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Dr. Scott A. Masten
Director
Office of Chemical Nomination and Selection
NIEHS/NTP
111 T.W. Alexander Drive
P.O. Box 12233
Research Triangle Park, North Carolina 27709

9 May 2007

Dear Dr. Masten:

We are writing to support the nomination of "artificial butter flavoring mixture and certain components: Acetoin and Diacetyl" as described in the notice and request for comments published in the *Federal Register* on 29 March 2007 (72 *Fed. Reg.* 14816).

The Flavor and Extract Manufacturers Association of the United States (FEMA) is the national association of flavor manufacturers and represents companies that produce the vast majority of flavors in the United States. FEMA has been very active in issues associated with respiratory health and safety in flavor manufacturing related to butter flavor and diacetyl since late 2001. A copy of FEMA's report, "Respiratory Health and Safety in the Flavor Manufacturing Workplace" is enclosed.

FEMA has much information to share as NTP develops a testing program for butter flavor, diacetyl, and acetoin. We are preparing information that we expect you will find useful and that addresses some of the deficits of the report dated January 2007 "Chemical Information Review Document for Artificial Butter Flavoring and Constituents" prepared by Integrated Laboratory Systems, Inc. FEMA would have been pleased to have provided this information as this report was being prepared if we had been contacted, or if we had been aware that the report was under preparation.

FEMA has enjoyed a productive relationship with NTP over the years and looks forward to working with NTP on a butter flavor/diacetyl/acetoin testing program. We expect to provide you with more information shortly.

Sincerely,

John B. Hallagan

Enclosure – FEMA report

FEMA

THE FLAVOR AND EXTRACT MANUFACTURERS ASSOCIATION OF THE UNITED STATES

AUGUST 2004

Respiratory Health and Safety in the Flavor Manufacturing Workplace

The Flavor and Extract Manufacturers Association of the United States

1620 I Street, N.W. | Suite 925 | Washington, D.C. 20006

Introduction

Maintaining safe and healthy workplaces is an issue of paramount importance to members of the Flavor and Extract Manufacturers Association (FEMA), the national association of the U.S. flavor industry. FEMA has over 120 member companies including flavor manufacturers, and companies using flavors to manufacture foods, beverages and other consumer products.

There is broad recognition that flavors are safe under their conditions of intended use in foods, beverages, and other consumer products (Hallagan and Hall, 1995). Reports of serious respiratory illness among workers in the microwave popcorn manufacturing industry (Kreiss et al., 2002) emphasize the importance of the proper handling of flavors when workers may be exposed to higher concentrations of flavors through different routes of exposure than consumers get from food. Ingredients that are innocuous when consumed in food may pose a health risk in the workplace due to exposure to much higher concentrations via inhalation, and certain conditions involved in processing, most notably, the use of heat or mixing that increases airborne exposure levels.

The manner in which some flavors may contribute to the development of respiratory illness in workers remains unclear. However, sound respiratory health and safety programs can be implemented without certainty on causation of observed effects. It is clear that flavors can be handled in such a manner that they are a minimal health risk.

Because of the great variability in a number of factors among flavor manufacturing facilities (such as size, number of employees, types of manufacturing

Flavoring Substances and Compounded Flavors

A flavor to be added to food is a complex mixture of individual flavoring substances that has been "compounded" to provide the desired taste perception, or "flavor." For example, the flavor humans perceive as "orange" is a complex mixture of over 100 individual substances that each contribute to the flavor as it is perceived.

There are over 2,000 individual single chemically-defined flavoring substances used by flavor manufacturers to formulate flavors. Natural extracts (e.g. vanilla extract) are also used to formulate flavors, and may be directly added to foods in the manufacturing process. Compounded flavors and extracts usually contain a solvent such as propylene glycol or triacetin to facilitate the use of the flavor.

The safety of flavors when they are added to foods has been thoroughly evaluated by the FEMA Expert Panel (e.g. Smith et al., 2003) and flavors are strictly regulated under their conditions of intended use in foods by the Food and Drug Administration (e.g. 21 CFR Parts 172, 182).

Individual flavoring substances are most often simple organic chemicals composed of carbon, hydrogen, nitrogen, oxygen, and sulfur with a molecular weight of 300 or less, and can either be isolated or extracted from the foods in which they occur naturally, or they may be chemically synthesized. Flavoring substances of molecular weight 100-120 tend to be of medium to high volatility due to their chemical structure. Substances of low volatility are often not effective as flavoring substances because they have little impact on the human olfactory system.

It is common for flavoring substances to be used in a compounded flavor in concentrations similar to the very low, "ppm" concentrations at which they are present naturally in food. The vast majority of individual flavoring substances are added to food in concentrations less than 0.01% (<100 ppm). Natural extracts and compounded flavors and extracts are often added to foods at levels <1.0%.

processes, flavoring substances used, building design, etc.), it is extremely difficult to provide generic recommendations on respiratory health and safety practices that will "fit" every facility. Therefore, it is best for each facility to be evaluated independently with respiratory health and safety practices tailored to meet the needs of each facility. This document contains information on how to accomplish this, in addition to important information on how to evaluate and reduce potential respiratory hazards in the flavor workplace.

This document will also be helpful for food and beverage manufacturers who use flavors in their products. This is especially true for workplaces in which large volumes of flavors are stored, handled, and incorporated into foods and beverages, and which use heat during food and beverage manufacture.

Identifying the Need for Action

All flavor manufacturing facilities should have a respiratory health and safety program that is appropriate for the operations and structure of the facility. The presence of certain key factors indicates that a review of a facility's respiratory safety program should be a high priority. These factors include:

- The presence of employees who experience symptoms of respiratory illness such as prolonged or work-related difficulty in breathing, shortness of breath on exertion, persistent coughing, wheezing, or chest tightness.
- The presence of employees who experience symptoms consistent with exposure to airborne irritants such as irritated or tearing eyes, skin rashes, and nasal irritation.
- Processes in flavor manufacture and handling that involve heating of flavor mixtures in open or only partially closed vessels.
- Processes in flavor manufacture and handling that result in significant air concentrations of particulate matter, such as the spray-dry manufacturing processes, and blending, packaging and use of dry and powdered flavors.
- Processes in flavor manufacture and handling that result in significant air concentrations of vapors from liquid flavors.
- Quality assurance and flavor testing activities that result in repeated exposures, even if single exposures are at seemingly low levels.

If any of these factors are present in your manufacturing workplace then it is strongly recommended that you pursue the actions described in this document. Please see page 4 for information on how to obtain assistance.

The Flavor Manufacturing Workplace

Conditions may exist for significant exposures to flavoring substances in typical flavor manufacturing facilities. For example, a person responsible for compounding a liquid flavor formulation or mixing a flavor into another food constituent may encounter circumstances in which exposure to vapors or particulate matter from flavoring substances occurs at many times the concentration encountered by a consumer using the product containing the flavor.

A variety of strategies are currently employed by flavor manufacturers to reduce the potential for workplace exposure to flavoring substances through inhalation. However, increased focus is called for on particular substances and processes that may present hazards. The spray-dry manufacturing process, handling liquid and powdered flavors, and research and development and quality assurance activities may provide opportunities for significant exposures. Engineering controls such as spot or local exhaust ventilation (e.g. "elephant trunks") and closed process vessels are commonly used during flavor compounding to control emissions. Fume hoods are commonly used in research and development laboratories.

One of the most important aspects of workplace health and safety is the identification of substances used in the workplace that may pose a respiratory hazard. These materials are discussed in this section, and Table 1 contains a list of single chemically-defined flavoring substances that, under certain circumstances, may pose respiratory hazards. This list may be revised as information becomes available.

How to Obtain Assistance

Assistance in establishing a sound respiratory safety program is readily available. You may choose to work with industrial hygiene consultants in your area using this report as an information resource, or you may choose to work with the "center of excellence" at National Jewish Medical and Research Center (NJRMC) in Denver, Colorado.

FEMA has worked with NJMRC to provide FEMA members with up-to-date information on respiratory safety so that they may maintain the safest workplace possible. Cecile Rose, M.D., M.P.H. and John Martyny, Ph.D., C.I.H. of NJMRC have provided FEMA and its members with expert consulting services related to respiratory safety programs since 1996.

You may contact Drs. Rose and Martyny directly at NJMRC, or by contacting John Hallagan at FEMA. If you wish to contact Drs. Rose and Martyny directly, please contact Dr. Rose at:

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Industrial hygiene consultants are likely to be available in your area should you choose to explore the option of obtaining services from a local provider. Among the factors to consider before retaining a service provider is to evaluate the provider's experience in respiratory safety issues.

1. Flavoring substances of interest—single chemically defined substances

Lower molecular weight substances in the following classes of flavoring substances may have volatility (indicated by a high vapor pressure) and irritant properties sufficient to result in a respiratory hazard when inhaled at high concentrations during certain food and flavor manufacturing and handling processes:

- Alpha, beta-unsaturated aldehydes and ketones
- Aliphatic aldehydes
- Aliphatic carboxylic acids
- Aliphatic amines
- Aliphatic aromatic thiols and sulfides

None of the substances in these classes of flavoring substances share chemical characteristics with recognized causes of the type of respiratory illness, bronchiolitis obliterans, that NIOSH has suggested is present in some workers in microwave popcorn manufacturing facilities (Kreiss et al., 2002; Horvath et al., 1969; King, 2000).

Only 46 of the more than 1,000 flavoring substances in these classes have permissible exposure limits (PELs) established by the U.S. Occupational Safety and Health Administration (OSHA). OSHA PELs for these substances are based primarily on the substances' widespread use in non-flavor manufacturing operations, and not on their use as flavoring substances. OSHA establishes PELs to protect work-

ers against the adverse health effects of exposure to substances identified as hazardous. PELs are enforceable regulatory limits on the amount or concentration of a substance in the air. PELs are established by OSHA based on data from 8-hour time-weighted exposures. Additional information on OSHA PELs is available on the OSHA website (www.osha.gov).

Table 1 lists single chemically-defined flavoring substances that are priorities for consideration as substances that may pose respiratory hazards in flavor manufacturing workplaces. Thirty-four substances are listed as "high priority" and 49 are listed as "low priority." Table 1 also contains a list of nine flavoring substances that are judged not likely to pose a respiratory hazard but that have been assigned OSHA PELs.

Priority levels were assigned based on available inhalation exposure data in animals and humans, chemical structure, and volatility. In many cases, data on a flavoring substance was used to evaluate the priority level for other structurally-related substances. It is important to note that in many cases relevant inhalation data for flavoring substances are limited and are often only available for flavoring substances that have other, larger-scale industrial uses. The assignment of priority levels required the application of significant judgment and also took into account the anecdotal information provided by numerous workers in the flavor industry who shared their valuable experience related to handling flavors.

The priority level is intended to identify substances that should receive attention as substances that may pose a respiratory hazard if used or handled in the workplace in an unsafe manner. The thirty-four high priority substances in Table 1 are candidates for higher levels of attention in the flavor workplace, and for greater focus in communication with workers and with customers. These substances merit a higher degree of attention related to the manner in which they will be handled and processed and should be carefully considered for the application of protective measures such as engineering controls, special handling procedures, and personal protective equipment.

High priority substances may have sufficient volatility and, based on an analysis of their structure, sufficient potential reactivity to pose a risk of respiratory injury when associated with any of the following factors:

- High exposure levels
- Repeated exposure at lower air concentrations
- Exposure associated with heat processing
- Exposure in the absence of appropriate safety measures including local and area ventilation, and proper process and engineering controls

For example, a manufacturing process that involves heating a high priority substance such as acetaldehyde, or a mixture containing a significant portion of acetaldehyde, should be carefully evaluated to assure that opportunities for exposure are minimized.

There are forty-eight substances listed as "low priority" in Table 1. These substances may pose hazards only in more extreme circumstances of exposure and merit a lower level of concern. For example, a low priority substance that is subjected to heating, and/or mixing or blending activities that could significantly increase air concentrations would merit attention to the need for appropriate safety measures.

For all flavoring substances, and other substances used to manufacture flavors, the review of each substance's material safety data sheet (MSDS) represents a basic and fundamental means for communication. MSDSs contain information useful to an assessment of risk in the workplace. Under the OSHA Hazard Communication Standard, MSDSs must be available to all workers, and all workers must be trained in their use (29 CFR Part 1910).

Among FEMA GRAS single chemically-defined flavoring substances, only acetaldehyde (an aliphatic aldehyde) and diacetyl (a ketone) have been associated with instances of serious respiratory illness as occurred in microwave popcorn manufacturing plants. Neither substance has been shown to be a cause of this respiratory illness, but the available data suggest an association.

Acetaldehyde, a commonly used flavoring substance and a natural food constituent, is a well-known respiratory irritant. It has an OSHA PEL, but its role in causing the type of respiratory illness seen in popcorn manufacturing facilities remains unclear. Exposure to acetaldehyde was mentioned in one report of illness at a flavor manufacturing facility (Lockey, 2002).

Diacetyl, a natural constituent of butter and other dairy products, and a flavoring substance commonly used in butter-type flavors, is cited by NIOSH as a marker of exposure in microwave popcorn manufac-

turing and as a substance that can cause airway injury in animal studies (NIOSH, 2003). Prior to its identification by NIOSH as being associated with respiratory illness in workers in microwave popcorn manufacturing, diacetyl was not considered a significant respiratory hazard and it has no OSHA PEL. Discussions with companies that manufacture diacetyl revealed no information suggesting any health effects, respiratory or other, from years of experience in manufacturing and handling diacetyl. However, it is appropriate to consider diacetyl a "high priority" substance based on the available data, and the need to be cautious given the association with respiratory illness noted by NIOSH.

The lists in Table 1 also contain information related to the amount (poundage) of each flavoring substance reported by the flavor industry to be used to formulate flavors in the United States on an annual basis during the most recent survey year, 1995 (Lucas et al., 1999). In general, these amounts are quite modest when compared to typical industrial-scale substances used in millions of pounds per year, and suggest some limitation on the extent of potential exposure. Sixteen of the 34 high priority substances have a reported 1995 poundage of <1,000 lbs. Of the flavoring substances determined to be high priority, the five largest annual volumes (excluding phosphoric acid which has a single very specific use) are for:

- Benzaldehyde—603,000 lbs.
- Acetaldehyde—321,000 lbs.
- Acetic acid—310,000 lbs.
- Diacetyl—211,000 lbs.
- Butyric acid—180,000 lbs.

2. Natural flavoring complexes

No natural flavoring complexes (e.g. essential oils and extracts) have been associated with the type of respiratory illness seen in microwave popcorn workers. None are known to cause bronchiolitis obliterans or similar diseases. Some natural flavoring complexes have long been known to be skin, and nasal and upper-respiratory tract irritants (e.g. mustard, garlic and onion oils, and capsaicin-containing oils and powders). Because the irritation potential of these materials is well-known, their use in flavor manufacture has generally not resulted in workplace injury or illness. They are routinely handled with appropriate caution and safety measures.

Many natural flavoring complexes are not thought to pose significant respiratory hazards in the workplace because, while they may contain naturally-occurring constituents in low concentrations that are considered potential hazards (e.g. acetaldehyde in lemon oil), other constituents in the natural mixture most often result in the mixture having a relatively low vapor pressure and therefore low volatility.

However, flavor manufacturing activities that involve mixing and/or heating of natural flavoring complexes may result in significant opportunities for exposure and should be treated with appropriate caution. Examples of natural flavoring complexes that may under certain circumstances result in skin, and nasal and upper-respiratory tract irritation include the following oils: balsam fir, bitter almond, garlic, grapefruit, lemon, lime, mustard, onion and orange. In addition, extracts and oils of the Capsicum species may contain significant amounts of capsaicin, a well-known irritant, and should be treated with appropriate caution.

Other "natural" materials, including some foods, are sometimes used to manufacture flavors and while none have been identified as risks for respiratory effects in the workplace, materials derived from butter and other dairy products should be handled with appropriate caution, especially when processes employing heat are involved.

3. Spray-dry and powdered flavors

Spray-dry flavors are a class of flavors in which the compounded flavor is attached to a carbohydrate substrate through the spray-drying manufacturing process. Spray-dry flavors may include a wide variety of flavor types including fruit, dairy, and savory flavors. The spray-dry manufacturing process provides opportunities for inhalation exposure.

Powdered flavors may be manufactured by various processes, including simple blending. Possible exposures to powdered flavors generally involve their handling in processes such as packing, transfer, and mixing. Handling powdered flavors is a potential source of exposure, and appropriate engineering and process controls and personal protection should be utilized. The same precautions also apply to handling spray-dried flavors that are generally powders in their finished form. Exposure to powdered flavors was mentioned in a report of respiratory illness in a flavor packaging facility in a 1986 NIOSH report (NIOSH, 1986).

Key Factors for Respiratory Safety Programs in the Flavor Industry

A series of incidents has focused attention on the possible role of flavors in the development of respiratory illness in flavor and food manufacturing facilities. Much effort has been devoted to determining the precise nature and cause of the respiratory illness seen in microwave popcorn manufacturing facilities but many uncertainties remain. Determination of the nature of the illness and its cause has been hampered by difficulties in obtaining direct access to potentially affected workers and their medical records, and the fact that in the vast majority of cases, the workers recall no particular event that may have led to their respiratory illness.

Despite these uncertainties, it is critically important for flavor manufacturers to understand that sound respiratory health and safety programs can and should be established in their facilities.

A respiratory health and safety program that will

Background on Respiratory Safety Issues

The 1986 NIOSH Health Hazard Evaluation

The possibility that exposure to flavors in the workplace may result in respiratory injury was noted in a 1986 Health Hazard Evaluation published by the National Institute of Occupational Safety and Health (NIOSH). NIOSH reported that two workers at a facility that mixed "liquid and powdered flavorings" for use in the baking industry were found to have serious lung disease. The report concluded that it is "probable that some agent in the mixing room . . . produced severe mixed obstructive lung disease . . ." Lung tissue samples (lung biopsy information) from the two workers were not available but the report concluded that "the clinical picture was more compatible with bronchiolitis obliterans than with emphysema." (NIOSH, 1986).

The 1996 Confidential Report to FEMA

In late 1996, a member-company reported to FEMA on a confidential basis that a worker developed a respiratory illness identified as bronchiolitis obliterans while working in the manufacture of flavors. Due to patient confidentiality issues, very little information was available at that time, and the cause of the illness could not be determined. Because of this initial report, FEMA sponsored a workshop in March 1997 to educate its members on respiratory safety practices.

Additional information related to this incident was obtained in subsequent years and was reported publicly for the first time in 2001 when a physician reported that five workers at a flavor manufacturing facility developed severe respiratory illness that may be associated with exposure to flavors. The physician later presented an abstract on these cases at the annual meeting of the American Thoracic Society in May 2002 reporting "an index case of BO" in one worker, and "an additional four workers with clinical findings consistent with BO." (Lockey, 2002). The abstract made no reference to whether lung biopsies were conducted on any of the five workers. The abstract also noted that, "A comprehensive review of the worksite identified multiple agents . . . as potential causative agents and most prominently acetaldehyde." The abstract concluded, "This case series indicates that the manufacturing of food flavors in relatively large amounts and at high concentrations and the use of aerosolized manufacturing processes may represent a respiratory hazard in susceptible workers."

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The 2001 NIOSH Report on the Gilster Mary Lee Microwave Popcorn Facility

In August 2001, NIOSH published an interim report on their investigation of respiratory illness in a microwave popcorn manufacturing facility (Gomaa, 2001). In that report, NIOSH stated, "Nine former workers from a microwave popcorn packaging plant were reported to have a severe lung disease, bronchiolitis obliterans, but no recognized causes of this rare condition were evident in the plant. . . . The survey findings are best explained by work-related bronchiolitis obliterans in relation to exposures arising in the mixing room but widely disseminated through other areas of the plant." The report also stated, "Strong exposure-response relationships existed between quartile of estimated cumulative exposures to diacetyl and respirable dust and frequency and degree of airway obstruction."

In April 2002, NIOSH provided additional comments on its investigation of the same microwave popcorn facility in the Morbidity Mortality Weekly Report (MMWR) published by the Centers for Disease Control (CDC). The MMWR reported "eight cases of fixed obstructive lung disease in former workers of a microwave popcorn factory. . . . All eight had a respiratory illness resembling bronchiolitis obliterans . . ." (CDC, 2002). The report noted that "Industrial hygiene sampling . . . detected approximately 100 VOCs in the plant air. Diacetyl, a ketone with butter-flavor characteristics, was measured as a marker for exposure to flavoring vapors." Information in the MMWR was elaborated in the New England Journal of Medicine in August 2002 (Kreiss et al., 2002), at a NIOSH-sponsored workshop in November 2003, and in a NIOSH "Alert" in December 2003.

The Flavor Industry Respiratory Safety Program

As part of its ongoing respiratory safety program, FEMA initiated a confidential incident reporting program in 2002 that provides flavor manufacturers with the opportunity to report respiratory safety concerns to FEMA in a confidential manner, and to obtain assistance if needed to maintain a safe workplace.

Extensive investigation by FEMA and its expert consultants, Drs. Rose and Martyny, found four employees in three companies with reported significant respiratory illness. All of the employees performed tasks that could result in exposure to flavors.

At Company 1, the available information suggests that one employee had "severe fixed airway obstruction" which is similar to the disease seen in some microwave popcorn workers. The employee underwent a lung biopsy. The employee's physician offered a differential diagnosis of chronic hypersensitivity pneumonitis noting, however, that "characteristic changes are not observed." This employee had consistent exposure to a flavor which employees had noted was irritating to their eyes and nasal passages. This flavor was noted to contain a variety of lactones, low concentrations of acetic and lactic acids, and low concentrations of diacetyl.

At Company 2, one employee was identified as having signs of exposure-related constrictive bronchiolitis after a lung biopsy. The biopsy also showed several signs inconsistent with exposure-related bronchiolitis and it remains unclear whether this employee's disease was the result of workplace exposure. This employee did not report consistent exposure to any particular type of flavor.

At Company 3, one employee's physician concluded that the employee had bronchiolitis obliterans based on a lung biopsy that, according to the physician, showed changes consistent with this disease. A second employee at Company 3 was seen by two physicians, one of whom (a general practitioner) con-

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cluded that the employee had work-related lung disease while a second physician, a pulmonologist, concluded that the symptoms were not work-related. This employee did not have a lung biopsy. A review of the available documentation by FEMA's consultant suggests that this employee's symptoms could be work-related. Both employees had direct exposure to butter-type flavors.

While there may be unreported cases of respiratory disease among workers in flavor manufacturing, it appears highly unlikely, based on the results of a two-year investigation, that there are significant numbers of workers with workplace-related respiratory disease. It appears that four workers in three different flavor manufacturing facilities may have serious workplace exposure-related respiratory disease. The information on two of the workers allows a higher degree of confidence that the disease is work-related. Causation remains unclear. As noted in the main section of this report, flavor manufacturers can take a number of actions to assure the safest possible workplace without having confirmation of causation.

be most likely to adequately protect workers should be oriented around five areas of emphasis:

1. Management and employee awareness through education and hazard communication
2. Exposure assessment
3. Medical surveillance
4. Material handling strategies and engineering controls for manufacturing, storage, packing and shipping facilities
5. Personal respiratory protection

1. Management and Employee Awareness Through Education and Hazard Communication

1.1 MANAGEMENT AND EMPLOYEE AWARENESS

Management should consistently seek to improve health and safety in the workplace and to anticipate and respond to new problems. Management must do more than simply be aware of relevant, specific OSHA requirements. In addition to specific duty requirements, the Occupational Safety and Health Act establishes a general duty for employers to provide a workplace that is free from "recognized hazards," and that is unlikely to cause death or serious physical harm.

Recent reports of severe respiratory illness among workers in microwave popcorn manufacturing facilities suggest that certain flavoring substances may present a respiratory hazard (NIOSH, 2003). These reports suggest the presence of a recognized hazard associated with butter-type flavors when they are handled improperly (e.g. heated flavor mixtures processed and handled without appropriate engineering controls or personal respiratory protection). Therefore, management and employees in flavor manufacturing facilities that manufacture butter flavors and other similar flavor-types should be made aware of possible respiratory hazards, and appropriate health and safety training should be conducted.

Thorough education and communication among both management and employees of flavor manufacturers are critical to the success of any workplace health and safety program. Task areas that merit focus include:

- Personnel who blend and mix flavors in bulk quantities, especially those exposed to heated flavors and the 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.

Formal, mandatory hazard communication and training sessions are recommended to assure that employees have the appropriate awareness of respiratory safety issues.

1.2 HAZARD IDENTIFICATION

Over 2,200 single chemically-defined flavoring substances and natural flavoring complexes are commonly used to formulate flavors. The vast majority of these materials have chemical and physical characteristics that would make it highly unlikely that they would pose a risk of respiratory injury in the workplace. Most of the materials are not very volatile and do not have a significant degree of reactivity.

However, some low molecular weight flavor substances may have sufficient volatility, and possibly reactivity, to pose a risk of respiratory injury when improperly handled. Table 1 contains a list of single chemically-defined flavoring substances that may pose potential respiratory hazards when improperly handled. Please see Section 1 of "The Flavor Manufacturing Workplace" for a detailed discussion of this list.

1.3 HAZARD COMMUNICATION—MSDSS

Clear communication of potential hazards is of critical importance. The OSHA Hazard Communications Standard (29 CFR Part 1910) establishes a minimum for hazard communication through its material safety data sheet (MSDS) requirements. The development and provision of MSDSs is an individual company obligation.

FEMA members have access to the Flavor and Fragrance Ingredient Data Sheet (FFIDS) program which provides information on workplace hazards that can be used to formulate MSDSs. A new procedure to update FFIDSs is being implemented to focus on high-priority flavoring substances that may pose a risk of respiratory injury.

1.4 HAZARD COMMUNICATION—LABELING

In addition to the various types of labeling required under relevant regulations, the labeling of bulk flavors may also be appropriate in certain circumstances to alert workers to potential respiratory hazards.

It is recommended that the following bulk flavors bear a label using the language described below, or language that conveys a similar warning.

- Containers of "high priority" neat substances such as acetaldehyde and diacetyl.
- Containers of compounded flavors (liquid and dry or powdered) that contain "high priority" flavoring substances in concentrations >1.0%.
- Any compounded flavors (liquid and dry or powdered) containing "high priority" or "low priority" flavoring substances in any concentrations that will be heated during processing.

WARNING—This flavor may pose an inhalation hazard if improperly handled. Please contact your workplace safety officer before opening and handling, and read the MSDS. Handling of this flavor that results in inhalation of fumes, especially if the flavor is heated, may cause severe adverse health effects.

It is recommended that the following bulk flavors bear a label using the language described below, or language that conveys a similar warning.

- Containers of neat "low priority" single chemically-defined substances.
- Containers of neat natural flavoring complexes.
- Containers of compounded flavors (liquid and dry or powdered) containing "high priority" single chemically-defined substances at concentrations <1.0%, or "low priority" single chemically-defined substances at any level.

ATTENTION—Safe flavors can be used in an unsafe manner. Please contact your workplace safety officer before opening and handling this flavor, and read the MSDS.

Information available from incidents in microwave popcorn manufacturing clearly demonstrates the importance to workplace safety of how flavors are handled and incorporated into food products (Gomaa, 2001; NIOSH 2003). However, it is apparent that flavor manufacturers and suppliers cannot in all instances know how their customer will use a flavor. In many instances, the customer chooses to keep information related to how they will use a flavor confidential to protect 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 warning statements suggested in this section provide a means for flavor manufacturers to interact with customers to seek to assure that customers

receive helpful information related to the safe handling and use of flavors.

2. Exposure Assessment

Environmental monitoring is a necessary component of a sound respiratory health and safety program. Monitoring at regular intervals can provide valuable information on potential exposures even if the chemicals causing respiratory injury have yet to be identified.

A critical issue in any monitoring program is identifying the appropriate substances to monitor. With respect to flavors, this issue is particularly difficult because there are no flavoring substances that have been confirmed to cause the type of respiratory illness seen among workers in microwave popcorn manufacturing.

However, an analysis of the characteristics of flavoring substances allows for the identification of those that may pose the highest risk for exposure in flavor manufacturing facilities. These substances are typically relatively volatile, allowing for respiratory exposure during certain manufacturing processes. In any event, if exposure to the more volatile substances is reduced, then exposure to other substances also present will likely be reduced as well.

We have focused our attention on single chemically-defined flavoring substances whose chemical characteristics and biological data suggest a high risk for exposure and possible respiratory injury—these substances are listed in Table 1. An environmental monitoring program can focus on these substances but should not ignore other substances that present indications of opportunities for exposure.

Monitoring of particulates should also be conducted to assure excessive exposure does not occur. Exposure to particulates was a potential contributing factor in the two incidents reported by NIOSH—the International Bakers workplace (NIOSH, 1986) and the Gilster Mary Lee microwave popcorn workplace (Gomaa, 2001).

3. Medical Surveillance

Medical surveillance is a key component of an effective respiratory health and safety program in the flavor industry. 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.

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 follow-up exams thereafter. It is important that spirometry testing follow the most recent American Thoracic Society guidelines for accurate testing.

Medical surveillance is especially important in circumstances such as existed in the microwave popcorn industry where causation of illnesses remains unclear, and it appears that the circumstances surrounding exposure may contribute significantly to the development of illness. In such circumstances, appropriate medical surveillance can identify health issues before progression to severe illness occurs, and when opportunities for reducing or eliminating exposure exist.

A sound medical surveillance program will facilitate the identification of respiratory symptoms and lung function abnormalities. Workers in microwave popcorn plants 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 in affected workers (Kreiss et al., 2002). 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 or if there are significant unexplained declines in employee lung function as measured by periodic spirometry.

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. Early detection is especially important with bronchiolitis obliterans because the disease is difficult to treat.

4. Material handling strategies and engineering controls for manufacturing, storage, packing and shipping facilities

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. 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 significant 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 to material handling strategies and engineering controls is inappropriate. However, a number of basic principles can greatly reduce opportunities for hazardous exposures.

In general, if workers involved in handling flavors can taste, see or smell flavoring substances then the identity of the flavoring substances should be explored, and if high priority substances are involved then an exposure assessment should be conducted using environmental monitoring. If it is determined that opportunities for exposure exist then changes in processes to reduce exposure (e.g. closed vessels and/or local ventilation) should be employed.

4.1 HEATING OF FLAVORS

Heating of flavors is of particular concern with regard to potential hazardous exposures. Heating will increase volatility and greatly increase air concentrations of flavoring substances. Mixing of heated flavors should be conducted in closed vessels with local ventilation. 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 then their exposures should be promptly evaluated by environmental sampling. If exposures are elevated then the proper personal protective equipment should be employed.

4.2 PRODUCT SUBSTITUTION

Awareness that specific substances are hazardous often results in the application of a simple industrial hygiene strategy—product substitution. Product substitution may be employed when it is known that a substance is hazardous and can be replaced with one that isn't.

Very few flavoring substances have been identified as respiratory hazards. Product substitution is not likely to be a useful strategy for flavor manufacturing for this reason, and because of the complex nature of compounded flavors consisting of many individual substances. The unique nature of the flavor imparted by certain substances, many of which are naturally-occurring constituents of food, make it difficult to identify substitutes that are effective.

4.3 FACILITY STRUCTURE AND ORGANIZATION

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.

4.4 VENTILATION

Flavoring substances and mixtures, whether liquid or dry, must be handled in such a way as to minimize the creation of airborne aerosols or particulate matter. 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 ("spot") ventilation (e.g. "elephant trunks") should be used. Dilution through general room ventilation seldom results in exposure reduction unless extremely high volumes of air are circulated.

4.5 MATERIAL HANDLING—FLAVOR COMPOUNDING AND PACKING ACTIVITIES

Simple flavor compounding activities such as mixing or pouring can result in significant exposures. This is emphasized by the first report of respiratory illness in a flavor-related facility (NIOSH, 1986). In this instance, workers were handling dry flavors (mixing and re-packing) in a workspace with no local ven-

tilation, and minimal general room ventilation. The workers also did not wear any personal respiratory protection.

Mixing activities also figured prominently in problems encountered in microwave popcorn manufacturing when workers were assembling the ingredients of the mixture to be present inside the popping bag. In these circumstances workers were exposed to heated mixtures of flavors, color additives, salt, and particulate matter from popcorn and packaging.

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. Simple, 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 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. The use of personal protective equipment may then need to be considered to minimize exposure.

4.6 MATERIAL STORAGE

Flavoring substances that are volatile 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 dry 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.

4.7 CLEANING OF VESSELS AND WORK AREAS

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 flavors. Automated cleaning processes will greatly reduce opportunities for exposure. In some instances, the most effective way to protect workers responsible for cleaning activities will be to use respirators.

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).

5. Personal respiratory protection

The implementation of appropriate process and engineering controls is preferable to simply providing employees with personal respiratory protection such as respirators. 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. OSHA also requires that employees wearing most types of respirators undergo medical clearance prior to their use.

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."

Under OSHA's Respiratory Protection Standard (29 C.F.R. Sec. 1910.134), the "primary objective shall be to prevent atmospheric contamination." Where, however, that is not feasible through engineering controls, respirators shall be used. 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 background information was published in the *Federal Register* notice announcing the standard (63 *Fed. Reg.* 1152. 8 January 1998).

Developing a Respiratory Safety Program for Flavor Manufacturing Facilities

A survey of FEMA members conducted in 2002 indicated that more than 90% of responding companies, representing a balanced cross-section of the membership, had a respiratory safety program. Responding companies had from three to >100 employees involved in flavor manufacture. Survey results suggested that the scope of respiratory safety programs varied.

Among respondents' respiratory safety programs, most included a medical examination, most commonly a questionnaire, with most medical examinations including spirometry as a component of the exam. A minority of the companies that reported including medical examinations in their program included annual exams.

Whole room ventilation was identified as the predominant engineering control. The use of local ventilation (e.g. "elephant trunks") was also reported by most companies. Personal respiratory protection (respirators) was reported to be commonly available for workers to use. Less than 5% of respondents reported using respirators "all of the time."

Information collected through site visits to facilities of FEMA members indicates that certain processes and activities that are commonly conducted in flavor manufacturing facilities warrant special attention. In general, any process or activity that results in increased air concentrations of flavors should be examined to determine the potential to increase the respiratory health risk, including:

- Any process or activity that results in the heating of flavors
- Manufacture and handling of liquid flavors
- Manufacture and handling of dry and powdered flavors
- Quality assurance and product testing activities that result in repeated exposures, even if a single exposure is of minor quantity

Because of the great variability in flavor manufacturing facilities, it is extremely difficult to provide recommendations on respiratory health and safety practices that will "fit" every facility.

Therefore, it is best for each facility to be evaluated independently with respiratory safety practices tailored to meet the needs of that facility. It is strongly recommended that each company conduct an audit of its existing respiratory health and safety program, and, if necessary, seek expert assistance. Several sources of expert assistance are available.

FEMA, and a number of its members, have worked with the National Jewish Medical and Research Center (NJMRC) through Cecile Rose, M.D., M.P.H., and John Martyny, Ph.D., C.I.H. Dr. Rose is an expert in pulmonary diseases including bronchiolitis, and Dr. Martyny is a certified industrial hygienist. Both have worked with the flavor industry since 1997, and have significant experience with flavors and flavor manufacturing. Information on contacting Drs. Rose and Martyny can be found on page 4.

Other sources of expert assistance include occupational medicine physicians and industrial hygiene consultants located in the communities where flavor manufacturing facilities are located.

OSHA Requirements

The Occupational Safety and Health Administration (OSHA) is the Federal agency responsible for workplace safety matters. The Occupational Safety and Health Act establishes that an employer's duty to employees is two-fold; specific duty requirements that mandate compliance with the workplace safety standards promulgated by OSHA, and a general duty requirement which requires employers to provide a workplace that is free from recognized hazards and that is unlikely to cause death or serious physical harm.

An employer can be found in violation of the general duty clause if the employer failed to render the workplace free of a recognized hazard that caused or was likely to cause death or serious physical harm, and there was a feasible and useful method to correct the hazard. This "general duty" can be used by OSHA to intervene when a workplace is deemed unsafe even if there is no violation of a "specific duty" requirement such as a specific OSHA standard. OSHA's standards can be found at 29 C.F.R. Parts 1900-1999.

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."

Under OSHA's Respiratory Protection Standard (29 C.F.R. Sec. 1910.134), the "primary objective shall be to prevent atmospheric contamination." Where, however, that is not feasible through engineering controls, respirators shall be used. 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 Federal Register notice announcing the standard can be found at 63 Fed. Reg. 1152 (8 January 1998).

While OSHA's respiratory safety standards apply to flavor manufacturers, there are few other specific, relevant requirements. There are no regulations or standards that apply specifically to the flavor industry. One of OSHA's primary mechanisms for regulating workplace inhalation exposures to potentially hazardous materials is through the establishment of permissible exposure limits (PELs). PELs are established by OSHA through the evaluation of relevant data that indicate that inhalation exposure above a certain level (the PEL) may present a workplace respiratory hazard, and that actions to control exposures may be necessary.

Under the OSHA Hazard Communication Standard, material safety data sheets (MSDSs) must be available to all workers, and all workers must be trained in their use (29 CFR Part 1910).

Customer Communication

Clear communication of potential hazards between flavor suppliers and their customers who use flavors in food, beverages and other consumer products is of critical importance. Communication with users of flavors should extend beyond the provision of an MSDS. We encourage the distribution of this report to manufacturers using flavors in their products.

More extensive and detailed communication with flavor users will help food, beverage, and consumer product manufacturers to focus more thoroughly on potential respiratory health and safety issues associated with their specific uses of flavors in manufacturing their products.

Also available is a brief statement targeted to assist manufacturers that use flavors in their products. This

statement, entitled "The Safe Handling of Flavors in Food, Beverage, and Consumer Product Manufacturing," is available from FEMA for your consultation and use. Please contact John Hallagan at FEMA (*Hondobear@aol.com*; 202.331.2333) for more information.

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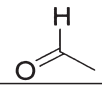
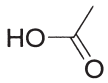
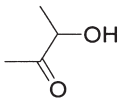
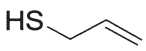
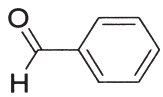
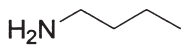
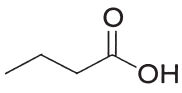
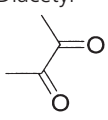
NOTE: Copies of these references are available from FEMA by contacting John Hallagan (*Hondobear@aol.com*, 202.331.2333).

TABLE 1

FEMA	CAS	Principal Name	Molecular Weight	Calculated Vapor Pressure Value	PEL Data[a,b]	1995 Reported Poundage[c] (lbs)
High Priority						
2003	75-07-0	Acetaldehyde 	44.05	750 mm Hg 20° C	PEL - TWA 200 ppm, 360 mg/m^3	321,000
2006	64-19-7	Acetic acid 	60.05	12 mm Hg 20° C	PEL - TWA 10 ppm, 25 mg/m^3	310,000
2008	513-86-0	Acetoin 	88.11	6.2 mm Hg 20° C		116,000
2035	870-23-5	Allyl mercaptan 	74.14	128 mm Hg 20° C		1
2053	12124-99-1	Ammonium sulfide $(NH_4)_2S$	68.15	2.88 X 10^{-15} mm Hg 20° C		660
2127	100-52-7	Benzaldehyde 	106.13	0.9 mm Hg 20° C		603,000
3130	109-73-9	Butylamine 	73.14	71 mm Hg 20° C	PEL - Skin ceiling limit TWA 5 ppm, 15 mg/m^3	0
2221	107-92-6	Butyric Acid 	88.11	0.7 mm Hg 20° C		180,000
2370	431-03-8	Diacetyl 	86.09	43 mm Hg 20° C		211,000

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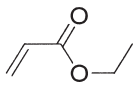
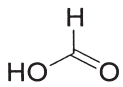
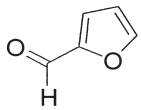
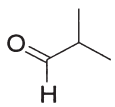
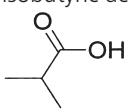
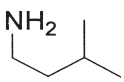
FEMA	CAS	Principal Name	Molecular Weight	Calculated Vapor Pressure Value	PEL Data[a,b]	1995 Reported Poundage[c] (lbs)
2418	140-88-5	Ethyl acrylate 	100.12	29 mm Hg 20° C	PEL - Skin TWA 25 ppm, 100 mg/m^3	11
2487	64-18-6	Formic Acid 	46.03	33 mm Hg 20° C	PEL - TWA 5 ppm, 9 mg/m^3	20,600
2489	98-01-1	Furfural 	96.09	1.7 mm Hg 20° C	PEL - Skin TWA 5 ppm, 20 mg/m^3	7,710
3779	6/4/7783	Hydrogen sulfide 	34.08	26.9 mm Hg 20° C	PEL - Acceptable ceiling concentration 20 ppm; Acceptable maximum peak above the acceptable ceiling concentration for an 8-hr shift is - 50 ppm for 10 minutes(once only, if no other measurable exposure occurs)	3
2220	78-84-2	Isobutyraldehyde 	72.11	140 mm Hg 20° C		1,100
2222	79-31-2	Isobutyric acid 	88.11	0.00037 mm Hg 20° C		8,750
3219	107-85-7	Isopentylamine 	87.17	40 mm Hg 20° C		1

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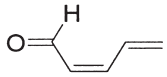
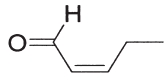
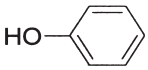
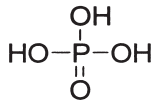
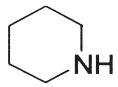
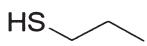
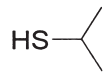
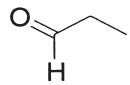
FEMA	CAS	Principal Name	Molecular Weight	Calculated Vapor Pressure Value	PEL Data[a,b]	1995 Reported Poundage[c] (lbs)
2716	74-93-1	Methyl mercaptan 	48.11	1.28 X 10^3mm Hg 20° C	PEL - ceiling limit TWA 10 ppm, 20 mg/m^3	52
2746	75-18-3	Methyl sulfide 	62.13	400 mm Hg 20° C		8,200
3217	764-40-9	2,4-Pentadienal 	82.1	15 mm Hg 20° C		0
3218	764-39-6	2-Pentenal 	84.12	50 mm Hg 20° C		3
3223	108-95-2	Phenol 	94.11	0.2 mm Hg 20° C	PEL - Skin TWA 5 ppm, 19 mg/m^3	9
2900	7664-38-2	Phosphoric acid 	67.02	0.03 mm Hg 20° C	PEL - TWA 1 mg/m^3	4,840,000
2908	110-89-4	Piperidine 	85.15	23 mm Hg 20° C		1,610
3521	107-03-9	Propanethiol 	76.16	120 mm Hg 20° C		120
3897	75-33-2	2-Propanethiol 	76.16	213 mm Hg 20° C		NA
2923	123-38-6	Propionaldehyde 	58.08	260 mm Hg 20° C		3,870

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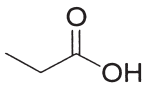
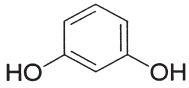
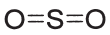
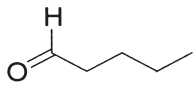
FEMA	*CAS*	*Principal Name*	*Molecular Weight*	*Calculated Vapor Pressure Value*	*PEL Data[a,b]*	*1995 Reported Poundage[c] (lbs)*
2924	79-09-4	Propionic acid 	74.08	3.0 mm Hg 20° C	PEL- TWA 10 ppm	44,400
2966	110-86-1	Pyridine 	79.10	16 mm Hg 20° C	PEL - TWA 5 ppm, 15 mg/m^3	71
3523	123-75-1	Pyrrolidine 	71.12	49 mm Hg 20° C		28
3898	5724-81-2	1-Pyrroline 	69.1	62.9 mm Hg 20° C		NA
3589	108-46-3	Resorcinol 	110.11	2.11 mm Hg 25° C	PEL-TWA 10 ppm; STEL 20 ppm (see Footnote d)	5
3039	7446-09-5	Sulfur dioxide 	64.06	224 mm Hg 20° C	PEL - TWA 5 ppm, 13 mg/m^3	4,100
3241	75-50-3	Trimethylamine 	59.11	1430 mm Hg 20° C	REL - TWA 10 ppm; STEL 15 ppm	870
3098	110-62-3	Valeraldehyde 	86.13	25.1 mm Hg 20° C	REL -TWA 50 ppm	140

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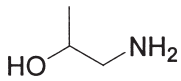
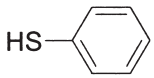
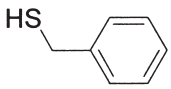
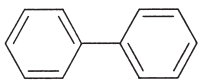
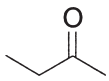
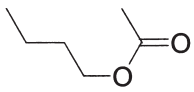
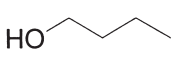
FEMA	CAS	Principal Name	Molecular Weight	Calculated Vapor Pressure Value	PEL Data[a,b]	1995 Reported Poundage[c] (lbs)
Low Priority						
3326	67-64-1	Acetone 	58.08	202 mm Hg 20° C	PEL - TWA 1000 ppm, 2400 mg/m3	400
3965	78-96-6	1-Amino-2-propanol 	75.13	0.511 mm Hg 20° C		NA
3616	108-98-5	Benzenethiol 	110.18	1.15 mm Hg 20° C	REL-ceiling limit TWA 0.1 ppm, 0.5 mg/m^3 (15 minutes)	4
2147	100-53-8	Benzyl mercaptan 	124.21	0.3 mm Hg 20° C		0
3129	92-52-4	Biphenyl 	154.21	0.00419 mm Hg 20° C	PEL - TWA 0.2 ppm, 1mg/m^3	0
2170	78-93-3	2-Butanone 	72.11	75 mm Hg 20° C	PEL - TWA 200 ppm, 590 mg/m^3	530
2174	123-86-4	Butyl acetate 	116.16	9.3 mm Hg 20° C	PEL- TWA 150 ppm, 710 mg/m^3	26,300
2178	71-36-3	Butyl alcohol 	74.12	4.4 mm Hg 20° C	PEL - TWA 100 ppm, 300 mg/m^3	13,300

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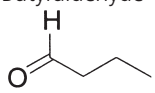
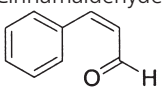
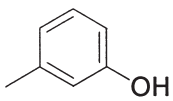
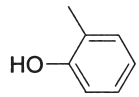
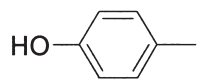
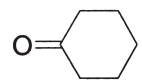
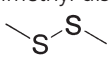
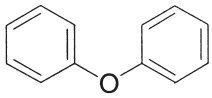
FEMA	*CAS*	*Principal Name*	*Molecular Weight*	*Calculated Vapor Pressure Value*	*PEL Data[a,b]*	*1995 Reported Poundage[c] (lbs)*
2219	123-72-8	Butyraldehyde 	72.11	87 mm Hg 20° C		340
2286	104-55-2	Cinnamaldehyde 	132.16	0.02 mm Hg 20° C		993,000
3530	108-39-4	m-Cresol 	108.14	0.238 mm Hg 25° C	PEL - Skin TWA 5 ppm, 22 mg/m^3. OSHA standard is for all cresols combined under CAS Number 1319-77-3 (*Federal Register* 7/5/89).	0
3480	95-48-7	o-Cresol 	108.14	0.2 mm Hg 20° C	PEL - Skin TWA 5 ppm, 22 mg/m^3. OSHA standard is for all cresols combined under CAS Number 1319-77-3 (*Federal Register* 7/5/89).	1
2337	106-44-5	p-Cresol 	108.14	0.07 mm Hg 20° C	PEL - Skin TWA 5 ppm, 22 mg/m^3. OSHA standard is for all cresols combined under CAS Number 1319-77-3 (*Federal Register* 7/5/89).	17
3909	108-94-1	Cyclohexanone 	98.15	2.94 mm Hg 20° C	PEL - TWA 50 ppm, 200 mg/m^3	NA
3536	624-92-0	Dimethyl disulfide 	94.2	22 mm Hg 20° C		4,170
3667	101-84-8	Diphenyl ether 	170.21	0.01 mm Hg 20° C	PEL - Vapor TWA 1ppm, 7mg/m^3	86

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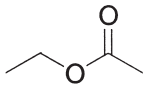
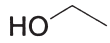
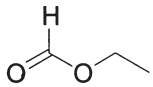
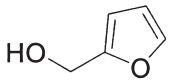
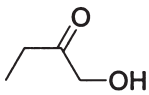
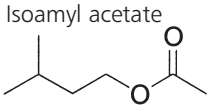
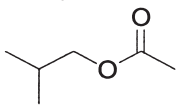
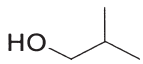
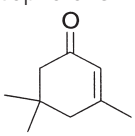
FEMA	CAS	Principal Name	Molecular Weight	Calculated Vapor Pressure Value	PEL Data[a,b]	1995 Reported Poundage[c] (lbs)
2414	141-78-6	Ethyl acetate 	88.11	74 mm Hg 20° C	PEL - TWA 400 ppm, 1400 mg/m^3	462,000
2419	64-17-5	Ethyl alcohol 	46.07	44 mm Hg 20° C	PEL - TWA 1000 ppm, 1900 mg/m^3	23,500,000
2434	109-94-4	Ethyl formate 	74.08	190 mm Hg 20° C	PEL - TWA 100 ppm, 300 mg/m^3	18,600
2491	98-00-0	Furfuryl alcohol 	98.1	0.5 mm Hg 20° C	PEL - TWA 50 ppm, 200 mg/m^3	410
3173	5077-67-8	1-Hydroxy-2-butanone 	88.11	0.511 mm Hg 20° C		0
2055	123-92-2	Isoamyl acetate 	130.19	4.0 mm Hg 20° C	PEL - TWA 100 ppm, 525 mg/m^3	441,000
2175	110-19-0	Isobutyl acetate 	116.16	13 mm Hg 20° C	PEL - TWA 150 ppm, 700 mg/m^3	35,600
2179	78-83-1	Isobutyl alcohol 	74.12	6.9 mm Hg 20° C	PEL - TWA 100 ppm, 300 mg/m^3	27,700
3553	78-59-1	Isophorone 	138.2	0.3 mm Hg 20° C	PEL - TWA 25 ppm, 140 mg/m^3	2

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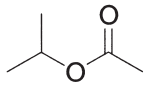
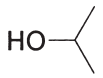
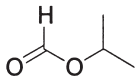
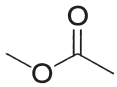
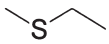
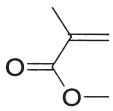
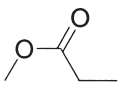
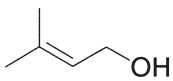
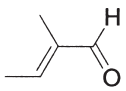
FEMA	CAS	Principal Name	Molecular Weight	Calculated Vapor Pressure Value	PEL Data[a,b]	1995 Reported Poundage[c] (lbs)
2926	108-21-4	Isopropyl acetate 	102.13	50 mm Hg 20° C	PEL - TWA 250 ppm, 950 mg/m^3	1,180
2929	67-63-0	Isopropyl alcohol 	60.1	33 mm Hg 20° C	PEL - TWA 400 ppm, 980 mg/m^3	176,000
2944	625-55-8	Isopropyl formate 	88.11	110 mm Hg 20° C		0
2676	79-20-9	Methyl acetate 	74.08	170 mm Hg 20° C	PEL - TWA 200 ppm, 610 mg/m^3	1,060
3860	624-89-5	Methyl ethyl sulfide 	76.16	119 mm Hg 20° C		NA
4002	80-62-6	Methyl methacrylate 	100.12	28 mm Hg 20° C	PEL - TWA 100 ppm, 410 mg/m^3	NA
2742	554-12-1	Methyl propionate 	88.11	68.7 mm Hg 20° C		270
3647	556-82-1	3-Methyl-2-buten-1-ol 	86.13	1.4 mm Hg 20° C		65
3407	497-03-0	2-Methyl-2-butenal 	84.12	17 mm Hg 20° C		3

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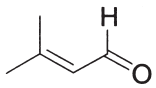
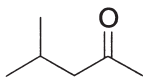
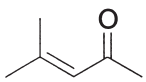
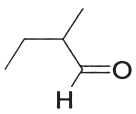
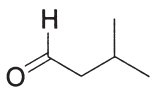
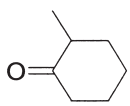
FEMA	CAS	Principal Name	Molecular Weight	Calculated Vapor Pressure Value	PEL Data[a,b]	1995 Reported Poundage[c] (lbs)
3646	107-86-8	3-Methyl-2-butenal 	84.12	6.14 mm Hg 20° C		0
2731	108-10-1	4-Methyl-2-pentanone 	100.16	15 mm Hg 20° C	PEL -TWA 100 ppm, 410 mg/m^3	19
3368	141-79-7	4-Methyl-3-penten-2-one 	98.15	7.9 mm Hg 20° C	PEL - TWA 25 ppm, 100 mg/m^3	0
2691	96-17-3	2-Methylbutyraldehyde 	86.13	25 mm Hg 20° C		33
2692	590-86-3	3-Methylbutyraldehyde 	86.13	29 mm Hg 20° C		3,290
3946	583-60-8	2-Methylcyclohexanone 	112.17	2.17 mm Hg 20° C	PEL - Skin TWA 100 ppm, 460 mg/m^3	NA
3875	67-68-5	Methylsulfinylmethane 	78.14	0.427 mm Hg 20° C		NA

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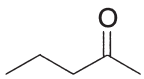
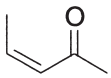
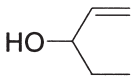
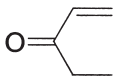
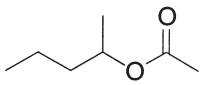
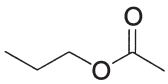
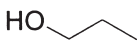
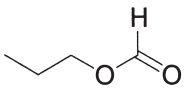
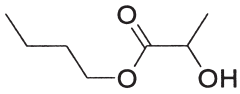
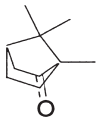
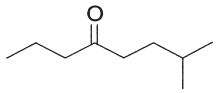
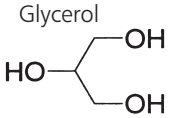
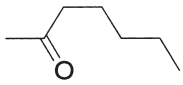
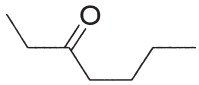
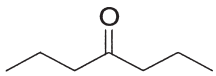
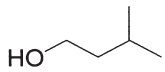
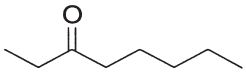
FEMA	CAS	Principal Name	Molecular Weight	Calculated Vapor Pressure Value	PEL Data[a,b]	1995 Reported Poundage[c] (lbs)
2842	107-87-9	2-Pentanone 	86.13	29 mm Hg 20° C	PEL - TWA 200 ppm, 700 mg/m^3	640
3417	625-33-2	3-Penten-2-one 	84.12	29 mm Hg 20° C		0
3584	616-25-1	1-Penten-3-ol 	86.13	6.0 mm Hg 20° C		20
3382	1629-58-9	1-Penten-3-one 	84.12	26 mm Hg 20° C		2
4012	626-38-0	2-Pentyl acetate 	130.19	7.22 mm Hg 20° C	PEL - TWA 125 ppm, 650 mg/m^3	NA
2925	109-60-4	Propyl acetate 	102.13	25 mm Hg 20° C	PEL - TWA 200 ppm, 840 mg/m^3	3,110
2928	71-23-8	Propyl alcohol 	60.1	15 mm Hg 20° C	PEL - TWA 200 ppm, 500 mg/m^3	8,470
2943	110-74-7	Propyl formate 	88.11	64 mm Hg 20° C		110

Other Flavoring Substances with OSHA/PEL's

2205	138-22-7	Butyl lactate 	146.19	0.5 mm Hg 20° C	REL-TWA 5 ppm	410

CONTINUED

FEMA	CAS	Principal Name	Molecular Weight	Calculated Vapor Pressure Value	PEL Data[a,b]	1995 Reported Poundage[c] (lbs)
2230	464-49-3	d-Camphor 	152.24	0.00563 mm Hg 20° C	PEL - TWA 2 mg/m^3	6,630
3537	108-83-8	2,6-Dimethyl-4-heptanone 	142.24	0.0147 mm Hg 20° C	PEL - TWA 50 ppm, 290 mg/m^3	0
2525	56-81-5	Glycerol 	92.10	<0.001 mm Hg 20° C	PEL - Glycerol mist - TWA 15 mg/m^3 (total dust); 5 mg/m^3 (respirable fraction)	3,620,000
2544	110-43-0	2-Heptanone 	114.19	2.6 mm Hg 20° C	PEL - TWA 100 ppm, 465 mg/m^3	2,280
2545	106-35-4	3-Heptanone 	114.19	2.8 mm Hg 20° C	PEL - TWA 50ppm, 230 mg/m^3	120
2546	123-19-3	4-Heptanone 	114.19	0.8 mm Hg 20° C	REL-TWA 50 ppm	130
2057	123-51-3	Isoamyl alcohol 	88.15	1.5 mm Hg 20° C	PEL - TWA 100 ppm, 360 mg/m^3 (for primary and secondary)	36,600
2803	106-68-3	3-Octanone 	128.22	1.6 mm Hg 20° C	TWA 25 ppm, 130 mg/m^3. OSHA lists standard for this material under CAS Number 541-85-5 (*Federal Register* 7/5/89).	12

[a] REL's listed only for substances without OSHA PEL's.

[b] PEL=OSHA Permissible Exposure Limit; REL=NIOSH Recommended Exposure Limit; STEL=Short Term Exposure Limit; TWA=Time Weighted Average

[c] NA=Not applicable because the 1995 Poundage survey included FEMA GRAS substances from GRAS 3 through GRAS 16 (up to GRAS number 3796).

[d] PEL for resorcinol subsequently rescinded and is currently not in force.

Additional Resources

American Thoracic Society

ATS is the professional society for pulmonary medicine physicians. ATS has a variety of resources relevant to respiratory health and safety. Especially important are the ATS guidelines on the proper conduct of spirometry and other pulmonary function tests.

- The ATS website is at: *www.thoracic.org*.

National Institute for Occupational Safety and Health

NIOSH is part of the Centers for Disease Control (CDC) and is the federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness. NIOSH is not a regulatory agency. Important NIOSH resources include:

- The NIOSH Alert, "Preventing lung disease in workers who use or make flavorings" available at *http://www.cdc.gov/niosh/docs/2004-110/*.
- The new NIOSH occupational respiratory disease surveillance program at *www.cdc.gov/niosh/topics/ORDS*.
- The NIOSH website is at: *www.cdc.gov/niosh*.

Occupational Safety and Health Administration

OSHA is the federal regulatory agency responsible for assuring the safety and health of workers by setting and enforcing standards; providing training, outreach and education; establishing partnerships; and encouraging continual improvement in workplace safety and health.

- While there are no OSHA standards specific to the flavor industry, the flavor industry is subject to OSHA's general standards at 29 C.F.R. Parts 1900-1999, and to OSHA established permissible exposure limits (PELs) for individual substances.
- OSHA's Respiratory Protection Standard can be found at 29 C.F.R. Sec. 1910.134.
- OSHA's website is at: *www.osha.gov*.

Patty's Industrial Hygiene and Toxicology

The fifth edition of this basic resource on industrial hygiene was published in 2000. The 12-volume set covers a variety of industrial hygiene issues and provides summaries of toxicology data on many chemicals used in manufacturing. Patty's is published by John Wiley & Sons and is available in book form and on-line.

Maintaining safe and healthy workplaces is a matter of utmost importance to FEMA and its members. FEMA consulted with experts on the development of this document and made extensive use of a wide variety of information resources. As described in detail in this report, the application of this information to your workplace is a function of specific aspects of your workplace and the products manufactured and handled. Because of the unique nature of each workplace, the information in this report should be considered only a general guide. FEMA is not responsible for either the use or nonuse of the information, or any actions, or failure to act, in any specific workplace based on reliance on this report. It is your individual responsibility to verify this information as it applies to your workplace before acting, and to comply with all relevant federal, state, and local laws and ordinances. We strongly urge you to consult with appropriate experts regarding the circumstances relevant to respiratory health and safety in your facilities.

The Flavor and Extract Manufacturers Association of the United States

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