3 Effects of Exposure in Employees

Information on the effects on employees' health of exposures to diacetyl and other flavoring compounds comes from case reports and case series and from cross-sectional and longitudinal medical and environmental surveys conducted at several flavoring and food manufacturing facilities (Table 3-1). NIOSH has conducted cross-sectional surveys as part of HHEs at six microwave popcorn plants where diacetyl-containing butter flavorings were used, at five flavoring manufacturing plants that used diacetyl and other flavoring compounds to produce different flavors for use in food products such as microwave popcorn, at a plant that used flavorings (including buttermilk flavoring) to produce baking mixes, and at three restaurants where grill cooks used butter-flavored oil. Academic researchers have also conducted studies at other food and flavoring manufacturing plants and at a chemical plant in the Netherlands that produced diacetyl. Surveillance with a longitudinal component has been conducted by NIOSH in two HHEs, by the California Department of Public Health, and by academic researchers.

At the time of most of these field investigations, which preceded the California diacetyl regulation implemented in December 2010, little 2,3-pentanedione was being used for artificial butter flavoring. When food manufacturers began to request that diacetyl percentage be less than 1% of flavoring constituents, flavor manufacturers sometimes did not inform their clients of the substitution of 2,3-pentanedione and other diacetyl substitutes [Boylstein 2012; Day et al. 2011; NIOSH 2009b]. Accordingly, populations with 2,3-pentanedione exposure without previous diacetyl exposure are difficult to identify. Thus, illness attributable to 2,3-pentanedione alone has not been studied.

3.1 Obstructive Lung Disease Consistent with Obliterative Bronchiolitis

The most significant health consideration for flavoring-exposed employees is the development of exertional dyspnea or findings consistent with obliterative bronchiolitis (also often called constrictive bronchiolitis, see discussion of terminology). Most textbooks characterize obliterative bronchiolitis as a rare disease with airways obstruction, defined by a decreased FEV_1 and a decreased FEV_1 to FVC ratio on spirometry testing. The magnitude of decline in FEV_1 determines the severity of the disorder. However, three recent case series of biopsy-confirmed obliterative bronchiolitis document that many cases have normal spirometry and, when abnormal, the spirometric pattern can be restrictive, obstructive, or mixed restrictive and obstructive in nature [Ghanei et al. 2008; King et al. 2011; Markopoulou et al. 2002]. Because of the historical assumption that obliterative bronchiolitis is an obstructive disease, the early NIOSH investigations focused on obstructive abnormalities.

Airways obstruction can occur in diseases such as smoking-related COPD (including emphysema and chronic bronchitis) and in asthma. In emphysema, the airways obstruction is usually

Table 3-1. Literature pertinent to flavoring health effects

Reference	Facility NIOSH evaluated	Study type(s), industry	Contribution*
Akpinar-Elci et al. [2004]	G	Case report, MICROWAVE POPCORN MANUFACTURING	Nine former employees at the index plant exhibited moderate to very severe fixed airways obstruction; five of the cases were on lung transplant lists.
Bailey et al. [2015]	R	Public health investigation, FOOD PRODUCTION	Coffee processing employees had excess shortness of breath and 2.7-fold risk of obstructive abnormalities; the group working in both high exposure areas (unflavored coffee grinding/packaging and flavoring room) had lower mean FEV_1/FVC ratio and percent predicted mid-expiratory flow than employees without such exposure.
Cavalcanti et al. [2012]	†	Case report, FOOD PRODUCTION	Four employees at a cookie manufacturing facility developed bronchiolitis within 1 to 3 years of employment.
Centers for Disease Control and Prevention (CDC) [2002]	G	Public health investigation, MICROWAVE POPCORN MANUFACTURING	Eight cases of fixed obstructive lung disease resembling bronchiolitis obliterans among former employees at the index plant resulted in identification of excess risk for mixers compared to packaging employees, with no cases outside of microwave production.
CDC [2007]	†	Case report and public health investigation, FLAVORING MANUFACTURING	Two cases of work-related bronchiolitis obliterans from two different plants resulted in a public health surveillance effort identifying five additional cases of severe fixed obstruction in young, non-smoking employees who worked in flavor compounding or packaging.
CDC [2013]	R	Case report, FOOD PRODUCTION	Two employees in the flavoring room of a coffee roasting plant developed fixed airways obstructive disease and were diagnosed with obliterative bronchiolitis by biopsy.
Halldin et al. [2013]	G	Cohort mortality follow-up, MICROWAVE POPCORN MANUFACTURING	Current and former employees studied by NIOSH in 2000–2003 had a 4-fold increase in mortality coded as chronic obstructive pulmonary disease in an 11-year follow-up through late 2011.
Kanwal et al. [2006]	G, J, K, L, N, O	Summary of six plant surveys, MICROWAVE POPCORN MANUFACTURING	Synthesis of six cross-sectional NIOSH surveys identified an industry-wide risk of fixed airways obstruction in five plants, one of which had mixing-area diacetyl exposures as low as 0.02 ppm. Mixers with longer work histories and packaging employees near nonisolated tanks of oil and flavorings had higher prevalences of respiratory symptoms and airways obstruction.

See footnotes at end of table.

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Table 3-1 (Continued). Literature pertinent to flavoring health effects

Reference	Facility NIOSH evaluated	Study type(s), industry	Contribution*
Kanwal et al. [2011]	G	Intervention study, MICROWAVE POPCORN MANUFACTURING	Ventilation and isolation of flavor mixing at the index plant resulted in one to three orders of magnitude reduction in diacetyl air concentrations in different areas. Employees with high past exposures had stable chest symptoms, decreased mucous membrane and skin symptoms, and higher prevalence of rapid declines in lung function than employees hired after interventions began. These new employees had lower symptom prevalences and higher lung function, demonstrating that intervention resulted in improved health for new employees.
Kim et al. [2010]	B,C†	Cross-sectional industry-wide public health investigation, FLAVORING MANUFACTURING	California flavoring employees had 2.7 times more severe airways obstruction than the general population. Risk factors for the 18 cases with obstruction among 467 employees were younger age, Hispanic ethnicity, liquid and powder production work, greater company diacetyl usage, and having a coworker with obstruction. Severity of obstruction was related to tenure. At least 12 employees had probable occupational fixed airways obstruction.
Kreiss et al. [2002]	G	Cross-sectional survey, MICROWAVE POPCORN MANUFACTURING	The 117 current employees at the index plant had 2.6 times the expected rates of respiratory symptoms and 3.3 times the expected rate of airways obstruction, with never-smokers having 10.8 times the expected rate. Quartile of cumulative exposure to diacetyl was related to the frequency and extent of airways obstruction.
Lockey et al. [2009]	L†	Longitudinal survey, MICROWAVE POPCORN MANUFACTURING	Study of 765 employees at four plants at two 6-month intervals showed significant FEV_1 declines in mixers, who also had an 8-fold risk of obstructive abnormality. Cumulative diacetyl exposure of 0.8 ppm-yr was associated with an odds ratio of 9.2 for obstruction.
NIOSH [1986]	A	Cross-sectional survey, FLAVORING MANUFACTURING	Two young employees with no known risk factors developed severe, fixed obstructive lung disease suggestive of bronchiolitis obliterans within 1 year of employment.
NIOSH [2003a]	N	Cross-sectional survey, MICROWAVE POPCORN MANUFACTURING	Elevated prevalence of airways obstruction when compared to national rates; all observed obstruction was fixed.

See footnotes at end of table.

(Continued)

Table 3-1 (Continued). Literature pertinent to flavoring health effects

Reference	Facility NIOSH evaluated	Study type(s), industry	Contribution*
NIOSH [2004a]	K	Cross-sectional survey, MICROWAVE POPCORN MANUFACTURING	A study of 157 employees in a plant having a mixing room employee previously diagnosed with fixed obstructive lung disease consistent with bronchiolitis obliterans found abnormal lung function in 6 of 13 mixers: 3 had fixed airways obstruction, and 3 had spirometric restriction.
NIOSH [2004b]	L	Cross-sectional survey, MICROWAVE POPCORN MANUFACTURING	A survey of 205 employees at a plant with a mixer previously diagnosed with severe fixed obstructive lung disease consistent with bronchiolitis obliterans, identified 3 of 12 mixers and 5 of 110 packaging employees with fixed airways obstruction and normal diffusing capacity.
NIOSH [2006]	G	Eight cross-sectional surveys, MICROWAVE POPCORN MANUFACTURING	Studies of 373 current employees over 2.75 years at the index plant determined that inhalation of butter flavoring compounds is a risk for occupational disease. Comparisons of employees hired before and after implementation of exposure controls document declines in the prevalence of eye, nose, and throat irritation. Large decreases in FEV_1 (> 300 mL or 10%) were observed in 4 of 9 mixers; one young mixer lost 2,800 mL over 2.75 years.
NIOSH [2007a]	B	Two cross-sectional surveys, FLAVORING MANUFACTURING	Two former employees and one current employee who made powdered flavorings (of 18 with current or previous production experience) had severe fixed obstructive lung disease consistent with bronchiolitis obliterans. Within months of the survey, one of these employees was diagnosed with bronchiolitis obliterans following biopsy.
NIOSH [2007b]	M	Cross-sectional survey, FOOD PRODUCTION	All three employees in a popcorn popping business developed symptoms of airways disease during their tenure; all were lifetime nonsmokers. One of the employees had significant reversible airways obstruction with some clinical evidence suggesting possible bronchiolitis obliterans in addition to asthma.

See footnotes at end of table.

(Continued)

Table 3-1 (Continued). Literature pertinent to flavoring health effects

Reference	Facility NIOSH evaluated	Study type(s), industry	Contribution*
NIOSH [2008]	C	Two cross-sectional surveys, FLAVORING MANUFACTURING	One of 14 employees with production experience had severe fixed airways obstruction (subsequently confirmed as bronchiolitis obliterans), and an additional production employee developed mild fixed obstruction following the loss of 1 liter in FEV_1 during a 4.5-month screening interval.
NIOSH [2009b]	E	Cross-sectional survey, FOOD PRODUCTION	At a plant using a newly reformulated flavoring that included 2,3-pentanedione, no obstruction was identified in the 22 employees tested. Participants had higher than expected rates of shortness of breath, physician-diagnosed asthma, and a restrictive pattern on spirometry (four cases ranging from mild to moderately severe), compared to U.S. adults. Some participants reported symptoms with a work-related pattern.
NIOSH [2009c]	F	Three cross-sectional surveys, FOOD PREPARATION	Studies of employees at three sites found higher prevalences of spirometric restriction, wheeze, dyspnea on exertion, nasal and eye irritation, and nasal allergies when compared to national rates. Cooks were 3–4 times more likely to report work-related respiratory symptoms. Fixed airways obstruction identified in two employees did not appear to be work-related.
NIOSH [2009d]	D	Cross-sectional survey, FLAVORING MANUFACTURING	This study of 34 employees found that bacterial products employees had higher prevalences of work-related eye symptoms and post-hire skin problems than flavoring employees; both groups reported lower respiratory symptoms related to the substances they handled at work. One employee was identified with fixed airways obstruction and two employees with restriction on spirometry.

See footnotes at end of table.

(Continued)

Table 3-1 (Continued). Literature pertinent to flavoring health effects

Reference	Facility NIOSH evaluated	Study type(s), industry	Contribution*
NIOSH [2011] Kreiss [2014]	I	Public health investigation, FLAVORING MANUFACTURING	Review of company-supplied spirometry tests identified 39 (37%) employees with evidence of some abnormality (either the most recent spirometry test showed restriction or obstruction; and/or longitudinal spirometry showed excessive decline over time, with most recent spirometry values still within the normal range). Employees currently in areas with higher potential for flavorings exposure were 5.8 times more likely to have abnormal declines in FEV_1 than employees in other areas.
NIOSH [2013] Cummings et al. [2014]	Q	Cross-sectional survey, FLAVORING MANUFACTURING	A survey of 367 employees at a plant that used thousands of chemicals found that employees that spent 1 hour or more daily in the production area had higher prevalences of spirometric abnormalities and low diffusing capacity. Employees with 7 or more years of tenure had lower mean values of percent predicted FEV_1, FVC, and diffusing capacity.
van Rooy et al. [2007]	†	Case report, Cross-sectional survey, DIACETYL MANUFACTURING	Four cases of bronchiolitis obliterans syndrome ([BOS] previously attributed to chronic obstructive pulmonary disease [COPD] or asthma) were identified in screening of 103 process operators in a retrospective cohort of production plant employees.
van Rooy et al. [2009]	†	Cross-sectional survey, DIACETYL MANUFACTURING	Excess respiratory symptoms and asthma indices occurred among 175 production plant employees compared to an internal reference group and a general population sample, with evidence of diacetyl exposure-response for FEV_1.

* The health effects listed use the terminology stated in the original report or publication (e.g., fixed obstruction, bronchiolitis obliterans, bronchiolitis obliterans syndrome).
† Referenced publication includes site(s) that NIOSH did not visit.

fixed (i.e., does not respond to bronchodilator medications), whereas in asthma, the airways obstruction is at least partially responsive to bronchodilators (reversible airways obstruction). Most employees who have developed obstructive lung disease while exposed to diacetyl and other flavoring compounds have had fixed airways obstruction. Additional medical tests in severely affected employees have generally revealed findings consistent with the irreversible obstructive lung disease obliterative bronchiolitis (discussed in detail in section 3.1.2). Serial lung function testing with spirometry indicates that affected employees can experience very rapid lung function declines.

Obstructive lung disease in employees exposed to diacetyl and other flavoring compounds was first reported in employees in the microwave popcorn industry. Scientific publications that have reported on the occurrence and natural history of the illness have used different diagnostic terms including fixed obstructive lung disease [CDC 2002], popcorn worker's lung [Schachter 2002], flavorings-related lung disease [Kanwal et al. 2006; NIOSH 2009a], clinical bronchiolitis obliterans [Kreiss et al. 2002], bronchiolitis obliterans syndrome [Akpinar-Elci et al. 2004], and flavoring-related bronchiolitis obliterans [Kreiss 2007]. Of the few surgical lung biopsies that have been performed in affected employees, some have been interpreted as showing evidence of "constrictive bronchiolitis" or "obliterative bronchiolitis" [Akpinar-Elci et al. 2004; Kanwal 2008]. The term *fixed obstructive lung disease* is the least specific of the terms. The term *popcorn worker's lung* refers to the population of employees in which the disease was first identified. The term *flavorings-related lung disease* refers to the full spectrum of lung diseases that may be related to flavorings exposure and is not necessarily limited to obstructive conditions. The terms *flavoring-related bronchiolitis obliterans*, *constrictive bronchiolitis*, and *obliterative bronchiolitis* refer to pathologic findings of inflammation and fibrosis primarily involving the bronchioles, leading to irreversible airflow limitation. Terminology is complicated by the fact that, historically, researchers have applied the term "bronchiolitis obliterans" to different distinct disorders that involve the bronchioles [King 2003; King and Kinder 2008]. The terms clinical bronchiolitis obliterans and bronchiolitis obliterans syndrome refer to those who are thought to suffer from this pathologic condition based on clinical findings, but have not undergone lung biopsy for pathological confirmation. Additional discussion regarding diagnostic terminology in relation to the different recognized forms of bronchiolitis is included in section 3.1.1.

3.1.1 Bronchiolar Disease and Terminology

Bronchiolitis obliterans refers to disease processes that show some degree of inflammation, narrowing, or obliteration of small airways (bronchioles) in the lung [King 2003; King and Kinder 2008]. Historically, bronchiolitis obliterans has been classified into two groups: *proliferative* bronchiolitis obliterans and *constrictive* bronchiolitis obliterans [King 2003; King and Kinder 2008]. The disorder known as bronchiolitis obliterans organizing pneumonia (BOOP) is included in the proliferative group. BOOP is characterized pathologically by intraluminal polyps in the respiratory bronchioles, alveolar ducts, and alveolar spaces accompanied by organizing pneumonia in the more distal parenchyma. Clinically it is usually associated with diffuse alveolar opacities on chest x-ray and computed tomography scan; pulmonary function testing may show a restrictive defect [King 2003; King and Kinder 2008]. BOOP was first described in 1985. Prior to this, many cases that matched the description for BOOP were classified as idiopathic bronchiolitis obliterans [King 2003; King and Kinder 2008]. The

American Thoracic Society and the European Respiratory Society have recommended the use of the term cryptogenic organizing pneumonitis (COP) instead of BOOP to avoid confusion with the disease constrictive bronchiolitis obliterans [ATS and ERS 2002]. While proliferative bronchiolitis can be idiopathic (e.g., COP), known associations include collagen vascular diseases (e.g., systemic lupus erythematosus), acute infections (e.g., influenza, mycoplasma), organ transplantation, and aspiration pneumonitis. Proliferative bronchiolitis is generally responsive to corticosteroid medications and is usually reversible [King and Kinder 2008].

Obliterative bronchiolitis (also referred to as constrictive bronchiolitis obliterans [ATS and ERS 2002], constrictive bronchiolitis [Schlesinger et al. 1998; Visscher and Myers 2006], and bronchiolitis obliterans [King 2003; King and Kinder 2008]) is a rare disorder characterized by alterations in the walls of respiratory and membranous bronchioles that cause concentric narrowing or complete obliteration of the airway lumen, without involvement of the distal lung parenchyma by inflammation or organizing pneumonia [King 2003; King and Kinder 2008]. In affected individuals, pulmonary function tests usually show airways obstruction and hyperinflation [King and Kinder 2008], but biopsy-confirmed cases may have normal or restrictive spirometry [Ghanei et al. 2008; King et al. 2011; Markopoulou et al. 2002]. Chest x-rays may be normal or show hyperinflation, peripheral attenuation of the vascular markings, and nodular or reticular opacities [King 2003]. The predominant finding of obliterative bronchiolitis on high-resolution computed tomography (HRCT) scan is heterogeneity of lung density due to mosaic perfusion and air trapping [King 2003; King and Kinder 2008]. Other findings of bronchiolitis on HRCT scan include centrilobular thickening, bronchial wall thickening, bronchiolar dilatation, and the tree-in-bud pattern. Cylindrical bronchiectasis is frequently associated with obliterative bronchiolitis; scans with both inspiratory and expiratory views are helpful because expiratory views are important in assessing air trapping [King 2003]. Identification of the obliterative bronchiolitis lesion on lung biopsy may be difficult because of its patchy distribution [Estenne et al. 2002; Schlesinger et al. 1998; Visscher and Myers 2006], often requiring step-sectioning and special staining to identify airway walls [King 2003; King and Kinder 2008]. The diagnosis is a multidisciplinary one involving a team with clinical, radiologic, and histopathologic expertise; HRCT evidence often replaces the need for surgical lung biopsy [King and Kinder 2008]. In comparison to proliferative bronchiolitis, obliterative bronchiolitis is generally unresponsive to corticosteroid medications and often progresses to more severe disease [King and Kinder 2008], although progression after exposure cessation is not characteristic of flavoring-related disease consistent with obliterative bronchiolitis [Akpinar-Elci et al. 2004].

As mentioned previously and discussed in detail in the next section (3.1.2), the medical evaluations of employees who have developed lung disease during exposure to diacetyl and other flavoring compounds have generally revealed findings consistent with obliterative bronchiolitis. Because of concerns for patient welfare and the invasive nature and imperfect sensitivity of lung biopsy for diagnosing obliterative bronchiolitis, most patients have been diagnosed based upon clinical findings. Despite the small number of lung biopsies conducted, findings consistent with obliterative bronchiolitis have been identified in multiple flavorings-exposed patients [Akpinar-Elci et al. 2004; NIOSH 2007a]. Patients exposed to sulfur mustard gas are another patient population where obliterative bronchiolitis has been diagnosed in a small subfraction of the patients while other patients are diagnosed using

contemporary clinical criteria, including HRCT scans [Ghanei et al. 2004a; Ghanei et al. 2004b; Ghanei et al. 2008; Rowell et al. 2009]. Other known causes of obliterative bronchiolitis include uncontrolled inhalation exposures to ammonia, chlorine, phosgene, nitrogen dioxide and sulfur dioxide, collagen vascular diseases (especially rheumatoid arthritis), infections, and organ transplantation (bone marrow, heart-lung, lung) [King and Kinder 2008].

Because of the difficulty of identifying the lesions of obliterative bronchiolitis on lung biopsy, and because the disease occurs commonly after heart-lung and lung transplants, in 1993 a committee sponsored by the International Society for Heart and Lung Transplantation proposed a clinical description for the disease termed bronchiolitis obliterans syndrome. The syndrome refers to graft deterioration secondary to persistent airflow obstruction as defined by pulmonary function changes with or without histolopathologic confirmation. Probable risk factors for BOS include acute graft rejection and cytomegalovirus pneumonitis [Estenne et al. 2002]. The term BOS has also been used in cases of obliterative bronchiolitis resulting from chemical injury and diagnosed using clinical criteria with or without biopsy [Akpinar-Elci et al. 2004; Ghanei et al. 2004a; van Rooy et al. 2007].

Because the terminology used in the peer-reviewed literature of flavorings-exposed employees has included several different accepted and frequently interchanged diagnostic terms, and indeed may have been influenced by the peer-review process itself, this criteria document sometimes provides the terms used in the cited papers and includes the criteria used in the patient evaluations.

3.1.2 Evidence from Field Studies

NIOSH first learned of the potential risk of obliterative bronchiolitis in microwave popcorn employees exposed to butter flavorings in August 2000 when they were asked by the Missouri Department of Health and Senior Services for technical assistance in investigating the occurrence of this illness in eight former employees (index cases) of a microwave popcorn plant (index Facility G)[CDC 2002]. NIOSH reviewed medical records for these employees and in November 2000 conducted a medical survey of current and former employees of this plant. Survey results and medical records review for the eight index cases and a current employee with lung disease showed several findings consistent with obliterative bronchiolitis. All cases had moderate to very severe airways obstruction (FEV_1s between 14.9% and 58.4% predicted), fixed in most cases; six of seven cases tested had increased residual volume consistent with air trapping. Diffusing capacity for carbon monoxide (DL_{CO}) was normal initially in five of seven cases tested. All cases had chest x-rays that were normal or showed hyperinflation. All eight cases that had HRCT scans showed marked bronchial wall thickening and mosaic attenuation with air trapping; five cases also showed mild cylindrical bronchiectasis. In two of three cases that underwent lung biopsy, the reviewing pathologist reported findings that supported or were consistent with a diagnosis of bronchiolitis obliterans [Akpinar-Elci et al. 2004]. These nine employees had developed a dry persistent cough, shortness of breath on exertion, and wheezing after a median of 1.5 years of employment. At the time of symptom onset, five of the employees had been working in the room where butter flavorings, salt, and colorings were combined with heated soybean oil. The other four employees had been working in the adjacent room where the oil and flavoring mixture was combined with kernel popcorn in microwavable bags (packaging area). None of these employees were initially diagnosed by their personal physicians as having obliterative bronchiolitis.

Initial diagnoses received by these employees included pneumonia, asthma, emphysema, bronchitis, COPD, hay fever, and sinusitis. Five of the employees had minimal smoking history. All nine employees had been prescribed oral corticosteroids, but none had improvement in lung function. Five of the employees had been placed on lung transplant waiting lists by their personal physicians [Akpinar-Elci et al. 2004].

3.1.2.1 Index plant lung function testing

The NIOSH medical survey at the index microwave popcorn plant (Facility G) in November 2000 included lung function testing with spirometry and DL_{CO}, chest x-rays, and a questionnaire [Kreiss et al. 2002; NIOSH 2006]. NIOSH compared the prevalences of respiratory symptoms, self-reported physician-diagnosed asthma and chronic bronchitis, and airways obstruction on spirometry to data from the Third National Health and Nutrition Examination Survey (NHANES III) [CDC 1996]. Of 135 current employees, 117 (87%) completed the questionnaire, and 97 (83%) of the survey participants worked in the microwave popcorn production areas of the plant. The remaining 20 survey participants worked in areas where butter flavorings were not used such as plain kernel popcorn packaging, offices, warehouse, and outside receiving. The prevalences of respiratory and systemic symptoms, mucous membrane irritation, and skin irritation were higher among employees in microwave popcorn production areas than in other areas. Among all survey participants, the prevalences of chronic cough and shortness of breath when hurrying on level ground or walking up a slight hill were 2.6 times higher than expected; the prevalence of wheezing was three times higher than expected. The prevalences of self-reported physician-diagnosed asthma and chronic bronchitis were 1.8 and 2.1 times higher than expected, respectively. Of the 116 employees who underwent spirometry, 21 had airways obstruction, 3.3 times higher than expected. Airways obstruction in nonsmokers was 10.8 times higher than expected, and only two employees with airways obstruction had a significant response to administered bronchodilator. Five of six employees in the quality control (QC) laboratory had airways obstruction; these employees popped up to 100 bags of microwave popcorn in microwave ovens per employee per 8-hour work shift. Of the 115 survey participants who had an x-ray, 111 had no abnormalities, two had evidence of emphysema, one had saber-sheath tracheal narrowing attributable to COPD or tracheal stenosis, and one had focal upper-zone scarring and atelectasis at the left lung base. DL_{CO} was normal in 96 of 103 employees tested, including all but one of those with airways obstruction.

3.1.2.2 Index plant environmental survey

In addition to the cross-sectional medical survey, NIOSH conducted a detailed environmental survey at the index microwave popcorn plant (Facility G) in November 2000 [Kanwal et al. 2011; NIOSH 2006]. The predominant VOC in the air of the plant was the butter flavoring compound diacetyl. All measurements above detectable limits (except where noted otherwise below) were subsequently corrected for underestimation inherent to NIOSH Method 2557 related to absolute humidity and days to extraction [Cox-Ganser et al. 2011]. The relative humidity and temperature measurements used for correction were available from in-facility area-specific and shift-specific measurements during all sampling, and sample-specific days to extraction were supplied by the laboratory. The mixing room had the highest mean air concentration of diacetyl (57.2 ppm); the next highest mean air concentration of diacetyl was in the packaging area for machine operators (2.8 ppm). The mean air concentration of diacetyl in the QC laboratory was 0.8 ppm, and for maintenance it was 0.9 ppm. The much higher prevalence of airways obstruction in QC employees, despite much lower average

air concentrations of diacetyl, may reflect an enhanced risk of peak flavoring exposures when microwaved bags of popcorn product were opened; peak exposures were also likely present in maintenance employees and mixers. Mean diacetyl air concentrations in other plant areas were less than 0.15 ppm.

These area-specific diacetyl concentrations and work history data provided by employees on the medical survey questionnaire were used to calculate estimated cumulative exposure to diacetyl for each survey participant. When survey participants were grouped into quartiles of increasing estimated cumulative exposure to diacetyl (corrected for underestimation by NIOSH Method 2557), the prevalence of any airways obstruction on spirometry was 14.3% in the lowest exposure quartile, 6.7% in the next lowest quartile, and 27.6% in the highest two exposure quartiles (statistically significant; *P* for trend = 0.04). The prevalences of abnormal spirometry, whether obstructed or restricted or mixed, by quartile were 21.4% for cumulative exposures < 0.82 ppm-yr; 16.7% for cumulative exposures between 0.82 and < 6.4 ppm-yr; 34.5% for cumulative exposures between 6.4 and < 19.2 ppm-yr; and 37.9% for cumulative exposures > 19.2 ppm-yr (statistically significant; *P* for trend = 0.04). Lung function as indicated by the average percent of predicted FEV_1 on spirometry was 93.5%, 95.8%, 86.5% and 84.3% in the lowest to highest quartiles (*P* for trend = 0.03) [Kreiss et al. 2002].

3.1.2.3 Findings of index plant follow-up surveys

NIOSH conducted seven follow-up medical and eight follow-up environmental surveys at the index microwave popcorn plant (Facility G) from 2001 to 2003 [Kanwal et al. 2011; NIOSH 2006]. These surveys were conducted to follow employee symptoms and lung function over time as exposures decreased with the implementation of engineering controls. NIOSH recommended a respiratory protection program for mixing room employees to minimize their exposures while engineering controls were being implemented; this program was initiated at the time of the November 2000 NIOSH survey. Starting in February 2001, the company began implementing several engineering controls to decrease air concentrations of flavoring compounds in the mixing room, the main source of air contaminants in the plant. An exhaust fan was installed in an outer wall of the mixing room to move contaminated air from this room to the outdoors and to maintain this room under negative air pressure relative to the rest of the plant. An air lock was installed at the entrance to the mixing room to further isolate the room from the rest of the plant. Local exhaust ventilation of the air space (headspace) above the contents of the heated flavoring tanks and the mixing tank in which flavorings are mixed into heated soybean oil was accomplished via ducts connecting the tank lids to the wall exhaust fan. A pump was installed to facilitate closed transfer of heated butter flavorings into the mixing tank. In 2002, the company constructed and began using a new mixing room that was more isolated from the packaging area than the original mixing room. In the packaging area, additional general dilution ventilation was implemented in 2001 along with local exhaust ventilation for seven heated holding tanks located on a mezzanine above the packaging lines that contained soybean oil and butter flavoring mixtures transferred via pipes from the mixing room. The entire mezzanine was walled off from the packaging area in 2003. Additional general dilution ventilation was also implemented in the QC laboratory in 2001. In 2003, all microwave ovens were eventually moved into a separate "popping room" adjacent to the QC laboratory with additional exhaust ventilation.

Compared to the mean diacetyl air concentrations NIOSH measured in November 2000,

concentrations measured in November 2001 were approximately 96% lower in the mixing room, 85% lower in the microwave popcorn packaging machine operator area, and 51% lower in the QC laboratory. After the implementation of a new, more isolated mixing room in fall 2002, mean diacetyl air concentrations in the microwave popcorn packaging machine operator area further declined to less than quantifiable limits (~0.004 ppm) in January 2003 [Kanwal et al. 2011].

In their analyses of data from the eight NIOSH medical surveys at Facility G from November 2000 to August 2003, NIOSH compared health outcomes in microwave popcorn production employees hired after the implementation of exposure controls to health outcomes in employees who had been working at the plant prior to the implementation of controls [Kanwal et al. 2011]. For these analyses, investigators classified employees according to their hire date as follows: "Group 1" consisted of employees who were already working at the plant at the time of the November 2000 survey (i.e., before exposure controls were implemented), and "Group 2" consisted of employees who started work at the plant after the November 2000 survey (i.e., after exposure controls were implemented and exposures had declined). Because of a high turnover rate among employees hired after the November 2000 survey, participation in more than one medical survey was much higher in Group 1 (100 of 146 [68%] Group 1 survey participants) than in Group 2 (86 of 227 [38%] Group 2 survey participants). Mean length of employment for Group 1 survey participants was approximately 6 years, compared to 6 months for Group 2 survey participants. For all Group 1 microwave popcorn production employees who participated in one of the last two surveys in February 2003 and August 2003 and in an earlier survey, NIOSH compared symptoms and lung function on their first survey to their last survey results. Most Group 2 employees who participated in more than one survey worked in the packaging area. Therefore, for all Group 2 packaging area employees who participated in more than one survey, investigators compared symptoms and lung function on their first survey to their last survey results. In Group 1, the only statistically significant change in symptom prevalence over time was a decline in reported eye, nose, or throat irritation. There were no statistically significant changes in the prevalence of airways obstruction or in mean percent predicted FEV_1. Based on data from employees' first surveys, packaging area employees in Group 2 had lower prevalences of respiratory symptoms and airways obstruction on spirometry, and mean percent predicted FEV_1 was significantly higher compared to packaging area employees in Group 1. All these differences were statistically significant except for usual cough. There were no statistically significant changes in the prevalences of symptoms, airways obstruction, or mean percent predicted FEV_1 from first to last survey in Group 2 packaging area employees [Kanwal et al. 2011]. Of interest is that 47% of all employees with abnormal spirometry tested by NIOSH (in Groups 1 and 2) were asymptomatic.

NIOSH conducted a mortality study on Facility G employees based on Social Security Administration vital status determination as of November 30, 2011 [Halldin et al. 2013]. The cohort consisted of employees with potential flavoring exposure: 356 current employees who had participated in any of the eight NIOSH cross-sectional medical surveys from November 2000 through August 2003 and 155 former employees tested by NIOSH at the county health department during that time period. There were 15 decedents altogether, not significantly different from the 17.39 expected. However, there were five COPD-associated multiple causes of death (International Classification of Diseases [ICD]-10 codes

J40-J44) coded among four decedents, for a standardized mortality ratio (SMR) of 4.3 (95% confidence interval [CI] 1.40–10.04). There is no specific ICD-10 code for obliterative bronchiolitis, so it is likely that death from the condition would be coded using a COPD classification code. Consistent with this, the specific code J44 "other COPD" was assigned as a multiple cause of death for the four decedents (0.98 expected; SMR = 4.10, 95% CI 1.12–10.49). Three of the four COPD-coded deaths occurred among former employees and employees employed before the company began to implement interventions to reduce diacetyl exposure (Group 1 above).

3.1.2.4 Other NIOSH microwave popcorn health hazard evaluations

NIOSH conducted HHEs that included cross-sectional medical and environmental surveys at five other microwave popcorn plants (Facilities J, K, L, N, and O) from 2001 to 2003 [NIOSH 2003a, b, c, 2004a, b]. These plants and the index plant (Facility G) were similar with regard to some production and exposure characteristics; however, there were some important differences as well [Kanwal et al. 2006]. The similarities in production and exposure characteristics at the six microwave popcorn plants evaluated by NIOSH were as follows:

(1) At each plant, one to three employees per work shift (i.e., mixers) measured butter flavorings (liquids, pastes, and powders) in open containers such as 5-gallon buckets and poured the flavoring into heated soybean oil in large (e.g., 500-gallon) heated mixing tanks, most of which had loose-fitting lids.

(2) Most mixers did not use respirators. Only one mixer at one plant reported consistent use of a respirator with organic vapor cartridges during mixing tasks.

(3) Mixers added salt and coloring to the oil and flavoring mixture, which was then transferred by pipes to nearby packaging lines to be combined with kernel popcorn in microwaveable bags.

(4) Employees on the packaging lines operated the packaging machines and facilitated the placement of the finished product into cartons and boxes.

In most plants, QC employees popped product in microwave ovens that were usually located in a separate QC laboratory. Other employees were located in warehouse and office areas. In separate areas of some plants, employees also packaged plain kernel popcorn in plastic bags without oil or flavorings. The six microwave popcorn plants differed in size as follows:

(1) Two small plants (Facilities J and O) had fewer than 15 employees, one or two mixing tanks, and one packaging line.

(2) One medium-sized plant (Facility N) had approximately 50 employees, one mixing tank, three holding tanks for heated oil and butter flavoring mixtures, and three packaging lines.

(3) The three largest plants (Facilities G, K, and L) had more than 100 employees, five or more tanks, and seven or more packaging lines.

In some plants, flavoring-mixing activities and tanks were in a separate room adjacent to the packaging area. In other plants, some or all tanks of heated oil and flavoring were adjacent to or were inadequately isolated from the packaging lines [Kanwal et al. 2006].

In addition to the employees with findings consistent with bronchiolitis obliterans at the index microwave popcorn plant, employees with fixed airways obstruction and air trapping on HRCT scans consistent with obliterative bronchiolitis were identified at four of the other five microwave popcorn plants where NIOSH conducted

HHEs [Kanwal et al. 2006]. Including the index plant, the three largest plants and one of the small plants had affected mixers [Akpinar-Elci et al. 2004; NIOSH 2003b, 2004a, b]. Like the index plant, the medium-sized plant had affected packaging area employees. At both of these plants, packaging area employees worked near tanks of heated oil and butter flavorings [NIOSH 2003a, 2006]. The biopsies of three of the six employees who underwent lung biopsy at the medium-sized plant were reported by the reviewing pathologists as having findings consistent with bronchiolitis obliterans [Kanwal et al. 2006; NIOSH 2003a]. Compared to mean diacetyl air concentrations measured at the index microwave popcorn plant, mean corrected diacetyl air concentrations at the other five microwave popcorn plants were lower: 0.02 to 0.83 ppm in the packaging areas and 0.63 to 1.54 ppm in the mixing rooms/areas [Kanwal et al. 2006].

NIOSH conducted analyses of aggregated data from the medical surveys conducted at the six microwave popcorn plants [Kanwal et al. 2006]. Only the data from the first survey at the index microwave popcorn plant were aggregated with the data from the surveys at the other plants. Compared to employees who had never worked as mixers, employees who had at least one day of experience mixing butter flavorings into heated soybean oil had statistically significant ($P < 0.05$) higher prevalences of respiratory symptoms and a statistically significant lower mean percent predicted FEV_1. Compared to mixers with 12 months or less experience, mixers with more than 12 months experience had higher prevalences of respiratory symptoms (shortness of breath was statistically significant) and airways obstruction on spirometry. Mean percent predicted FEV_1 was 82% in mixers with more than 12 months experience compared to 95% in mixers with 12 months or less experience ($P = 0.004$). The same pattern of higher prevalences of respiratory symptoms and worse lung function in ever mixers (who had ever worked at least one day mixing flavorings in oil) and in mixers with more than 12 months experience was still evident after index plant data were excluded from the analyses [Kanwal et al. 2006]. Compared to packaging area employees at plants where tanks of heated oil and butter flavorings were isolated from the packaging lines, packaging area employees at plants where tanks were adjacent to or inadequately isolated from the packaging lines had higher prevalences of respiratory symptoms and airways obstruction on spirometry and lower mean percent predicted FEV_1 (29% vs. 10% for wheezing, $P = 0.001$; 14% vs. 5% for airways obstruction, $P = 0.06$; $P > 0.05$ for all other comparisons). Of 27 packaging area employees with airways obstruction at plants where tanks were adjacent to or inadequately isolated from the packaging lines, 21 of 23 who were administered a bronchodilator had fixed airways obstruction. After excluding index plant data from the analyses, packaging area employees in plants where tanks were adjacent to or inadequately isolated from the packaging lines still had higher prevalences of airways obstruction (11.5% vs 5.5%; not statistically significant) and wheezing (25% vs 10.7%, $P = 0.01$) compared to packaging area employees at plants where tanks were isolated. The prevalences of other respiratory symptoms were similar in both groups. The findings across the six plants suggested that those employee groups with peak exposures, sometimes with relatively low average exposures, had higher prevalences of chest symptoms or pulmonary function abnormalities than those employees without intermittent high exposures [Kanwal et al. 2006].

3.1.2.5 Results of private surveys

A large food company hired private consultants to conduct medical and environmental surveys at the company's four microwave popcorn plants [Lockey et al. 2009; White et al. 2010].

One of the company's plants, Facility L, was among the six microwave popcorn plants evaluated by NIOSH. A mixer at this plant had developed severe airways obstruction and other findings consistent with obliterative bronchiolitis. The investigators conducted spirometry tests three times at each plant from February 2005 through January 2006. During this time, 765 full-time employees worked at the four plants. Four employees were not tested because of significant cardiovascular disease or pneumonia, and four had unusable tests. The investigators excluded from subsequent analyses the test results of 11 office employees and 21 employees with a history of asthma that began prior to employment and who were taking asthma medications. The investigators classified employees into five groups for data analyses: (1) non-mixers (i.e., employees in the packaging line area, warehouse, or shipping/receiving areas), (2) mixers with mixing experience before the company implemented mandatory use of powered air-purifying respirators (PAPRs) with an assigned protection factor of 25 for mixers in April 2003, (3) mixers who only had mixing experience after implementation of mandatory use of PAPRs, (4) mechanics and supervisors who spent more than 30 minutes per month in the mixing room, and (5) quality assurance employees who popped approximately 50 bags of microwave popcorn per day. The investigators identified the following statistically significant associations from their data analyses:

(1) Work as a mixer before the implementation of mandatory PAPR use was associated with a decrease in the FEV_1 percent of predicted of 6.1% for non-Asian males and 11.8% for Asian males, in comparison to employees with no mixing room or quality assurance employment ($P = 0.03$ and $P = 0.02$, respectively).

(2) Having a cumulative diacetyl exposure greater than or equal to 0.8 ppm-yrs was associated with a decrease in the FEV_1 percent of predicted of 10.3% for non-Asian and 12.7% for Asian males, compared to having a cumulative diacetyl exposure less than 0.8 ppm-years.

(3) Among non-Asian males, work as a mixer before the implementation of mandatory PAPR use was associated with an 8-fold increased risk of airways obstruction (95% CI 2.26–29.24), and work as a mixer after the implementation of mandatory PAPR use was associated with a 5.7-fold increased risk of airways obstruction (95% CI 1.23–26.24).

(4) Having a cumulative diacetyl exposure greater than or equal to 0.8 ppm-yrs was associated with airways obstruction (odds ratio 9.2, 95% CI 2.29–36.75).

To assess for evidence of rapid lung function decline, the investigators identified employees with a progressive increase or decrease in FEV_1 of greater than 8% or 330 mL over 12 months among employees who participated in all three spirometry tests [Lockey et al. 2009]. They found no association between current diacetyl exposure (less than 0.05 ppm or greater than/equal to 0.05 ppm) and a short-term persistent increase or decrease in FEV_1, adjusted for pack-years of smoking and body mass index. Of 39 mixers with mixing experience before the implementation of mandatory PAPR use, five had airways obstruction. Three of the five had bronchodilator administered, and all three had a bronchodilator response. Three of the five had HRCT scans; two of the scans showed air trapping on the expiratory view. The investigators concluded that, "The contribution of exposure to butter flavouring with diacetyl to these clinical findings is uncertain." Three mixers who began mixing after the implementation of mandatory PAPR use were found to have airways obstruction. Preplacement spirometry was not available for these individuals. One of the three employees had pre-existing asthma, and

the other two had long smoking histories (24 and 63 pack-years, respectively). The investigators concluded that the airways obstruction in these three individuals was likely due to asthma and smoking but could not rule out the possibility that short-term exposure to diacetyl contributed to the airways obstruction when respirators had not been used 100% of the time. Analyses of 6 years of spirometric follow-up of these four plant cohorts are pending.

3.1.2.6 Field studies at flavoring manufacturing plants

Employees at several flavoring manufacturing plants have developed severe fixed airways obstruction and other findings consistent with obliterative bronchiolitis [Kanwal 2008]. The first known publicly available report of bronchiolitis obliterans in flavoring manufacturing employees is a 1986 report of a NIOSH HHE at Facility A that manufactured flavors for the baking industry [NIOSH 1986]. At this plant, two young previously healthy male employees (28 and 30 years old; nonsmokers) who prepared batches of flavorings developed severe fixed obstructive lung disease within 7 months of employment. Each employee developed progressive shortness of breath on exertion and nonproductive cough 4 to 5 months after starting work. Pulmonary function testing within 1 to 2 months of symptom onset revealed an FEV_1 of 1.2 and 0.7 liters, respectively, in the two employees. NIOSH reported that one employee had a "mild" response to bronchodilators and the other had a "minimal" response. Neither employee showed significant improvement in lung function within 1 to 2 years after they stopped working at the plant. Diffusing capacity was initially normal in both employees, and chest x-rays were normal or showed hyperinflation. NIOSH concluded that, even without pathological confirmation, the clinical picture was more compatible with bronchiolitis obliterans than with emphysema. One of the two employees was relocated to work in the loading dock but eventually left the job 11 months after starting work at the plant because of shortness of breath. The other employee left the job when he was identified with severe fixed airways obstruction 5 months after starting work at the plant in the same job. Two current mixers with 5 to 6 years of experience were asymptomatic and had normal lung function on spirometry. Two other former mixers (36 and 38 years old) had asymptomatic airways obstruction on spirometry. One had moderately severe airways obstruction and a normal chest x-ray; the other had mild airways obstruction, normal DL_{CO}, and a normal chest x-ray. Both were former smokers.

At the time of the NIOSH HHE at Facility A, mixers produced flavors by mixing liquid flavor compounds into dextrose and corn starch powder in large blenders. This included using both 300-pound and 500-pound capacity "day mixers" (ribbon blenders), and a 1,500-pound capacity Littleford Mixer [NIOSH 1986]. Employees used approximately 200 Food and Drug Administration (FDA)-approved flavor compounds to produce different flavors. A list of commonly used ingredients at this plant included diacetyl. A supplied-air respirator system had been installed several months before the first employee to develop severe fixed airways obstruction had started work. Management had required employees to wear respirators when weighing or adding the flavors or base ingredients to the mixers. However, employees did not always wear respirators during clean-up activities where exposure to powdered flavors was possible. NIOSH concluded that it was probable that some agent in the mixing room produced severe fixed obstructive lung disease in two employees. They did not identify a specific etiologic agent, but suspected an airborne agent because the lung was the only affected organ and because air sampling by the Indiana Division of Labor had revealed high dust exposures. The Indiana

Division of Labor collected 20-minute air samples that showed dust air concentrations of 20 mg/m^3 in an employee's breathing zone and 2.5 mg/m^3 inside the hood of an employee's supplied-air respirator. NIOSH analyzed bulk ingredient samples for levels of proteolytic enzymes and endotoxin. They did not identify proteolytic activity in any of the samples; endotoxin levels were "below levels seen in other workplaces where endotoxin has been associated with large decrements in FEV_1" [NIOSH 1986]. Air sampling for specific flavoring compounds was not conducted.

A cluster of cases consistent with obliterative bronchiolitis among production employees at a flavoring manufacturing company was reported by Dr. James Lockey at the 2002 American Thoracic Society International Conference [Lockey et al. 2009]. After identification of an index case of biopsy-documented bronchiolitis obliterans at this plant, a survey of the workforce identified an additional four employees with clinical findings consistent with obliterative bronchiolitis. All five employees with these findings had normal spirometry tests at the start of employment. These employees went on to develop moderate to severe fixed airways obstruction. For 4 to 5 years after cessation of exposure to flavoring compounds, the affected employees had no further declines in their lung function.

In 2007, the California Department of Public Health reported that seven flavoring manufacturing employees from four California plants had severe fixed airways obstruction [CDC 2007]. NIOSH conducted HHEs that included cross-sectional medical and environmental surveys at two of these plants (Facilities B and C) [NIOSH 2007a, 2008]. Facility B produced liquid and powdered flavorings; powdered flavorings were produced by combining liquid flavoring compounds such as diacetyl with powder ingredients in ribbon blenders. Out of a workforce of 36 at the time of the NIOSH survey, 12 worked in the flavoring production room. Before July 2006, management provided production employees with 3M® N95 filtering-facepiece respirators for voluntary use. In 2005, a 42-year-old production employee who had worked for 7 years primarily making powdered flavorings developed cough and progressive shortness of breath. Medical tests conducted by this employee's personal physicians revealed the following: fixed airways obstruction with an FEV_1 of 0.55 liters (18% of predicted) on spirometry, an HRCT scan of the chest that showed small areas of patchy ground-glass opacities in the lungs, a follow-up computed tomography (CT) scan that revealed a small amount of scarring in the right lower lobe and lingula (part of the left lung) and resolution of the ground-glass opacities, and an open lung biopsy that was interpreted as showing peribronchial fibrosis and some granulomas. An occupational pulmonary medicine physician who evaluated this employee favored a diagnosis of bronchiolitis obliterans over hypersensitivity pneumonitis. This employee stopped working at the plant in December 2005 because of severe cough and shortness of breath on exertion. In the July 2006 NIOSH medical survey, spirometry testing in this employee again showed severe fixed airways obstruction (FEV_1 of 0.54 liters; 21% of predicted). Another former employee and a current employee who had worked in powdered flavoring production also had severe fixed airways obstruction on NIOSH spirometry tests. The FEV_1 was 1.11 liters (32% of predicted) for the former employee and 0.78 liters (23% of predicted) for the current employee. The current employee with severe airways obstruction reported a past history of asthma but said that he was asymptomatic when he began working at the plant. He reported the onset of difficulty breathing within 2 weeks of starting work in powdered flavoring production. He had been relocated to the warehouse just before the NIOSH survey because of severe shortness of breath on exertion.

An open lung biopsy was interpreted by the reviewing pathologist as showing bronchiolitis obliterans. An additional current production employee was found to have mild restriction on spirometry; the rest of the medical survey participants (31 of 36 current employees and three former employees) had normal spirometry tests [NIOSH 2007a].

NIOSH conducted an HHE at a second flavoring manufacturer (Facility C) over several visits to the plant from October 2006 to July 2007 [NIOSH 2008]. This plant produced liquid and powdered flavorings (encapsulated and nonencapsulated powders) and colors. Nonencapsulated powdered flavorings were produced by combining liquid flavoring compounds such as diacetyl with powder ingredients in ribbon blenders. Encapsulated powdered flavorings were produced by drying a slurry (a mixture of powdered and liquid ingredients) in a spray dryer. With encapsulated powder flavors, volatile flavor ingredients such as diacetyl are enclosed within an encapsulant material to decrease volatility. Out of a workforce of 47 at the time of the NIOSH survey, 12 were production employees. Forty-one employees participated in the first NIOSH medical survey conducted from October 30, 2006, to November 1, 2006. Of 41 employees tested, 3 had abnormal spirometry: a laboratory/QC employee had mild restriction, a flavoring production employee had borderline obstruction, and an employee in the warehouse with several years of experience in flavoring production had severe fixed airways obstruction. This last employee had started working at the plant in powdered flavoring production in 1995 at age 26. He used an N95 filtering facepiece respirator from 1995 to 1999 and then started using a full-face, negative-pressure, air-purifying respirator; he was not fit-tested for either respirator. Because of respiratory symptoms, he was reassigned to liquid flavoring production in 2000. In April 2006, he was reassigned to the warehouse. His personal physician diagnosed chronic rhinitis in 2003 and acute bronchitis in 2004. A spirometry test in March 2005 showed severe fixed airways obstruction (FEV_1 20% of predicted). In May 2005, a pulmonologist diagnosed bronchiectasis of unknown etiology based on HRCT scan of the chest. The employee was hospitalized twice for his lung condition. NIOSH spirometry testing in October 2006 showed severe fixed airways obstruction (FEV_1 17.9% of predicted). On follow-up spirometry testing by NIOSH at the plant in March 2007 his FEV_1 was 20.7% of predicted. The flavoring employee who had borderline airways obstruction on NIOSH testing in October 2006 was found to have mild fixed airways obstruction in March 2007; his FEV_1 had dropped approximately one liter (percent predicted FEV_1 declined from 86% to 64%).

NIOSH performed an HHE in 2007 that included a medical and environmental survey at a flavoring manufacturer (Facility D) in Wisconsin [NIOSH 2009d]. At the time of the HHE, this plant manufactured flavors, colors, and bacterial blends used as silage inoculants and probiotics. One of the flavor products produced at this plant is starter distillate, a diacetyl-containing distillate of a milk stock produced from fermented dairy cultures. The diacetyl concentration in this distillate was 4.5%. Other flavor products made at this plant included powdered encapsulated starter distillates and other butter flavors produced by spray drying, and other liquid flavors. The NIOSH medical survey included a questionnaire, spirometry testing, and methacholine challenge testing (to identify airways hyperresponsiveness as occurs in asthma). Of 40 employees in production areas, the quality control laboratory, the warehouse, and in maintenance who were invited to participate in the medical survey, 34 agreed to participate. Of these 34 employees, 15 worked in jobs where they could potentially be exposed to flavoring-related compounds

including diacetyl. Of 10 former employees who had worked in flavoring production areas and were invited to participate in the medical survey, three agreed to participate. Of the 15 current employees with jobs in which they could potentially be exposed to flavoring-related compounds including diacetyl, one employee with a pre-employment history of asthma was found to have mild fixed airways obstruction mixed with restriction. NIOSH recommended that this employee pursue additional medical evaluation to look for further evidence of obliterative bronchiolitis or another illness; follow-up results were not available to NIOSH. In addition to the employee with mild fixed airways obstruction (mixed with restriction), two employees had restrictive abnormalities. Of the 15 employees with potential exposures to flavoring-related compounds, five reported having currently active physician-diagnosed asthma. All five were diagnosed with asthma before starting work at the plant; no employees reported recurrence after hire of pre-existing asthma that had been inactive for 2 or more years prior to hire. Two of 11 employees with normal spirometry who underwent methacholine challenge testing were found to have airways hyperreactivity. Both of these employees had physician-diagnosed asthma before coming to work at the plant.

In 2012, NIOSH conducted a cross-sectional medical survey at a flavoring company (Facility Q) in Kentucky in which two former employees had received physician diagnoses of obliterative bronchiolitis [Cummings et al. 2014; NIOSH 2013]. Of 357 employees with spirometry, 13 had obstruction (of whom 2 of 10 responded to bronchodilator), 15 had restriction, and 2 had mixed obstruction and restriction. The prevalences of abnormal spirometry were not elevated in relation to NHANES III expected rates, adjusted for age, sex, race/ethnicity, smoking status, and body mass index. However, participating employees had statistically significant excesses of wheeze in the last 12 months, sinusitis or sinus problems in the last 12 months, phlegm on most days for three consecutive months during the year, a diagnosis of hay fever, a lifetime diagnosis of asthma, and current asthma, when compared to the U.S. adult population. Shortness of breath was twice as common in those with 7 or more year's tenure, and remained significant in a model adjusted for age and smoking status. Work-related breathing trouble, wheeze, nasal symptoms, sinusitis, eye symptoms, and cough were all statistically significantly increased in employees currently using flavoring compounds compared to remaining employees, and these work-related symptoms remained significantly associated with flavoring compound use in models adjusted for age and smoking status. Participating employees who spent an hour or more daily in production areas had twice the prevalence of any spirometric abnormality and three times the prevalence of low diffusing capacity than other participants. Mean lung function parameters (expressed as percent predicted) were significantly lower in participants with tenure of 7 or more years and those who spent one or more hours daily in production areas. Differences in lung function could not be explained by age, smoking status, or employment at another flavoring plant, and persisted in analyses stratified by ever having been in production. The association of symptoms and lung function parameters with exposure indices suggested that they resulted from workplace exposures. Diacetyl was not used in the plant during the NIOSH air sampling, but 2,3-pentanedione was detected in two air samples collected with evacuated canisters in a liquid compounding room where fruit and cheese flavor recipes were being prepared.

3.1.2.7 Lung disease in flavoring manufacturing employees

The California Department of Public Health provided information on a flavoring production

employee who developed bronchiolitis obliterans while working at another California flavoring plant [California Department of Public Health 2007; CDC 2007]. This employee primarily prepared powdered flavorings by pouring "diacetyl and other liquid ingredients through a hole on the blender lid." He started working at the plant in October 2001 at the age of 27. Two years later he developed progressive shortness of breath on exertion, decreased exercise tolerance, intermittent wheezing, left-sided chest pain, and a productive cough. In November 2003, his physician prescribed antibiotics and bronchodilators for suspected bronchitis and allergic rhinitis. He stopped working in January 2004, but his shortness of breath continued to worsen. An HRCT scan of his chest showed cylindrical bronchiectasis in the lower lobes, with scattered peribronchial ground-glass opacities. Spirometry in April 2004 showed severe fixed airways obstruction (FEV_1 28% of predicted). Lung volume measurements showed severe air trapping. Diffusing capacity was normal. A follow-up HRCT with inspiratory and expiratory views in October 2004 showed central peribronchiolar thickening with central airway dilatation and subtle areas of mosaic attenuation scattered throughout the lungs, predominantly in the right lower lobe [CDC 2007].

In 2006, Cal/OSHA and the California Department of Public Health developed a lung disease prevention program for employees of California flavoring manufacturing plants. In analyses of aggregated medical surveillance data (questionnaire and spirometry results) from 467 employees at 16 companies who had usable questionnaires and acceptable spirometry tests, 18 employees (3.9%) from six companies with 315 participating employees had airways obstruction [Kim et al. 2010]. This prevalence was similar to that expected in comparison to national data from NHANES III [CDC 1996]. However, the distribution by severity of obstruction was highly skewed, with six mild cases, seven moderate, one severe, and the remaining four very severe. The prevalence of severe and very severe obstruction combined was 2.7 times higher than expected overall (95% CI 1.2–6.4) and 15 times higher than expected in employees less than 40 years old (95% CI 5.1–44.1). Sixteen obstructed cases worked in four companies using ≥ 800 pounds of diacetyl annually compared to two obstructed cases in companies using less diacetyl (prevalence of 5.3% versus 1.2%), for an odds ratio (OR) of 4.5 (95% CI 1.03–19.9). The prevalence of obstruction in employees currently doing any production task was 4.5% compared to 2.0% in production support employees (laboratory technicians/scientists, quality control technicians, maintenance/repair employees, warehouse employees, and truck drivers) and 2.3% in office employees. Of the 18 employees with obstruction, 14 currently worked in production, two worked in production support (one had just moved from production because of dyspnea), one with previous production experience currently worked in the office, and one could not be classified. Tenure was statistically significantly higher in employees with moderate or worse obstruction than in employees with mild obstruction (1.5 versus 9.0 years; $P = 0.02$). Half of the 18 employees with obstruction reported no chest symptoms (five of six employees with mild obstruction and four of seven with moderate obstruction). Of the 13 with documented postbronchodilator spirometry, 12 had fixed obstruction (including all four with severe or very severe obstruction). Of the 12 of 18 with obstruction who had medical evaluation results submitted to the California Department of Public Health, eight were diagnosed by their physicians to have either bronchiolitis obliterans (one biopsy-confirmed) or fixed obstruction related to flavorings; all eight had moderate to very severe disease [Kim et al. 2010]. Some of the cases included in this analysis of California

flavoring employee surveillance data were presented above in the descriptions of two NIOSH HHEs at California flavoring plants (Facilities B and C).

3.1.2.8 Lung disease in diacetyl production employees

Lung disease consistent with obliterative bronchiolitis was reported among employees of a plant in the Netherlands that produced diacetyl [van Rooy et al. 2007]. From 1960 through 2003 when diacetyl production ceased, 206 employees had potentially been exposed to diacetyl at this plant. Of 196 employees still alive, 175 consented to participate in a medical survey conducted by Dutch investigators. The survey included a questionnaire, spirometry, and review of medical files of the Occupational Health Service. Employees with possible airways obstruction on screening spirometry were referred for additional medical evaluation including an HRCT scan with inspiratory and expiratory views. Of the 175 survey participants, 102 worked as "process operators." The other participants worked in other jobs such as the quality control laboratory, "technical service," management, research and development, and logistics. Four employees were found to have fixed airways obstruction. One of these four employees (with a predicted FEV_1 of 72%) refused further evaluation. FEV_1 percent predicted in the other three employees, all process operators, ranged from 35% to 42%. All three employees had evidence of air trapping on HRCT scan expiratory views. One of these three employees underwent a thoracoscopic lung biopsy that did not show evidence of obliterative bronchiolitis. Two of these three employees were nonsmokers who had initially been diagnosed with COPD; the third employee (with a 14 pack-year smoking history) had initially been diagnosed with COPD and asthma. Two of these three employees developed shortness of breath on exertion within a year or two of starting work at the plant at ages 45 and 39 years. The other employee developed shortness of breath at age 52, 14 years after starting work. A fourth employee (process operator; nonsmoker) with severe fixed airways obstruction and findings compatible with obliterative bronchiolitis on HRCT scan was identified among survey nonparticipants after the survey. During production of diacetyl, employees were also potentially exposed to acetoin, acetaldehyde, and acetic acid. The diacetyl plant was one of several in operation at the production site; all process employees also worked at other chemical plants at the production site. The investigators noted that "Among the gaseous chemicals identified in the plants, only ammonia and chlorine were of potential concern for bronchiolitis obliterans, but none of the cases reported having had significant exposure to these agents" [van Rooy et al. 2007]. Regarding diacetyl exposures, 26 area samples (82–219 minutes) and 4 personal task-based samples (33–90 minutes) were taken between 1995 and 2003. Many jobs were not sampled. These data were insufficient for quantitative risk assessment over the period of plant operation from 1960 to 2003.

The investigators who evaluated the workforce of the diacetyl-producing plant in the Netherlands compared respiratory symptom and asthma prevalence among male employees to data from the Dutch section of the European Community Respiratory Health Survey [van Rooy et al. 2009]. Compared to the Dutch European Community Respiratory Health Survey population, the diacetyl plant workforce had significantly higher prevalences of continuous trouble with breathing, daily cough, and asthma attacks. Compared to a minimally exposed internal comparison group, process operators (including the three with severe fixed airways obstruction and evidence of air trapping on HRCT scan expiratory views who were identified in the medical survey [van Rooy et al. 2007]) and quality control laboratory

employees reported ever trouble with breathing significantly more often. Operators also reported significantly more shortness of breath in the last year. Spirometry test results for the 149 white male diacetyl plant employees did not differ significantly from the Dutch European Community Respiratory Health Survey population after adjusting for smoking history. The investigators were not able to demonstrate an exposure-response relationship between relative cumulative exposure to diacetyl and FEV_1. However, they had previously demonstrated an average 292 mL decrement in FEV_1 in process operators in comparison to a minimally exposed internal reference group [van Rooy et al. 2007].

Available information on TWA and peak exposures to diacetyl in flavoring and diacetyl manufacturing plants where employees have developed findings consistent with obliterative bronchiolitis indicates that employees' exposures in these plants may have been similar to employees' exposures at microwave popcorn plants. At one flavoring plant [NIOSH 2007a], the mean TWA diacetyl exposure from full-shift air sampling in the powdered flavoring production area was 2.73 ppm. Measurements made with partial-shift air sampling during the production of butter and vanilla powdered flavorings showed a diacetyl exposure of 25.9 ppm. Employees' real-time diacetyl exposures during the packaging of these powders were as high as 204 ppm. At a second flavoring plant [NIOSH 2008], mean TWA diacetyl air concentrations from full-shift air sampling in November 2006 (area and personal samples combined) were 0.46 ppm in liquid flavoring production and 0.34 ppm in powdered flavoring production. A task-based personal air sample measured a diacetyl air concentration of 11 ppm when an employee poured diacetyl from a 55-gallon drum into multiple 5-gallon containers over a 10-minute period. At the diacetyl production plant in the Netherlands where Dutch investigators identified four former employees with severe fixed airways obstruction and evidence of air trapping on HRCT scan expiratory views, task-specific diacetyl exposures ranged from 3 to 396 mg/m^3 (0.6 ppm to 83 ppm) during discharge of diacetyl from a reactor vessel into containers [van Rooy et al. 2007]. The measured diacetyl exposures at these three plants are comparable to exposures (corrected for absolute humidity and days to extraction) measured at the six microwave popcorn plants evaluated by NIOSH. In the mixing room at the index microwave popcorn plant (Facility G), the mean TWA diacetyl air concentration from area samples in November 2000 was 57.2 ppm. At the three other microwave popcorn plants where mixers developed findings consistent with obliterative bronchiolitis, TWA diacetyl exposures from personal samples were 0.31 ppm, 0.69 ppm, and 1.33 ppm [NIOSH 2003b, 2004a, b]. Real-time measurements at one of these plants showed that a mixer's diacetyl exposures increased up to 80 ppm to 120 ppm when he added liquid butter flavorings to a mixing tank [NIOSH 2004a].

3.1.2.9 Other food production case reports

In addition to cases consistent with obliterative bronchiolitis in flavoring manufacture, diacetyl manufacture, and microwave popcorn production, case reports have surfaced in other food production industries in which flavorings are introduced into food products. In cookie manufacture with artificial butter flavoring in Brazil, four cases of bronchiolitis were described in young men, aged 24 to 27 years, who had worked between 1 and 3 years handling flavorings in preparation of cookie dough [Cavalcanti et al. 2012]. One of the four had confirmation of bronchiolitis obliterans on open lung biopsy, and the remaining three were diagnosed on the basis of consistent chest symptoms (cough, progressive dyspnea,

and wheezing); moderate to severe mixed obstructive and restrictive spirometry; abnormal chest CT findings of lung hyperinflation, air trapping, bronchial thickening, and mosaic perfusion; and persistence of spirometric findings in 4 years of follow up. Two cases had partial response to bronchodilators and one case had ground-glass opacity.

In a coffee production plant, two cases have biopsy confirmation of obliterative bronchiolitis among employees with artificial flavorings exposure in the production of roasted coffee beans and ground coffee [CDC 2013]. An additional three cases from the same plant were reported by Dr. Jeffrey Levin in an abstract at the 2013 American Thoracic Society International Conference. In 2012, NIOSH conducted an HHE at this coffee production plant involving 75 current employees (88% participation)[Bailey et al. 2015]. Excluding the five sentinel former employees (all never-smokers under age 42), standardized morbidity ratios were elevated 1.6-fold for shortness of breath and 2.7-fold for obstructive spirometric abnormalities. The sum of diacetyl and 2,3-pentanedione air concentrations were equivalent in the flavoring room and in the grinding/packaging area of unflavored coffee. The subgroup of employees who currently worked in both coffee flavoring and grinding/packaging of unflavored coffee had significantly lower mean FEV_1/FVC ratio and percent predicted mid-expiratory flow than employees without such exposure. In addition to the sentinel former employee cases, six current employees had abnormalities suggestive of obliterative bronchiolitis and five additional employees had suspect work-related asthma. NIOSH investigators could not separate risks of employees in unflavored coffee grinding/packaging from risks of flavored coffee production because most employees' exposures were similar during their work tenure.

3.2 Restrictive Spirometry in Flavoring-exposed Workforces

NIOSH work on flavoring-related lung disease concentrated on obstructive spirometric abnormalities between 2000 and 2008 because the classic textbook description of obliterative bronchiolitis described an obstructive disease. NIOSH included employees with mixed obstructive and restrictive spirometry among the obstructed because NIOSH assumed that air trapping explained their decreases in forced vital capacity. Had NIOSH added employees with mixed obstructive and restrictive disease to those with pure spirometric restriction, NIOSH would have had excesses of restriction similar to those of obstruction in comparison to general population prevalences in some field investigations. NIOSH now has evidence from several investigators outside of the flavoring lung disease field that the clinical spectrum of biopsy-confirmed obliterative bronchiolitis includes both restrictive spirometry and normal spirometry, as well as those with fixed obstructive spirometry [Ghanei et al. 2008; King et al. 2011; Markopoulou et al. 2002]. NIOSH summarizes the evidence concerning spirometric restriction in flavoring-exposed employees in this section.

Spirometric restriction is defined as a FVC below the lower limit of normal and an FEV_1/FVC ratio that is normal. Lung diseases involving scarring (fibrosis), and inflammation of the interstitium or alveolar spaces commonly are accompanied by spirometric restriction. Examples of these lung diseases are hypersensitivity pneumonitis, pneumoconioses, and BOOP in which bronchiolar changes extend into the alveolar spaces. Non-pulmonary causes of spirometric restriction are poor effort or incomplete exhalation maneuvers, obesity, and neuromuscular weakness. Low lung volumes such as total lung capacity

and low residual volume support pulmonary causes of spirometric restriction, but normal lung volumes do not rule out lung pathology accounting for spirometric restriction [Boros et al. 2004].

The proportions of abnormal spirometry that were restrictive in the three case series of biopsy-documented constrictive bronchiolitis are instructive. In dyspneic U.S. soldiers, 3 of 38 soldiers had restriction (2 with low diffusing capacity), 2 had obstruction (1 with low diffusing capacity), and one had mixed restriction and obstruction (with low diffusing capacity). The remaining soldiers had normal spirometry and lung volumes, although 19 had low diffusing capacity [King et al. 2011]. Of 15 cases of chronic dyspnea and cough following sulfur mustard exposure 20 years previously, 13 had normal spirometry, one had restriction, and one had obstruction; all had pathologic evidence of bronchiolar disease. The cases with biopsy-documented constrictive bronchiolitis all had normal spirometry, and the two with the abnormal spirometry had chronic cellular bronchiolitis [Ghanei et al. 2008]. Of 19 cases of biopsy-documented obliterative bronchiolitis, six had normal spirometry (although 2 had isolated gas trapping), 11 had obstruction, one had restriction, and one had a mixed pattern [Markopoulou et al. 2002]. This last case series originated from a clinical referral center without common exposures. These pathologic case series suggest two conclusions. First, abnormal spirometry is insensitive to pathologic obliterative bronchiolitis that results in symptoms warranting clinical evaluation. Second, the finding of restriction in populations with cases of fixed airways obstruction consistent with obliterative bronchiolitis is likely to be part of the spectrum of obliterative bronchiolitis, although the differential diagnosis in individual employees requires investigation.

3.2.1 Index Plant Findings Regarding Restriction

Among the former employees who developed findings consistent with obliterative bronchiolitis while working at the index microwave popcorn plant (Facility G), lung function tests in one employee showed a reduced total lung capacity and reduced residual volume in addition to airways obstruction. These reduced lung volumes indicate that this employee had restrictive lung disease as well as airways obstruction [Akpinar-Elci et al. 2004]. This former employee also had a low carbon monoxide diffusing capacity and was unusual among the former employee cases in having some reversibility after ceasing employment at the microwave popcorn [Akpinar-Elci et al. 2004].

In the first cross-sectional survey of the index plant (Facility G), 10 of 116 employees had isolated abnormal FVC, of whom 7 had low total lung capacity; 11 employees had isolated airways obstruction. An additional 10 employees had both low FVC and airways obstruction, for a total of 21 of 116 employees having any restrictive spirometric pattern. None of those with any restriction had radiologic interstitial abnormalities. When the prevalence of any restrictive abnormality was examined by cumulative exposure quartile (using exposure estimates corrected for humidity and time to extraction), a trend for exposure response relationship was evident: From lowest to highest exposure quartile, the prevalence of any restriction was 10.7%, 13.3%, 20.7%, and 24.1% (P = 0.08). During follow up of these plant employees, one employee with rapidly falling pulmonary functions in a restrictive pattern underwent open lung biopsy. The pathology report documented caseating lung granulomas around airways, but grossly normal areas of lung were not sampled for examination of possible obliterative bronchiolitis. Cultures and stains for microorganisms did not yield an infectious etiology, and the physician concluded

Table 3-2. Distribution of spirometric abnormalities in flavoring-exposed employees by facility, reference, facility type, and type of spirometric abnormality

Facility NIOSH evaluated	Reference	Facility type	Current employees tested	Spirometric abnormalities		Restrictive abnormalities		Obstructive abnormalities	Mixed obstructive and restrictive abnormalities
				N	%	N	%*		
G	Kreiss et al. [2002]	Microwave popcorn	116	31	26.7	10	32.3	11	10
N	NIOSH [2003a]	Microwave popcorn	35	7	20.0	2	28.6	2	3
K	NIOSH [2004a]	Microwave popcorn	86	13	15.1	7	53.8	3	3
L	NIOSH [2004b]	Microwave popcorn	205	29	14.1	10	34.5	12	7
G	NIOSH [2006]	Microwave popcorn	368	75	20.4	36	48.0	24	15
B	NIOSH [2007a]	Flavor manufacturer	34	2	5.9	1	50.0	0	1
C	NIOSH [2008]	Flavor manufacturer	41	3	7.3	1	33.3	1	1
D	NIOSH [2009d]	Flavor manufacturer	28	3	10.7	2	66.7	0	1
E	NIOSH [2009b]	Food production	22	4	18.2	4	100.0	0	0
F	NIOSH [2009c]	Food preparation	104	20	19.2	15	75.0	4	1
B,C†	Kim et al. [2010]	Flavor manufacturer	467	59	12.6	41	69.5	10	8
I	NIOSH [2011]	Flavor manufacturer	106	34	32.1	30	88.2	3	1
G	Halldin et al. [2013]	Microwave popcorn	356	57	16.0	27	47.4	16	14
			155‡	50	32.3	23	46.0	10	17
Q	NIOSH [2013]	Flavor manufacturer	357	30	8.4	15	50.0	13	2
R	Bailey et al [2015]	Food production	69	7	10.2	2	2.9	5	0

*Percentage of abnormal pulmonary function tests (PFTs) classified as restriction

†Referenced publication includes site(s) that NIOSH did not visit

‡Former employees

that the abnormalities were related to occupational flavoring exposures [Kreiss 2012].

3.2.2 NIOSH Findings of Restrictive Spirometry at Other Microwave Popcorn Plants

Most microwave popcorn plant populations surveyed cross-sectionally by NIOSH had similar proportions of restrictive, obstructive, and mixed abnormalities among those employees with abnormal pulmonary functions (Table 3-2). In the three large microwave popcorn plants (Facilities G, K, and L), the restrictive proportion of abnormal spirometry ranged from 32.3% to 53.8%. These proportions are similar to those cited in two case series of biopsy-documented constrictive bronchiolitis, which were 50% in the case of U.S. soldiers in Iraq and Afghanistan [King et al. 2011] and Iranians following sulfur mustard exposure, in which the pathology included proliferative bronchiolitis [Ghanei et al. 2008]. In the three large microwave popcorn plants, the proportion of mixed restrictive and obstructive spirometry in those with abnormal spirometry was similar to the proportion with pure obstructive and pure restrictive abnormalities. In the consecutive clinical case series [Markopoulou et al. 2002], the much lower proportion of restrictive abnormalities may be explained by the prevailing understanding a decade ago that obliterative bronchiolitis is an obstructive disease.

3.2.3 NIOSH Findings of Restrictive Spirometry at Flavoring Manufacturing Plants

As in the microwave popcorn investigations, flavoring manufacturing workforces with cases consistent with obliterative bronchiolitis have also had employees with restrictive spirometry, with proportions of restriction among those with abnormal spirometry ranging from 28.6% to 88.2% (Table 3-2).

NIOSH found an unusually high prevalence of a restrictive spirometric pattern among production employees at a flavoring manufacturing plant (Facility I) in Indiana [NIOSH 2011]. Among the 106 employees with interpretable spirometry test results obtained by the company, 30 (28%) had a restrictive pattern (22 with a mild abnormality, six with a moderate abnormality, one with a moderately severe abnormality, and one with a severe abnormality). In addition, three employees had obstructive abnormalities, and one had a very severe mixed abnormality. Combining all spirometric abnormalities with those with only excessive decline in FEV_1 in the subset of employees with serial abnormalities, 39 (37%) employees had abnormal findings. In comparison to the U.S. general population, the employee prevalence of restrictive spirometric abnormalities was 3.8 times higher than expected, after adjustment for race, ethnicity, sex, age, smoking status, and body mass index. NIOSH later detected an error in abstraction of smoking information from company spirometry reports and corrected this comparison to 3.7 [Kreiss 2014]. NIOSH also found evidence of rapid lung function decline in this workforce (section 3.3) with a 7.0-fold risk of excessive decline in the subgroup of production employees with higher potential for flavorings exposure (later corrected to 5.8) [Kreiss 2014]. Average declines in percent predicted FEV_1 and FVC for the employees with four annual measurements were in a pattern consistent with the evolution of restrictive lung disease. As in other flavoring plants, chemical exposures were diverse, although diacetyl was used nearly daily. Personal samples of diacetyl obtained by the company using NIOSH Method 2557 (uncorrected for absolute humidity and days to extraction) ranged to 0.76 ppm and area measurements to 10.2 ppm. Company samples in 2008–2009 using OSHA methods (not requiring correction) ranged to 1.9 ppm for personal and 2.9 ppm for area samples.

A company-sponsored re-analysis of Facility I spirometry data reported finding that no flavoring compounds, including diacetyl, had produced an increased risk of abnormal spirometric findings or longitudinal changes in spirometry [Ronk et al. 2013]. The study confirmed an excess risk of abnormal restrictive spirometry reported by NIOSH investigators with a similar prevalence ratio of 3.3 (95% CI 2.2–4.6) in comparison to the general population reflected in NHANES III. The authors offered the inadequacy of the NHANES III study population as a comparison group, despite adjusting for age, sex, and body mass index, because the national data were largely drawn from urban centers, and the authors alleged that the flavoring employees in a large city in Indiana were largely agrarian. As an alternative comparison group, the authors described the employee group with lower potential for flavoring exposure as an internal control group with no or minimal exposure, also referring to them as an administrative group. However, all employees in the medical surveillance program were in production areas, and company data documented measurable diacetyl in all production areas, including worrisome measurements in packaging which was classified in the NIOSH health hazard evaluation as having lower potential for exposure. Thus, the similar distribution of abnormal restrictive spirometry across the production workforce, without regard to higher and lower potential for flavoring exposure, remained unexplained and cannot be attributed to misclassification of lung disease by spirometry, variable quality spirometry, or body habitus, also mentioned by the authors. The most likely explanation for the 3.3–3.7 increased odds for restrictive disease in the Facility I workforce is that risk for work-related abnormality existed across both groups of production area employees in comparison to the national predicted estimate.

The Ronk et al. [2013] study conclusion that none of the flavoring compounds caused work-related spirometric abnormalities hinges on absence of association of pulmonary function abnormalities or decrements in employees with tenure in higher potential for flavoring exposure areas. The authors explain the difference in findings between their "negative" study and the NIOSH findings of work-related spirometric abnormalities by a NIOSH methodologic flaw in not taking account of correlated measures of serial lung functions. However, the authors misrepresent NIOSH analyses in which the outcome variables were the slopes of spirometric changes, expressed as mL/year, based on linear regression as a smoothing function. NIOSH also used categorical outcomes of excessive spirometric decline. Neither of these NIOSH outcomes reflected correlated serial data. In addressing serial (correlated) spirometry measures, Ronk et al. [2013] used generalized estimating equation modeling, which is a reasonable approach. However, the authors chose an exchangeable correlation structure, which assumes that the variation between any two measures is equal; this assumption would not appear appropriate for pulmonary function test measures at varying intervals. Measures taken at a 6-month interval would likely be more correlated than measures at several-year intervals, as occurred in the Facility I spirometry data set. The generalized estimating equation models assume that cumulative tenure is linearly related to the change in spirometry measures, which may not be the case in a short-latency health effect as has occurred in flavoring-exposed employees. The Ronk et al. [2013] paper omits report of average changes in FEV_1 and FVC per year in their model without workplace covariates, which might have indicated unusually high average decrements per year. NIOSH had found that the average FVC decline in the employee population was 108 mL/year, about 3.5-fold the expected decline of approximately 30 mL/year.

Ronk et al. [2013] separately modeled tenure in work areas with higher potential for exposure and tenure in liquid compounding with the apparent assumption that the remainder of the plant population had zero tenure (exposure), which is simply false. In particular, the liquid compounding tenure model ignores tenure in other higher potential for exposure jobs, which would clearly result in no associations with their work parameters. In contrast, the simpler NIOSH analyses of decline in lung function by areas with higher and lower potential for flavoring exposure demonstrated that both average declines and excessive decline differed between the two groups of production employees in statistically significant ways. These simple methods were not affected by correlated measurements.

A subsequent Indiana Occupational Safety and Health Administration (IOSHA) compliance investigation of Facility I reported hydrogen sulfide exposures above the NIOSH level immediately dangerous to life and health of 100 ppm [IOSHA 2012]. Hydrogen sulfide can result in obliterative bronchiolitis. IOSHA measured high concentrations of diacetyl (well above the proposed recommended exposure limit) in the packaging area that NIOSH had classified as lower potential for exposure. Thus, the diversity of exposures encountered by employees in this flavoring facility precluded identifying a specific cause(s) of the excess lung disease. However, the burden of likely occupational disease, reflected in the excess of restrictive spirometry and excessive annualized decline in spirometry, requires control of flavoring vapors, flavoring-related particulates, and hydrogen sulfide.

NIOSH found a high prevalence of a restrictive pattern on spirometry among employees at a plant (Facility E) where production employees combined liquid and powdered flavorings with flour, sugar, salt and other solid ingredients to produce baking mixes [NIOSH 2009b]. Of 41 employees, 23 (including 18 of 27 production employees) participated in a NIOSH medical survey that included spirometry testing. Of 22 employees with interpretable spirometry results, four (18%) had a restrictive pattern. All other spirometry tests were normal. The prevalence of restriction was approximately three times greater than expected compared to U.S. general population data from NHANES III [CDC 1996]. From June 2007 through May 2008, the company had used a buttermilk flavoring that contained 15% to 20% diacetyl. The company began using a reformulated buttermilk flavoring that contained less than 1% diacetyl in July 2008. The reformulated buttermilk flavoring contained 2,3-pentanedione, a diacetyl substitute that contains an additional methyl group. Use of the buttermilk flavoring was reported to be infrequent. In an industrial hygiene survey conducted by NIOSH from September 30, 2008, to October 2, 2008, diacetyl was detected qualitatively in screening air samples obtained with thermal desorption tubes and analyzed with gas chromatography/mass spectrometry according to NIOSH Method 2549. However, the diacetyl air concentrations were too low to be quantified or detected with the modified OSHA Method PV2118. In a second industrial hygiene survey conducted by NIOSH in May 2009, air sampling with OSHA Method 1013 again did not reveal detectable or quantifiable concentrations of diacetyl; however, one personal sample showed an air concentration of 2,3-pentanedione of 91 ppb, and a corresponding area sample showed an air concentration of 78 ppb. Area air sampling with an additional method under development, in-tube derivatization with 1,2-phenylenediamine (section 2.2.5 above), did not detect diacetyl but did show 2,3-pentanedione in several areas, at concentrations ranging from 48 to 95 ppb. The sample that showed an air concentration of 95 ppb was obtained in the same area where a sample obtained with OSHA Method 1013 showed an air concentration of 78 ppb [Day et al. 2011].

In 2008 NIOSH conducted an HHE of three cafeterias located at three different office buildings in New York City (Facilities F) [NIOSH 2009c]. The HHE request was motivated by concern about diacetyl in butter-flavored cooking oils used on grill surfaces. Laboratory analyses of bulk samples of butter and two samples of one brand of cooking oil used at the three facilities did reveal diacetyl. Air samples obtained by NIOSH at the three facilities showed that air concentrations of diacetyl were below the limit of detection (0.02 ppm). NIOSH conducted a medical survey that included a questionnaire and spirometry tests. Approximately 80% of the workforce at the three facilities participated in the medical survey (116 of 141 employees completed the questionnaire; 104 of 111 employees who underwent spirometry testing had a valid test). Five employees (5%) had airways obstruction, and two of these five employees had fixed obstruction. Both employees with fixed obstruction had started work at their current facility after butter-flavored cooking products were no longer in use. All five employees with obstruction denied having ever worked as professional cooks. Fifteen employees (14%) had restriction on spirometry, for a prevalence that was twice as high as expected compared to general population data from NHANES III [CDC 1996]. Five of the 15 had body mass indices over 30. Only three of the 15 reported cooking experience, and 13 reported cleaning experience. Compared to employees who did not cook at work, employees who reported cooking among their job duties were twice as likely to report asthma-like symptoms; more than three times as likely to report shortness of breath after exercise, cough, and work-related wheezing; approximately five times more likely to report work-related shortness of breath following exercise; and more than twice as likely to report work-related nasal symptoms. Employees who reported cleaning among their job duties were three times more likely to report asthma-like symptoms or shortness of breath while hurrying on level ground or walking up a slight hill than employees who did not clean at work. Employees who reported cleaning hot surfaces at work were almost four times more likely to report shortness of breath following exercise than those who had not cleaned hot surfaces at work.

In these field investigations in microwave popcorn production, flavoring production, and food preparation, clinical evaluations of employees with spirometric restriction are unavailable, with the exception of the two employees at Facility G [Akpinar-Elci et al. 2004; Kreiss 2012]. One reason for the absence of pathophysiologic data is the previous focus of NIOSH investigators and clinicians on obstructive lung disease. Although the evolving literature now documents that obliterative bronchiolitis can manifest with normal or restrictive spirometry as well, NIOSH did not examine evidence for work-relatedness of restrictive disease and FEV_1 decline until reporting the findings in 2011 from medical surveillance data for flavoring Facility I [Kreiss 2014; NIOSH 2011]. A published case report exists of BOOP in an employee with exposure to spices and flavorings in making snack foods [Alleman and Darcey 2002] which has resulted in permanent impairment 10 years later [NIOSH unpublished data]; the role of flavorings in this case with restriction remains unclear. Because obstructive abnormalities are insensitive for pathologic obliterative bronchiolitis, future work should evaluate dyspnea and any spirometric abnormalities.

3.3 Rapid Lung Function Decline

Indirect and direct evidence shows that employees exposed to flavoring-related compounds can experience excessive lung function decline, whether within the normal range of spirometry or in those with either restrictive or obstructive

spirometric abnormalities. Indirect evidence comes from reviews of medical records and work histories of flavoring-exposed employees who developed obliterative bronchiolitis. In a case series summarizing the eight affected former employees and one additional current employee at the index microwave popcorn plant (Facility G), the median length of employment prior to symptom onset was 1.5 years; the median duration of employment was 2 years [Akpinar-Elci et al. 2004]. At a company that manufactured flavors for the baking industry (Facility A), two flavoring production employees developed respiratory symptoms and severe fixed airways obstruction within 7 months of starting work at the plant [NIOSH 1986]. Although these employees did not have baseline spirometry tests before they began working with flavorings, it is unlikely that their lung function was already significantly decreased when they started work. Production jobs such as preparing the oil and flavoring mixture for microwave popcorn production and mixing liquid and powder flavor ingredients in flavoring manufacture often require the employee to lift 50- to 100-pound containers. It is unlikely that employees could have performed such tasks if their lung function was already severely compromised when they started work. Some affected employees stopped working when they could no longer do the job because of severe shortness of breath on exertion, while others were relocated to less strenuous jobs [NIOSH 1986, 2007a, 2008]. Severe airways obstruction as seen in obliterative bronchiolitis is rare in the general population. Data from NHANES III show that, among individuals less than 50 years old (including both smokers and never-smokers), the prevalence of obstruction with an FEV_1 less than 40% of predicted is 0.1% (1 in 1,000 people) [CDC 1996].

Direct evidence that employees exposed to flavoring-related compounds can experience rapid lung function decline comes from exposed employees who have had serial spirometry tests. Normal average FEV_1 decline is about 30 mL/year, and percent predicted FEV_1 does not usually change in the absence of disease because the predicted value is age corrected [Redlich et al. 2014]. Three of the affected former employees from the index microwave popcorn plant (Facility G) had declines in their FEV_1 percent of predicted of approximately 20% to 30% over approximately 2 years [Akpinar-Elci et al. 2004]. NIOSH evaluated data from the eight NIOSH medical surveys at the index microwave popcorn plant for evidence of rapid lung function decline [Kanwal et al. 2011]. The investigators chose as the criterion for rapid decline a decrease in FEV_1 of 300 mL and/or 10% from an employee's initial (baseline) spirometry test to the employee's last spirometry test. This criterion was similar to a threshold developed based on a study of coal miners evaluated over time with spirometry of high technical quality in which the researchers concluded that "when healthy working males perform spirometry according to American Thoracic Society standards, a yearly decline in FEV_1 greater than 8% or 330 mL should not be considered normal…" [Wang and Petsonk 2004]. The sensitive criterion used by the investigators, who did not annualize declines, was chosen because of the potential severity of the irreversible health outcome and the high technical quality of the pulmonary function tests, which allows for a sensitive cutpoint. For their analysis of the data from the surveys at the index microwave popcorn plant, investigators excluded survey participants with fewer than three interpretable spirometry tests because interpretation of change over time based on only two tests is less reliable [Pellegrino et al. 2005].

Of the 88 survey participants who participated in three or more NIOSH medical surveys at the index microwave popcorn plant (Facility G) and had started working there prior to the

implementation of exposure controls ("Group 1"), 19 (22%) had FEV_1 declines of greater than 300 mL and/or 10% from their first to their last spirometry test. Four of these 19 employees had worked at some point in the mixing room, including one employee who experienced a 1,300-mL decline from the first test in November 2000 to the next test 5 months later; the next spirometry test 4 months after the second test showed an additional decline in FEV_1 of 600 mL, resulting in the employee leaving employment. This employee's FEV_1 continued to fall after leaving employment, with a total fall of 2,800 mL over 2.75 years, representing a decline from 96% of predicted FEV_1 to 39% of predicted FEV_1. In comparison to survey participants who began working at the plant before the company started implementing exposure controls, only 3 (7%) of 41 survey participants with three or more spirometry tests who were hired after the company began implementing controls ("Group 2") had FEV_1 declines of greater than 300 mL and/or 10% from their first to their last spirometry test [Kanwal et al. 2011]. Of the 27 Group 1 employees who participated in all eight medical surveys, mean annualized decline in FEV_1 in the first year of follow-up was 144 mL per year. Annualized decline in the second year of follow-up fell to 40 mL per year as exposures were controlled, and the annualized decline fell to 22 mL per year in the third year of follow-up, a rate of decline consistent with normal aging-related lung function decline [Kreiss 2007].

NIOSH identified rapid lung function decline at a flavoring plant where a production employee had developed severe fixed airways obstruction [NIOSH 2008]. Another flavoring production employee at this plant had borderline airways obstruction on his first spirometry test, which is defined as a normal FEV_1 with a FEV_1/FVC ratio below the lower limit of normal. This employee was found to have mild fixed airways obstruction on his second test 5 months later; his FEV_1 had declined approximately one liter in the 5 months between tests.

NIOSH found evidence of excessive lung function decline among flavoring production employees at a flavoring manufacturing company (Facility I) in Indiana [NIOSH 2011]. Diacetyl was used nearly daily in the plant and was measured in the air in many areas of the plant. In the course of an HHE at this facility, NIOSH reviewed results of spirometry tests obtained by the company on 112 production employees. Interpretable spirometry results were available for 106 current and former production employees. NIOSH compared the results of each employee's spirometry test to reference values based on U.S. population data on healthy nonsmokers from NHANES III [Hankinson et al. 1999]. The investigators calculated changes in FEV_1 over time for 70 employees with more than one spirometry test result. To assess abnormal excessive declines in FEV_1, they determined the average within-person variation in FEV_1 to be 5%. Using spirometry longitudinal data analysis (SPIROLA), a NIOSH freeware program that adjusts for data quality (within-person variation) and length of follow up [NIOSH 2010], NIOSH found that 19% (13) of employees with serial spirometry had excessive decline in FEV_1 based on a 12.4% longitudinal decline supplemented by a reference decline of 30 mL/year. Five of the 13 still had spirometry values within the normal range despite their excessive declines. Employees currently working in areas with higher potential of flavorings exposure had 7.0-fold odds (later corrected to 5.8) [Kreiss 2014] of having excessive FEV_1 decline (95% CI 1.3–38.2, corrected to 1.2–28.8) in comparison to employees who were not currently working in areas with higher potential for exposure. The areas with higher potential for flavorings exposure included dry blend, extract and distillation, liquid compounding, process flavors, and spray dry areas. The

employees in these areas had 2.8 times greater average annual declines in FEV_1 than employees in other areas. The 18 production employees who had annual tests for 4 years (2006–2009) had average changes in their percent predicted FEV_1 and FVC measurements that declined in parallel with stable FEV_1/FVC ratios suggestive of an average tendency toward evolution of restrictive spirometry. Historical measurements of diacetyl and other flavoring compounds were insufficient to evaluate quantitative exposure-response relations. NIOSH also found a high prevalence (28%) of a restrictive pattern on spirometry tests in this workforce (section 3.2.3).

Company-sponsored re-analyses of the longitudinal spirometry data using generalized estimating equation models were interpreted as not showing any exposure-related declines in longitudinal spirometry measures [Ronk et al. 2013]. However, as noted earlier, the paper used an internal control group of production employees with diacetyl exposure as a control group, assumed zero tenure (reflecting zero exposure) for subgroups in the lower potential for exposure "control" group, and an exchangeable correlation structure for modeling that is not suitable for differing intervals of spirometric measures. See section 3.2.3 for further details.

The California Department of Public Health received serial spirometry test data for 416 flavor manufacturing employees administered from 2004 until early 2009, of whom 9.6% (40) had abnormal FEV_1 decline [Kreiss et al. 2012]. Abnormal FEV_1 decline rates (per person-month of follow up) were greater at companies using ≥ 800 lbs/year diacetyl than at companies using lesser amounts (7.3 versus 3.0 per 1,000 person-months, $P = 0.01$) and greater in companies previously shown to have four-person clusters of spirometric obstruction than at companies with no or only one employee with obstruction. Using only high quality serial spirometry data on a subset of 289 employees, 21 (7.3%) had abnormal decline using the 4% within-individual variation that characterized this subset [NIOSH 2010]. Only one of the 21 had airways obstruction; this employee lost 23.9% (−980 mL) of his baseline FEV_1 over 25 months. Only five of the 21 employees had abnormal restrictive spirometry on one or more tests, three of whom developed restriction on their last test. The remaining 15 employees with excessive FEV_1 decline were within the normal range of FEV_1. The greatest annualized FEV_1 decline in the group with good quality data was −2534 mL/year (−1700 mL in 8 months), and the average annualized FEV_1 loss in this group was −85 mL/year. The mean FEV_1 change for employees in companies using ≥ 800 lbs/yr of diacetyl was −113.6 mL/yr compared to −51.6 mL/yr in companies using less diacetyl ($P = 0.06$).

Other investigators have examined rapid declines in flavoring-exposed or diacetyl-exposed employees. The bronchiolitis obliterans syndrome cases identified in the Dutch diacetyl manufacturing plants had accelerated declines in FEV_1, with one case having an annualized decline of 175 mL/year from 1995 to 2003 [van Rooy et al. 2007]. In contrast, in a microwave popcorn manufacturing cohort studied over 12 months, no relationship was demonstrated between current exposure level (dichotomized at 0.05 ppm) and an abnormal decrease in FEV_1 (found in 7% of employees using a criterion of a greater than 320 mL or 8% decline over one year), adjusted for pack-years of smoking and body mass index [Lockey et al. 2009].

As indicated in the studies above, different approaches have been used by investigators over time to define excessive or rapid decline in FEV_1. These include percentage decline with various criteria, absolute decline with various criteria, normative population-based criteria for longitudinal limits of decline over various time intervals, and spirometry quality-adjusted

criteria, all of which are discussed in Chapter 9, section 9.5.

3.4 Asthma

At the index microwave popcorn plant and at one of the other five microwave popcorn plants that NIOSH evaluated (Facilities G and L), the prevalence of self-reported physician-diagnosed asthma was approximately two times higher than expected [NIOSH 2004b, 2006]. This suggests the possibility that some employees exposed to diacetyl and other flavoring compounds may be at increased risk for asthma (reversible airways obstruction) while others might be at risk for obliterative bronchiolitis (fixed airways obstruction). However, few of the survey participants with airways obstruction at these two plants who were administered a bronchodilator medication had a significant response (i.e., their airways obstruction was fixed); therefore, it is possible that some of these individuals had a different lung disease and that asthma may have been a misdiagnosis. Some employees at microwave popcorn plants and flavoring plants who were initially diagnosed with asthma were ultimately found to have fixed airways obstruction and other findings consistent with obliterative bronchiolitis [Akpinar-Elci et al. 2004; van Rooy et al. 2007].

It is possible that individuals with pre-existing asthma may experience an exacerbation of their asthma due to the irritant properties of diacetyl or similar vapors. Many asthmatics react nonspecifically with bronchospasm to strong odors. Diacetyl has been reported to be a sensitizer in a rodent local lymph node assay, and other diketones, including 2,3-pentanedione, 2,3-hexanedione, 3,4-hexanedione and 2,3-heptanedione, have similar potency as sensitizers [Anderson et al. 2013]. Some aldehydes found in flavoring manufacturing plants are sensitizers. If sensitization to diacetyl or another chemical were to occur in a susceptible individual, that individual might develop allergic-type asthma, with diacetyl exposure triggering airways obstruction and respiratory symptoms. In the coffee manufacturing plant investigation (Facility R), evidence for occupational asthma among current and former employees consisted of sensitization to coffee and castor bean antigens known to be exposures in the industry, and exacerbation of asthma was reported in relation to roasting area smoke and dusts [Bailey et al. 2015].

NIOSH conducted an HHE at a small plant (Facility M) where employees popped popcorn in heated oil and applied flavorings (including butter flavorings) prior to packaging [Sahakian et al. 2008]. Before 2002, they had used diacetyl-containing salt, and they used butter-flavored oil at the time of the survey. All three employees (lifelong nonsmokers) who had ever worked at the company developed respiratory disease while working there. One former employee had a mixed pattern of airways obstruction and restriction on spirometry; the airways obstruction was responsive to administered bronchodilator. This employee eventually died as a result of his respiratory disease. "Status asthmaticus with acute cardiopulmonary arrest" was listed as the primary diagnosis on the hospital discharge summary. Of the two other employees who had symptoms of asthma, one had an FEV_1 that improved by 480 mL (11%) and an FVC by 510 mL (8%) within the normal ranges after bronchodilator administration. The other employee had abnormal airways resistance of 322% of predicted; 19% improvement of the mid-maximal forced expiratory flow after bronchodilator; and improvement in FEV_1 of 6% after bronchodilator. While employed at the plant, all three employees experienced worsening of their respiratory symptoms on the days they worked. HRCT scans of the chest showed findings suggesting possible bronchiolitis obliterans in the employee who died and in one of

the other two employees. Air sampling results indicated that aldehydes were the predominant type of VOC in the plant air during production processes. Air samples obtained with thermal desorption tubes and analyzed with gas chromatography/mass spectrometry according to NIOSH Method 2549 showed that diacetyl was present in the plant air. However, the 2-hour and 4-hour diacetyl concentrations were less than the minimal detectable concentrations of 0.02 and 0.01 ppm respectively with NIOSH Method 2557 [NIOSH 2007b].

3.5 Mucous Membrane Irritation (Eye, Upper Respiratory)

Eye, nose, and throat irritation has been frequently reported by employees in NIOSH medical surveys at microwave popcorn plants and flavoring manufacturing plants. At the index microwave popcorn plant (Facility G), among employees who started work in microwave popcorn production prior to the implementation of exposure controls, approximately 65% reported eye, nose, or throat irritation on their first medical survey. Only 33% of these employees reported eye, nose, or throat irritation on their last survey after exposures had declined. Microwave popcorn packaging area employees who started work after exposures had declined had a similar lower prevalence of irritant mucosal symptoms (25%) [NIOSH 2006]. At the two small microwave popcorn plants NIOSH evaluated (Facilities J and O), most employees reported eye and/or nasal irritation [NIOSH 2003b, c]. At one of these two plants (Facility J), several employees developed severe eye irritation and blurred vision when the company started using a new butter flavoring [NIOSH 2003b]. After the company stopped using the new flavoring and halted production for several days, the employees' eye problems resolved. At one of the large microwave popcorn plants NIOSH evaluated (Facility K), management implemented use of full-facepiece respirators for mixing room employees soon after the company began producing microwave popcorn (before the respiratory hazard from butter flavoring vapors had been recognized), because these employees experienced severe eye irritation from butter flavoring vapors [NIOSH 2004a]. However, employees did not wear respirators consistently at all times during which they might be exposed [NIOSH 2004a]. At another microwave popcorn plant evaluated by NIOSH (Facility L), 83% of employees in the mixing room reported nasal irritation [NIOSH 2004b]. All laboratory and warehouse employees who participated in the NIOSH medical survey at a flavor manufacturer (Facility B) reported post-hire nasal irritant symptoms; 80% of employees in the production room and the laboratory reported post-hire eye irritation [NIOSH 2007a]. Of employees who had ever worked in production at another flavor manufacturer (Facility C), 93% reported post-hire eye irritation [NIOSH 2008]. One employee reported eye burning from exposure to diacetyl and starter distillate during a NIOSH survey at a third flavoring producer (Facility D) [NIOSH 2009d].

3.6 Dermatologic Effects

Of the former employees who developed findings consistent with obliterative bronchiolitis while working at the index microwave popcorn plant (Facility G), one employee also developed a severe skin rash [Akpinar-Elci et al. 2004]. The employee developed thick keratotic plaques and fissures of the palms and soles, associated with dystrophic fingernails. Skin punch biopsy revealed mild acanthosis and spongiosis with focal superficial epidermal necrosis and an associated subepidermal dense lymphohistiocytic infiltrate. Patch testing showed early and late reactions to two butter flavorings and

late reactions to six other butter flavorings, all used in the plant. This employee's dermatitis improved when he stopped work.

Prevalences of reported post-hire skin problems at microwave popcorn plants and flavoring plants have ranged from 12% at one of the six microwave popcorn plants (Facility N) NIOSH evaluated [NIOSH 2003a] to 36% among production employees at a flavoring plant (Facility B). Post-hire skin problems were reported by 60% of employees who primarily made liquid flavorings at this plant [NIOSH 2007a].

3.7 Discussion

Medical evaluations of employees who have developed progressive shortness of breath while working at several microwave popcorn plants and flavoring plants have shown findings consistent with the severe irreversible lung disease obliterative bronchiolitis. Some affected employees have experienced extremely rapid declines in lung function, with severe airways obstruction occurring within several months of the start of exposure to flavoring compounds [Akpinar-Elci et al. 2004; NIOSH 1986]. Whether restrictive lung disease is part of the spectrum of obliterative bronchiolitis in flavoring-exposed employees remains incompletely evaluated, although restrictive spirometry has been a common finding; in one plant, excessive FEV_1 declines in a restrictive pattern appear to be associated with potential for flavorings exposure. Employees as young as 22 years old have been affected by obstructive disease. Some affected employees have been placed on lung transplant waiting lists by their physicians because of the severity of their disease [Akpinar-Elci et al. 2004], and some flavoring-exposed employees have received lung transplants. The findings from investigations and studies conducted at multiple plants have revealed a link between exposure to diacetyl and risk for severe occupational lung disease. These findings meet the criteria that are often used to determine if the results of multiple studies indicate that an exposure is the likely cause of specific health effects [Gordis 1996; Hill 1965].

The first of these criteria is *temporality*: the exposure precedes disease development. Evidence of this comes from the many instances where initially asymptomatic diacetyl-exposed employees developed progressive shortness of breath within months of starting work and then were found to have severe fixed airways obstruction [Kreiss et al. 2002; NIOSH 1986; van Rooy et al. 2007]. Additionally, NIOSH documented rapid falls in lung function in exposed employees with initially normal spirometry at three plants [NIOSH 2006, 2008, 2011]. Lockey et al. reported at the 2002 American Thoracic Society International Conference that five flavoring employees who developed moderate or severe fixed airways obstruction had normal spirometry at the start of employment [Lockey et al. 2009]. California public health surveillance showed that excessive FEV_1 decline occurred in employees in flavor manufacturing plants that participated in a preventive program attempting to lower flavoring exposures [Kreiss et al. 2012].

Temporality requires the exposure to precede disease development, and the inverse is that new disease cases should decline in a population with *cessation of exposure*, an evaluation by intervention or "experiment". Follow-up medical and environmental surveys at the index microwave popcorn plant (Facility G) revealed evidence of decreased lung disease risk with control of exposures. In employees hired before exposures were controlled, the prevalences of respiratory symptoms and airways obstruction and mean percent predicted FEV_1 did not change significantly over time (consistent with an irreversible disease). However, employees hired after exposures were controlled had lower prevalences of respiratory symptoms

and airways obstruction and higher mean percent predicted FEV_1 on their first medical survey than employees hired before exposures were controlled, and these findings did not change significantly over time [Kanwal et al. 2011; NIOSH 2006]. Additionally, among 27 employees who participated in all eight NIOSH medical surveys from 2000 to 2003, annualized declines in FEV_1 improved from 144 mL per year to 40 mL per year to 22 mL per year, the last being consistent with normal aging-related lung function decline [Kreiss 2007]. Similarly, the former employee index cases with clinical bronchiolitis obliterans had stable FEV_1 within about 2 years of exposure cessation [Akpinar-Elci et al. 2004].

Another criterion is *strength of the association*: the magnitude of the apparent health risk due to the exposure. In analyses of data from the initial NIOSH medical survey at the index microwave popcorn plant (Facility G), the prevalence of airways obstruction among nonsmoking current employees was approximately 11 times higher than expected in comparison to national data from NHANES III. It was approximately three times higher than expected in older smokers [Kreiss et al. 2002]. In analyses of California flavoring employee surveillance data, the prevalence of severe airways obstruction was approximately three times higher than expected among all employees compared to national data. The prevalence in employees less than 40 years old was 15 times higher than expected [Kim et al. 2010].

The criterion of *replication of findings* (and *strength of the association*) between diacetyl exposure and development of severe occupational lung disease is apparent in the number of plants where employees have been affected and the number of production employees in these plants. The six microwave popcorn plants NIOSH evaluated represent a large segment of the microwave popcorn industry in the United States. Employees who developed findings consistent with obliterative bronchiolitis at these plants prepared the mixture of butter flavorings and soybean oil ("mixers") or worked nearby in the packaging area. Four of the six microwave popcorn plants NIOSH evaluated had affected mixers [Kanwal et al. 2006]. Each of these plants had one to three mixers per work shift at the time of the NIOSH HHEs. The occurrence of multiple cases of severe airways obstruction in such a small job category (approximately 20 mixers across the six plants) is far greater than expected when compared to the U.S. population prevalence of severe airways obstruction from NHANES III data (0.1%, or 1 in 1,000, in individuals less than 50 years old, including smokers and never-smokers) [CDC 1996]. A similar magnitude of risk exists in some flavoring companies. At least six flavoring production employees developed findings consistent with obliterative bronchiolitis at three flavoring plants (Facilities A, B, and C) where NIOSH conducted medical surveys. There were approximately 30 production employees across these three plants at the time of the NIOSH HHEs [NIOSH 1986, 2007a, 2008].

Consistency is also supported by the occurrence of lung disease consistent with obliterative bronchiolitis in diacetyl-exposed employees in at least eight flavoring manufacturing plants, a diacetyl production plant, a cookie manufacturing plant, and a coffee production plant [Akpinar-Elci et al. 2004; CDC 2007; Kanwal et al. 2006; Kim et al. 2010; NIOSH 1986, 2007a, 2008; van Rooy et al. 2007]. Private consultants who conducted medical and environmental surveys at four microwave popcorn plants owned by one large food company also found in their data analyses that a history of working as a mixer and higher cumulative exposure to diacetyl were associated with decreased lung function [Lockey et al. 2009].

Additional criteria to support a causal link between diacetyl exposure and severe lung

disease include *biologic plausibility, dose-response relationship,* and *consideration of alternate explanations. Biologic plausibility* is supported by experimental studies of diacetyl toxicity summarized in Chapter 4.

NIOSH found evidence of a *dose-response relationship* (i.e., worse lung disease or more employees affected with higher diacetyl exposure) in analyses of medical survey data from the index microwave popcorn plant (Facility G) and in analyses of aggregated data from medical surveys at the index plant and five additional microwave popcorn plants. The analyses of data from the initial survey at the index plant showed an increasing prevalence of abnormal spirometry with increasing quartiles of estimated cumulative diacetyl exposure [Kreiss et al. 2002]. Analyses of aggregated data from surveys at the six microwave popcorn plants showed higher prevalences of respiratory symptoms and worse lung function in mixers with more than 12 months experience and in packaging area employees at plants where heated tanks of oil and flavorings were not adequately isolated, compared to less exposed comparison groups [Kanwal et al. 2006]. Additional evidence of a *dose-response relationship* was found in analyses of California flavoring employee surveillance data. An analysis of obstruction by amount of plant diacetyl use showed that there were 16 employees with obstruction in four companies that used more than 800 pounds of diacetyl annually compared to two employees with obstruction in companies that used less diacetyl (prevalence of 5.3% versus 1.2%), for an OR of 4.5 (95% CI 1.03–19.9) [Kim et al. 2010].

In diacetyl-exposed employees with severe fixed airways obstruction and other findings of obliterative bronchiolitis, a *consideration of alternate explanations* should take into account the fact that while obstructive lung diseases such as asthma and smoking-related emphysema are common in the general population, severe airways obstruction is rare, especially in young individuals. Asthma is characterized by episodes of reversible airways obstruction—some individuals with severe or inadequately treated asthma can develop fixed airways obstruction. However, asthma does not appear to be a possible explanation for cases of severe lung disease among diacetyl-exposed employees for the following reasons:

(1) Most affected employees denied having any pre-existing lung disease or symptoms at the start of exposure.

(2) Once shortness of breath developed, it did not improve when employees were away from the workplace as would be expected in employees with occupational asthma (either new onset asthma or exacerbation of pre-existing asthma).

(3) Employees' illnesses did not improve when they took medications for asthma such as bronchodilators and corticosteroids.

(4) Most employees did not have a significant response to administration of bronchodilators in any of their spirometry tests (i.e., airways obstruction was fixed).

While some diacetyl-exposed employees who developed severe lung disease were smokers, the natural history of smoking-related disease and the results of medical evaluations of affected employees make it unlikely that the cases of severe fixed airways obstruction among diacetyl-exposed employees are smoking-related. Compared to the normal decline in lung function that occurs with aging (FEV_1 declines approximately 30 mL/year), in a subset of smokers lung function declines more rapidly (FEV_1 declines on average approximately 45–70 mL/year). An estimated 10%–15% of all smokers develop clinically important airflow obstruction [Ryu and Scanlon 2001]. Smokers who experience rapid lung function decline will typically start to become short of breath once their FEV_1 falls below 60% of predicted; this usually occurs

around age 50. Severe airways obstruction (e.g., FEV_1 less than 40% predicted) typically does not occur before 55–60 years of age [Wise 2008]. Several diacetyl-exposed employees developed severe fixed airways obstruction while still in their 20s and 30s. Any smoking history among these affected employees (as well as in affected employees younger than 50) would not explain their severe fixed airways obstruction. Additional evidence against smoking as a cause of severe lung disease in these employees is the fact that most employees' DL_{CO} measurements were normal. In airways obstruction due to smoking-related emphysema, DL_{CO} is reduced.

Obliterative bronchiolitis is known to occur as a result of a variety of infections, exposures, or nonpulmonary diseases. Examples include overexposure to highly irritating gases or vapors such as chlorine, ammonia, and nitrogen oxides or in association with connective tissue diseases such as systemic lupus erythematosus and rheumatoid arthritis, or in organ transplant recipients. The diacetyl-exposed employees who developed severe fixed airways obstruction did not have histories or medical evaluation findings to suggest that they had developed obliterative bronchiolitis from another exposure or medical condition. Airways obstruction can also occur due to diseases that affect other airways besides the bronchioles such as bronchiectasis or upper airway lesions [Ryu and Scanlon 2001]. However, individuals with airways obstruction from such other causes typically have characteristic history, physical exam, and medical test findings that usually serve to reveal the nature of the illness (e.g., copious sputum in someone with bronchiectasis or evidence of upper airway obstruction on spirometry). Such findings were not apparent in diacetyl-exposed employees who developed severe fixed airways obstruction.

Investigations of severe lung disease consistent with obliterative bronchiolitis among diacetyl-exposed employees have provided substantial evidence of a causal relationship between diacetyl exposure and development of this disease. Exposure preceded disease development, and lung disease risk decreased with control of exposures. Analyses of data from workplace medical and environmental surveys revealed a strong, consistent association of the disease with diacetyl manufacture, use of diacetyl in flavoring production, and use of diacetyl-containing butter flavorings in microwave popcorn production. The investigations have also shown evidence of a dose-response effect, and animal and other laboratory studies have provided evidence of biologic plausibility. Medical evaluations of affected employees did not identify alternative explanations for their illness besides their workplace exposure to diacetyl and other flavoring compounds. Accordingly, the criteria for interpreting epidemiologic associations as causal have all been met by the body of investigation presented in this criteria document for a recommended standard.

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