waite and J. Lockey, unpublished

observations communicated at a NIOSH meeting, 31 October 2006, Morgantown, West Virginia, USA).

Regulatory control of diacetyl exposure does not exist [29•], apart from the duty of employers to provide work environments free of recognized hazards. In the summer of 2006, labor organizations petitioned the federal Occupational Safety and Health Administration (OSHA) and its California counterpart for an emergency temporary standard for diacetyl exposure. For 30 California flavor manufacturers, California OSHA has instituted a consultation program that requires companies to disclose their medical screening and exposure assessment results to the California Department of Health Services. This program may result in information that could establish industry-wide risk factors, extent of the risk of different chemical constituents, and exposure-response relations. Across the United States in the meantime, some incentive for future control of flavoring exposures exists because of the liability of flavoring manufacturers for cases of bronchiolitis obliterans occurring among workers of their customers [30].

Research needs

Little published inhalation toxicity information exists for most flavoring chemicals. For its designation of priority chemicals, FEMA also considered volatility, irritancy, structural reactivity, poundage used, and anecdotal reports from its members. Additional work on structure–activity relations is a research priority and can guide needed inhalation toxicology research. In the absence of knowing specific chemical causes, engineering interventions must be evaluated for their effectiveness in protecting worker respiratory health in longitudinal evaluation of pulmonary function and other medical surveillance. Paired postintervention medical and exposure surveillance is critical, because safe levels of exposure to individual flavoring ingredients are unknown. Flavoring exposure characterization alone following engineering interventions cannot be interpreted with regard to health protection.

In contrast to the information about the industry-wide risk in microwave popcorn production, epidemiology is still unavailable regarding the extent of risk, risk factors, and effectiveness of interventions in flavoring manufacture. Downstream manufacture of other flavored food products is another avenue requiring research characterization of obstructive lung disease risk. Misdiagnosis of bronchiolitis obliterans as asthma, bronchitis, or emphysema is common, and worker surveys require measuring spirometry with and without bronchodilator to assess fixed airflow limitation. Three population-based studies have shown excess bronchitis or chronic obstructive pulmonary disease (COPD) in food production workers [31–33]. The recognition that flavoring exposure results in fixed airways obstruction from bronchiolitis obliterans should motivate research to assess what proportion of the observed excess airways disease in food production workers is accounted for by flavorings exposure.

Implications

Flavoring-related fixed airways obstruction prompts investigation of other settings in which excess COPD exists in occupations and industries. The fraction of COPD attributable to work in the US adult general population may be 20% overall and 31% in never smokers [31]. Consistent with the dearth of information regarding flavorings, little inhalation toxicology exists for other volatile organic chemicals. Many of the occupations and industries with excess smoking-adjusted COPD prevalence have volatile chemical exposures, such as office building services (from cleaning compounds), repair services and gas stations, agriculture, armed forces, transportation and trucking [31], spray painting, and chemical processors [32]. Aspirated hydrocarbons are known to damage the lungs, but inhaled solvents also may lead to obstructive physiology. Solvent exposure is associated with asthma in identical twins discordant for this condition [34], with wheezing in farmers with daily solvent use [35], and with emphysema in metal polishers [36]. In the general population, blood 1,4-dichlorobenzene concentrations, a volatile organic chemical found in air fresheners, toilet bowl deodorants, and mothballs, is associated with lower FEV_1 [37•]; concurrent exposure to fragrances common in these household products was not examined. Investigation of bronchiolitis obliterans in flavoring-exposed workers is a paradigm for study of other volatile exposures, which may account for obstructive disease in both occupational groups and the general population.

Conclusion

Since 2000, knowledge regarding flavoring-related lung disease has mushroomed and allowed recognition of antecedent outbreaks of disease whose etiology was unknown or which went unreported. Pressure from industry, media, labor advocates, and public agencies are resulting in more work, which will likely motivate further publications, prevention efforts, and future research.

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References and recommended reading

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- • 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. 209).

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