7 Basis of the Recommended Standards for Diacetyl and 2,3-Pentanedione

In the Occupational Safety and Health Act of 1970 (Public Law 91–96), Congress mandated that NIOSH develop and recommend criteria for identifying and controlling workplace hazards that may result in occupational illness or injury. In fulfilling this mandate, NIOSH has reviewed the relevant human and/or animal data to assess the health effects of diacetyl and 2,3-pentanedione; assessed the risks of occupational exposure; characterized anticipated employee exposures; and developed recommended criteria for exposure limits, exposure monitoring, engineering and work practice controls, and medical monitoring.

The basis for the RELs is described in this chapter. The primary objective of the recommendations for diacetyl is to reduce loss of lung function associated with diacetyl exposure because diacetyl (and potentially related diones) has been shown to cause potentially fatal obliterative bronchiolitis in employees. The NIOSH REL for 2,3-pentanedione would be identical to that for diacetyl but is slightly higher based upon the limitations of the analytical method.

7.1 Health Effect Studies of Employees Exposed to Diacetyl

As detailed in Chapter 3, medical evaluations showed that employees exposed to diacetyl developed progressive shortness of breath while working at several microwave popcorn plants and flavoring plants, findings consistent with the severe irreversible lung disease obliterative bronchiolitis. Obliterative bronchiolitis, sometimes characterized by spirometric abnormality, has been described in employees in the microwave popcorn and flavor-manufacturing industries [CDC 2002, 2007; Kanwal et al. 2006]. Some affected employees have experienced extremely rapid declines in lung function, with severe airways obstruction in some cases occurring within several months of the start of exposure to flavoring compounds [Akpinar-Elci et al. 2004; NIOSH 1986]. Employees as young as 22 years old have been affected. 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]. The findings from investigations and studies conducted at multiple plants presented in Chapter 3 have established a link between exposure to diacetyl and risk for severe occupational lung disease. These findings meet the standard criteria used to determine causation: that an exposure is the likely cause of specific health effects [Gordis 1996; Hill 1965]. Investigations of severe lung disease consistent with obliterative bronchiolitis among diacetyl-exposed employees have provided clear evidence of a causal relationship between diacetyl exposure and development of this disease.

7.2 Toxicological Studies of Diacetyl

In rats, acute exposures to diacetyl or diacetyl-containing butter flavoring vapors cause necrosis in the epithelial lining of nasal and pulmonary airways. Rats inhaling vapors of butter flavoring that contained diacetyl developed multifocal necrotizing bronchitis one day after a 6-hour exposure. The mainstem bronchus was the most affected intrapulmonary airway. However, nasal airways were more affected than intrapulmonary airways. Necrosuppurative rhinitis was seen in rats inhaling butter flavoring vapors at concentrations that did not cause damage in intrapulmonary airways [Hubbs et al. 2002]. As a single agent acute exposure in rats, diacetyl caused epithelial necrosis and inflammation in bronchi at concentrations of ≥290 ppm and caused epithelial necrosis and inflammation in the trachea and larynx at concentrations of ≥220 ppm [Hubbs et al. 2008]. In a pattern similar to that of airway damage from diacetyl-containing butter flavoring vapors, diacetyl causes greater damage to nasal airways than to intrapulmonary airways in rats [Hubbs et al. 2008].

In mice, inhaling diacetyl at concentrations of 200 or 400 ppm for 6 hours/day for up to 5 days caused respiratory tract changes similar to those seen in rats inhaling diacetyl or diacetyl-containing butter flavoring vapors [Morgan et al. 2008]. Subchronic diacetyl inhalation caused significant histopathological changes in mice at all concentrations studied. Peribronchial lymphocytic infiltrates were seen at terminal sacrifice at 12 weeks in all subchronically exposed mice inhaling 100 ppm diacetyl and in some mice inhaling 25 or 50 ppm diacetyl. Using a CFD-PBPK model, the rodent pathologic changes, though at higher regions in the respiratory tract, were consistent with the human bronchiolar pathology once differential nasal scrubbing, size of airway, and target organ doses were accounted for [Gloede et al. 2011; Morris and Hubbs 2009]. In rats in which nasal scrubbing was bypassed by administering a single dose of 125 mg/kg diacetyl via intratracheal instillation, histopathological alterations characteristic of bronchiolitis obliterans ensued, including damage to airway epithelium [Palmer et al. 2011].

NIOSH concludes that the toxicological responses to diacetyl observed in animal studies support the conclusions of the epidemiologically-based risk assessment for this compound. The animal-based risk assessment presented in Chapter 6 further 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.

7.3 Quantitative Risk Assessment for Deriving the Recommended Exposure Limit

NIOSH has reviewed the literature on diacetyl toxicology and exposures in the workplace and subsequently conducted a quantitative risk assessment. Results from this comprehensive review demonstrate a causal relationship between diacetyl exposure and development of severe occupational lung disease. The quantitative risk assessment used to derive the REL was based solely on human (employee) data, but the results were informed and supported by animal risk assessments. On the basis of a quantitative risk assessment of data collected in a series of NIOSH health hazard evaluations (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 FEV_1/FVC ratio and percent predicted FEV_1 and an exposure-associated incidence of 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). Excess lifetime risks in the range of 1:1,000 corresponded to working lifetime diacetyl exposure of approximately 5 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 an REL at that level.

7.4 Objectives

The NIOSH objective in establishing 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 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 included sampling and analytical feasibility and the achievability of engineering controls.

A variety of risk estimates were evaluated and presented in Chapter 5. NIOSH has historically targeted excess risks predicted to be in the range of approximately 1 per 1,000 in establishing RELs (see Chapter 5, Tables 5-34, 5-35 for risk estimates). In occupational exposure to diacetyl, the ultimate health effect of concern is obliterative bronchiolitis, a debilitating, sometimes fatal, and irreversible effect. The goal is to prevent the respiratory impairment that precedes the appearance of obliterative bronchiolitis. There are validated analytical methods that can be used to effectively measure employee exposures at the selected level. Additionally, information from site visits indicates that the REL is achievable with engineering controls where diacetyl is used or handled [Eastern Research Group 2009; Kanwal et al. 2011].

7.5 Recommended Exposure Limits

7.5.1 Recommended Exposure Limit for Diacetyl

On this basis, NIOSH recommends a REL of 5 ppb for diacetyl (as a 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) will help protect employees.

NIOSH is also recommending a STEL for diacetyl of 25 ppb for a 15-minute time period. The establishment of a short-term exposure limit 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. Some limited evidence of this type of dose-rate effect is available in animal studies [Hubbs et al. 2008]. On the basis of general industrial hygiene principles, the STEL, which is five times the REL, would serve to reduce peak exposures and tend to reduce overall employee exposures to diacetyl. The selection of a STEL that is five times the REL is based upon past precautionary practice [Federal Register 1997]. In the absence of a STEL in workplaces complying with the NIOSH REL for diacetyl of 5 ppb TWA, employees could theoretically be exposed to 2,400 ppb diacetyl for 1 minute or 480 ppb for 5 minutes in an 8-hour day with no additional exposure the remaining part of their 8-hour shift. The STEL for diacetyl of 25 ppb would limit those exposures to a possible peak of 375 ppb for 1 minute and 75 ppb for 5 minutes and should prevent acute irritation from brief high exposures.

7.5.2 Recommended Exposure Limit for 2,3-Pentanedione

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]. Morphologic data suggest that 2,3-pentanedione can cause airway epithelial damage similar to the damage caused by diacetyl [Hubbs et al. 2012; Morgan et al. 2012; Morgan et al. 2016]. Rats repeatedly inhaling 2,3-pentanedione at concentrations ≥ 150 ppm for up to 2 weeks develop fibrosis of intrapulmonary airways, a morphologic change similar to obliterative bronchiolitis in humans [Morgan et al. 2016]. Recently, more than 3500 genes were found to be upregulated in RNA isolated from the fibrotic bronchi of 2,3-pentanedione exposed rats [Morgan et al. 2015]. Some of the up-regulated genes were ones previously implicated in fibrosis, including transforming growth factor-β2, interleukin-1α, interleukin-18, interleukin-33, and fibronectin. In addition, at high exposure concentrations, messenger RNA changes were noted in the brain of rats after acute 2,3-pentanedione inhalation [Hubbs et al. 2012].

The toxic potency of the two materials appears to be comparable in mice exposed by inhalation (see Chapter 6, section 2 for a full discussion). Given the structural similarity between diacetyl and 2,3-pentanedione and the evidence published, NIOSH would prefer to recommend an identical REL for diacetyl and 2,3-pentanedione. However, OSHA Method 1016, the validated analytical method available for 2,3-pentanedione, can only reliably quantify 2,3-pentanedione at concentrations 9.3 ppb and above. Therefore the NIOSH REL for 2,3-pentanedione, while informed by the toxicological potential, is based upon the limitations of the analytical method and is established at 9.3 ppb. This REL for 2,3-pentanedione will result in a residual risk of lung disease similar to diacetyl, but may be higher. It does not imply that 2,3-pentanedione is safer than diacetyl. Because the REL is established at the reliable quantitation level, no AL is established for 2,3-pentanedione.

Because of their structural similarity, concerns for short-term exposures to 2,3-pentanedione also apply. Accordingly, a STEL for 2,3-pentanedione is established at 31 ppb (i.e., the lowest concentrations the method can sample accurately during a 15-minute time period). The NIOSH REL for 2,3-pentanedione of 9.3 ppb and STEL of 31 ppb would limit exposures to a possible peak of 465 ppb for 1 minute and 93 ppb for 5 minutes. Because of the concern for potential dose-rate effects, NIOSH recommends STELs for diacetyl and 2,3-pentanedione to reduce peak exposures to employees.

Maintaining diacetyl and 2,3-pentanedione concentrations at or below the RELs and STELs requires the implementation of a comprehensive safety and health program that includes engineering controls, exposure monitoring, routine medical surveillance, and employee training in good work practices. Specific recommendations for these components can be found in Chapters 2, 8, 9, and 10 of this document.

7.6 Rationale for the Recommended Exposure Limit

The recommendation to limit occupational exposures to diacetyl to an 8-hour TWA of 5 ppb is based on data from human quantitative risk assessment with additional rationale provided by animal toxicological studies. From the human studies, 5 ppb represents a reasonable summary of estimates from several concordant approaches to risk assessment. Although smoking affects the excess lifetime risk estimates, a full treatment for the purpose of developing separate REL recommendations on smoking status would require including interactions between smoking and diacetyl exposure histories for which NIOSH believes there is insufficient historical information and statistical power to implement. Furthermore, there is no precedent for developing standards that are specific to smoking status. NIOSH also recommends an AL of 2.6 ppb to help protect employees from exposure to diacetyl above the 5 ppb REL and a STEL of 25 ppb to limit peak exposures and protect against dose-rate effects. Engineering controls and work practices are available to control diacetyl exposures below the REL (and the AL) in workplaces. OSHA Method 1012 is a validated analytical method that can be used to effectively measure employee exposures to diacetyl. Establishing the recommended exposure limits for diacetyl is consistent with the mission of NIOSH mandated in the Occupational Safety and Health Act of 1970.

7.7 Controlling Diacetyl and 2,3-Pentanedione Exposures in the Workplace

In general, many industries have implemented engineering controls to reduce exposure and risk of disease among their employees. Many of the processes where diacetyl and 2,3-pentanedione are manufactured, handled, or used are similar to other industries and may allow for common approaches to reducing employee exposure. These processes include blending, mixing, and handling of flavoring compounds in liquid and powder form. A 3-year study of a microwave popcorn production facility showed that the use of exposure controls can dramatically reduce diacetyl concentrations in mixing rooms and for all production employees [Kanwal et al. 2011]. As a result of the implementation of exposure controls, average combined personal and area diacetyl air concentrations declined an order of magnitude in the mixing room (from 57.2 ppm to 2.88 ppm) while concentrations in the quality control laboratory (from 0.82 ppm to < LOD) and packaging area (from 2.76 ppm to < LOD for machine operators) declined to below detectable limits. These interventions included providing general room exhaust ventilation to the mixing room and local exhaust ventilation for the heated flavoring and mixing tanks. Closed transfer processes were implemented through the installation of a pump to transfer heated butter flavorings from the holding tanks to oil/flavor mixing tanks. The building of an enclosure for all oil/flavor holding tanks and installing local exhaust ventilation on all tanks further reduced exposures to employees in the packaging area of this plant. In the final survey conducted following the implementation of all engineering and process controls, personal diacetyl exposures for all employees/job categories in the plant were below detectable limits with the exception of mixers which ranged from below the LOD to 12.6 ppm.

The design concepts required for working with hazardous materials include specification of general ventilation, local exhaust ventilation, maintenance, cleaning and disposal, personal protective equipment, exposure monitoring, and medical surveillance [Naumann et al. 1996]. Bag emptying, bag filling, charging tanks, benchtop weighing and handling, and drum filling and emptying are a few of the production processes of concern. Other more specialized processes (for example, candy panning, a process in which candy pieces in a rotating drum are sprayed with chocolate or other flavoring compounds; coffee roasting; commercial fry-cooking) may also result in employee exposure. Special attention should be given to manual handling of flavoring compounds, particularly in heated processes, and when spraying flavoring compounds. Research on food industry practices 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.

Although many job categories can be effectively controlled to levels below the REL, tasks associated with transfer of diacetyl may continue to pose risk to the employees even following the implementation of controls. For example, mixers may continue to be exposed at levels above the REL when handling butter flavorings and from tank emissions. However, these exposures can be reduced through the implementation of closed transfer systems and local exhaust ventilation approaches discussed in Chapter 8. NIOSH acknowledges that the frequent use of personal protective equipment, 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) airborne concentrations of diacetyl or 2,3-pentanedione (e.g., pouring, mixing, packaging) above the REL 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 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.

7.8 Hazards Associated with Diacetyl Substitutes

Much has been made of the possible removal/substitution of diacetyl and 2,3-pentanedione from the flavor manufacturing or food production industries. A health benefit from substitution can only be realized if the substitute is safer than diacetyl or 2,3-pentanedione. However, the current knowledge on toxicity of available substitutes is limited; few if any have OELs, and therefore exposure to substitutes should be controlled.

There is reason to think that, like diacetyl, other alpha-dicarbonyl compounds would have a tendency to cause protein cross-links [Miller and Gerrard 2005]. The reactivity of the alpha-dicarbonyl compounds is enhanced by electron-attracting groups and decreased by electron donors [Roberts et al. 1999]. Alpha-dicarbonyl compounds can inactivate proteins, principally through reactions with the amino acid, arginine [Epperly and Dekker 1989; Saraiva et al. 2006]. The related alpha-dicarbonyl flavoring, 2,3-pentanedione, has been reported to be even more reactive with arginine groups than diacetyl [Epperly and Dekker 1989].

While the focus of this document is on diacetyl and 2,3-pentanedione, NIOSH has concern about other flavoring substitutes with structures similar to diacetyl or moieties that are biologically active and capable of producing similar toxic effects as diacetyl. Therefore, NIOSH recommends that such exposures also be considered and controlled to concentrations as low as possible, taking into account potential additive effects of flavoring compounds.

The guidance recommendations presented in Chapter 8 regarding control of exposures are applicable not only to diacetyl and 2,3-pentanedione, but also to their substitutes and other flavorings and flavoring compounds used in this industry. The control of exposures is discussed in detail in Chapter 8, but several LEV systems described have been shown to be particularly effective in controlling diacetyl and would be expected to work well for similar compounds. Ventilated backdraft workstations used for small batch mixing have been evaluated in two field studies conducted in flavoring production plants. The field studies showed reductions in exposure of 90%–97% when performing mixing tasks using these stations [NIOSH 2008a]. Also, the use of controls to reduce employee exposure during pouring and mixing of ingredients in a commercial mixer has been evaluated in a flavoring production plant [NIOSH 2008b]. The use of LEV at the mixing tank helps to maintain the vessel at a negative pressure and contain evaporative emissions. NIOSH evaluated the impact of a ventilated tank lid on the exposure of an employee during the mixing of a food flavoring [NIOSH 2008b]. The use of the ventilated tank lid resulted in a reduction of approximately 76% exposure. Most of the exposure during the evaluated mixing process was attributed to tasks performed outside of the hood. Ventilated tank lids have also been recommended by the British Health and Safety Executive (HSE) to contain vapors during the mixing of liquids with other liquids or solids [Health and Safety Executive 2003].

7.9 Summary

The following points summarize the relevant information used as the basis for the NIOSH recommendation for limiting occupational exposure to diacetyl and 2,3-pentanedione:

- Airborne exposures to diacetyl and 2,3-pentanedione have been characterized as potentially hazardous based on a review of the available literature regarding both human exposure and animal studies.
- Human health and animal data indicate a causal relationship between diacetyl exposure and development of obliterative bronchiolitis. Studies show a progressive shortness of breath for employees at several microwave popcorn plants and flavoring plants as well as employees who have experienced rapid declines in lung function.
- Rats repeatedly inhaling 2,3-pentanedione at concentrations ≥ 150 ppm for up to 2 weeks develop fibrosis of intrapulmonary airways, a morphologic change similar to obliterative bronchiolitis in humans. Inhalation studies on mice produced similar results.
- Risk assessment using data from both animal and inhalation human studies indicates that a diacetyl REL of 5 ppb as a TWA for up to 8 hours/day during a 40-hour workweek would be appropriate to achieve a 1/1,000 excess lifetime risk. Further, NIOSH recommends a STEL of 25 ppb to limit peak exposures and protect against dose-rate effects. An AL of 2.6 ppb is recommended to ensure that employee exposures are routinely below

the REL for diacetyl and to ensure that all control efforts (engineering controls, medical surveillance, and work practices) are in place and working properly.

- Given evidence that 2,3-pentanedione can cause airway epithelial damage and the structural similarity of 2,3-pentanedione to diacetyl, NIOSH recommends a 2,3-pentanedione REL of 9.3 ppb as a TWA for up to 8 hours/day during a 40-hour workweek. The REL for 2,3-pentanedione is based upon the reliable quantitation limit for the analytical method and does not imply that 2,3-pentanedione is of lower toxicity than diacetyl. Further, NIOSH recommends a STEL of 31 ppb to limit peak exposures on the same basis of analytic method limitation.
- Data gathered on diacetyl exposure demonstrated that engineering controls and work practices currently available can control diacetyl exposures below the REL. A validated analytical method can be used to effectively measure employee exposures at these levels.

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