Executive Summary

Diacetyl and its substitute, 2,3-pentanedione, are widely used flavoring compounds. There have been extensive reports of serious respiratory disease and decreased lung function in employees exposed to diacetyl. The NIOSH objective in establishing recommended exposure limits (RELs) for diacetyl and 2,3-pentanedione is to reduce the risk of respiratory impairment (decreased lung function) and the severe irreversible lung disease obliterative bronchiolitis associated with occupational exposure to these compounds. In this disease the smallest airways in the lungs, the bronchioles, become scarred and constricted, blocking the movement of air. In addition, maintaining exposures below the RELs will help prevent other adverse health effects including but not limited to irritation of the skin, eyes, and respiratory tract in exposed employees. The recommendation to limit exposure to diacetyl and 2,3-pentanedione is based upon data from human and animal studies and the quantitative risk assessment; however, additional considerations include sampling and analytical feasibility and the achievability of engineering controls.

Diacetyl is used extensively in the food flavoring and production industries, and occupational exposure to this substance has been associated with severe respiratory impairment and the disease obliterative bronchiolitis. 2,3-Pentanedione, which has been used as a substitute for diacetyl, is also of concern because of structural similarities with diacetyl and because animal studies show similar toxicity for the respiratory tract [Hubbs et al. 2012; Morgan et al. 2012; Morgan et al. 2016].

The first observation of obliterative bronchiolitis in a food production employee may have occurred in 1985 in a facility where diacetyl was listed among ingredients used in making flavorings for the baking industry [NIOSH 1985]. The link between exposure to diacetyl and lower pulmonary function was confirmed in the early 2000s, and research further showed that diacetyl exposure leads to a decrease in pulmonary function [Kreiss et al. 2002]. Occupational exposures to diacetyl have been assessed in a variety of food production and flavoring facilities [Kanwal et al. 2006; Martyny et al. 2008; NIOSH 2003a, b, 2004a, b, 2006, 2007, 2008a, b, 2009, 2011].

Another compound, acetoin, was present along with diacetyl in many of the workplaces where obliterative bronchiolitis occurred in employees who made or used diacetyl [Kullman et al. 2005; van Rooy et al. 2007]. However, current data indicate that acetoin is considerably less hazardous than diacetyl and it does not have the reactive α-dicarbonyl group, which has been implicated in the toxicity of diacetyl and 2,3-pentanedione [Hubbs et al. 2016; National Toxicology Program 2015; Zaccone et al. 2013].

Mean diacetyl air concentrations measured at the first microwave popcorn facility where obliterative bronchiolitis was reported were highest in the mixing room (57.2 parts per million [ppm]), followed by the packaging area (2.8 ppm) [Kanwal et al. 2011]. Mean personal diacetyl air concentrations at five other microwave popcorn plants were lower: 0.023 to 1.16 ppm in the mixing room and 0.35 to 1.33 ppm in the packaging rooms/areas [Kanwal et al. 2006]. Mean full-shift diacetyl air concentrations measured

at flavor manufacturing facilities ranged from 0.07 ppm to 2.73 ppm [Kanwal et al. 2006; Martyny et al. 2008; NIOSH 2003a, b, 2004a, b, 2006, 2007, 2008a, b, 2009, 2011].

In addition to cases consistent with obliterative bronchiolitis in flavoring manufacturing, diacetyl manufacturing, and microwave popcorn production, case reports have surfaced in other industries in which flavorings are introduced. In cookie manufacturing 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]. 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]. In 2012, NIOSH conducted a health hazard evaluation (HHE) 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.

Investigations of severe lung disease consistent with obliterative bronchiolitis among diacetyl-exposed employees presented in Chapter 3 have provided substantial evidence of a causal relationship between diacetyl exposure and development of this disease. These findings in conjunction with laboratory experiments providing biological plausibility, meet the standard criteria used to determine causation: that an exposure is the likely cause of specific health effects [Gordis 1996; Hill 1965].

NIOSH has reviewed the literature on diacetyl toxicology and exposures in the workplace and subsequently conducted a quantitative risk assessment. The quantitative risk assessment used to derive the REL was based solely on human (employee) data, but the results were informed and corroborated by animal risk assessments. On the basis of a quantitative risk assessment of data collected in a series of NIOSH health hazard investigations (full description in Chapter 5), NIOSH has concluded that employee exposure to diacetyl is associated with a reduction in lung function. Specifically, a statistically significant exposure-associated reduction in the forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio and percent predicted FEV_1 ($ppFEV_1$) and an exposure-associated estimated incidence of symptomatic obstructive lung disease were observed. NIOSH quantified these exposure-response relationships and determined the exposure levels that correspond to a variety of risks (Chapter 5, Table 5.35). Lifetime risks in the range of 1:1,000 corresponded to working lifetime diacetyl exposure of approximately 5 parts per billion (ppb). Once the risks were characterized, NIOSH examined the analytical methods (OSHA Methods 1012 and 1016) and available engineering controls and determined that they supported establishing a REL at that level.

It should be noted that diacetyl and 2,3-pentanedione are found in cigarette smoke [Fujioka and Shibamoto 2006; Pierce et al. 2014; Polzin et al. 2007] and some flavored e-cigarettes [Allen et al. 2016; Farsalinos et al. 2015]. As extensively discussed in Chapter 3, increased prevalence of airway obstruction and decreased FEV_1 can be identified in smokers who are exposed to diacetyl in comparison to prevalence in smokers in the U.S. population. Most importantly, because diacetyl causes obstructive lung disease and because smoking causes obstructive lung disease, the presence of diacetyl in cigarette smoke in no way diminishes the need to control diacetyl exposures in employees.

NIOSH concludes that the toxicological responses to diacetyl observed in animal studies support the conclusions of the epidemiologically-based risk assessment for diacetyl. Further, the animal-based

risk assessment presented in Chapter 6 corroborates the epidemiologic assessment by demonstrating a causal link between diacetyl exposure and respiratory health effects and by showing a clear dose-response relationship in exposed animals as was observed in employees exposed to diacetyl in the epidemiologic assessment.

On this basis, NIOSH recommends a REL of 5 ppb for diacetyl as a time-weighted average (TWA) for up to 8 hours/day during a 40-hour workweek. NIOSH has determined that employees exposed to diacetyl at this level for 8 hours a day, 40 hours a week for a 45-year working lifetime should have no more than a 1/1,000 excess risk of lung function falling below the lower limit of normal due to diacetyl exposure.

To ensure that employee exposures are routinely below the REL for diacetyl, NIOSH also recommends using an action level (AL) of 2.6 ppb with the exposure monitoring program to ensure that all control efforts (engineering controls, medical surveillance, and work practices) are in place and working properly. When exposures exceed the AL, employers should take corrective action (determine the source of exposure, identify methods for controlling exposure) to ensure that exposures are maintained below the REL. NIOSH has concluded that the use of an AL in conjunction with periodic monitoring of employee exposures (described in Chapter 10) is helpful to protect employees.

NIOSH is also recommending a short-term exposure limit (STEL) for diacetyl of 25 ppb for a 15-minute time period. The establishment of a STEL is based on the concern that peak exposures may have greater toxicity than the same total dose spread out over a longer period of time.

2,3-Pentanedione is used in many operations; it is structurally similar to diacetyl because it is a 5-carbon alpha diketone, whereas diacetyl is a 4-carbon alpha diketone. Published toxicology studies indicate that 2,3-pentanedione exposure can cause damage to the lining of airways similar to that caused by diacetyl in laboratory studies [Hubbs et al. 2012; Morgan et al. 2012; Morgan et al. 2016]. Therefore, NIOSH recommends controlling occupational exposure to 2,3-pentanedione to a level comparable to that recommended for diacetyl. However, analytical limitations allow 2,3-pentanedione to be reliably measured only above 9.3 ppb. This recommended exposure limit is slightly higher than the recommended exposure limit for diacetyl. NIOSH recommends keeping exposure to 2,3-pentanedione below 9.3 ppb in an 8-hour average during a 40-hour work week. NIOSH has estimated that employees exposed to 2,3-pentanedione at this concentration should have a similar risk of decreased pulmonary function as employees exposed to diacetyl. NIOSH also recommends a short-term exposure limit for 2,3-pentanedione of 31 ppb during a 15-minute period.

Research into various flavoring industries has led to the development of engineering controls that may help reduce employee exposure to diacetyl, 2,3-pentanedione, and other chemicals. Chapter 8 describes engineering controls for the industries where diacetyl is handled or used within products. Table 8.2 in Chapter 8 provides a summary of NIOSH-evaluated engineering control efficiencies for the mixing of food flavorings. NIOSH acknowledges that the frequent use of personal protective equipment (PPE), including respirators, may be required for some employees who handle diacetyl, 2,3-pentanedione, diacetyl-containing flavorings or flavored products. The frequent use of PPE may be required during job tasks for which (1) routinely high airborne concentrations of diacetyl or 2,3-pentanedione (e.g., pouring, mixing, packaging) exist, (2) the airborne concentration of diacetyl or 2,3-pentanedione is unknown or unpredictable, and (3) job tasks are associated with highly variable airborne concentrations because of environmental conditions or the manner in which the job task is performed. In all work environments

where diacetyl, 2,3-pentanedione, diacetyl-containing flavorings, or flavored products are found control of exposure through engineering controls should be the highest priority.

NIOSH recommends that employers develop and implement comprehensive occupational safety and health programs to protect employees with potential exposure to diacetyl, 2,3-pentanedione, and other potentially hazardous flavoring compounds. This program should include periodic exposure and medical evaluation and monitoring exposure controls and appropriate employee training on potential health effects, respiratory protection, and use of controls. Employers should (1) determine employee exposure to diacetyl, 2,3-pentanedione, and other flavoring compounds used in the workplace; (2) evaluate the effectiveness of work practice and engineering controls; and (3) facilitate the selection of appropriate personal protective equipment. Because diacetyl and 2,3-pentanedione are found in cigarette smoke [Fujioka and Shibamoto 2006; Pierce et al. 2014; Polzin et al. 2007] and e-cigarettes, NIOSH also recommends that all employers make tobacco cessation programs available to employees and have workplaces that are free of tobacco smoking and vaping with flavored nicotine delivery systems [NIOSH 2015].

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. Because of the potentially rapid progression and grave consequences of flavoring-related lung disease, it is important that the medical monitoring program director be able to quickly evaluate clinical data and make medical judgments about appropriate diagnostic and therapeutic measures, including medical removal. For this reason, the medical monitoring program director should be a licensed physician with training and experience in identifying and preventing occupational lung disease. The medical program that includes the following:

- good quality spirometry testing for pulmonary function
- medical evaluation for employees found with abnormal spirometry
- removal from exposure pending medical evaluation
- analysis of group medical surveillance and longitudinal spirometry data to assess work-related risk factors on the basis of job, task, area, and other exposure indices

The purpose of this epidemiologic surveillance is to assist monitoring physicians in assessing the likelihood of work-related causes of abnormalities and to prioritize interventions, if needed. Identifying excessive declines in spirometry, even if absolute spirometric values remain within the normal range, offers the best opportunity to intervene before progression to symptomatic impairment and to prevent the development of clinically significant occupational lung disease. The rapid onset and progression of diacetyl-related lung disease requires more frequent medical monitoring evaluations be done than with slowly progressive occupational lung diseases, such as silicosis and coal employees pneumoconiosis. While the focus of this document is on diacetyl and 2,3-pentanedione, NIOSH has concern regarding other volatile and reactive flavorings potentially capable of producing similar toxic effects. Therefore, NIOSH recommends that such exposures be carefully considered and controlled in consultation with workplace safety professionals and the recommendations contained within this criteria document.