9 Medical Monitoring and Surveillance of Exposed Employees

Despite attempts to control exposure to diacetyl, 2,3-pentanedione, and similar flavoring compounds, some employees may develop health effects as a result of insufficient control, additive effects, intermittent peak exposures, susceptibility, unmeasured flavoring compounds in powdered form, or unrecognized hazardous exposures. Medical monitoring and surveillance of employees exposed to diacetyl and similar flavoring compounds are important, as these employees are at risk of rapidly developing severe irreversible lung disease. The rapid onset and progression of diacetyl-related lung disease requires that more frequent medical monitoring evaluations be done than for slowly progressive occupational lung diseases such as silicosis and coal worker's pneumoconiosis. The most important component of an effective medical monitoring program for an employee exposed to diacetyl and similar flavoring compounds is to carefully follow spirometry test results over time, comparing current to past test results to identify excessive declines in lung function [California Department of Public Health 2012]. Spirometry tests must be of high quality to allow valid interpretation of lung function changes over time. This chapter provides information on how to conduct effective medical monitoring of these employees. The chapter also provides examples that illustrate how medical surveillance can identify workplace risk factors.

Medical Monitoring

Medical monitoring of employees, sometimes called medical screening, involves periodic medical follow up for early detection of work-related disease. The intended benefit of early detection is to identify disease in early stages when steps can still be taken to prevent progression from pre-clinical to clinical disease or from milder to more symptomatic disease. This approach is called secondary prevention because it attempts to ameliorate or at least halt the progression of health effects that have already occurred. Evidence of early disease identified through medical monitoring serves as a sentinel event or warning that other employees might be at risk for the same exposures and outcomes. This warning should stimulate efforts to evaluate the workplace to identify possible risk factors for exposures that can be controlled. Systematic evaluation and use of medical monitoring data obtained from individual employees to better protect a population of employees is an important component of the overall medical surveillance program. This approach contributes to the goal of primary prevention, to prevent disease from developing in other employees.

Medical Surveillance

The systematic analysis of aggregated results over time constitutes medical (epidemiologic) surveillance of trends in symptoms or functional changes that can be assessed in relationship to jobs, tasks, and exposures [Silverstein 1990]. For medical monitoring to serve surveillance purposes, a formal process should be in place to assure that data from a screened employee population is evaluated in aggregate at regular intervals. Epidemiologic analysis of medical

results and questionnaire and/or administrative data to evaluate for possible risk factors for disease can result in understanding what actions need to be prioritized to decrease the risk of subsets of employees and can document the effectiveness of interventions over time in preventing flavoring-related health effects.

9.1 Medical Monitoring Program Director

The medical monitoring program director should be a licensed physician with training and experience in identifying and preventing occupational lung disease. This is because flavoring-related lung disease can progress rapidly and have grave consequences, so it is important to assure that the medical monitoring program director can quickly evaluate clinical data and make medical judgments about appropriate diagnostic and therapeutic measures, including medical removal. This individual (hereafter referred to as "the medical monitoring program director") should ensure that the monitoring program collects high quality data, including relevant questionnaire data and high quality spirometry tests that adhere to ATS/ERS technical guidelines for spirometry [Miller et al. 2005], or the most recent equivalent guidelines. The medical monitoring program director should also ensure that medical monitoring data is appropriately evaluated for surveillance purposes, including evaluation of aggregated results to identify risk factors and opportunities to better prevent flavoring-related lung disease.

The employer should ensure that the medical monitoring program director is familiar with the natural history of flavoring-related lung disease and is knowledgeable about operating a spirometry program that maintains high test accuracy, precision and validity. The employer should provide the following to the medical monitoring program director:

- A copy of the NIOSH Alert, "Preventing Lung Disease in Workers Who Use or Make Flavorings" [NIOSH 2003];
- A copy of this criteria document;
- A description of work areas, job categories, and work tasks;
- A description of any personal protective equipment to be used by employees; and
- Results of any environmental sampling related to potential flavorings exposures.

9.2 Employees to Include in the Medical Monitoring Program

All permanent, temporary, and contract employees who work in or enter areas where diacetyl, 2,3-pentanedione, or similar flavoring compounds or products that contain these compounds are used or produced should be included in the medical monitoring program. Employees who work in or enter these areas for a total of 40 or more hours per year should be included in the medical monitoring program. In addition to production employees, employees who are periodically exposed such as supervisors, warehouse employees, laboratory employees, quality assurance/control employees, shipping and receiving employees, maintenance employees, janitorial employees, and office employees should also be included in the program, as employees with lung function abnormalities were identified in nonproduction jobs during several NIOSH HHE investigations [Kanwal et al 2006; Kanwal et al 2011]. Employees with past experience in such jobs or performing such duties should be included in the monitoring program for one year and longer if abnormalities are present [California Department of Public Health 2012].

To achieve the intent of primary and secondary prevention, employers have an interest in

attaining a high rate of employee participation in regular medical monitoring. Voluntary participation should be encouraged at a time and place convenient to employees and should be provided at no cost to employees.

9.3 Medical Monitoring Program Elements

The medical monitoring evaluation should include a questionnaire to obtain health and exposure information and spirometry to assess lung function. The questionnaire data from all employees in a medical monitoring program should be entered into a database along with spirometry results for use in epidemiologic analyses for medical surveillance. These analyses may reveal associations between health outcomes and exposure variables such as work tasks and practices that can be addressed to decrease lung disease risk (see section 9.9).

9.3.1 Questionnaire

The purpose of the questionnaire is to obtain standardized information on demographics, work history, exposures, personal risk factors such as smoking and health history. The medical monitoring program director can use information from the questionnaire when assessing the employee at each evaluation. Because employees with biopsy-documented obliterative bronchiolitis may have normal spirometry, chest symptoms such as exertional shortness of breath merit attention as suggestive of an occupational lung condition requiring employee education and follow up. Similarly, persons with abnormal spirometry, despite absent chest symptoms, may have occupational lung disease requiring attention.

Work history questions should allow employees to correctly indicate the specific job titles they have held at their current employer. For each job title, the questionnaire should collect information on specific work tasks and practices that may affect the employee's exposure to diacetyl and similar flavoring compounds. For example, for an employee whose job requires direct handling of diacetyl-containing flavorings, specific questions might address how often a particular task is performed, the amounts of flavorings used, whether open or closed containers of flavorings are used, and whether respiratory protection is used, including the type of respirator used and when it is worn. To help the medical monitoring program director develop appropriate questions on jobs and exposures, the employer should provide the medical monitoring program director with the specific job titles of potentially exposed employees, a description of the work tasks for each job that may be associated with potential for exposure to diacetyl and similar flavoring compounds, and the types of personal protective equipment (e.g., respirators) and other measures that employees have available to them to minimize exposures in each job. A visit to the plant by the medical monitoring program director to view the production process may provide additional useful information for questionnaire development.

The questionnaire should contain questions on the presence or absence of respiratory symptoms such as shortness of breath on exertion, cough, and wheezing; respiratory illnesses such as asthma, emphysema, chronic bronchitis, and COPD; and the dates of diagnosis. Additional questions might inquire about work-related nasal, ocular, and dermal symptoms. The American Thoracic Society Respiratory Symptom Questionnaire [Ferris 1978] or the NHANES III questionnaire [CDC 1994] can provide standardized questions. Examples of questions NIOSH has used in HHE medical surveys of flavoring-exposed employees can be

found in NIOSH HHE reports at http://www.cdc.gov/niosh/hhe/.

While respiratory symptom information is important in the assessment of employees exposed to diacetyl and similar flavoring compounds or products that contain these compounds, the medical monitoring program director should not conclude that an employee's exposures are below harmful levels solely by the absence of respiratory symptoms. Employees may not experience respiratory symptoms early in the course of excessive lung function decline. NIOSH medical surveys of flavoring-exposed employees have identified airways obstruction [Kreiss et al. 2002] and excessive declines in lung function [NIOSH 2008] in employees who did not report respiratory symptoms. Similarly, about half of the employees with airways obstruction found in surveillance of California flavoring manufacturing employees had no chest symptoms [Kim et al. 2010]. Absence of symptoms does not negate the need for clinical differential diagnosis and evaluation of employees with spirometric abnormalities.

The medical monitoring program director should counsel employees identified as having pre-existing lung disease on their initial evaluation regarding the potential risks of working in areas where they may be exposed to diacetyl and other flavoring compounds. The medical monitoring program director should also explain that it may be hard to determine the relative contributions of work exposures vs. pre-existing lung disease to any future abnormal lung function declines. Such employees should also be referred to their personal physician for additional evaluation and recommendations regarding potential exposure to these substances.

9.3.2 Spirometry

Every employee in the medical monitoring program should have a spirometry test at each evaluation irrespective of respiratory symptom status. Evaluation of lung function over time is the most important component of medical monitoring for identifying possible work-related lung disease in employees exposed to diacetyl and similar flavoring compounds (see section 9.6). High quality spirometry tests are necessary to allow the medical monitoring program director to correctly interpret the results and make appropriate recommendations to the employee and the employer. Accurate spirometry measurements depend on four key elements: (1) a trained technician who can obtain valid test results, (2) a reliable and accurate spirometer, (3) an approved testing protocol, and (4) a spirometry quality assurance program directed by a laboratory supervisor or the medical monitoring program director.

9.3.2.1 Persons administering the spirometry examination

Each person administering spirometry examinations should successfully complete a NIOSH-Approved Spirometry Training Course (information at http://www.cdc.gov/niosh/topics/spirometry/training.html) or equivalent and maintain valid certificates. The medical monitoring program director may also benefit from this training. The ATS/ERS [Miller et al. 2005] and the American College of Occupational and Environmental Medicine (ACOEM) [Townsend 2011] endorse the content of NIOSH-approved spirometry training and also recommend refresher training for spirometry technicians. Both the ATS/ERS and ACOEM recommend ongoing review of spirometry tests for quality after training to identify and correct any aspects of the technician's performance that have resulted in poor quality tests. The medical monitoring program director should provide for ongoing review of test quality and feedback to technicians about opportunities for improvement. The combination of initial training, refresher training, electronic feedback from spirometers during

testing, and ongoing review of test quality with timely feedback to technicians can help a program achieve a high proportion of technically acceptable spirometry tests [Redlich et al. 2014]. Certification of acceptable spirometry test administration is an additional means of addressing quality concerns (National Board for Respiratory Care [NBRC 2016]; American Association for Respiratory Care [AARC 2011]).

9.3.2.2 Spirometer specifications

Spirometry testing equipment should meet the ATS/ERS guidance for standardization of spirometry or most recent equivalent [Miller et al. 2005], specifications for spirometer accuracy and precision, and real-time display size and content. Written verification from a third party testing laboratory (not the manufacturer or distributor) that the model of spirometer being used has successfully passed its validation checks as required by the most current ATS/ERS protocol should be requested from the spirometer manufacturer.

9.3.2.3 Spirometry testing protocol and reporting information

Administration of spirometry tests should follow the ATS/ERS guidance for standardization of spirometry or most recent equivalent

Testing Procedures	1. Spirometer calibration checks should be performed using a currently calibrated (per manufacturer recommendations) 3-liter syringe on each day of testing [Miller et al. 2005]. A copy of the spirometer calibration report should be maintained in either electronic or hard copy form. 2. Spirometry should be performed in the same documented position (either sitting or standing) during the baseline and all subsequent tests. 3. A minimum of three forced exhalation maneuvers producing "acceptable curves" on the spirometry report should be characterized by the following: ▪ Lack of hesitation (back-extrapolation volume should be less than 5% of FVC or 150 mL, whichever is larger) ▪ No cough in the first second of the maneuver ▪ No evidence of airflow cessation, variable effort, leak, obstructed mouthpiece, positive or negative zero flow error(s), or extra breath(s) ▪ Acceptable end-of-test criteria (≤ 25 mL increase in volume for 1 second or a maneuver longer than 15 seconds) 4. Less than 150 mL difference between the two highest FVC measurements and the two highest FEV_1 measurements is the goal.
Spirometry Predicted Values	If spirometry software allows a choice of predicted values, NHANES III or the most recent equivalent should be used [Hankinson et al. 1999] as they are based on a large sample of the U.S. population. Because predicted values are not available from NHANES III for Asian people born in the United States, these predicted values may be estimated by multiplying the NHANES III Caucasian predicted values for FEV_1 and FVC by 0.88 [Hankinson et al. 2010; Redlich et al. 2014]. In the future, it will be preferable to use Asian-specific equations for predicted values, such as from NHANES Plus data, when they are available. If spirometry software does not include lower limits of normal values, the spirometry reference value calculator at http://www.cdc.gov/niosh/topics/spirometry/RefCalculator.html can be used to calculate lower limits of normal for NHANES III reference values.

Figure 9-1. Spirometry guidelines for testing procedures and interpretation

[Miller et al. 2005]. These guidelines outline the criteria to follow to ensure overall test results are valid (Figure 9-1). The technician should be able to view real-time testing displays as specified in the most recent ATS/ERS spirometry standardization. On-site back-up of the results should include spirometry test reports and retention of all spirometry test results in printed or electronic format. Spirometry test reports for the employee's health record should contain, at a minimum, the employee's age, height, sex, race, and weight; numerical values and volume-time and flow-volume spirograms for at least the three best valid expiratory maneuvers; normal reference value set used; employee position during testing (standing or sitting); dates of test and last calibration check; ambient temperature and barometric pressure (volume spirometers); and the technician's unique identification number or initials. The name, postal mailing and contact e-mail addresses, and telephone and fax numbers of the facility completing the spirometry test results and forms should also be recorded.

9.3.2.4 Spirometry quality assurance

A comprehensive spirometry quality assurance program is necessary to minimize the rate of invalid test results. This program should include all of the following components: instrumentation calibration checks, automated maneuver and test session quality checks, and ongoing monitoring of test quality. Testing personnel should be fully familiar with and adhere to the current ATS/ERS guidelines for instrument calibration check procedures. Calibration check procedures should include daily (day of testing) leak checks (for volume spirometers) and volume accuracy checks (performed at different speeds of injection for flow spirometers) and according to the frequency established by the current ATS/ERS spirometry standardization statement. Instrument calibration check records should be maintained by the provider for as long as the related employees' medical reports are maintained. Spirometer software should automatically perform quality assurance checks on expiratory maneuvers during each spirometry testing session. Messages should alert the technician to maneuver acceptability errors and test session nonrepeatability. Each spirometry test session should have the goal of obtaining three acceptable with two repeatable forced expiratory maneuvers, as defined by the current ATS/ERS spirometry standardization statement. Because all spirometry software packages are not able to identify all the possible technical errors encountered during testing, NIOSH developed a poster that provides guidance to identify and correct common testing errors and improve spirometry test quality [NIOSH 2011a]. This document has been translated into several languages and can be accessed at http://www.cdc.gov/niosh/docs/2011-135/. Providers should utilize physicians or other qualified healthcare professionals with expertise in evaluation and interpretation of spirometry to conduct ongoing monitoring of test quality. Determination of quality requires review of the flow-volume and volume-time curves for each acceptable maneuver and comparison of the two highest FEV_1 and FVC measurements [Townsend 2011]. When suboptimal quality tests with potential for improvement are identified, the reviewing physician or other appropriate healthcare professional should provide feedback to the appropriate technician(s) along with specific suggestions for improvement. Some studies have found evidence that providing regular feedback to technicians improves test quality and decreases variability. In two studies where extensive feedback was provided to technicians on the quality of their tests, the investigators found lower measures of variability for their test measurements than in other studies where extensive feedback to technicians was not provided [Enright et al. 1991; Malmstrom et al. 2002]. In these studies, the technicians received immediate feedback from the spirometry device

on the acceptability of a forced exhalation maneuver and on the overall quality of the test. The investigators also provided ongoing review of the quality of their tests and gave feedback to the technicians; additional technician training was provided as needed. Test quality in these studies was graded using an A, B, C, D, F scale. In a study of a workplace spirometry testing program, use of a new spirometer that provided technicians with feedback during the test led to increases in the mean FEV_1 and mean FVC of the study group, compared to use of an older spirometer without feedback capability [Banks et al. 1996].

With poor quality tests, some employees' results that are truly normal may be considered abnormal, and employers may incur costs for lost work time in follow-up testing and clinical evaluation. In addition, employees may suffer needless worry, risks of unnecessary medical tests, and may be subject to workplace discrimination or even job loss. An example of an incorrect interpretation due to a poor quality test is the finding of a restrictive abnormality because the test subject did not exhale long enough during the maneuver; this results in a falsely low FVC. High quality spirometry tests are also necessary for comparison of spirometry results over time, an important consideration for flavoring-exposed employees. Low quality spirometry has greater variability in test results; over time, decreased precision may cause the medical monitoring program director to incorrectly identify whether an employee has had an excessive decline in lung function from one test to the next.

In reviewing the quality of spirometry tests performed for employers by private healthcare providers, NIOSH has identified instances where the quality of most tests was poor and thus not useful for assessing lung function changes over time [Kanwal et al. 2011; Kreiss et al. 2012; NIOSH 2004b, 2006]. High quality spirometry minimizes the variability in the results caused by technical aspects (i.e., how the test was conducted) so that changes in spirometry measurements over time reflect true changes in lung function more accurately. In California public health surveillance, only one of 13 commercial providers of surveillance spirometry for flavoring employees who reported results to the California Department of Public Health met a minimum quality criterion of 80% of test sessions with FEV_1 of good quality [Kreiss et al. 2012]. Employers of flavoring-exposed employees should be aware of the characteristics of high quality spirometry programs so they can evaluate the quality of spirometry services offered by medical providers, monitor performance, and take corrective actions if necessary. OSHA and NIOSH have published an information sheet on spirometry for employers [NIOSH 2011b].

9.4 Frequency of Medical Monitoring Evaluations

Newly hired employees and current employees should have baseline evaluations before they are allowed to work in or enter areas as previously described where they may be exposed to diacetyl, 2,3-pentanedione, or similar flavoring compounds. Employees in the medical monitoring program should be evaluated with a questionnaire and spirometry every 6 months due to the potentially rapid development of flavoring-related lung disease [Redlich et al. 2014]. If an employee exposed to diacetyl or similar flavoring compounds is identified as likely having lung disease from this exposure, then all employees who perform similar job tasks or have a similar or greater potential for exposure should be evaluated every 3 months. More frequent evaluation (every 3 months) is also appropriate for employees with excessive decline in FEV_1 and similarly exposed employees. Identification of flavoring-related lung disease or excessive FEV_1 decline should

also trigger an environmental assessment to identify and correct potential sources of hazardous exposures. Although interpretation of excessive decline is challenging for short intervals between testing because of measurement error, the increased numbers of tests may facilitate improvement of spirometry quality and increasing monitoring physicians' confidence in trends that may be occurring. The 3-month schedule should be maintained until factors that may have led to excessive exposure have been corrected and 12 months have passed during which no additional employees with likely flavoring-related lung disease are identified. Employees should be instructed to report to their occupational health service or supervisor any new persistent or worsening shortness of breath, cough, wheezing, or other respiratory symptoms that last more than 6 weeks. Such employees should be immediately evaluated by the medical monitoring program director. All employees who have been in the monitoring program should have a final evaluation at the end of employment [California Department of Public Health 2012].

9.5 Reporting Medical Monitoring Results

The medical monitoring program director or designee should review and interpret questionnaire and spirometry results, including assessing spirometry quality. During an employee's scheduled visit for a medical monitoring program evaluation, the medical monitoring program director or designee should inquire about the employee's knowledge of the potential risk from exposure to diacetyl, 2,3-pentanedione, or similar flavoring compounds and of how to minimize the risk. The medical monitoring program director or designee should educate employees as needed [California Department of Public Health 2012], and encourage employees to report any new persistent respiratory symptoms to their supervisor or the monitoring physician. At the end of each evaluation visit or as soon as possible thereafter, the medical monitoring program director should provide the employee with a written report describing the following items:

- The results of any medical tests performed on the employee
- The medical monitoring program director's opinion regarding any abnormalities detected during the evaluation and recommendations for further evaluation and treatment
- Whether or not the employee has any detected medical condition which would place the employee at increased risk to health from exposure to diacetyl, 2,3-pentanedione, or similar flavoring compounds
- Recommendations, if necessary, for reducing the employee's exposure to diacetyl, 2,3-pentanedione, or similar flavoring compounds
- Any recommended limitation upon the employee's use of personal protective equipment.

The medical monitoring program director should inform the employer in writing of the following:

- Any recommendations for limiting the employee's workplace exposures (e.g., reducing exposure to diacetyl, 2,3-pentanedione, or similar flavoring compounds by removal, or limitations of the employee's duties or activities) or on the employee's use of personal protective equipment
- A statement that the physician has informed the employee of the results of the medical examination and any medical conditions that require further evaluation or treatment.

The specific condition, issue, or concern resulting in recommendations for limiting the employee's exposure to diacetyl, 2,3-pentanedione, or similar flavoring compounds or on the employee's use of personal protective equipment should not be specified in the write-up to the employer without the employee's consent. Also, any aspect of the employee's medical history that has no bearing on whether the employee should continue to work in areas where diacetyl, 2,3-pentanedione, or similar flavoring compounds are used should not be revealed to the employer. A copy of the medical monitoring program director's written opinion provided to the employer should also be provided to the employee.

9.6 Early Identification of Affected Employees

Early recognition of employees with lung disease due to exposure to diacetyl, 2,3-pentanedione, or similar flavoring compounds is essential to prevent rapid progression to severe irreversible disease. Identifying affected employees will also stimulate prevention efforts so that risk to other employees is minimized. The most effective means for identifying affected employees early is careful evaluation of results of serial spirometry tests of employees in the medical monitoring program. Symptom reports alone are not a reliable indicator of early disease, as many employees with early disease will be asymptomatic. However, symptom reports of exertional shortness of breath can reflect pathologic obliterative bronchiolitis even when spirometry remains normal [Kreiss 2013].

At each evaluation of an employee in the medical monitoring program, the medical monitoring program director should compare the results of the current spirometry test to the baseline (pre-exposure) test, or to the test with the highest values if post-hire spirometry values were higher than at baseline. The most important finding that may indicate development of lung disease from exposure to diacetyl, 2,3-pentanedione, or similar flavoring compounds is an abnormal decline in the FEV_1. An employee's longitudinal test results may reveal an abnormal decline in FEV_1 compared to baseline even when each individual test value is found to be normal because it is above the LLofN calculated from the reference population [Townsend et al 2011; Kreiss et al. 2012; Redlich et al. 2014]. While such test results might not meet the criteria for an abnormality such as airways obstruction or spirometric restriction, an abnormal decline in FEV_1 may indicate early disease in this case and should be further evaluated. Additionally, any new abnormality on spirometry compared to baseline should prompt further evaluation. Flavoring-exposed employees with obstructive abnormalities (FEV_1/FVC ratio and FEV_1 less than the LLofN) need additional medical tests to assess whether they have obliterative bronchiolitis. Employees with restrictive abnormalities (FVC less than LLofN and normal FEV_1/FVC ratio) also need additional medical tests to differentiate between nonlung causes and lung causes of spirometric restriction, including obliterative bronchiolitis [Ghanei et al. 2008; King et al. 2011; Markopoulou et al. 2002].

The criteria for an abnormal excessive decline in the FEV_1 depend on the quality of the spirometry tests performed as part of the medical monitoring program and the time period of follow-up [Redlich et al. 2014]. ATS/ERS and ACOEM have stated that a decline in FEV_1 over one year should exceed 15% before being considered clinically meaningful [Pellegrino et al. 2005; Townsend 2011]. By this criterion, someone with a baseline FEV_1 of 4 liters would

have to experience a decline of at least 600 mL for the results to be considered abnormal.

Because lung disease caused by flavorings can progress rapidly, it is useful to identify those potentially at risk before so much lung function is lost [Kreiss et al. 2002; NIOSH 2006, 2007]. Some studies indicate that when ATS/ERS criteria for spirometry quality are followed and high standards of quality are achieved, a threshold less than 15% can indicate an abnormally rapid decline in FEV_1 in a year. In a study that used data from a spirometry surveillance program for coal miners, Wang and Petsonk [2004] found that the 5th percentile for FEV_1 declines over 6 months in all employees studied was 320 mL (7.8%). In stable employees (those employees whose FEV_1 slope over 5 years was less than 90 mL/year), it was 300 mL (7.1%). In healthy employees (those employees without symptoms or methacholine responsiveness over 5 years), it was 280 mL (6.5%). The quality of spirometry data in this study reflected a within-person variation of 3% that is rarely achievable. Within-person variation of 6% is typical for spirometry programs, and an assumption of that level of variability was used by ATS to develop its recommendation for using 15% loss of FEV_1 as a threshold [Redlich et al. 2014].

In another study that used data with a within-person variation of 4% from a spirometry surveillance program for thousands of employees at a large chemical company, Wang et al. [2006] found that the 5th percentile values for FEV_1 decline for testing at one-year intervals were 380 mL (10.4%) in men and 280 mL (10.6%) in women. These studies suggest that in a medical monitoring program that follows ATS/ERS criteria and achieves high quality spirometry, an FEV_1 decline of 10% or higher in one year or less can be considered abnormal and used as a threshold for further medical evaluation of the employee. ACOEM now accepts this 10% criterion after allowing for expected average annual loss due to aging in high risk settings when the relationship between longitudinal results and endpoint disease is clear, as in flavoring-exposed employees [Townsend 2011]. Lower quality spirometry programs have the disadvantage of only being able to detect larger declines in FEV_1 as abnormal.

NIOSH has developed a computer program, SPIROLA, to help spirometry programs measure their within-person variation in FEV_1 as a measure of the precision of spirometry obtained by the spirometry providers (an indication of spirometry quality across the providers' programs). SPIROLA also provides a longitudinal limit of decline (LLD) for each individual tested, a threshold for determining abnormal loss of FEV_1 that is adjusted for the quality of the provider's spirometry program [NIOSH 2010]. The LLD allows the spirometry provider to determine if an individual's serial spirometry results suggest an excessive decline in lung function and allows higher quality programs to identify smaller changes in lung function as abnormal (http://www.cdc.gov/niosh/topics/spirometry/spirola-software.html). The advantage of using relative lower LLD and 5th percentile approaches over the 15% criterion in flavorings-exposed microwave popcorn employees has been demonstrated [Chaisson et al. 2010].

9.7 Continuity of Medical Monitoring

Employers may change medical providers of medical monitoring services. Employers should ensure that prior medical monitoring program directors transfer medical monitoring records, including spirometry tests and questionnaires, to new medical monitoring program directors. If necessary to gain access, employers or new providers should ask employees to sign releases allowing new providers to obtain previous medical monitoring and surveillance records from previous provider(s).

9.8 Tests Used in Medical Monitoring

9.8.1 Spirometry

The first step in evaluating an employee whose medical monitoring spirometry test shows either an excessive decline in FEV_1 (even if individual test results are still above the LLofN) or a new abnormality (e.g., obstructive, restrictive, or mixed spirometric abnormality) compared to baseline is to repeat the test within one month to confirm the change. If the repeat spirometry test confirms an excessive decline in FEV_1 or other abnormality, the employee should be referred for more extensive pulmonary function tests (PFTs) (described below). The medical monitoring program director may request these and other necessary tests or refer the employee to a pulmonary medicine physician at no cost to the employee.

9.8.2 Other Pulmonary Function Tests

The referred employee should receive complete PFTs that include spirometry with an assessment of bronchodilator response, DLCO, and static lung volumes. Most employees who have developed lung disease while being exposed to diacetyl and similar flavoring compounds have not had a response to bronchodilator [Akpinar-Elci et al. 2004; Kim et al. 2010]. In other words, they had fixed airways obstruction with an FEV_1 and/or FVC increase less than 12% and 200 mL after bronchodilator) [Pellegrino et al. 2005]. DL_{CO} in affected employees with airways obstruction has usually been normal, although some individuals with advanced disease have had a low DL_{CO} [Akpinar-Elci et al. 2004]. Lung volume measurements have shown a normal or elevated total lung capacity (TLC) and an increased residual volume, consistent with air trapping [Akpinar-Elci et al. 2004]. Individuals with moderate to severe airways obstruction may have a mixed obstructive/restrictive (reduced FEV_1, FEV_1/FVC ratio, and FVC) pattern of spirometry because air trapping decreases the FVC. The actual underlying physiology can be clarified by determining lung volumes.

9.8.3 High-resolution Computerized Tomography

Employees found to have fixed airways obstruction or other abnormalities on complete PFTs should have additional evaluation with a high-resolution computerized tomography (HRCT) scan of the chest with inspiratory and expiratory views. Heterogeneous air trapping during expiration has been the most common finding in flavoring-exposed employees with fixed airways obstruction. Other common findings include cylindrical bronchiectasis, bronchial wall thickening, and a mosaic pattern of attenuation. Centrilobular nodules may also be seen [Cox et al. 2014]. Patchy ground glass opacities have been observed less commonly. These findings may not be present despite obliterative bronchiolitis documented by biopsy [King et al. 2011]. HRCTs have not been systematically performed in flavoring-exposed employees with restrictive pulmonary function abnormalities or with excessive FEV_1 declines within the normal range of FEV_1. Specialist consideration of the diagnostic utility of this test is suggested.

9.8.4 Lung Biopsy

It is not routinely necessary to obtain a lung biopsy to diagnose obliterative bronchiolitis in employees exposed to diacetyl or 2,3-pentanedione when spirometry and HRCT results are consistent with the diagnosis. While some physicians might desire biopsy confirmation, it is important to recognize that the patchy nature of obliterative bronchiolitis and lack of familiarity of some pathologists with the techniques necessary to identify bronchiolar lesions may prevent identification of the disease on biopsy. HRCT has become the method of choice for assessing

bronchiolar morphology, often replacing surgical lung biopsy [King and Kinder 2008].

Physicians caring for another population at high risk for obliterative bronchiolitis, lung transplant patients, use a similar noninvasive approach. Obliterative bronchiolitis commonly occurs after patients receive a lung transplant. Because this disease is difficult to identify on biopsy, the International Society for Heart and Lung Transplantation developed 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 biopsy confirmation [Estenne et al. 2002]. The term bronchiolitis obliterans syndrome has also been applied to flavoring-exposed employees without surgical lung biopsies [Akpinar-Elci et al. 2004; van Rooy et al. 2007], but may lead to confusion because flavoring-related obliterative bronchiolitis differs in natural history from post-transplant bronchiolitis obliterans syndrome, which is relentlessly progressive.

There are some situations, described in the next section, where lung biopsy is appropriate for diagnosis. To obtain adequate tissue for diagnosis, a thoracoscopic or open lung biopsy should be obtained. Obtaining wedge biopsies from multiple lobes is recommended, as this approach increases the diagnostic yield [Devakonda et al. 2010]. Transbronchial lung biopsies are not useful for evaluating clinical obliterative bronchiolitis in employees exposed to diacetyl, 2,3-pentanedione, or similar compounds.

9.8.5 Determining Diagnosis Responsible for Lung Disease

Determination of the diagnosis responsible for lung disease in an employee exposed to diacetyl, 2,3-pentanedione, or similar flavoring compounds should take into account the changes identified in medical monitoring spirometry tests, the results of complete PFTs and of HRCT scans of the chest, the course of the employee's illness over time, and medical, work, and personal risk factor history.

In an exposed employee with evidence of clinical obliterative bronchiolitis on PFTs or HRCT scans and no other identifiable cause for the disease, biopsy is not necessary. The noninvasive clinical findings alone are sufficient to conclude that an exposed employee likely has clinical obliterative bronchiolitis and should no longer be exposed to diacetyl, 2,3-pentanedione, or similar flavoring compounds. When clinically apparent lung disease occurs in several employees at a particular plant, the need for biopsy confirmation in each employee is usually unnecessary.

When HRCT is normal in dyspneic employees, particularly if the PFTs are restrictive or normal, lung biopsy has a role. Some medical surveys of flavoring-exposed employees have revealed an increased prevalence of an isolated restrictive pattern on spirometry (i.e., without concurrent airways obstruction), but static lung volume measurements of TLC and biopsies have not been available in these studies to confirm restrictive lung disease [Kreiss 2012; NIOSH 2009, 2011c]. The evidence for restrictive and normal pulmonary functions in obliterative bronchiolitis is in patients exposed to other lung hazards, such as sulfur mustard gas and in U.S. soldiers serving in Iraq and Afghanistan, some of whom had sulfur dioxide exposure. Despite evidence from three biopsy-confirmed case series of obliterative bronchiolitis [Ghanei et al. 2008; King et al. 2011; Markopoulou et al. 2002], many pulmonary and occupational medicine specialists are not aware of the range of spirometric findings in this disease and may be reluctant to diagnose obliterative bronchiolitis in patients with

spirometric restriction or normal spirometry without pathologic confirmation. Employees who develop restrictive abnormalities or who have excessive parallel FEV_1 and FVC declines should have assessment of lung volumes, diffusing capacity, and HRCT to differentiate between restrictive lung disease and other causes of restrictive spirometric patterns. Further evaluation of restrictive lung disease for a specific diagnosis should be pursued as clinically appropriate and may require biopsy. Case reports of pathologic findings in dyspneic flavoring-exposed employees with restrictive or normal spirometry will be of interest in further guidance for clinicians responsible for the lung health of such employees.

The evaluating physician should exclude alternative causes of respiratory disease such as work-related asthma (new onset asthma or exacerbation of pre-existing asthma). An employee with no past asthma history who experiences post-hire recurrent respiratory symptoms and has airways obstruction responsive to bronchodilator on PFTs (reversible airways obstruction) may have new onset asthma due to workplace exposures. If an employee with asthma symptoms does not have changes over time on medical monitoring spirometry, a methacholine or mannitol challenge test may be necessary to determine if the employee has airways hyperresponsiveness as occurs in asthma. Worsening symptoms in an employee with pre-existing asthma may be due to exposure to diacetyl, similar flavoring compounds, or other agents in the workplace [Sahakian et al. 2008]. An important consideration for diacetyl-exposed employees with worsening pre-existing asthma or new onset reversible airways obstruction is that this may actually reflect early disease that may ultimately progress to clinical obliterative bronchiolitis. An employee at a California flavoring plant who had stable pre-existing asthma (no symptoms at time of hire) developed progressive shortness of breath and was found to have severe fixed airways obstruction on PFTs; a lung biopsy showed evidence of bronchiolitis obliterans [NIOSH 2007]. Employees with worsening pre-existing asthma or new onset reversible airways obstruction should be evaluated with an HRCT scan of the chest to determine if findings consistent with clinical obliterative bronchiolitis are present. However, because HRCT abnormalities may be insensitive in detecting early or mild disease, such asthmatic employees require careful and frequent follow-up [King et al. 2011].

An employee exposed to diacetyl, 2,3-pentanedione, or similar flavoring compounds who has normal pre-exposure spirometry and subsequently develops fixed airways obstruction and has evidence of air trapping on complete PFTs or on HRCT scan, or has an excessive decline in FEV_1 and whose pulmonary function does not improve after exposure cessation, likely has clinical obliterative bronchiolitis due to this exposure.

In exposed employees who smoke, fixed airways obstruction should not be attributed to smoking if there is no evidence of emphysema on medical tests. Clinically significant emphysema occurs in a subset of smokers after many years of smoking; it is uncommon in smokers less than 50 years old [Wise 2008]. In middle-aged and older smoking employees, work history, clinical course, and medical tests are important in attempting to differentiate between smoking-related COPD and flavoring-related obstruction. Smoking explains about 80% of COPD in the United States, with about 15% attributable to work exposures. Smoking diacetyl-exposed employees appear to have lower excess risk of obstruction than never-smoking flavoring-exposed employees [Kreiss et al. 2002].

9.9 Response to Identification of Work-related Lung Disease

Employees with abnormalities identified on medical monitoring spirometry should be counseled about the risks of further exposure and that removal from exposure is prudent because of the irreversibility of the disease, short latency, and often rapid progression. Employees who receive a diagnosis of flavoring-related lung disease or who have findings on medical evaluation that indicate likely clinical obliterative bronchiolitis or other lung disease due to workplace exposures should be placed on work restrictions to prevent any further exposure to flavoring compounds or other substances in the workplace that may cause their lung disease to worsen. Personal protective equipment is the least effective means for controlling employee exposures. The proper use of personal protective equipment requires a high level of employer and employee involvement and commitment to be effective. The use of respiratory protection is not equivalent to removal from exposures because employees may still be exposed due to incomplete compliance, selection of an inappropriate respirator, or respirator malfunction [California Department of Public Health 2012]. If possible, employers should offer affected employees the opportunity to transfer to available jobs in work areas that have minimal or nonexistent exposures. Such employees should retain seniority, wages, and benefits.

Employers of an employee with confirmed or likely flavorings-related lung disease should arrange for an industrial hygiene evaluation of the plant areas where the employee had been assigned. The evaluation may identify aspects of the production process or work practices where control strategies can be implemented to minimize exposures. This may prevent additional employees from developing work-related lung disease. Medical monitoring evaluations of employees in these areas should increase in frequency from every 6 months to every 3 months, with a return to 6-month intervals after factors that may have led to excessive exposure have been corrected and 12 months have passed during which no additional employees with likely flavoring-related lung disease are identified (see section 9.4).

When informed, employers should record all flavoring-related lung disease cases in the OSHA Form 300 Logs of Work-Related Injuries and Illnesses.

9.10 Medical Surveillance Analyses

A workplace assessment conducted after identification of a sentinel case of work-related lung disease may reveal sources of uncontrolled exposures from particular aspects of production processes and work practices that can be improved to prevent other employees from becoming affected. However, this approach may not identify all such risk factors for hazardous exposure in a given workplace. Additional risk factors may be identified through a medical monitoring and surveillance program, which includes the use of epidemiologic techniques for analyses of aggregated data obtained from evaluations of all employees in a medical monitoring program. Such analyses show trends and distributions of health outcomes by exposure variables such as work area, job category, and work task. In some instances, the results of such analyses may provide early evidence of risk factors that can be addressed before employees develop significant lung disease. Because production processes and work practices in manufacturing plants that use diacetyl or similar flavoring compounds or products that contain these compounds vary from plant to plant, medical surveillance may also allow identification of risk factors unique to

a particular plant. For these reasons, systematic evaluation of medical monitoring data is an important component of medical monitoring and surveillance programs for employees exposed to diacetyl or similar flavoring compounds. If the medical monitoring program director is not able to conduct such analyses, the employer or medical monitoring program director should arrange for consultants with expertise in epidemiology to undertake this task. Two examples below show how medical surveillance can help to identify lung disease risk factors in the workplace.

Example 1. At the plant where microwave popcorn employees were first identified as being at risk for severe fixed airways obstruction consistent with clinical obliterative bronchiolitis from exposure to butter flavoring vapors (index facility G), four known affected former employees had worked in the mixing room as mixers of oil and butter flavorings, and four other affected former employees had worked on the packaging lines near the mixing room. A medical survey of current employees showed that the prevalence of airways obstruction on NIOSH spirometry tests was 3.3 times higher than expected in comparison to U.S. population data, a finding that was consistent with the known disease in former employees. The environmental assessment showed that air concentrations of the butter flavoring compound diacetyl were highest in the mixing room. The next highest exposures were in the packaging line area because of contamination from the mixing room, which was not isolated from the rest of the plant. Diacetyl air concentrations in other parts of the plant were lower. Analyses of the medical and environmental data showed a dose-response relationship between abnormal spirometry and quartiles of estimated cumulative exposure to diacetyl [Kanwal et al. 2011; Kreiss et al. 2002; NIOSH 2006].

Additional analyses of the medical survey data revealed an unexpected finding: Among current employees, the highest prevalence of airways obstruction was found in QC laboratory employees, five of six (83%) of whom had airways obstruction [Kreiss et al. 2002]. These employees popped approximately 100 bags of microwave popcorn in microwave ovens per 8-hour shift. The mean time-weighted average diacetyl air concentration in the QC laboratory was 0.8 ppm compared to approximately 57.2 ppm in the mixing room and 2.8 ppm for machine operators in the packaging line area. QC laboratory employees may be at risk for lung disease because they experience intermittent peak exposures to vapors of diacetyl from microwave popcorn bags during and after popping in microwave ovens; mixers experience similar intermittent peaks when they add butter flavorings to tanks of heated oil [NIOSH 2003]. Another possible explanation is that the much higher temperatures that occur in microwave popping (compared with the temperatures in heated tanks of oil and butter flavorings) increase the volatilization of other chemicals. QC laboratory employees' exposures may be substantially different from those of other production employees; diacetyl air concentrations alone may not be a satisfactory predictor of risk for these employees. Because of this evidence of risk to QC laboratory employees, NIOSH recommended implementing exposure controls in the QC laboratory in addition to the mixing room and packaging line area [Kanwal et al. 2011; NIOSH 2006].

In evaluations at five other microwave popcorn plants, NIOSH found evidence of affected mixers in four plants and evidence of affected packaging line employees in one plant [Kanwal et al. 2006]. No other plant had an elevated prevalence of airways obstruction in QC employees. Fewer bags of microwave popcorn were popped per employee per day in those plants, and the mean time-weighted average diacetyl air concentrations in the QC laboratories were lower than at index facility G.

Example 2. At a microwave popcorn plant where a young mixing room employee developed moderately severe fixed airways obstruction and other findings consistent with clinical obliterative bronchiolitis, management had put a mandatory respirator use policy for mixing room employees in place soon after the company first started production. In addition to using respirators, the company had also ventilated and isolated the mixing room from the rest of the plant and had local exhaust ventilation for tanks of heated oil and butter flavorings. Butter flavorings were handled in open containers as they were at other microwave popcorn plants. The respirators used were full facepiece respirators with organic vapor cartridges and particulate filters. Included in the questionnaire that NIOSH administered to current employees during a medical survey at the plant were questions about respirator use for the following work tasks: (1) weighing or handling open containers of flavorings, (2) pouring flavorings into tanks in the mixing room, (3) pouring other ingredients into tanks in the mixing room, (4) checking the levels in the tanks, and (5) other duties in the mixing room. Thirteen current employees reported ever having worked as a mixer; six had abnormal lung function on NIOSH spirometry tests. The reported percentages of time these employees used respirators during these activities ranged from 0% to 100%. The median reported percentage of time was 20% for all activities, except for those where other ingredients (not flavorings) were poured into tanks in the mixing room where the median was 50% [NIOSH 2004a]. These results showed that employees were not fully compliant with management's respirator use policy; management was able to address this problem through employee education and enforcement of the policy. Had the company become aware of this problem earlier by regularly collecting and evaluating information on respirator use during medical monitoring evaluations, it could have increased compliance with respirator use and thus minimized some employees' exposures to butter flavoring compounds. (Before 2001 when NIOSH informed microwave popcorn companies of the risk of severe lung disease to employees exposed to butter flavorings, the company had been unaware of the respiratory toxicity potential of diacetyl. The company had implemented a mandatory respirator use policy for mixing room employees many years earlier to prevent severe eye irritation that employees had experienced when handling certain flavorings.)

Thus, analysis of population data generated by medical monitoring and surveillance programs plays an important role in primary prevention by helping employers of flavoring-exposed employees to recognize and take steps to characterize and correct hazardous conditions. Recognition can require epidemiologic evaluation of medical monitoring, population, and environmental data. It is therefore important for employers to ensure that this applied epidemiology is provided as part of the medical monitoring and surveillance program.

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