1 Introduction

1.1 Purpose

This document presents the criteria and components of a recommended standard necessary to reduce or eliminate significant risk of health impairment from exposure to diacetyl and 2,3-pentanedione and prevent flavorings-related lung disease. This document was developed in accordance with the Occupational Safety and Health Act of 1970 [29 U.S.C. 669(a)(3); 29 U.S.C. 671(c)(1)]. This Act charges NIOSH with recommending occupational safety and health standards and developing criteria for toxic materials. These criteria are to describe exposures that are safe for various periods of employment, including but not limited to the exposures at which no employee will suffer diminished health, functional capacity, or life expectancy as a result of his or her work experience.

The purpose of the criteria document is to evaluate the scientific literature concerning potential health effects, toxicology, risk assessment, engineering controls, work practices, personal protective equipment, and recommendations pertaining to diacetyl and 2,3-pentanedione. The criteria document provides a basis for the REL for diacetyl and 2,3-pentanedione, although compliance with this recommended standard is not the sole objective. The intended outcome of the document is to reduce occupational exposures to diacetyl and 2,3-pentanedione and thereby prevent flavorings-related lung disease through hazard guidance implementation. In their entirety, the RELs and the guidance are intended to help employers develop a more healthful work environment. The RELs and guidance will also provide useful information to help employees actively participate in their own protection.

1.2 Scope

This criteria document contains a review of relevant scientific information related to diacetyl and 2,3-pentanedione, and provides the rationale and criteria for establishing appropriate risk management recommendations. The basis for developing a criteria document on diacetyl and 2,3-pentanedione is described in this chapter. Chapter 2 provides an overview of studies conducted to characterize occupational exposure to diacetyl and 2,3-pentanedione. Chapter 3 describes the health effects observed in employees exposed to diacetyl and other flavoring compounds. Chapter 4 describes toxicology research from diacetyl and 2,3-pentanedione, while Chapters 5 and 6 describe the assessment of risk based on available human and animal data. Chapter 7 provides the basis for the RELs for diacetyl and 2,3-pentanedione. Chapter 8 describes procedures for informing employees about the safety of diacetyl and diacetyl substitutes as well as engineering interventions that could significantly reduce exposures when appropriately applied and fully operational. Also included in Chapter 8 are recommendations for establishing globally harmonized system for classification and labelling (GHS) classifications for diacetyl and 2,3-pentanedione based on the revised OSHA hazard communication standard. Additionally, recommendations for an effective respiratory protection program are provided. Chapter 9 provides medical surveillance guidelines for the ongoing evaluation of the health status of employees. Chapter 10 describes the components of an effective exposure monitoring program and work practices that when implemented correctly, can reduce occupational exposures. Finally, Chapter 11 presents key research needs.

This document results from a review of all relevant literature on diacetyl and 2,3-pentanedione, and describes selected studies which characterize exposures and discusses techniques shown to be effective in reducing those exposures. Published literature through October 2016 was used and extracted from databases including but not limited to PubMed, NIOSHTIC-2, Web of Knowledge, Toxline, and Chem Abstracts. The literature search was developed to identify critical scientific data relevant to workplace safety and health including physical and chemical properties, human health effects, laboratory testing, chemical toxicokinetics, toxicity, engineering controls, personal protective equipment and function, risk management, and modeling systems that are relevant to diacetyl and 2,3-pentanedione. The literature was searched using specific terminology for each scientific discipline. Evaluated data sources included peer reviewed journal articles, government publications, and peer reviewed data sources, high caliber professional practice manuals (i.e., ACGIH 2012 and FEMA 2012) and high-quality information submitted to government dockets. In a few instances personal communications are cited where authors were contacted for additional clarification. The information that was identified in the comprehensive literature search was evaluated with considerations that included if the studies were peer-reviewed, if the data were generated with standardized protocols, if the exposure conditions were described in detail, confounders and existing information in peer reviewed journals. Specific studies pertaining to workplace exposure assessment, human health effects, and toxicology were specifically identified and are described in Chapters 2, 3, and 4 respectively.

1.3 Background

Diacetyl is one of the main components in butter flavoring that imparts a buttery taste, and it has been identified as a prominent volatile organic compound (VOC) in air samples from microwave popcorn plants and flavoring manufacturing plants [Akpinar-Elci et al. 2004; Ashley et al. 2008; Kanwal 2003; Kanwal et al. 2006; Kanwal and Martin 2003; Martyny et al. 2008; NIOSH 2004a; Parmet and Von Essen 2002]. Diacetyl is used as a natural and artificial flavoring ingredient and aroma carrier in bakery products, dairy products, snack foods, and more. It is mainly used as a butter flavoring but is also used in the flavor formulation of a number of other flavors, including but not limited to strawberry, caramel, hazelnut, and butterscotch. It is also present as a natural byproduct in some fermented food products such as beer and roasted food products such as coffee. Occupational exposures in the flavoring and food production industries have been associated with respiratory disease, including obliterative bronchiolitis, an uncommon lung disease often characterized by fixed airways obstruction. Obliterative bronchiolitis refers to disease processes that show some degree of inflammation, narrowing, or obliteration of small airways (bronchioles) in the lung and is discussed in more detail in Chapter 3, specifically section 3.1.1. Although a causative relationship between diacetyl and respiratory disease has been observed, diacetyl may not be the only flavoring compound related to health impairment. Other flavoring ingredients such as acetaldehyde, butyric acid, and acetoin, have been present in workforces with adverse health effects [Lockey et al. 1998; van Rooy et al. 2007]. In addition, new diacetyl substitutes with little or no toxicological information related to occupational safety and health are being used in production.

Day et al. [2011] observed the flavoring compound 2,3-pentanedione in food production facilities. This compound has been used as a diacetyl substitute in many flavor manufacturing facilities because it has a related chemical structure and similar flavor properties to diacetyl. Published reports on the toxicity of 2,3-pentanedione from experimental inhalation studies with rats indicate that exposure causes airway epithelial damage similar to that produced by diacetyl [Hubbs et al. 2012; Morgan et al. 2012].

No state or national registries are available to identify potential cases of obliterative bronchiolitis among employees. In 1985, two employees with fixed obstructive lung disease suggestive of obliterative bronchiolitis were observed in a facility where flavorings with diacetyl were made for the baking industry [Kreiss et al. 2002; NIOSH 1986]. Catastrophic fixed airways disease suggestive of obliterative bronchiolitis was observed in these two former mixing employees who were young nonsmokers with job tasks that involved blending corn starch and flour with various flavorings. Two additional employees who formerly had mixing responsibilities also had otherwise unexplained obstruction, whereas two current mixers were unaffected. A review of common ingredients listed diacetyl among other flavoring compounds.

In the microwave popcorn industry, the first occurrences of obliterative bronchiolitis were observed in the year 2000 when eight employees formerly employed in a microwave popcorn facility were diagnosed with the disease [Kreiss et al. 2002]. The observation of this case series led to the identification of another case of obliterative bronchiolitis in a separate facility [Parmet 2002]. Since then, numerous cases of obliterative bronchiolitis have been observed in the microwave popcorn industry [Akpinar-Elci et al. 2004; CDC 2002; Ezrailson 2002; Kanwal et al. 2006; NIOSH 2003, 2004a, b, 2006; Parmet 2002; Schachter 2002]. In addition, a retrospective epidemiologic study found cases of obliterative bronchiolitis in employees who were employed in a diacetyl manufacturing plant with exposures to diacetyl, acetoin, acetic acid, and acetaldehyde [van Rooy et al. 2007].

In 2004 and 2006, two cases of obliterative bronchiolitis among employees who made food flavorings were reported to the California Department of Public Health (CDPH). An industry-wide public health investigation performed by CDPH, the California Occupational Safety and Health Administration (Cal/OSHA), and NIOSH initially found an additional five employees with severe, fixed obstructive lung disease [CDC 2007]. Outreach to the industry regarding the diacetyl hazard, including Cal/OSHA consultation site visits, prompted quick implementation of exposure controls and medical surveillance programs. A longer-term effort was focused on companies' installation of effective engineering controls and further assessment of medical surveillance findings over time by CDPH and NIOSH. A cross-sectional analysis of medical surveillance data from 16 companies confirmed the risk of lung disease among employees at companies using diacetyl [Kim et al. 2010]. In 2010, California issued the first occupational standard for diacetyl [California Code of Regulations. Title 8, §5197].

Employees within the flavoring production industry have complex exposures in terms of the physical form of the agents (vapors, mists, and airborne dusts) and the number of different chemicals used. Although thousands of flavoring compounds are in use, few have occupational exposure limits. The Flavor and Extract Manufacturers Association (FEMA) reports that of the more than 1,000 flavoring compounds considered to be potential respiratory irritants or hazards, only 46 have established OSHA permissible exposure limits (PELs) [FEMA 2012]. Given the lack of occupational exposure limits for most flavoring compounds, assessing workplace exposures and developing exposure control guidance are critical to help reduce the risk of flavorings-related lung disease.

In 2010, California promulgated a regulation for occupational exposure to food flavorings containing diacetyl that requires installation of exposure controls to reduce exposures to the lowest feasible levels. In 2012, the American Conference of Governmental Industrial Hygienists (ACGIH) published a threshold limit value® of 0.010 ppm 8-hour TWA with a STEL of 0.020 ppm for diacetyl [ACGIH 2012]. In 2014, the European Commission published the Recommendation from the Scientific Committee on Occupational Exposure Limits of 0.02 ppm 8-hour TWA with a STEL of 0.10 ppm for diacetyl [EU 2014].

1.4 Chemical and Physical Properties

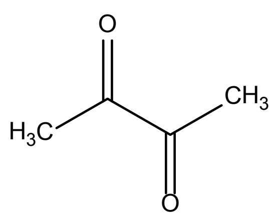
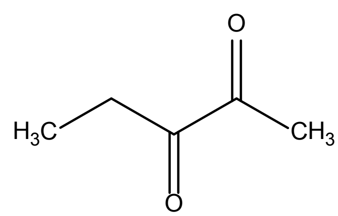
The compound diacetyl has Chemical Abstract Service (CAS) number 431-03-8 and has several synonyms including 2,3-butanedione (International Union of Pure and Applied Chemistry nomenclature), 2,3-butadione, 2,3-diketobutane, biacetyl, dimethyl diketone, and dimethylglyoxal. The compound 2,3-pentanedione has CAS number 600-14-6 and is also referred to by the name acetyl propionyl. Both diacetyl and 2,3-pentanedione are alpha diketones or vicinal diketones (also referred to less specifically as alpha dicarbonyls), which means that their molecular structures contain two carbonyl functional groups that are adjacent to one another, and the carbon molecules attached to the oxygen molecules are also attached to only carbon molecules. A listing of physical and chemical properties of diacetyl and 2,3-pentanedione and their molecular structures is presented in Table 1-1.

The odor threshold of diacetyl and 2,3-pentanedione has been reported by many studies [Buttery et al. 1997; Hall and Andersson 1983; Leksrisompong et al. 2010; Nagata and Takeuchi 1990; Sega et al. 1967]. It is not uncommon for odor threshold values reported in the literature to range over four orders of magnitude for the same chemical [AIHA 1989]. Odor threshold variability can result from the source of data, the characteristics of human olfactory response, and the differences in experimental methodology [AIHA 1989]. The following criteria were used to analyze the diacetyl and 2,3-pentandione odor threshold literature: (1) only primary odor threshold sources that were found in the literature and that were written in English were used; (2) only sources that clearly indicated the type of threshold being measured as a detection or recognition threshold were used; (3) sources that used a panel of at least five judges to account for the range of olfactory sensitivity in the population were used; and (4) sources that presented the different concentrations of odor samples in a way that eliminated olfactory fatigue were used. The geometric mean of the selected values was reported in Table 1-1 [AIHA 1989].

1.4.1 How Diacetyl and 2,3-Pentanedione are Prepared

Diacetyl can be synthesized chemically from four starting materials: (1) from methyl ethyl ketone, either by converting it into an isonitroso compound and then hydrolyzing with hydrochloric acid or by partial oxidation of methyl ethyl ketone over a copper or vanadium oxide catalyst [Aquila et al. 2001;

Table 1-1. Chemical and physical properties

Property	Diacetyl	2,3-Pentanedione
CAS #	**431-03-8**	**600-14-6**
Synonyms	2,3-butanedione; biacetyl; dimethyl diketone; dimethylglyoxal; 2,3-diketobutane [Merck and Co. Inc. 2006]	Acetylpropionyl [Lide 2008]
Molecular formula	$C_4H_6O_2$	$C_5H_8O_2$
Molecular weight	86.090 [Lide 2008]	100.117 [Lide 2008]
Molecular structure		
Density	0.9808 g/mL (18°C) [Lide 2008]	0.9565 g/mL (19°C) [Lide 2008]
Refractive index	1.3951 (20°C) [Lide 2008]	1.4014 (19°C) [Lide 2008]
Melting point	−1.2°C [Lide 2008]; −2.4°C [IPCS 2009]; −4°C [Fischer Scientific 2007]	−52°C [Merck Chemicals International 2010]
Boiling point	88°C [Lide 2008]; 88°C [IPCS 2009]	108°C [Lide 2008]; 110°C–112°C [Merck Chemicals International 2010]; 112°C [Chem Service Inc. 1988]
Vapor density	3	3.45
Vapor pressure	52.2 mm Hg (20°C) [Sigma Aldrich 2010]	21.4 mm Hg (20°C) [Merck Chemicals International 2010]
Saturated vapor concentration [Perez 1991]	184 g/m^3 (20°C); 246 g/m^3 (20°C)	117 g/m^3 (20°C)
Water solubility	200 g/L (25°C) [IPCS 2009]	60 g/L (15°C) [Merck Chemicals International 2010]
Flash point, closed cup	6°C [IPCS 2009]; 7°C [Sigma Aldrich 2010]	18°C [Merck Chemicals International 2010]
Autoignition temperature	365°C [IPCS 2009]; 345°C [Sigma Aldrich 2010]	265°C [Merck Chemicals International 2010]
Explosive limits in air	2.4% (V) – 13% (V) [IPCS 2009]	1.8% (V) – 10.9% (V) [Merck Chemicals International 2010]
Odor	Quinine odor, vapors have chlorine-like odor [Merck and Co. Inc. 2006]; strong rancid, chlorine-like, butter-like [Fischer Scientific 2007]	Fruity/pleasant [Chem Service Inc. 1988]

See footnotes at end of table.

(Continued)

Table 1-1 (Continued). Chemical and physical properties

Property	Diacetyl	2,3-Pentanedione
CAS #	**431-03-8**	**600-14-6**
Odor detection threshold	0.27 ppb [Hall and Andersson 1983; Nagata and Takeuchi 1990] (odor measurement of diacetyl vapor-air mixtures). Note: geometric mean of two literature reported threshold values with a geometric standard deviation of 5.33 ppb. 0.84 ppb [Buttery et al. 1997; Leksrisompong et al. 2010; Sega et al. 1967] (odor measurement of diacetyl vapor in the headspace above aqueous solutions, diacetyl concentrations in solution converted to air concentrations using Henry's Law constant). Note: geometric mean of three literature reported threshold values with a geometric standard deviation of 1.44 ppb. 1.2 ppb [Lawless et al. 1994] (recognition threshold) Note: not a geometric mean because obtained from a single source.	15 ppb [Hall and Andersson 1983] (odor measurement of 2,3-pentanedione vapor-air mixtures). Note: compared to 1.4 ppb for diacetyl obtained from the same reference.[¶] 9.4 ppb [Buttery et al. 1997] (odor measurement of 2,3-pentanedione vapor in the headspace above aqueous solutions, 2,3-pentanedione concentration in solution converted to an air concentration using Henry's Law constant). Note: compared to 0.70 ppb for diacetyl obtained from the same reference.[¶]
Octanol/water partition coefficient, Log P_{ow}	−1.34 [IPCS 2009]	−0.85 [Illovo Sugar Limited 2010]
Henry's Law Constant*	2.95×10^{-5} atm-m^3/mol*; 1.75×10^{-5} atm-m^3/mol at 25°C[Strekowski and George 2005]; 1.35×10^{-5} atm-m^3/mol at 25°C [Betterton 1991]; 1.75×10^{-5} atm-m^3/mol at 25°C [Snider and Dawson 1985]	4.7×10^{-5} atm-m^3/mol*
Appearance	Yellowish green liquid [Merck and Co. Inc. 2006]; green-to-yellow liquid [IPCS 2009]	Dark yellow liquid [Lide 2008]; [yellow to green yellow liquid [OSHA 2014]
Electron impact mass spectrum, m/z (%)	43 (100%), 15 (34%), 86 (11%), 14 (10%), 42 (7%), 13 (3%), 26 (2%), 29 (2%) [Nottingham University 1983]	43 (100%), 29 (69%), 57 (35%), 27 (30%), 15 (26%), 100 (10%), 26 (9%), 14 (9%) [Nottingham University 1983]
Infrared spectrum	1715.6 cm^{-1}, 1420.7 cm^{-1}, 1353.2 cm^{-1}, 1115.5 cm^{-1}, 537.2 cm^{-1} [Pouchert 1985]	2982.5 cm^{-1}, 1715.1 cm^{-1}, 1408.0 cm^{-1}, 1349.6 cm^{-1}, 1094.2 cm^{-1}, 908.7 cm^{-1}, 581.4 cm^{-1} [Pouchert 1985]

*Estimated as a ratio of vapor pressure to water solubility

National Toxicology Program 2007]; (2) from 2,3-butanediol, by oxidative dehydrogenation of 2,3-butanediol over a copper or silver catalyst [National Toxicology Program 2007]; (3) from acetoin (obtained by electrochemical oxidation of methyl ethyl ketone), by reacting acetoin with molecular oxygen in the presence of a copper oxide catalyst [Aquila et al. 2001]; or, (4) from 1-hydroxyacetone (obtained by dehydrogenation of 1,2-propanediol), by the acid-catalyzed condensation of 1-hydroxyacetone with formaldehyde [National Toxicology Program 2007].

Diacetyl is also a byproduct of fermentation. Natural diacetyl is used in the form of starter distillate, a concentrated flavor distillate, which may contain different concentrations of diacetyl depending on production conditions [Burdock 1997].

The compound 2,3-pentanedione is also naturally produced by fermentation and is recovered from dairy waste to be used as a flavoring ingredient [Miller et al. 1998]. The chemical synthesis of 2,3-pentanedione is achieved in the following ways: (1) the condensation of lactic acid and an alkali metal lactate [Miller et al. 1998]; (2) the acid-catalyzed condensation of 1-hydroxyacetone with paraldehyde [Lambrecht et al. 2004]; or (3) the oxidation of 2-pentanone with excess sodium nitrite and diluted hydrochloric acid in the presence of hydroxylamine hydrochloride [Burdock 1997].

1.5 Production Uses and Applications

The flavor manufacturing industry commonly uses diacetyl and 2,3-pentanedione during flavor formulation production. Flavor formulations are then sold to downstream users for the production of flavored food products. Flavored food production is the process of manufacturing food and beverage products that contain added flavor formulations or flavorings to enhance or modify the taste of the product. Examples of flavored food products include bakery products such as cake mixes, flour and margarines, dairy products such as cheese and yogurt, snack foods such as soft spreads and crackers, beverages such as soft drinks, in addition to candy, ice cream, frozen foods, and many other food and beverage products. The addition of concentrated flavorings including diacetyl is a cost effective way to impart the desired properties to manufactured food items.

In flavor formulations, diacetyl and 2,3-pentanedione are typically found as components in liquid solutions but can also be added to powders in dry mixtures to create a solid particulate formulation. Many volatile compounds are also encapsulated in an amorphous carbohydrate, producing more stable products with more manageable properties. Encapsulated powder flavorings are often created with a spray dryer, which converts a slurry mixture into a powder in which the flavorings are surrounded by the powder instead of simply coating the powder. When the encapsulated powder comes into contact with moisture, the flavor is released quickly and completely [Ubbink and Schoonman 2002].

The percentage of diacetyl or 2,3-pentanedione in a particular flavor formulation varies widely depending upon the product and its use. In past years, microwave popcorn contained the highest proportion of diacetyl ranging from 1% to 25% diacetyl [Hallagan 2007]. The diacetyl content in flavor formulations has declined rapidly as many manufacturers have reduced or substituted diacetyl with other flavoring compounds with similar characteristics, such as 2,3-pentanedione. Most confectionary flavors contain up to 1% diacetyl while marshmallow production uses up to 5% [Hallagan 2007].

Starter distillate, produced by fermenting milk with starter cultures, contains diacetyl in the range of 1% to 5% and is often used as a flavor enhancer in the dairy industry. Diacetyl is the major flavor component of starter distillate, constituting as much as 80% to 90% of the mixture's organic flavor compounds [FDA 2009]. A NIOSH health hazard evaluation (HHE) at a modified dairy production company found concentrations of airborne diacetyl ranging up to 2.14 parts per million on a full-shift TWA basis [NIOSH 2009].

Diacetyl is also used as a chemical modifier of arginine residues in proteins in studying glycation (the nonenzymatic browning of foods or the nonenzymatic binding of sugar and protein molecules in the body) [Saraiva et al. 2006]. Other uses for diacetyl include reactant/starting material in chemical or biochemical reactions, analytical reagent, antimicrobial/preservative, electron stabilizing compound and modifier of radiation response for chemical and biological systems, and photoinitiator/photosensitizer in polymerizations [National Toxicology Program 1994].

1.6 Potential for Exposures

It is difficult to quantify the number of employees directly involved with flavor manufacturing and more specifically having exposure to diacetyl or diacetyl substitutes in the United States. According to the Environmental Protection Agency (EPA) Non-Confidential Inventory Updating Report, diacetyl had an aggregate production volume between 10,000 and 500,000 pounds in 2002 [EPA 2002]. The North American Industry Classification System (NAICS) category 311, the most relevant category, indicates nearly 1.5 million employees are employed in food manufacturing. Bureau of Labor Statistics and Department of Commerce data provide a breakdown of a portion of that number into categories shown in Table 1-2. According to the FEMA, whose members account for approximately 95% of all flavors produced in the United States, a total of 6,520 employees work directly in flavor manufacturing or related laboratory activities in membership companies [Hallagan 2010].

Initial research concerning occupational exposure to diacetyl has focused on employees who directly produce flavorings or use them in the microwave popcorn industry. However, the employment figures for the food production industry suggest that some other employees have potential exposure to diacetyl and other food flavorings. For example, respiratory issues have been anecdotally reported for cheese production (Wisconsin), yogurt production (Ohio), and potato chip manufacturing [Alleman and Darcey 2002].

Employers in the food manufacturing sector are generally small business owners with 89%

Table 1-2. Breakdown of employees in various categories of the food manufacturing industry

Category description	No. of employees	NAICS code	Ref.
Bakeries and tortilla manufacturing	280,900	3118	[BLS 2008]
Other food manufacturing	164,100	3119	[BLS 2008]
Dairy product manufacturing	129,100	3115	[BLS 2008]
Sugar and confectionery product manufacturing	70,800	3113	[BLS 2008]
Beverage industry	177,000	3121	[BLS 2008]

of establishments employing fewer than 100 employees and nearly 53% of establishments employing fewer than 10 employees [United States Census Bureau 2004]. Industries that comprise food manufacturing can be found in every state in the United States; however, concentrations of specific industries are found in general geographic locations. For example, in 2004, 33% of the cheese manufacturing employees employed in the United States were in Wisconsin, and 20% of employees employed in the fruit and vegetable preservation industry were in California [BLS 2007].

There is increasing likelihood that various substances will be used as substitutes for diacetyl or 2,3-pentanedione. The potential for both employees' exposure and disease from exposure to these substitutes still remains largely unstudied.

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References

29 U.S.C. 669(a)(3). Research and related activities. United States Code. Washington, DC: U.S. Government Printing Office, Office of the Law Revision Counsel.

29 U.S.C. 671(c)(1). National Institute for Occupational Safety and Health. United States Code. Washington, DC: U.S. Government Printing Office, Office of the Law Revision Counsel.

ACGIH [2012]. 2012 TLVs® and BEIs®: threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists Signature Publications.

AIHA [1989]. Odor thresholds for chemicals with established occupational health standards. Dupraz C, Brosseau L, Guy H, May M, Reed L, eds. Fairfax, VA: American Industrial Hygiene Association.

Akpinar-Elci M, Travis WD, Lynch DA, Kreiss K [2004]. Bronchiolitis obliterans syndrome in popcorn production plant workers. Eur Respir J *24*(2):298–302.

Alleman T, Darcey DJ [2002]. Case report: bronchiolitis obliterans organizing pneumonia in a spice process technician. J Occup Environ Med *44*(3):215–216.

Aquila W, Botzem J, Brunner M, Fuchs H, Krause W, Pandl K, Schäfer-Lüderssen U [2001]. Process for the preparation of α-diketones from ketols or ketals from ketols. US Patent 6316676, filed February 28, 2001, and issued November 13, 2001.

Ashley K, McKernan LT, Burroughs E, Deddens J, Pendergrass S, Streicher RP [2008]. Analytical performance criteria. Field evaluation of diacetyl sampling and analytical methods. J Occup Environ Hyg *5*(11):D111–116.

Betterton E [1991]. The partitioning of ketones between the gas and aqueous phases. Atmos Environ *25A*:1473–1477.

BLS (Bureau of Labor Statistics) [2007]. Food manufacturing. http://www.bls.gov/oco/cg/cgs011.htm. Date accessed: October 2007.

BLS (Bureau of Labor Statistics) [2008]. National Employment Matrix, 2008–18, for NAICS 3113, 3115, 3118, and 3119. http://www.bls.gov/emp/ep_table_108.htm. Date accessed: December 2010.

Burdock GA [1997]. Encyclopedia of food and color additives. Boca Raton, FL: CRC Press, p. 2115.

Buttery RG, Ling LC, Stern DJ [1997]. Studies on popcorn aroma and flavor volatiles. J Agr Food Chem *45*(3):837–843.

California Code of Regulations. Title 8, §5197.

CDC (Centers for Disease Control and Prevention) [2002]. Fixed obstructive lung disease in workers at a microwave popcorn factory—Missouri, 2000–2002. MMWR *51*(16):345–347.

CDC (Centers for Disease Control and Prevention) [2007]. Fixed obstructive lung disease among workers in the flavor-manufacturing industry—California, 2004–2007. MMWR *56*(16):389–393.

Chem Service Inc. [1988]. Material safety data sheet, 2,3-pentanedione, O-818.

Day G, LeBouf R, Grote A, Pendergrass S, Cummings K, Kreiss K, Kullman G [2011]. Identification and measurement of diacetyl substitutes in dry bakery mix production. J Occup Environ Hyg *8*(2):93–103.

EPA [2002]. Non-confidential inventory updating report. http://www.epa.gov/iur/tools/data/2002-vol.html. Date accessed: March 2011.

EU [2014]. Recommendation from the Scientific Committee on Occupational Exposure Limits for diacetyl. SCOEL/SUM/149.

Ezrailson EG [2002]. Bronchiolitis in popcorn-factory workers. N Engl J Med *347*(24):1980–1982; author reply 1980–1982; discussion 1980–1982.

FDA (Food and Drug Administration) [2009]. Code of Federal Regulations, Title 21, Volume 3, Part 184, Direct food substances affirmed as generally recognized as safe, 21 CFR184.1278, diacetyl. U.S. Government Printing Office.

FEMA [2012]. Respiratory health and safety in the flavor manufacturing workplace. In: The flavor and extract manufacturers association of the United States. Washington, DC: p. 28.

Fischer Scientific [2007]. Material safety data sheet, 2,3-Butanedione, 99%. http://fscimage.fishersci.com/msds/03275.htm. Date accessed: November 2009.

Hall G, Andersson J [1983]. Volatile fat oxidation products. I. Determination of odour thresholds and odour intensity functions by dynamic olfactometry. Lebensmittel-Wissenschaft+ Technologie= Food science+ technology.

Hallagan J [2007]. Letter of June 20, 2007, from John Hallagan, General Counsel Flavor Extract Manufacturers Association, to Len Welsh, Acting Director, California Occupational Safety and Health Administration, distributed at the California OSHA Public Advisory Meeting, July 10, 2007.

Hallagan J [2010]. Letter of October 19, 2010, from John Hallagan, General Counsel Flavor Extract Manufacturers Association, based upon 2010 Industry Survey, to L. McKernan, Education and Information Division, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Department of Health and Human Services.

Hubbs AF, Cumpston AM, Goldsmith WT, Battelli LA, Kashon ML, Jackson MC, Frazer DG, Fedan JS, Goravanahally MP, Castranova V, Kreiss K, Willard PA, Friend S, Schwegler-Berry D, Fluharty KL, Sriram K [2012]. Respiratory and olfactory cytotoxicity of inhaled 2,3-pentanedione in Sprague-Dawley rats. Am J Pathol *181*(3):829–844.

Illovo Sugar Limited [2010]. Pentanedione, safety data sheet according to EC regulation No. 1907/2006.

IPCS (International Programme on Chemical Safety) [2009]. International Chemical Safety Card, 2,3-Butanedione. http://www.inchem.org/documents/icsc/icsc/eics1168.htm. Date accessed: March 2014.

Kanwal R [2003]. Letter of July 2, 2003, from R. Kanwal, Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Department of Health and Human Services, to Frank Morrison, Nebraska Popcorn. Clearwater, NE.

Kanwal R, Kullman G, Piacitelli C, Boylstein R, Sahakian N, Martin S, Fedan K, Kreiss K [2006]. Evaluation of flavorings-related lung disease risk at six microwave popcorn plants. J Occup Environ Med *48*(2):149–157.

Kanwal R, Martin S [2003]. Letter of May 13, 2003, from R. Kanwal and S. Martin, Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Department of Health and Human Services, to Keith Heuermann, B.K. Heuermann Popcorn, Inc. Phillips, NE.

Kim T, Materna B, Prudhomme J, Fedan K, Enright PL, Sahakian N, Windham G, Kreiss K [2010]. Industry-wide medical surveillance of California flavoring manufacturing workers: cross-sectional results. Am J Ind Med *53*(9):857–865.

Kreiss K, Gomaa A, Kullman G, Fedan K, Simoes EJ, Enright PL [2002]. Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. N Engl J Med *347*(5):330–338.

Lambrecht S, Franke O, Zahlman K [2004]. Process for the preparation of 2,3-pentanedione. U.S. Patent 6720456, filed November 7, 2002, and issued April 13, 2004.

Lawless HT, Antinone MJ, Ledford RA, Johnston M [1994]. Olfactory responsiveness to diacetyl. J Sens Stud *9*(1):47–56.

Leksrisompong P, Barbano DM, Foegeding AE, Gerard P, Drake M [2010]. The roles of fat and pH on the detection thresholds and partition coefficients of three compounds: diacetyl, δ-decalactone and furaneol. J Sens Stud *25*(3):347–370.

Lide D, ed. [2008]. CRC handbook of chemistry and physics. Boca Raton, FL: CRC Press.

Lockey JE, Levin LS, Lemasters GK, McKay RT, Rice CH, Hansen KR, Papes DM, Simpson S, Medvedovic M [1998]. Longitudinal estimates of pulmonary function in refractory ceramic fiber manufacturing workers. Am J Respir Crit Care Med *157*(4 Pt 1):1226–1233.

Martyny JW, Van Dyke MV, Arbuckle S, Towle M, Rose CS [2008]. Diacetyl exposures in the flavor manufacturing industry. J Occup Environ Hyg *5*(11):679–688.

Merck and Co. Inc., ed. [2006]. The Merck index. 14th ed. Whitehouse Station, NJ: Merck and Co. Inc.

Merck Chemicals International [2010]. 2,3-Pentanedione. http://www.merck-chemicals.com/2-3-pentanedione/MDA_CHEM-818555/p_HMKb.s1LnGcAAAEWhuEfVhTl]. Date accessed: December 2010.

Miller DJ, Perry SM, Fanson PT, Jackson JE [1998]. Condensed phase preparation of 2,3-pentanedione. U.S. Patent 5831130, filed April 24, 1997, and issued November 3, 1998.

Morgan DL, Jokinen MP, Price HC, Gwinn WM, Palmer SM, Flake GP [2012]. Bronchial and bronchiolar fibrosis in rats exposed to 2,3-pentanedione vapors: implications for bronchiolitis obliterans in humans. Toxicol Pathol *40*(3):448–465.

Nagata Y, Takeuchi N [1990]. Measurement of odor threshold by triangle odor bag method. Bull Jpn Environ Sanit Cent *17*:77–89.

National Toxicology Program [1994]. 2,3-Butanedione. CAS Number 431-03-8. http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/431-03-8.pdf. Date accessed: December 2010.

National Toxicology Program [2007]. Chemical information review document for artificial butter flavoring and constituents: diacetyl [CAS No. 431-03-8] and acetoin [CAS No. 513-86-0]. http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/Artificial_butter_flavoring.pdf. Date accessed: March 2011.

NIOSH [1986]. Hazard evaluation and technical assistance report: International Bakers Services, Inc, South Bend, IN. By McConnell R, Hartle R. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health, NIOSH HETA Report No. 1985–0171–1710.

NIOSH [2003]. Hazard evaluation and technical assistance report: Agrilink Foods Popcorn Plant, Ridgway, IL. By Sahakian N, Choe K, Boylstein R, Schleiff P. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, NIOSH HETA Report No. 2002–0408–2915.

NIOSH [2004a]. Hazard evaluation and technical assistance report: American Pop Corn Company, Sioux City, IA. By Kanwal R, Boylstein R, Piacitelli C. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, NIOSH HETA Report No. 2001–0474–2943.

NIOSH [2004b]. Hazard evaluation and technical assistance report: ConAgra Snack Foods, Marion, OH. By Kanwal R, Kullman G. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, NIOSH HETA Report No. 2003–0112–2949.

NIOSH [2006]. Hazard evaluation and technical assistance report: Gilster-Mary Lee Corporation, Jasper, MO. By Kanwal R, Kullman G, Fedan K, Kreiss K. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, NIOSH HETA Report No. 2000–0401–2991.

NIOSH [2009]. Hazard evaluation and technical assistance report: Chr. Hansen, Inc., New Berlin, WI. By Sahakian N, Kullman G, Dunn K, Kanwal R. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, NIOSH HETA Report No. 2007–0327–3083.

Nottingham University [1983]. Eight peak index for mass spectra. 3rd ed. Nottingham, UK: The Mass Spectrometry Data Centre, The Royal Society of Chemistry.

OSHA [2014]. Chemical sampling information, 2,3 pentanedione. https://www.osha.gov/dts/chemicalsampling/data/CH_260240.html. Date accessed: September 2014.

Parmet AJ [2002]. Bronchiolitis in popcorn-factory workers. N Engl J Med *347*(24):1980–1982; author reply 1980–1982; discussion 1980–1982.

Parmet AJ, Von Essen S [2002]. Rapidly progressive, fixed airway obstructive disease in popcorn workers: a new occupational pulmonary illness? J Occup Environ Med *44*(3):216–218.

Pouchert CJ, ed. [1985]. The Aldrich library of FT-IR spectra. Edition I, Volume I. Milwaukee, WI: Aldrich Chemical Co.

Saraiva MA, Borges CM, Florencio MH [2006]. Non-enzymatic model glycation reactions: a comprehensive study of the reactivity of a modified arginine with aldehydic and diketonic dicarbonyl compounds by electrospray mass spectrometry. J Mass Spectrom *41*(6):755–770.

Schachter EN [2002]. Popcorn worker's lung. N Engl J Med *347*(5):360–361.

Sega GM, Lewis MJ, Woskow MH [1967]. Evaluation of beer flavor compounds. Proceedings of the annual meeting of the ASBC *25*:156–164.

Sigma Aldrich [2010]. Material safety data sheet, No. B85037, 2,3- butanedione. http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=D3634&brand=SIGMA&PageToGoToURL=http%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Fsigma%2Fd3634%3Flang%3Den. Date accessed: December 2009.

Snider JR, Dawson GA [1985]. Tropospheric light alcohols, carbonyls, and acetonitrile: concentrations in Southwestern United States and Henry Law data. J Geophysical Res: Atmos *90*(ND2):3797–3805.

Strekowski RS, George C [2005]. Measurement of Henry's Law Constants for acetone, 2-butanone, 2,3-butanedione, and isobutyraldehyde using a horizontal flow reactor. J Chem Eng Data *50*(3):804–810.

Ubbink J, Schoonman A [2002]. Flavor delivery systems. In: Kirk RE, Othmer DF, eds. Kirk-Othmer encyclopedia of chemical technology. 4th ed. Cary, NC: John Wiley and Sons, Inc., pp. 527–563.

United States Census Bureau, United States Department of Commerce [2004]. Spice and Extract Manufacturing. 2002 Economic Census. Manufacturing Industry Series. Volume: EC02–311942(RV).

van Rooy FG, Rooyackers JM, Prokop M, Houba R, Smit LA, Heederik DJ [2007]. Bronchiolitis obliterans syndrome in chemical workers producing diacetyl for food flavorings. Am J Respir Crit Care Med *176*(5):498–504.