THE FLAVOR AND EXTRACT
MANUFACTURERS ASSOCIATION
OF THE UNITED STATES

JULY 2024

Respiratory Health and Safety in the Flavor Manufacturing Workplace

2024 Update

Introduction

Maintaining safe and healthy workplaces is a matter of utmost importance to FEMA and its members. In August 2004 FEMA published the first edition of the report *Respiratory Health and Safety in the Flavor Manufacturing Workplace* containing information to help flavor manufacturers protect workers from respiratory hazards in the workplace. A second edition of the report was published in April 2012, and this, the third edition, provides new information to assist flavor manufacturers in maintaining safe and healthy workplaces.

There is broad recognition that flavors are safe when ingested under their conditions of intended use in food (Hallagan *et al.*, 2020). However, the initial report from the National Institute for Occupational Safety and Health (NIOSH) of serious respiratory disease, and in some instances skin and eye irritation, among workers in the microwave popcorn manufacturing industry (Gomaa *et al.*, 2001; Akpinar-Elci *et al.*, 2004; Kanwal *et al.*, 2006) brought new attention to the importance of the proper handling of flavors by flavor and food manufacturing workers because they may be exposed to higher concentrations of flavors through inhalation than consumers get through food. Several reviews describe historical aspects of the focus on workplace safety issues in flavor and food manufacturing (NIOSH, 2003; FEMA, 2004; Clark and Winter, 2015; Hallagan, 2017; Kreiss, 2017; Wallace, 2017). The establishment of the Occupational and Inhalation Exposures Program by the National Institute of Environmental Health and Safety (NIEHS) and the National Toxicology Program (NTP) further emphasizes the focus on potential occupational inhalation exposures (Ryan, 2021).

The application of the information in this report to flavor manufacturing workplaces is a function of the specific aspects of workplaces and the products handled and manufactured therein. Because of the unique nature of flavor manufacturing workplaces, the information in this report should be used only as a resource. This report is not a comprehensive survey and summary of the relevant literature on any topic. Some documents referred to in this report may be accessed through the links provided while other reports may be retrieved through the usual appropriate means.

Like the 2004 and 2012 editions of this report, this edition is not a respiratory safety standard but is intended to share information that flavor manufacturers may find helpful in maintaining safe workplaces. FEMA is not responsible for the use or non-use of the information, or any action or failure to act, in any specific workplace based on reliance on this report. It is the responsibility of users of this report to verify information at it applies to specific workplaces before acting and to comply with relevant local, state, and federal laws and regulations. FEMA strongly urges users of this report to consult with appropriate experts, including industrial hygienists, pulmonologists, and occupational and environmental health and safety professionals regarding specific circumstances relevant to respiratory

health and safety in their flavor manufacturing facilities.

About This Edition

This edition contains new information related to regulations, guidance, and other helpful information published by the Occupational Safety and Health Administration (OSHA), the National Institute for Occupational Safety and Health (NIOSH), and others that has become available since 2012. OSHA announced significant changes to the federal Hazard Communication Standard (HCS) in 2012 (OSHA, 2012) to be consistent with the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) developed under an extensive program within the United Nations (U.N., 2023). Additional changes were announced in 2024 again to be consistent with the GHS (OSHA, 2024a). Hazard communication, and many resources available for compliance, are discussed in later sections of this report. Of significance is the NIOSH "Criteria Document" (McKernan *et al.*, 2016), and other information from NIOSH (*e.g.* Dunn *et al.*, 2015) published since 2012. Also included in this edition is information on numerous scientific studies on diacetyl and related flavoring substances that have been published since 2012 including studies published by NIOSH staff, staff from the National Toxicology Program (NTP), and others.

The focus on flavoring substances that may pose a respiratory safety risk if not handled properly in this edition remains on diacetyl and other volatile short-chain α-dicarbonyl substances such as 2,3-pentanedione. These substances have also been referred to as α-diketone substances. The mechanism of action of volatile short-chain α-dicarbonyl substances and the potential for resultant respiratory toxicity has been described by Hubbs *et al.*, 2019. New rodent inhalation toxicology studies conducted by the NTP and NIOSH that indicate that while attention should remain focused on the volatile short-chain α-dicarbonyl substances diacetyl and 2,3-pentanedione (Hubbs *et al.*, 2012; Morgan *et al.*, 2012; Morgan *et al.*, 2016; NTP, 2018), acetoin should not be considered to represent the same level of concern as diacetyl and 2,3-pentanedione (Hubbs *et al.*, 2019; NTP, 2023; Card *et al.*, 2023).

While the focus remains on volatile short-chain α-dicarbonyl substances, new resources available from OSHA, NIOSH, and others, and the significant amount of new information gained since the publication of the 2012 edition means that there is no longer a need to precautionarily prioritize substances using the parameters described in the 2004 and 2012 editions of this report. The new information, and new resources, described in later sections of this report, indicate that prioritization as described formerly in Table 1 of the previous editions of this report is no longer needed.

Workplace Safety Regulatory Requirements

Federal

The federal Occupational Safety and Health Act establishes that an employer's duty to employees is two-fold: specific duty requirements that mandate compliance with workplace safety standards promulgated by OSHA, and a general duty requirement to that requires employers to provide a workplace that is free from recognized hazards and that is unlikely to cause death or serious physical harm to employees (see 29 U.S.C. Sec. 654).

There is no federal workplace safety standard specifically for the flavor manufacturing industry. OSHA initiated a rulemaking process regarding occupational exposures to diacetyl in January 2009 through an Advance Notice of Proposed Rulemaking (ANPR) that requested relevant information related to workplace exposures to diacetyl (74 *Fed. Reg.* 3938. 21 January 2009) but OSHA withdrew the ANPR two months later (74 *Fed. Reg.* 11329. 17 March 2009) and did not pursue rulemaking further. However, OSHA made clear in its National Emphasis Program for Facilities that Manufacture Food Flavorings Containing Diacetyl (OSHA, 2009) that the agency relies heavily on the General Duty Clause of the Occupational Safety and Health Act (Section 5(a)(1) of the Act) for broad authority over flavor manufacturing in general, and specifically for potential exposure to diacetyl. An OSHA inspection under the National Emphasis Program for flavor manufacturing resulted in a flavor manufacturer receiving citations for deficiencies in hazard communication, respiratory protection, and personal protective equipment (Lee, 2012). Before initiating the National Emphasis Program for flavor manufacturing, OSHA implemented a National Emphasis Program for Microwave Popcorn Manufacturing Plants which can also provide useful information for flavor manufacturers (OSHA, 2007).

In addition to the General Duty Clause, the flavor industry is subject to a number of OSHA regulatory requirements. As discussed in the subsequent section of this report on occupational exposure limits (OELs), OSHA has established OELs as permissible exposure limits (PELs) for only a small number of flavoring substances. OSHA PELs have the force of regulation and may be a source of citations if they are determined to be exceeded by OSHA. An annotated list of PELs can be found on the OSHA website (OSHA, 2024b).

The federal HCS applies to flavor manufacturing. The HCS requires that chemical manufacturers, distributors, and importers evaluate the chemicals that they produce and provide hazard information to downstream employers and employees by providing safety data sheets (SDSs), and labeling containers and vessels in compliance with the HCS. As discussed in the subsequent section on hazard communication and labeling, OSHA guidance and other resources are available to assist flavor manufacturers in their compliance

activities.

Flavor manufacturers should be familiar with, and comply with, the OSHA Respiratory Protection Standard (29 C.F.R. 1910.134). Failure to comply with this standard remains a common source of OSHA citations. Other OSHA regulations that are relevant to flavor manufacturing include, but are not limited to, injury and illness reporting (OSHA, 2023), and OSHA's confined space regulations (29 CFR 1910.146) that may apply to some flavor manufacturers employing large vessels or tanks in their operations. Guidance on confined space entry and work is available from OSHA (https://www.osha.gov/confined-spaces) and the National Fire Protection Association (NFPA, 2022).

California

In 2006, the California Division of Occupational Safety and Health (Cal/OSHA) implemented the Flavor Industry Safety and Health Evaluation Program (FISHEP) with the assistance of FEMA. This program resulted in workplace safety consultations by Cal/OSHA with flavor manufacturers operating in California. FISHEP assisted California flavor manufacturers in maintaining safe workplaces and provided important information used in the adoption of a workplace safety regulation specifically for flavor manufacturing in California in 2010 (C.C.R. Title 8, Section 5197) The regulation contains a "1% cutoff" for diacetyl in compounded flavors and contains provisions related to flavoring substances considered as "alternatives" to diacetyl – acetoin, 2,3-pentanedione (acetyl propionyl), diacetyl trimer, 2,3-hexanedione, and 2,3-heptandione. The state's final statement of reasons explains the rationale for the regulations (California Occupational Safety and Health Standards Board, 2009). While there has been little activity with this regulation in recent years, the regulation remains in force and flavor manufacturers in California should follow its requirements. California remains the only state or federal agency to promulgate workplace safety regulations specific for flavor manufacturing workplaces.

Government Agency Guidance and Advice

OSHA and NIOSH maintain web pages on flavorings-related lung disease. The OSHA page can be found at www.osha.gov/SLTC/flavoringlung/index.html and the NIOSH page at http://www.cdc.gov/niosh/topics/flavorings. NIOSH also has a science blog on diacetyl and food flavorings at http://blogs.cdc.gov/niosh-science-blog/2008/11/10/diacetyl/. Among other available resources is an OSHA Worker Alert (OSHA, 2010).

In 2015, NIOSH published the report, *Best Practices – Engineering Controls, Work Practices, and Exposure Monitoring for Occupational Exposures to Diacetyl and 2,3-Pentanedione* (Dunn *et al.*, 2015). The following year NIOSH published the nearly 400-page "Criteria Document," *Criteria for a Recommended Standard – Occupational Exposure to Diacetyl and 2,3-Pentanedione* (McKernan *et al.*, 2016). This report contains a wealth of information and covers a number of critical subjects including exposure monitoring and control, recommended OELs for

diacetyl and 2,3-pentandione, and medical monitoring of workers. Although this report focuses on diacetyl and 2,3-pentanedione, the respiratory health and safety principles described in the report have relevance to potential exposures to other flavoring substances and to flavor manufacturing in general.

Important information is also available through the NIOSH program of Health Hazard Evaluations (HHEs) that describe evaluations on a variety of workplaces. NIOSH HHE reports are available on the NIOSH website at www.cdc.gov/niosh/hhe/. Several types of facilities relevant to the flavor industry have been evaluated by NIOSH. HHEs for flavoring manufacturing facilities include Kanwal and Kullman (2007), Bailey *et al.* (2008), Sahakian *et al.* (2009), and Cummings *et al.*, (2013a). While there have been no additional HHEs on flavor manufacturing since 2013, NIOSH has continued to evaluate potential occupational exposures to diacetyl and 2,3-pentanedione in other industries such as dairy food manufacturing facilities (Bailey and Piacitelli, 2013), snack food manufacturing facilities (Cummings *et al.*, 2013b; Hawley *et al.*, 2016), pet food manufacturing (LeBouf *et al.*, 2014), vaping shops (Zwack *et al.*, 2018), and coffee processing facilities (Bailey *et al.*, 2020).

Respiratory Health and Safety in Flavor Manufacturing Facilities

Introduction

Reports of respiratory illness in flavor manufacturing indicate the need for respiratory health and safety programs in these facilities (Lockey *et al.*, 2002; FEMA, 2004; VanRooy *et al.*, 2007; VanRooy *et al.*, 2009; Kanwal and Kullman, 2007; Bailey *et al.* 2008; Sahakian *et al.* 2009; Kreiss, 2012; Lee, 2012; Cummings *et al.*, 2013a). Previous editions of this report (FEMA, 2004; FEMA, 2012) together with FEMA-sponsored workshops, and consistent sharing of relevant workplace safety information with FEMA members up to the present have helped many flavor manufacturers to make enduring changes in processes, procedures, and communication to provide employees with workplaces free from respiratory safety risk. This report describes numerous resources that flavor manufacturers may consult to develop respiratory health and safety programs for their facilities. This report is not intended to be exhaustive but rather to identify resources to assist flavor manufacturers as they develop their own respiratory health and safety programs.

Flavor manufacturing facilities vary greatly in size, structure, age, manufacturing technologies employed, flavoring substances

stocked and handled, types of flavors manufactured, and many other characteristics, and therefore present significant variability in opportunities for exposure to flavoring substances as described by Martyny *et al.* (2008) who evaluated potential diacetyl exposures in sixteen flavor manufacturing facilities. Manufacturing processes may range from simple blending and packaging to more complicated processes that include repeated heating of flavoring substances that are mixed and heated again, extraction at room temperature and with heat, and other processes that may result in opportunities for exposure. Some facilities have extensive automated processes that minimize opportunities for exposure while others have little automation and rely on workers manipulating large quantities of flavors and other materials by hand during the formulation and packing processes. Because of this great variability, "one size fits all" solutions for respiratory health and safety programs are not appropriate. The following sections of this report summarize a framework for developing a respiratory health and safety program for flavor manufacturing facilities.

Hazard identification

More than 3,000 chemically-defined flavoring substances and natural flavoring complexes are commonly used to formulate flavors. The vast majority of flavoring substances have chemical and physical characteristics that would make it unlikely that they would pose a risk of respiratory injury in the workplace. Most of the substances are not significantly volatile and do not have a significant degree of reactivity. However, some low molecular weight chemically-defined flavoring substances may have sufficient volatility and/or reactivity to pose a risk of respiratory injury when improperly handled.

The U.S. Food and Drug Administration (FDA) is responsible for the regulation of the addition of flavoring substances to food through several regulatory pathways (Hallagan *et al.*, 2020). Inhalation data are not required by FDA to establish regulatory authority to use substances as flavors added to food so historically the focus on potential toxicity has been on the ingestion route of exposure. As a result, relatively few flavoring substances have been studied for potential inhalation toxicity. In addition to there being few flavoring substances with inhalation toxicity data, the interpretation and relevance of the results of inhalation studies in rats and mice is often constrained by the significant anatomic and physiologic differences between rodents and humans (Morgan *et al.*, 2008; Morris and Hubbs, 2009; Morgan *et al.*, 2012; SOT, 2018). For example, unlike humans, rodents are obligate nose-breathers and the human nasal cavity is shorter, has fewer turbinates, and a smaller surface area for removal of reactive chemicals compared with the rodent nasal cavity.

Even though there are difficulties in studying inhalation exposures in rodents, information on occupational inhalation exposures to diacetyl has generally been supported by the results of animal inhalation toxicity studies of diacetyl indicating a variety of effects on the respiratory tracts of rats and mice

(*e.g.* Hubbs *et al.*, 2002; Hubbs *et al.*, 2004; Hubbs *et al.*, 2008; Goravanahally *et al.*, 2014; NTP, 2018). A number of studies and models have explored potential mechanisms of toxicity for diacetyl (Palmer *et al.*, 2011; Hubbs *et al.*, 2012; More *et al.*, 2012; Dworak *et al.*, 2013; Zaccone *et al.*, 2013; Zaccone *et al.*, 2015; Hubbs *et al.*, 2016; Brass and Palmer, 2017; Cichocki and Morris, 2017). Hubbs *et al.*, (2019) reviewed much of this work and described new mechanistic data that implicate α-dicarbonyl compounds, including diacetyl, in airway injury and flavorings-related lung disease.

A significant number of animal studies on diacetyl and its close structural relative, 2,3-pentanedione, support maintaining attention on these substances in flavor and food manufacturing (*e.g.* Anderson *et al.*, 2013; Morgan *et al.*, 2016; Anders, 2017; Flake and Morgan, 2017; NTP, 2018; NTP, 2023). Several structurally-related substances, 2,3-hexanedione, 3,4-hexanedione, and 2,3-heptanedione do not appear to have the same level of potential toxicity as diacetyl and 2,3-pentanedione. While acetoin may be converted to diacetyl through oxidation under certain conditions that may occur during handling (McKernan *et al.*, 2016), studies by Hubbs *et al.*, (2019), and NTP (2023), and an analysis of the NTP studies (Card *et al.*, 2023) demonstrate that acetoin itself does not have significant potential for respiratory toxicity when inhaled under the conditions of the Hubbs *et al.* and NTP studies.

In 2023 NIOSH initiated an occupational exposure study of four terpenes used as flavoring substances, α-pinene, *b*-pinene, delta-3-carene, and *d*-limonene, in a variety of workplaces and occupational exposure scenarios, including flavor manufacturing (Christensen, 2023). The rationale for the NIOSH terpene exposure study is the observation of a variety of toxic effects in rodent inhalation studies conducted by the National Toxicology Program (NTP). These studies include two-year chronic toxicity/carcinogenicity studies in rats and mice on α-pinene administered by inhalation. Information on the findings from these studies has not been made publicly available yet but other reports from NTP on *in vitro* studies suggest a focus on the potential carcinogenicity of α-pinene oxide, a metabolite reported in rodents following inhalation exposure to α-pinene (Fernando *et al.*, 2021; Waidyanatha *et al.*, 2021; Waidyanatha *et al.* 2022).

The IFRA-IOFI Labelling Manual 2023 (IFRA-IOFI, 2023), developed and maintained jointly by the International Fragrance Association (IFRA) and the International Organization of the Flavor Industry (IOFI), contains useful information on potential inhalation hazards through the assignment of classifications according to the UN GHS guidance (OSHA, 2024; U.N., 2023). Other information useful in hazard identification are data from the FEMA poundage surveys. Data from surveys conducted for the years 1995, 2005, 2010, 2015, and 2020 represent the amount of each FEMA GRAS flavoring substance estimated to "disappear" (be available for use) into the U.S. food supply in a given year (*e.g.* Harman *et al.*, 2023). This information allows

for an estimate of the trends in use for flavoring substances.

Assessment of potential exposures

An exposure assessment often is a first step in assessing the need for employing methods to reduce exposures to potentially hazardous substances. Monitoring at regular intervals for the presence of certain vapors and particulates when reliable methods are available can provide valuable information on potential exposures and can guide the implementation of effective controls. A critical issue in any monitoring program is identifying the appropriate substances to monitor. NIOSH has focused on diacetyl and 2,3-pentanedione in flavor and food manufacturing and provides a thorough discussion of analytical methods and sampling in the NIOSH Criteria Document (McKernan *et al.*, 2016). The *NIOSH Manual of Analytical Methods* (NMAM) is a compilation of methods used by the agency and is a key resource (NIOSH, 2020).

OSHA included a description of analytical methods for a number of flavoring substances including diacetyl in its National Emphasis Program for flavor manufacturing (OSHA, 2009). Also relevant are reports by Cox-Ganser *et al.* (2011) and Day *et al.* (2011) on analyzing for diacetyl and 2,3-pentanedione. Boylstein *et al.* (2006) analyzed diacetyl and dust emissions from butter flavorings used to manufacture microwave popcorn, and Rigler and Longo (2010) described the methods they used to analyze butter flavors and natural butter for diacetyl content. Rincon-Delgadillo *et al.* (2012) described analyses for diacetyl in butter starter distillate and certain dairy foods.

Analyzing emissions from individual compound flavors presents a number of challenges due to variability in composition and conditions under which the analysis is performed. Due to these challenges, exposure modeling may be useful in certain instances (AIHA, 2020). Angelini *et al.* (2016) refined the ECETOC-TRA (European Centre for Ecotoxicology and Toxicology of Chemicals—Target Risk Assessment) model using correction factors to more realistically assess occupational respiratory exposure in flavor and fragrance manufacturing settings. Their refined model overestimated exposures for 98% of the values obtained compared with the experimental values measured in real conditions whereas the ECETOC-TRA model overestimated exposures for only 37% of the values obtained compared to the experimental values. Given the importance of ensuring that estimates of exposure obtained through modeling software are overestimated rather than underestimated, the Angelini *et al.* method offers a useful refinement to the ECETOC-TRA modeling software.

The importance of environmental monitoring is also emphasized by the workplace exposure study NIOSH has initiated on four terpenes (α-pinene, b-pinene, delta-3-carene, and *d*-limonene) in which NIOSH will evaluate a variety of workplaces, including flavor manufacturing, as a prelude to a possible health effects study if it is determined that significant exposures occur (Christensen, 2023). NIOSH identified analytical methods for

the terpenes relevant to this study (NIOSH, 2020a; NIOSH 2020b).

Occupational Exposure Limits

In the U.S., occupational exposure limits (OELs) include permissible exposure limits (PELs) established by OSHA that have the force of regulation, threshold limit values (TLVs) and short-term exposure limits (STELs) established by the American Conference of Government Industrial Hygienists (ACGIH) that are voluntary guidelines, and proposed OELs developed by others. It is important to note that OELs apply to specific routes of potential exposure in occupational settings. For example, OELs are commonly established for potential occupational inhalation and dermal exposures. Very few FEMA GRAS flavoring substances have occupational exposure limits (OELs) of any kind. As of 2024, less than 1.0% of FEMA GRAS flavoring substances have OELs. An annotated list of PELs is available on the OSHA website (OSHA, 2024b).

Diacetyl and related substances such as 2,3-pentanedione have not been assigned PELs or STELS by OSHA. While a number of OELs have been proposed for diacetyl and 2,3-pentandione (*e.g* Maier *et al.*, 2010; Egilman *et al.*, 2011; ACGIH, 2024; Beckett *et al.*, 2019; Card *et al.*, 2023) the OELs recommended by NIOSH in its 2016 report, C*riteria for a Recommended Standard – Occupational Exposure to Diacetyl and 2,3-Pentanedione* (McKernan *et al.*, 2016) are the most widely recognized. NIOSH recommended exposure limits (RELs) for diacetyl and 2,3-pentanedione are 5 ppb/8 hour time-weighted average (TWA) and 9.3 ppb/8 hour TWA, respectively. NIOSH also recommended short-term exposure limits (STELs) for each substance – 25 ppb/15 minutes for diacetyl and 31 ppb/15 minutes for 2,3-pentanedione.

As discussed in the Hazard Identification section of this report, NIOSH has initiated an exposure study in a variety of workplaces on four terpenes: α-pinene, *b*-pinene, delta-3-carene, and *d*-limonene. While there are no PELs for the four terpenes, the OSHA PEL for turpentine, of which α-pinene is the predominant terpene, is 100 ppm/8 hr TWA. The ACGIH TLVs for turpentine, α-pinene, *b*-pinene, and delta-3-carene are 20 ppm/8 hr. TWA for each material. Relevant analytical methods are available from NIOSH (NIOSH, 2020a; NIOSH 2020b). The NIOSH exposure study is expected to continue for several years and while there is significant uncertainty whether inhalation exposure to α-pinene and other terpenes pose a hazard and risk in the flavor manufacturing workplace, it is worthwhile to consider action in the face of this uncertainty, and out of an abundance of caution, to reduce occupational exposure to these terpenes.

OELs may be established and enforced in other countries and regions. For example, in 2017 the European Union adopted occupational exposure limits for diacetyl of 0.02 ppm/8-hour TWA, and a STEL of 0.1 ppm (EU, 2017). Card *et al.* (2023) provide a summary of OELs for diacetyl and 2,3-pentanedione in several countries and regions but note the difficulties in verifying some of them. Flavor manufacturers and users should check

regulations and available guidance in the jurisdictions in which they operate for relevant OELs.

Occupational Exposure Banding

Occupational exposure banding, also referred to as control or hazard banding, may be useful in the absence of an OEL for a possible occupational exposure hazard. These techniques represent a process of assigning substances into bands or categories based on a substance's toxicological potency and the risk of adverse health effects that may be associated with exposure. The result of this process is an occupational exposure band (OEB) which is a range of exposure concentrations where worker health can be expected to be protected (AIHA, 2021). Given the small number of flavoring substances with OELs, OEB approaches may be helpful in certain instances. Numerous resources are available to explore the development of OEBs (McKernan *et al.*, 2016a; Scheffers *et al.*, 2016; AIHA, 2021; NIOSH, 2021; Mercer, 2023).

Management and Employee Awareness Through Education, Training and Hazard Communication

Even though there have been significant efforts made for more than twenty years by FEMA, NIOSH, and OSHA to increase awareness of the potential workplace hazards associated with diacetyl and other flavoring substances, it is impossible to assure that all flavor and food manufacturers are aware of the potential hazards. Exposure limits, even when adopted and enforced, do not guarantee protection from occupational injury because potential hazards often go unrecognized until relevant data become available or until there is a sentinel event. Workers and employers may not know the identity of every substance to which they are exposed.

Thorough education and communication among both management and employees of flavor manufacturers are critical to the success of any workplace health and safety program. Formal, mandatory hazard communication and training sessions assure that employees have the appropriate awareness of respiratory safety issues. Task areas that merit focus include:

- Personnel who blend and mix flavors in bulk quantities, especially those exposed to heated flavors, and the powder flavor and spray-dry manufacturing processes
- Personnel who pack flavors (liquid or dry)
- Quality assurance personnel and flavorists who may have repeated exposure to flavors even though exposure may be in smaller amounts

Hazard communication - SDSs

Clear communication of hazards is of critical importance to employers and employees who may have occupational exposures to hazardous chemicals. Flavor manufacturers and suppliers cannot in all instances know how their customers will use a flavoring substance. In many instances, a customer may choose to keep information on how they will use a flavoring substance confidential to pro-

tect valuable trade secret information related to their products. In other instances, customers may communicate to a supplier how they plan to use a flavor but then modify their plans. The OSHA Hazard Communication Standard (OSHA, 2012; OSHA, 2024a; 29 CFR Parts 1910,1915, and 1926; www.osha.gov/hazcom) establishes a minimum for hazard communication through its safety data sheet (SDS) and labeling requirements using the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) as explained by OSHA (OSHA, 2012; OSHA, 2024a) and the United Nations (U.N., 2023).

The HCS requires that chemical manufacturers, distributors, and importers provide SDSs for chemicals to downstream users that contain information on the physical and health hazards identified for the chemical along with safety precautions and protective measures that should be employed when handling, storing and transporting the chemical. The development and provision of SDSs is an individual company obligation. FEMA does not, and has never, compiled or published SDSs, or reviewed or approved company SDSs. FEMA has assisted members in meeting their hazard communications obligations only by serving as one source for potentially relevant information.

The preambles to the HCS final rules (OSHA, 2012; OSHA, 2024a) contain information helpful in complying with the HCS. Other resources available from government agencies include OSHA's guidance issued in 2007 on hazard communication as it relates to diacetyl (OSHA, 2007). OSHA has informally stated that its 2007 guidance also applies to 2,3-pentanedione although OSHA did not revise the guidance to include this flavoring substance. OSHA also issued general guidance on enforcement (OSHA, 2015) and hazard classification (OSHA, 2016). Significant resources are available in the Hazard Communication section of the OSHA website including interpretation letters OSHA has issued explaining the standard. The NIOSH Criteria Document contains helpful information. NIOSH has noted issues and concerns with hazard communication related to diacetyl and 2,3-pentanedione (LeBouf *et al.*, 2019).

In addition to commercial databases and consulting firms, several resources are available to FEMA members to assist them in compiling SDSs. A key resource available to FEMA members is the IFRA-IOFI Labelling Manual 2023 (IFRA-IOFI, 2023). The IFRA-IOFI Labelling Manual 2023 provides information on hazard identification and the harmonization of hazard statements for hazard communications purposes consistent with the requirements of the GHS and can be accessed through the Member Resources section of the FEMA website (www.femaflavor.org) using FEMA members' access to the IOFI Member Network (www.iofi.org). Helpful information can also be found in the OSHA GHS Compliance Guide published by FEMA and the International Fragrance Association North America (FEMA/IFRANA, 2014).

Hazard communication - labeling

In addition to hazard communication through the provision of SDSs, the HCS man-

dates labeling containers, packages and vessels containing hazardous materials (29 CFR 1910.1200(f)) providing an additional opportunity for flavor manufacturers to interact with customers to assure that customers receive helpful information related to the safe handling and use of flavors in their production processes. The resources described above for compiling SDSs including the OSHA GHS Compliance Guide (FEMA-IFRANA, 2014) and the IFRA-IOFI Labelling Manual 2023 are also helpful in complying with HCS labeling requirements. If flavor manufacturers choose to provide supplementary labeling in addition to labeling required by regulation such additional language should not be substituted for, or used in lieu of, any of the requirements of the HCS labeling provisions at 29 CFR 1910.1200(f).

Controlling Potential Exposures

Employing the basic principles that comprise the well-recognized industrial hygiene hierarchy of controls (Cullinan *et al.*, 2017) can greatly reduce opportunities for hazardous exposures in flavor manufacturing facilities:

- Elimination of the potentially hazardous substance
- Substitution for the potentially hazardous substance
- Engineering controls to reduce/prevent possible exposures
- Administrative controls to reduce/prevent possible exposures
- Personal protective equipment to protect against exposures

Product elimination and substitution

In some instances it is not possible to eliminate or substitute for potentially hazardous flavoring substances because alternatives are not available, or because of the difficulty in achieving the desired flavor profile. However, through substitution it may be possible to reduce the concentration of a potentially hazardous substance in the compounded flavor. Product substitution may be employed when it is suspected that a substance may be hazardous and can be replaced with one that is not. The unique nature of the flavor imparted by certain substances, many of which are naturally-occurring constituents of food, may make it difficult to identify substitutes that function properly in the food to which they are added and that meet consumer expectations.

The history of concerns associated with occupational inhalation exposures to butter flavors illustrates issues that arise in product elimination and substitution strategies. As information became available in the early to mid-2000s related to occupational exposures to butter flavors containing diacetyl (Gomaa *et al.*, 2001; Kreiss *et al.*, 2002; NIOSH, 2003; FEMA, 2004) the flavor industry began to identify potential substitutes for diacetyl that would meet consumer expectations. In exploring potential substitutes for diacetyl, the flavor industry initially focused on 2,3-pentanedione, an α-dicarbonyl substance that is a close structural relative of diacetyl and has a flavor profile more similar to diacetyl than longer-chain α-dicarbonyl flavoring substances 2,3-hexanedione, 3,4-hexandione,

and 2,3-heptanedione.

In 2010 OSHA published a "Worker Alert" on diacetyl and potential substitutes noting that "some diacetyl substitutes may also cause harm" and stated that 2,3-pentandione, 2,3-hexanedione, and 2,3-heptanedione "have not been proven to be safe" in potential workplace exposure settings (OSHA, 2010). NIOSH requested information on flavoring substances that may be used as substitutes (76 *Fed. Reg.* 1434. 10 January 2011). FEMA provided information to NIOSH on six flavoring substances that it was aware of that may serve as substitutes for diacetyl: the α-dicarbonyl substances 2,3-pentanedione, 2,3-hexanedione, 3,4-hexandione, 2,3-heptanedione, and acetoin and diacetyl trimer. Subsequently it became apparent that butter starter distillate could be used as a substitute for diacetyl but this material is known to contain relatively high levels of diacetyl (LSRO/FASEB, 1980; FDA, 1982) and should not be considered a safe substitute for diacetyl. FEMA has learned that diacetyl trimer is not used as a substitute for diacetyl and it has had no reported use in FEMA's recent poundage surveys. An environmental monitoring study conducted by NIOSH at a microwave popcorn production plant evaluated eight different butter flavorings for the presence of "diacetyl substitutes." The substitutes included acetoin in five samples, 2,3-pentanedione in four, and 2,3-hexanedione in one (Boylstein, 2012). Acetoin is not a volatile short-chain α-dicarbonyl flavoring substance but imparts a "buttery" flavor and, based on recent rodent inhalation studies, does not represent the same level of concern as diacetyl and 2,3-pentanedione (Hubbs *et al.*, 2019; NTP, 2023; Card *et al.*, 2023).

A number of groups have published rodent studies evaluating the potential inhalation toxicity of potential diacetyl substitutes. Several studies have evaluated the comparative potential toxicity of diacetyl and 2,3-pentanedione and found that both substances are associated with similar rodent respiratory tract toxicity, among other effects (Morgan *et al.*, 2008; Hubbs *et al.*, 2012; Morgan *et al.*, 2012). In 2013, NIOSH published a HHE on a flavoring manufacturing facility where it appears that illness may have arisen from exposure to 2,3-pentanedione used as an alternative to diacetyl (Cummings *et al.*, 2013a). As a result of these findings, NIOSH focused attention on diacetyl and 2,3-pentanedione in their Criteria Document (McKernan *et al.*, 2016). Singal *et al.* (2012) reported the results of an inhalation study of 2,3-pentanedione in rats using whole body exposures of 8.8, 17.5, and 35 ppm of for two weeks. No respiratory tract toxicity was observed at the lowest concentration tested, 8.8 ppm. The authors note that the 8.8 ppm no-adverse-effect level concentration is significantly higher than the REL of 9.3 ppb/8 hour TWA proposed for 2,3-pentandione by NIOSH (McKernan *et al.*, 2016). With respect to other α-dicarbonyl flavoring substances, a comparative study demonstrated similar potential of diacetyl, 2,3-pentanedione, 2,3-hexanedione, 3,4-hexanedione, and 2,3-heptanedione to induce dermal irritation and sensitization in mice (Anderson *et al.*, 2013).

The National Toxicology Program (NTP)

published the results of two-week and three-month inhalation studies in rats and mice with 2,3-pentanedione and acetoin (NTP, 2023). In the 2,3-pentanedione studies, rats and mice were exposed to 2,3-pentanedione vapors at concentrations up to 100 ppm. In the acetoin studies, rats and mice were exposed to acetoin vapors at concentrations up to 800 ppm. NTP concluded, "Under the conditions of this inhalation study, there were no significant exposure-related adverse effects in rats or mice exposed to acetoin for 2 weeks or 3 months. Exposure to 2,3-pentanedione via whole-body inhalation for 3 months caused significant adverse effects primarily in the respiratory tract but also in the eyes, of rats and mice." (NTP, 2023).

Engineering and Administrative Controls

Flavoring substances and mixtures, whether liquid or dry, should be handled in such a way as to minimize the disbursement of airborne aerosols or particulate matter (McKernan *et al.*, 2016). This means that mixing, blending and other physical manipulation activities should be performed in closed systems when possible. When systems must remain open then local exhaust ventilation should be used. Fume hoods are commonly used in research and development laboratories. Dilution through general room ventilation is generally not recommended and seldom results in exposure reduction unless extremely high volumes of air are circulated, and may even result in a greater number of workers being exposed.

A key aspect of evaluating potential risk of exposure for flavoring substances is volatility. The molecular weight and calculated vapor pressure of flavoring substances are helpful in assessing volatility. Heating increases volatility and therefore air concentrations of flavoring substances and, thus, is of particular concern with regard to potentially hazardous respiratory exposures. Mixing of heated flavors should be conducted in closed vessels with local ventilation. To minimize emission of volatile chemicals into the air, heated processes should be maintained at the lowest possible temperature. Workers should not open heated vessels to conduct visual inspections in such a way as to create an opportunity for exposure. In instances when workers must work near open vessels that are heated and cannot be closed or do not have local ventilation, potential exposures should be promptly evaluated by environmental sampling, and if potential exposures are elevated, then proper personal protective equipment should be employed.

Flavor compounding activities such as mixing or pouring can result in significant exposures. In most instances, mixing of liquid and dry flavors should be conducted in fully or partially closed vessels with local ventilation. Opportunities for the generation of airborne particles and aerosols should be minimized. Proper pouring techniques for liquid and dry flavors can greatly reduce opportunities for exposure.

For liquid flavoring substances, techniques can be adopted that pipe material into mixing vessels so that workers do not have to pour. In some instances, it is appropriate to pipe in liquids below the surface of solutions

in vessels to minimize splashing. This is particularly important for volatile substances. For dry and powdered flavors, pouring should be conducted in such a way that the generation of airborne particulates is minimized to reduce potential exposures as well as the potential for static buil*d*-up and combustible dust explosions. Proper pouring techniques such as pouring slowly close to the mixing vessel can greatly minimize airborne particulates. Mixing ingredients in an order in which dry ingredients are added last to liquid mixtures also can minimize particulate generation. Local exhaust ventilation is the most effective control for these operations. Systems can be designed that will allow easy pouring and at the same time control exposures.

Packaging activities can result in significant opportunities for exposure, especially when dry flavors are filled into bags, boxes or drums under pressure. Closed systems should be used when possible but, unless there is an unusually high degree of automation, workers will have opportunities for exposure as filled containers must be replaced with empty ones, and when containers must be sealed and closed. The use of personal protective equipment may be employed to minimize exposure.

Flavoring substances with a higher degree of volatility should be stored in cooled storage areas. Substances such as acetaldehyde are often stored in cooled rooms and are often also used in flavor manufacture in a cooled state. Liquid and powdered flavors should ideally be stored in store-rooms with their own air handler that has minimum recirculation. In some instances, flavor facilities have negative air flow in storage areas to reduce opportunities for exposure.

Cleaning of process vessels that contained liquid flavors or viscous mixtures, or work areas with spilled material, especially with steam or heated water, may create opportunities for exposure to flavoring substances. Similarly, cleaning vessels or areas used to manufacture or mix powdered flavors with compressed air may also result in airborne particulates. It is important that cleaning activities be conducted in a manner that does not result in significant air concentrations of flavors and other materials present in the vessel. Cleaning areas should be isolated and contained to prevent the dissemination of airborne flavoring substances. Automated cleaning processes will greatly reduce opportunities for exposure and should be employed wherever possible. In some instances, the most effective way to protect workers responsible for cleaning activities will be to use personal protective equipment. It is also important that adequate care be exercised if workers are to enter or partially enter equipment in order to clean it. In addition to concerns about possible respiratory exposures, in some instances, cleaning activities involving vessel entry may be subject to the requirements of OSHA's confined space regulations (29 CFR 1910.146).

Opportunities for exposure can be greatly decreased by segregating functions that involve the handling of flavors from functions that do not. For example, a flavor compounding, packing, or shipping area should not share space with a sales office. Flavor production areas should be separate from non-production

areas, and they should not share the same air handler. Air flow and air pressure through a building or space should flow from areas of no or low potential hazard to those with higher levels of potential hazard. The areas of highest potential hazard should have negative air pressure in relation to adjacent spaces to reduce the potential for the migration of hazardous materials from that space.

A number of resources are available to assist flavor manufacturers in employing engineering and administrative controls including NIOSH's Best Practices document (Dunn *et al.*, 2015), the NIOSH Criteria Document (McKernan *et al.*, 2016), NIOSH's engineering controls database (NIOSH, 2016), NIOSH's directory of engineering controls (NIOSH, 2015), and the guide on local exhaust ventilation systems available from the American National Standards Institute (ANSI)/American Society of Safety Professionals (ASSP) (ANSI/ASSP, 2018). Also informative are Dunn *et al.* (2008), Hirst *et al.*, (2014), and Cullinan *et al.* (2017). Significant resources are also available from ACGIH (www.acgih.org) and the American Industrial Hygiene Association (ww.aiha.org).

Personal respiratory protection

The implementation of appropriate process, engineering and administrative controls is preferable to simply providing employees with personal respiratory protection. However, respirators do have a role in many respiratory health and safety programs. Critical to their success is the selection of the proper respirator for the conditions present in a given facility, the proper fit of that respirator to the person using it, and the training in its use, maintenance and storage (Cowan *et al.*, 2016). OSHA also requires that employees wearing most types of respirators undergo medical clearance prior to their use.

Under OSHA's Respiratory Protection Standard (29 C.F.R. 1910.134), the "primary objective shall be to prevent atmospheric contamination." Where, however, that is not feasible through engineering controls, respirators shall be used. In terms of specific duty requirements relevant to protection against respiratory hazards, OSHA regulations require that personal protective equipment must be provided to employees whenever necessary to address chemical or other hazards which are "capable of causing injury or impairment in the function of any part of the body through absorption, inhalation or physical contact" (29 C.F.R. Sec. 1910.134). The regulations contain a range of requirements including the proper selection of respirators, standard procedures for use, training of employees, respirator maintenance, and other safety measures. The standard and relevant historical background information was published in the Federal Register notice announcing the standard (63 *Fed. Reg.* 1152. 8 January 1998). In addition to resources available in the Personal Protective Equipment section of the OSHA website (www.osha.gov), NIOSH's National Personal Protective Technology Laboratory publishes information on NIOSH-certified respiratory protection products (NIOSH, 2024).

Medical surveillance

Early detection, correct diagnosis, and sound management of lung disease from workplace exposures is of critical importance (Rose, 2017). Medical surveillance is a key component of an effective respiratory health and safety program. This is especially the case when it is difficult to identify a specific causative agent for an observed effect and when symptoms and/or lung function abnormalities may be the first clue to an exposure-related problem. Appropriate medical surveillance can identify health issues before progression to severe illness occurs, and when opportunities for reducing or eliminating exposure exist. The importance of medical surveillance is emphasized by the experience with California-based flavor manufacturers (Kim *et al.*, 2010; Kreiss *et al.*, 2012).

Medical surveillance should include an evaluation at the time of hire, and at least annually thereafter. The exam should include both a medical and occupational history and a pulmonary function component. Spirometry is a simple and inexpensive way to monitor pulmonary function status and should be included in the exam at hire and in periodic follow-up exams thereafter with some recommending follow-up exams every six months (McKernan *et al.*, 2016). It is important that spirometric evaluation follow the most recent American Thoracic Society/European Respiratory Society guidelines for accurate testing (Graham *et al.*, 2019), and it is important that results from testing be analyzed by consistent criteria (Kreiss *et al.* 2011; Ronk *et al.*, 2013; Rose, 2017).

A sound medical surveillance program will facilitate the identification of respiratory symptoms and lung function abnormalities. As reported by NIOSH (McKernan *et al.*, 2016), some workers in microwave popcorn manufacturing facilities, and in a few flavor manufacturing facilities, exhibited findings of fixed airway obstruction manifested by symptoms of cough (often without the production of phlegm) and shortness of breath after exertion as well as spirometric abnormalities (*e.g.* decreased FEV-1, a parameter of airflow). Frequent or persistent symptoms of eye, nose, throat or skin irritation have also been reported by NIOSH in some affected workers (McKernan *et al.*, 2016). A plan should be in place to refer employees for further medical follow-up and evaluation if such symptoms and lung function abnormalities are identified in the surveillance examinations (McKernan *et al.*, 2016). Further medical attention is also required in case of significant unexplained declines in employee lung function as measured by periodic spirometry, even if spirometry measures remain within normal limits (Kreiss *et al.*, 2011).

It is particularly important to note that bronchiolitis obliterans, a very serious lung disease, has been implicated in cases of respiratory illness seen in microwave popcorn manufacturing plants and in flavor manufacturing facilities. Early detection of symptoms and spirometric abnormalities through a medical surveillance program will allow workers to seek timely follow-up and may prevent progression of disease. Symptoms and/or spirometric abnormalities in one worker should

prompt timely evaluation of other workers at the facility. Early detection is especially important with bronchiolitis obliterans because the disease is generally irreversible.

For Additional Information

This report contains references and summary information on resources that flavor manufacturers may use to develop respiratory health and safety programs for their facilities. Other resources include occupational medicine physicians and industrial hygiene consultants. FEMA strongly urges users of this report to consult with appropriate experts regarding specific circumstances relevant to respiratory health and safety in flavor manufacturing facilities.

Consultants can be identified through the consultant directory maintained by AIHA (www.aiha.org). Please contact John Hallagan (Hondobear@aol.com) or Christie Harman (charman@femaflavor.org) at FEMA if you would like to discuss this report.

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