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Diacetyl Exposures in the Flavor Manufacturing Industry

J.W. Martyny,[1] M.V. Van Dyke,[1] S. Arbuckle,[2] M. Towle,[1] and C.S. Rose[1]

[1]National Jewish Medical and Research Center, Division of Environmental and Occupational Health Sciences, Denver, Colorado
[2]CoorsTec - Safety, Golden, Colorado

Recently, worker exposures to diacetyl, a chemical used in the production of butter popcorn, has been linked to bronchiolitis obliterans, a severe lung disease. This chemical is also used in the flavor industry to confer a buttery flavor to many food products, with more than 228,000 pounds used in 2005. Diacetyl exposures were monitored at 16 small- to medium-sized flavor facilities to determine potential diacetyl exposures. A total of 181 diacetyl samples (both personal and area samples) were obtained, and a number of real-time samples were collected using an IR spectrometer. Samples were obtained during liquid and powder compounding operations at the facilities as well as during laboratory and QC operations. The personal and area samples ranged from non-detectable (<0.02 ppm) to as high as 60 ppm. Ninety-two (51%) of the samples were below the limit of detection, and the mean diacetyl concentration for all processes was 1.80 ppm. Mean diacetyl levels during powder operations were generally higher (4.24 ppm) than mean diacetyl levels during liquid operations (2.02 ppm). Maximum real-time diacetyl exposures during powder operations could reach as high as 525 ppm. These results are similar to exposures measured by NIOSH in popcorn facilities where lung disease was found; however, the duration of use and frequency of use may be significantly lower.

Keywords 2,3-butanedione, bronchiolitis obliterans, butter flavor, butter popcorn, flavorings, lung disease

Address correspondence to: J.W. Martyny, National Jewish Medical and Research Center, Division of Environmental and Occupational Health Sciences, 1400 Jackson Street, Denver, CO; e-mail: martynyj@njc.org.

INTRODUCTION

In 2002, a report of severe lung disease in employees at a microwave popcorn plant was published by investigators from the National Institute for Occupational Safety and Health (NIOSH).(1) NIOSH subsequently investigated a total of six U.S. microwave popcorn facilities(2) and found an association between the production of butter-flavored microwave popcorn and risk for airways obstruction with features of bronchiolitis obliterans. Extensive environmental sampling suggested that the most likely causative exposure was to diacetyl, a ketone used to impart butter flavoring during the production of microwave popcorn.

Following recognition of potential risk to workers exposed to butter flavorings, individual flavor manufacturing companies, of which a number are members of the Flavor and Extract Manufacturers Association of the United States (FEMA), requested consultation from investigators at the National Jewish Medical and Research Center to determine exposures and lung health risk among flavor manufacturing employees. A multipronged effort with 16 flavor companies to (*a*) characterize exposures to chemicals of concern (including diacetyl, acetoin, acetaldehyde, benzaldehyde, and acetic acid); (*b*) recommended appropriate engineering controls to reduce exposures; and (*c*) provide respiratory protection programs in smaller flavor companies was begun in 2003. This article describes the steps in flavor manufacturing and presents findings from this industrial hygiene effort.

BACKGROUND

Diacetyl (2,3-butanedione, dimethyl diketone, 2,3-diketobutane) (CAS # 431-03-8) is a ketone commonly used in the flavor industry to impart a buttery flavor to food products. In addition to its commercially synthesized form used in the flavor industry, diacetyl is a naturally occurring substance produced during bacterial fermentation and is found in butter, red and white wines, brandy, roasted coffee, ensilage, and many other fermented foods.(3) In 2005, the most recent year for which information is available, use of diacetyl as reported by FEMA totaled 103,420 kilograms (228,000 pounds).(4)

Diacetyl has a vapor pressure of 43 mm Hg at 20°C and a molecular weight of 86.09. At low concentrations, diacetyl has a familiar and, to many, pleasing butter aroma; at higher concentrations (>30 ppm), it is an irritant to the upper respiratory tract and eyes. Exposure to high concentrations (>190 ppm) of diacetyl-containing butter flavor and to pure diacetyl resulted in necrosis of nasal and airway epithelium in rats exposed in a whole-body inhalation chamber for 6 hr.(5,6)

Diacetyl is used in a wide variety of liquid and powdered flavors. As diacetyl imparts a butter-like taste and aroma to products, it is generally found in the highest relative concentration in buttery flavors. However, diacetyl also is present in lower quantities in many other flavored products, including caramel, butterscotch and vanilla flavors, and muffin and cake mixes. As the composition of most flavored products is usually a closely guarded trade secret, the exact percentages of diacetyl are not generally reported.

Diacetyl is only one of more than 2000 chemicals and natural flavorings used by the flavor industry. In a recent industry publication, FEMA experts reviewed available scientific information on human and animal inhalation exposure, chemical structure, and volatility for many of the chemicals used in the flavor industry.[7] This review identified 34 flavor chemicals as "high priority" indicating the chemical "may pose a respiratory hazard if used or handled in the workplace in an unsafe manner."[(p.5)] Forty-nine flavor chemicals were identified as "low priority" indicating the chemical "may pose hazards only in extreme circumstances of exposure."[(p.5)] Diacetyl is currently listed as a "high priority" chemical by FEMA even though it currently does not have an Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL).

In part, because the flavor manufacturing industry is a subset of the food industry, there has been little recognition of potential risks from exposure to flavor ingredients. Prior to 2001, diacetyl had not been implicated as a cause of occupational lung disease. Moreover, flavor companies vary widely in size and product specialty, making generalization about risk difficult. Flavor manufacturers range from small companies with fewer than 10 production employees to large companies with several hundred production employees. Variability occurs in the quantities and types of materials mixed. Some facilities concentrate on producing a particular type of product, such as savories, fruit or berry products, vanilla extracts, or dairy flavors. Companies may also specialize in liquid or powder compounds. Some companies may produce flavor quantities in excess of 3500 L per batch, while other facilities mix amounts less than 19 L per batch. Despite this variability, steps in the production process for most flavor manufacturers are similar.

Prior to this project, liquid and powder compounding in many flavor facilities was carried out in semi-enclosed areas with few if any local exhaust ventilation controls. The average liquid compounding area may range from 16 m^2 to as many as several hundred square meters. Areas for powder operations are generally larger, with high ceilings to contain the large ribbon blenders. Most powder operations are performed in areas at least 100 m^2, with a ceiling height of 7 m. General ventilation in the facilities varies depending on location, with businesses in colder climates having large heating and air-conditioning units; facilities in warmer climates are more likely to rely on outdoor ventilation.

Initial Steps in Flavor Production

Most flavor facilities unload pure liquid diacetyl in a large warehouse receiving area. This location also may serve as the area where the finished flavor product is shipped to customers. After pure diacetyl and other flavor production chemicals are brought into the receiving area, containers are opened and small samples (less than 100 mL) are collected by quality control (QC) personnel. Quality control usually consists of sensory tests to evaluate the color, texture, taste, and odor of an incoming chemical. For diacetyl, a plastic strip is placed into an incoming sample, and a second strip is inserted into a sample from a previous shipment. A comparison is made by passing one and then the other under the nose of the individual conducting the testing. Occasionally, analyses including gas chromatography analysis are done.

After quality control approval, the diacetyl is taken to a raw ingredient storage area that is usually in a separate area from finished product storage. As pure diacetyl is flammable, it is frequently stored in an area served by a hazardous materials ventilation system consisting of floor level exhaust vents. In some facilities, these areas are refrigerated.

The manufacture of flavors consists of three basic steps:

(1) Concentrate compounding, that is, the addition of precise quantities of raw flavor chemicals and ingredients to a single container
(2) Flavor compounding, involving the addition of flavor concentrates to larger quantities of carrier liquids or binder powders to create the final flavor product.
(3) Packaging the final flavor product for shipment.

These steps are described in more detail below, and particular processes with potential worker exposure to flavor chemicals are discussed.

Concentrate Compounding

The initial concentrate compounding step is similar whether the final product is to be a powder or a liquid. In most companies, there is a specific area or room where this initial concentrate compounding step is conducted: the oil room or liquid compounding room. The process begins when a production worker (compounder) receives a product sheet or recipe specifying quantities and types of chemicals and raw materials necessary for the product. The compounder gathers these materials one at a time and stages them in the area to be weighed. Chemicals and raw materials are weighed carefully and added to a stainless steel container generally ranging from 4 to 19 L. As ingredients are added, they are frequently stirred using a pneumatic mixer.

During our initial evaluations, these containers were usually not covered, and mixing was seldom conducted in an area equipped with local exhaust ventilation. Diacetyl amounts in the initial concentrate may consist of quantities ranging from a few milliliters to several liters. Some products may require special handling, such as heating or dissolving in a liquid before their addition to the stainless steel container. Once the initial flavor concentrate has been well mixed, it may be transported to other areas of the facility for either liquid or powder flavor compounding. It is at this point that liquid compounding and powder compounding take different pathways.

Liquid Flavor Compounding

After initial compounding is complete, liquids are frequently taken to another area and mixed with carrier solutions (water, alcohols or other solvents). This portion of the process usually requires larger containers with capacities of 1000 to 1900 L. Mixing containers are almost always stainless steel and are frequently fitted with a valve mechanism to allow gravity draining of the product after mixing.

Three methods are used to add flavor concentrates and carrier liquids to mixing containers. The most common method involves simply pouring large quantities of carrier solution into the tank using a forklift or drum pouring device. Pouring the liquid chemical from the forklift into the container often results in turbulence and potential worker exposure to droplet aerosols as well as vapors. The flavor concentrates are usually added to the tank after the carrier by manually pouring the concentrate into the mixing tanks. If diacetyl is present in the concentrate, exposures to diacetyl aerosols and vapors may occur.

A second method involves a pumping system. Most facilities have small, mobile pneumatic pumps that can be used to transfer carrier liquids from a 190-L drum into a larger container. The pumps can quickly complete the transfer, but they take time to set up, disconnect, and clean. Because of these time constraints, pumps are usually not used unless large amounts of product are to be transferred. Some companies have gravity feed lines for products that are frequently used; a container is simply moved to the proper line, the valve opened, and the product dispensed into the tank. Flavor concentrates are usually added by hand pouring that may result in droplet and vapor exposure.

A third method involves transferring carrier chemicals out of a 190-L drum, 8 to 20 L at a time, into a small container that is then poured into the larger container. This method often results in worker exposure when the material is poured out of the drum and again when it is poured into the larger container. Because this method is time-consuming, it is not commonly used. The concentrates are normally poured by hand into the carrier tank.

During and/or after the materials are added, the final mixture is mixed automatically for a specified period of time, usually with a large bladed mixer. Mixing may occur for a short time (15–30 min) or for an hour or more as dictated by the compounding sheet. Occasionally, the mixture may be heated as it is mixed. The large mixing vessel may or may not be covered; however, as recognition of lung health risk has spread, most facilities have installed vessel lids during mixing. Few companies provided headspace ventilation control at the top of the tanks prior to and during this consultation program, although more controls were installed as a result of this program.

Liquid Flavor Packaging

After liquid flavor mixing has been completed, the product may be packaged immediately or held in a covered container until it is convenient to package. In many facilities, compounders do not complete the packaging, and there is a separate job category of packagers. Liquid packaging commonly requires either a pump or gravity to transfer the product to containers. In some cases, the process is as simple as opening a valve at the bottom of the tank and filling the appropriately sized containers. When large quantities are to be packaged into small containers, a pumping system is usually used to fill the containers. Some facilities use different filling mechanisms that enable the packagers to fill multiple bottles at a time. In all cases, containers are filled, capped, and labeled, then stacked on a pallet and sent to shipping.

After the finished product has been packaged, the compounding and mixing vessels are cleaned. In most cases, large containers are cleaned in place using a warm, soap solution and a high-pressure water spray. This use of a warm (38°–43°C) cleaning solution may result in increased exposure to diacetyl vapors. The container may also be brushed or wiped with a sponge, requiring a worker to bend over the tank during cleaning. Smaller containers are usually washed in the sink with soap and water. In smaller facilities, either packagers or compounders clean the mixing containers. In larger facilities, workers may be assigned exclusively to cleanup. Exposure to remnant flavoring chemicals may occur during these cleanup efforts.

Powder Flavor Compounding

Powder compounding is similar to liquid compounding in that both begin with mixing of liquid compounds. In some cases, powder processing may be as simple as adding liquids from the initial stage to a large base powder and then mixing the two. In other cases, liquids are mixed into a portion of the carrier to reduce clumping and then added to a larger quantity of powder. In this case, the initial quantity to be mixed is usually quite small, less than 23 kg of powder.

Most of the mixing vessels, whether they are 4-kg or 1360-kg mixers, are ribbon blenders that are loaded from the top. With larger ribbon blenders, a platform allows the operator to stand at the top of the mixer for loading. Most powders come in 23-kg bags that are slit open, and the contents are poured directly into the mixer. The powders may consist simply of carrier powders but may be powdered ingredients, including powdered diacetyl. Relatively few ribbon blenders are equipped with local exhaust at the loading port, and the operator is frequently exposed to particulate matter when powder is poured into the mixer and when the bag is folded up and discarded.

After the ingredients are added, the ribbon blender is turned on and large internal paddles mix the powder in a horizontal tube. Normally, the tube remains stationary and the paddles move internally. The top of the mixer through which the materials are loaded usually has a gasket seal to prevent material from leaking from the mixer into the room. We noted circumstances where the gasket material had worn off and fine powders with low moisture content entered the workplace via the top of the mixer, resulting in a fine dust contaminating the entire mixing room with potential worker exposure.

Powder Flavor Packaging

Powder flavors are mixed until uniform, then packaged. The packaging operation uses a chute at the bottom of the mixer with a handle that opens a valve, allowing powder to flow into the final container, usually a 7-kg to 11-kg box. A fine powder with low moisture content will flow easily into the boxes. If the powder is moist or coarse, the flow may be impeded and spout vibration may be necessary to keep the powder flowing. This can be accomplished either with the use of an automatic vibrating screen or by the worker tapping on the chute that delivers the powder. In either case, exposure to the powdered chemical may result.

Some mixers are equipped with local exhaust ventilation at the interface between the box to be loaded and the delivery chute. This device is designed to collect particulate matter and vapors released both when the powder is dropped through the chute and when the powder lands in the packaging container. The fill level is usually determined by the weight of the box as measured by a scale at the filling location. Frequently, the box will have a plastic lining that is tugged up and tied by a worker when the box is full. In some cases, tugging and tying of the plastic lining is not in close proximity to the ventilation control system, resulting in substantial worker exposure to the powdered flavor particulate matter and vapors.

After the boxes are filled, they are usually placed on a pallet and taken to the shipping area or to finished product storage. The large mixers are then cleaned using high-pressure water to rinse out the powder. High-pressure water is also frequently used to rinse down the floors and walls in the powder mixing area. Mixing may be ongoing during the cleaning process. Aerosols containing flavor chemicals may be released during vessel rinsing.

Occasionally, when small powder batches are mixed, the resulting mixture is sieved to ensure a uniform particle size. Often, the operator simply removes the powder from the mixer and sieves it by hand. Exposures during this process are very high, with the operator usually having visibly contaminated clothing after the operation is complete.

Spray Drying

Some powder flavors are produced by a spray drying process. This process involves atomizing a slurry or suspension of flavor concentrate and binder in a gas-fired drying tower to remove the moisture. Exposures from spray drying operations are very similar to powder mixing. The powder and flavor concentrate are added to the top of the spray dryer to form a slurry, which is atomized into the drying tower and drops to the bottom of the tower as a finely divided, dry powder. These powders are packaged in the same way as powdered flavors described previously. However, because these powders are very fine, the powder easily escapes from the chute, even with a local exhaust system present, and may result in exposures to workers in the vicinity.

Product Development

Product development in a laboratory setting occurs in most facilities but involves relatively fewer workers and smaller quantities than in production operations. Compounding is similar to the weighing and mixing that occurs in the production operation but is usually much faster and involves individual flavorists working on a particular product at their laboratory bench top. The process may be conducted under a hood, depending on the type of product being developed and whether the compounds used are malodorous or hazardous. Mixing is usually conducted in a beaker with a stirring magnet. After the product is mixed, it is tested for taste, texture, and color to meet customer specifications.

METHODS

The companies for whom we provided industrial hygiene (IH) consultation contacted us directly to request assistance. Companies were located in eastern, midwestern, and western states, with the largest number in California, where state OSHA efforts have encouraged flavor companies to seek industrial hygiene assistance.

We began our industrial hygiene evaluation at each facility by obtaining information about facility layout, products utilized, health and safety plans, and employee numbers. We then arranged with each company to conduct air sampling on product mixtures that used either high percentages ($>1\%$) of diacetyl or required heating diacetyl. This approach was designed to obtain worst-case diacetyl exposures during the sampling period. Based on the products to be compounded on the day of our evaluation, we formulated a sampling plan. In most facilities, we measured airborne levels of other chemicals of concern as well (including acetic acid, benzaldehyde, acetaldehyde and acetoin), but these results are not discussed here.

We collected both personal and area air samples for each process. The personal samples were obtained only on employees directly participating in the selected processes. Area samples were taken as close to the process as feasible. All samples were "process samples" in that sampling was conducted only during the time that the flavor was being compounded, mixed, and packaged, and not for an entire 8-hr shift. This process time also included time spent gathering flavor ingredients and during cleanup where applicable. Most processes ranged from 1 to 3 hr in total duration. As most employees were exposed only during the process time, the results of sampling should not be treated as 8-hr time-weighted averages (TWAs). Bystander exposures to employees working in the vicinity of the diacetyl operations were possible, and we assessed these potential exposures based on area samples.

Samples for diacetyl were taken in accordance with NIOSH Method 2557 using personal sampling pumps that were pre- and post-calibrated daily to a flow rate of approximately 150 cc/min.[8] All samples were shipped on ice via overnight mail to an AIHA-accredited laboratory for analysis within 7 days. Information provided by NIOSH after the completion

TABLE I. Outdoor Relative Humidity Levels during Diacetyl Sampling

Company Code	Minimum Relative Humidity (%)	Maximum Relative Humidity (%)	Average Relative Humidity (%)
A	72	94	80
A	37	65	47
B	79	88	84
C	56	88	73
D	25	63	38
E	70	100	86
E	50	93	63
F	54	72	62
F	67	88	80
F	47	78	63
G	57	81	67
H	46	68	53
I	61	74	69
I	48	66	58
J	25	84	30
J	53	80	65
K	16	77	36
L	69	81	73
M	37	81	57
M	47	84	63
N	57	88	73
O	24	56	37
P	44	67	53

Note: Relative humidity levels obtained from www.wunderground.com/history/airport for the zip code in which the facility was located.

of this program indicated that this sampling method is significantly affected by humidity.[8] At humidity levels exceeding 30%, there is reportedly a dramatic underestimation of actual diacetyl concentrations. During our sampling efforts, there were no instances where the mean outside relative humidity was less than 30% relative humidity (Table I), suggesting that our results likely underestimate actual diacetyl concentrations. However, for comparison purposes, most data regarding diacetyl concentrations in other industries were also collected using this methodology.[1,2]

In six flavor facilities, we collected real-time measurements of airborne diacetyl concentrations using an Innova 1312 photoacoustic infrared (IR) spectrometer (Innova AirTech Instruments, Ballerup, Denmark). This instrument is a portable, subpart per million chemical analyzer that provides real-time measurements of diacetyl vapor concentration. The instrument included a filter on the sampling tube to remove particles from the sample stream and protect the detection chamber. For diacetyl detection, an optical filter (#977) with a center wavelength of 11.1 μm was used. The instrument was calibrated yearly to a diacetyl standard by the factory representative, and the results were internally adjusted for humidity. Data and observations regarding the activities of employees working on specific flavor formulations were manually recorded to determine which processes or process steps were associated with higher diacetyl exposures. Logged, minute-by-minute data were downloaded into an Excel Spreadsheet for analysis.

All data were entered into a Microsoft Access database and then into a Microsoft Excel spreadsheet for analysis. Samples that were below the lower limit of detection were treated as half the limit of detection for analytical purposes.

RESULTS

We measured airborne diacetyl levels from a total of 16 small- to medium-sized flavor companies ranging in size from as few as 10 to as many as 130 employees. The companies employed an average of 24 production employees (range 3–76) and an average of 12 laboratory and quality control personnel (range 1–25). A total of 181 diacetyl samples were obtained including 105 (58%) personal samples and 76 (42%) area samples (Tables II and III). In most cases, the area samples were collected in the same area where an employee with a personal sample was working; in some cases, area samples were collected in administrative or warehouse locations to characterize the concentrations of the diacetyl throughout the plant.

Results ranged from non-detectable (<0.01 ppm) to a high of 60 ppm. The highest level of diacetyl was obtained from a personal sample worn by a worker heating an approximately 1000-L butter flavor mixture while wearing a respirator (Table II). Ninety-two (51%) of the samples were below the

TABLE II. Personal Sample Results for Diacetyl at 16 Plants

Company	Number of Samples	Number <LOD (%)	Mean (ppm)	Median (ppm)	Range (ppm)
A	8	3 (38)	5.86	0.18	<0.01–32.00
B	7	2 (29)	0.18	0.08	<0.01–0.65
C	4	0	6.49	1.60	0.77–22.00
D	2	0	0.36	0.36	0.08–0.63
E	6	0	6.44	3.00	0.18–21.00
F	14	5 (36)	1.04	0.07	<0.02–8.30
G	3	0	0.81	0.74	0.18–1.50
H	1	1 (100)	NA	NA	0.09
I	4	0	15.26	0.48	0.07–60.00
J	21	11 (52)	3.01	0.16	<0.02–21.00
K	5	1 (20)	0.47	0.50	<0.01–0.98
L	4	1 (25)	0.09	0.08	0.04–0.14
M	8	7 (88)	0.08	0.07	<0.02–0.18
N	11	10 (91)	0.03	0.01	<0.02–0.07
O	6	4 (67)	0.04	0.02	<0.01–0.09
P	1	1 (100)	NA	NA	<0.02
Total	105	46 (44)	2.48	0.14	<0.01–60.00

Note: Half the LOD was used in the calculation of mean and median values. NA = Not Applicable.

TABLE III. Area Sample Results for Diacetyl at 16 Plants

Company	Number of Samples	Number <LOD (%)	Mean (ppm)	Median (ppm)	Range (ppm)
A	4	3 (75)	0.07	0.01	< 0.01–0.24
B	0	0	NA	NA	NA
C	3	1 (33)	3.71	0.11	<0.01–11.00
D	3	0	3.65	0.85	0.10–10.00
E	10	5 (50)	1.32	0.08	<0.01–6.60
F	8	5 (63)	0.07	0.06	< 0.01–0.21
G	2	1 (50)	0.56	0.56	<0.01–1.10
H	2	2 (100)	<0.01	<0.01	<0.01
I	7	2 (29)	1.41	0.09	<0.07–9.00
J	11	5 (45)	1.70	0.31	<0.01–8.30
K	5	3 (60)	0.31	0.02	< 0.01–1.20
L	2	0	0.10	0.10	0.01–0.12
M	2	2 (100)	<0.10	<0.10	<0.18–<0.22
N	7	7 (100)	<0.01	<0.01	<0.01–<0.04
O	9	9 (100)	<0.01	<0.01	<0.01–<0.09
P	1	1 (100)	NA	NA	<0.02
Total	76	46 (61)	0.91	0.07	< 0.01–11.00

Note: Half the LOD was used in the calculation of mean and median values. NA = Not Applicable.

LOD (generally less than 0.02 ppm). The mean diacetyl concentration for all of the process samples was 1.80 ppm and the median was 0.10 ppm. The median diacetyl levels by company ranged from a low of <0.01 ppm to a high of 1.50 ppm.

Table II shows diacetyl concentrations for personal samples obtained from production workers participating directly in a process using diacetyl. Forty-six (44%) of these samples were below the LOD (approximately 0.01 ppm). The overall mean diacetyl level was 2.48 ppm. For personal samples, individual company mean diacetyl levels ranged from non-detect (<0.01 ppm) to a high of 15.26 ppm. Company median diacetyl levels ranged from non-detect (<0.01 ppm) to a high of 3.0 ppm, with an overall median level for all companies of 0.14 ppm.

Table III shows results of a total of 76 diacetyl area samples obtained at the facilities. Not all of these samples were taken in the work areas, since some were taken in administrative areas to determine potential diacetyl vapor movement into those areas. Forty-six (61%) of the samples were below the LOD. The overall mean was 0.91 ppm, and the overall median was 0.07 ppm. Mean levels of diacetyl by company ranged from non-detect (approximately 0.01 ppm) to a high of 3.71 ppm. Median levels per company ranged from non-detect to a high of 0.85 ppm, with an overall median of 0.07 ppm. Not surprisingly, area sampling results were generally lower than personal sample results.

Table IV shows personal diacetyl sample results sorted by type of process. We obtained the largest number of samples for liquid compounding, a process common to all of the flavoring companies. Twenty-nine (44%) of the personal samples taken during liquid compounding operations were below the LOD. The mean diacetyl level for liquid compounding was 2.00 ppm, with a median level of 0.08 ppm. The highest level observed, 60 ppm, occurred during a process involving the use of a heated liquid diacetyl mixture. Mean diacetyl levels for powder compounding operations were significantly higher ($p < 0.03$) than those in liquid compounding operations, with only nine (29%) of the samples below the detection level.

Product development processes are similar to actual routine compounding processes except they involve much smaller quantities of diacetyl, are of shorter duration, and are frequently carried out under a laboratory hood. Only one of three laboratory-based process development operations sampled was above the LOD (approximately 0.05 ppm) at 0.14 ppm. The duration of this sample and the process was only 8 min. Personal samples taken on quality control employees were also low, with only one of six (14%) of the sample results above the detection level at 0.18 ppm.

Table V shows the mathematically calculated 8-hr TWA for the personal samples by process type. The TWAs are calculated assuming the samples represent the only diacetyl exposure for the applicable 8-hr period. Because many flavor companies do not use diacetyl on a daily basis, the potential for exposure to more than one process using diacetyl in a single day is not high. The table shows that mean and median TWA diacetyl exposures are less than 0.01 ppm for workers in both process development and QC. The mean TWA for liquid compounders was 0.91 ppm, with a median of 0.01 ppm. Powder compounders had the highest exposure, with a mean TWA of 0.71 ppm and a median of 0.32 ppm. The mean diacetyl exposure for liquids is influenced by a single sample of 60 ppm.

TABLE IV. Process Personal Sample Results

Process	Number of Samples	Mean Sampling Time[A]	Number <LOD (%)	Mean (ppm)	Median (ppm)	Range (ppm)
Powder Compounding	31	141 (96)	9 (29)	4.24	1.50	<0.01–32.00
Liquid Compounding	63	118 (85)	29 (44)	2.00	0.08	<0.01–60.00
Research and Development	3	31 (24)	2 (67)	0.11	0.11	<0.18–0.14
Quality Control	7	87 (141)	6 (86)	0.09	0.08	<0.01–0.18

Note: Half the LOD was used in the calculation of mean and median values.
[A]Standard deviation, sampling time in minutes.

TABLE V. Process Personal Sample Results as an 8-Hour TWA Assuming No Further Diacetyl Exposure

Process	Number of Samples	Mean (ppm)	Median (ppm)	Range (ppm)
Powder Compounding	31	0.71	0.32	<0.004–3.94
Liquid Compounding	63	0.91	0.01	<0.004–43.5
Research and Development	3	0.01	0.003	<0.004–0.017
Quality Control	7	0.01	0.004	<0.003–0.01

Note: Half the LOD was used in the calculation of mean and median values.

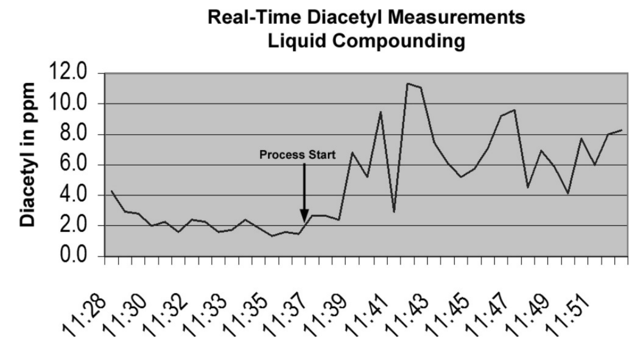

FIGURE 1. Real-time diacetyl levels during a typical liquid compounding operation obtained using an Innova 1312 photoacoustic infrared spectrometer

If that finding is removed from the analysis, the mean TWA for liquid compounders was 0.23 ppm, while the median remained 0.01 ppm.

Area sampling results during processes using diacetyl are shown in Table VI. These concentrations are generally less than the process exposures reported for the personal samples. The mean for all of the area samples obtained was 0.89 ppm and the median was 0.04 ppm. Four out of 17 (24%) of the area samples taken during powder operations were below the LOD, with a mean of 1.62 ppm and a median of 0.37 ppm. Area samples taken during liquid operations were below the LOD 54% of the time, with a mean of 0.80 ppm and a median of 0.05 ppm. For both liquid and powder processes, the mean diacetyl levels measured by area samples were less than half of the levels measured by personal samples. Eighty percent of area samples collected in the product development, QC, and administrative areas were below the limit of detection. There was a single high sample of 10 ppm in the QC area that was collected while preparing a sample for gas chromatograph analysis.

Real-time, direct-reading diacetyl samples were collected at six of the facilities using an IR spectrometer. These samples provide a more detailed picture of the fluctuation of diacetyl levels at different steps of each process. These samples also show short-term, high concentrations that may result from specific process steps. The direct-reading samples were normally taken in the breathing zone of the operator, although if the operator left the area the analyzer continued to run in that area. For that reason, the mean diacetyl levels reported by the real-time analyzer were generally higher than were the personal samples worn by the operator.

Figure 1 is a graph of the diacetyl level fluctuations observed during a typical liquid operation from start to finish. Figure 2 is a graph of diacetyl levels observed during a typical powder operation. In both cases, there are several peaks in diacetyl levels during the process. These peaks were associated with the addition of diacetyl to the process, the addition of other compounds creating turbulence, mixing or heating operations, covering or uncovering the containers, or packaging the materials. Powder operations appeared to have higher peaks than did the typical liquid operations we observed. This may be related to increased worker handling in powder mixing.

Table VII shows a summary of the real-time diacetyl sampling results for the flavor production processes monitored. Quality control processes, especially sampling of incoming chemicals or mixtures, were typically short duration processes that resulted in peak exposures ranging from 0.9 ppm to 35.2 ppm. Testing of finished products took slightly longer and resulted in higher maximum exposures, ranging from 116.2 ppm to 125.2 ppm. Similar to what we found through personal sampling, the mean exposures were low for all QC exposures, ranging from 0.6 ppm to 15.0 ppm. Liquid compounding operations resulted in higher exposure levels, especially if the operation involved agitation of the liquid as occurred during pouring.

TABLE VI. Process Area Sample Results

Process	Number of Samples	Mean Sampling Time^A (Std. Dev.)	Number <LOD (%)	Mean (ppm)	Median (ppm)	Range (ppm)
Powder compounding	17	129 (78)	4 (24)	1.62	0.37	<0.01–8.30
Liquid compounding	37	181 (101)	20 (54)	0.80	0.05	<0.01–11.00
Research and development	2	20 (3)	2 (100)	<0.10	NA	<0.10
Quality control	7	44 (38)	6 (86)	1.47	0.05	<0.01–10.00
Administration	8	211(103)	7 (88)	0.01	0.01	<0.01–0.01

Note: Half the LOD was used in the calculation of mean and median values.

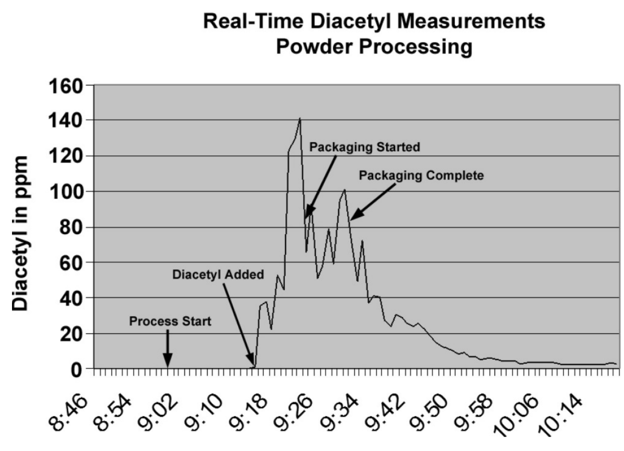

FIGURE 2. Real-time diacetyl levels in a typical powder operation obtained using an Innova 1312 photoacoustic infrared spectrometer

Maximum exposure levels during mixing ranged from 5.4 ppm to a high of 187.8 ppm. Peak exposures during liquid packaging were somewhat lower, ranging from 1.5 ppm to 8.4 ppm, likely due to the dilution of diacetyl in the final product. Powder compounding operations had the highest maximum exposure levels, with a high of 525 ppm measured during one process. Mean levels also appeared to be higher during powder operations than during liquid compounding operations, suggesting an extended time period of exposure for these operations.

DISCUSSION

There is increasing evidence for the risk of developing irreversible obstructive lung disease, BO, from exposure to diacetyl contained in artificial butter flavoring. This occupational lung disease was first described in 2001 in microwave popcorn workers, where cumulative exposure to diacetyl was found to be associated with increasing risk for BO.(1) Since then, investigations of additional microwave popcorn production facilities, diacetyl production workers, and flavor workers have supported the causal link between exposure to diacetyl in flavorings and risk for accelerated loss of lung function.(2,9–16)

Before this discovery, there was little concern about potential risks from chemical exposures in flavor workers. Because most artificial food flavors are “generally recognized as safe” for consumption, the possibility of damage from inhalation exposure during manufacturing received little attention. Although the flavor industry uses more than 2000 chemicals to manufacture flavor additives for foods, most of these chemicals, including diacetyl, do not have OSHA PELS. Few of the small- to medium-sized flavor companies with whom we consulted had pre-existing exposure monitoring or respiratory protection programs in place at the time of our initial industrial hygiene consultation. Thus, we found many opportunities for

TABLE VII. Real-Time Diacetyl Sampling Results

Process	Operation	Minimum (ppm)	Maximum (ppm)	Mean[A] (ppm)
QC	Raw Product Analysis	1.3	35.2	6.3
QC	Raw Product Analysis	2.7	11.1	5.0
QC	Raw Product Analysis	0	0.9	0.6
QC	Raw Product Analysis	0	1.5	1.0
QC	Raw Product Analysis	0	6.8	4.0
QC	Raw Product Analysis	6.7	15.0	8.0
QC	Raw Product Analysis	1.5	5.4	2.2
QC	Finished Product Analysis	1.9	116.2	10.7
QC	Finished Product Analysis	2.8	125.2	15.0
Liquid Comp.	Mixing	1.3	11.4	4.8
Liquid Comp.	Mixing	0.9	7.3	2.4
Liquid Comp.	Mixing	1.8	5.4	3.6
Liquid Comp.	Mixing	3.0	5.8	4.2
Liquid Comp.	Mixing	0	1.63	0.2
Liquid Comp.	Mixing	0	187.8	13.8
Liquid Comp.	Mixing	0	10.8	9.8
Liquid Comp.	Packaging	0.1	1.5	0.8
Liquid Comp.	Packaging	0.8	8.4	2.5
Liquid Comp.	Pouring	2.7	37.3	19.4
Liquid Comp.	Adding Water	18.8	184	87.7
Powder Comp.	Mixing	0.1	10.2	7.17
Powder Comp.	Mixing	9.6	19.4	11.6
Powder Comp.	Mixing	0	123	35
Powder Comp.	Mixing	0	525	164
Powder Comp.	Mixing	0	34	4.4
Powder Comp.	Mixing	37	287	100
Powder Comp.	Mixing	0.6	8.6	3.2
Powder Comp.	Sifting	21	53	42
Powder Comp.	Sifting	0	86.5	16.2
Powder Comp.	Pouring	6.7	231.3	52.5
Powder Comp.	Packaging	9.7	195	32.6
Powder Comp.	Packaging	50.6	101	75
Powder Comp.	Packaging	19	76	36
Powder Comp.	Packaging	0	84.4	10.5
Powder Comp.	Cleaning	15.3	20.1	17.1
Powder Comp.	Cleaning	2.2	2.8	2.5

Note: Samples were taken using an Innova 1312 photoacoustic infrared spectrometer.
[A]Mean is an average of all points taken during the sampling period.

primary prevention, even in the face of uncertainty regarding safe levels of exposure to diacetyl.

Our data suggest that diacetyl levels in small- to medium-sized flavor manufacturing facilities are widely variable, ranging from the limit of detection (<0.01 ppm) to as high as 60 ppm, with a mean of 1.80 ppm and a median of 0.10 ppm. These ranges are lower than those reported in the microwave popcorn plant with the index cases of BO, where diacetyl levels ranged from less than 0.01 ppm to 98 ppm, with a mean of 8.1 ppm.[10] Since we focused on measuring worst-case diacetyl exposures at the flavor production facilities, our results may not be representative of day-to-day operations. Moreover, because we sampled as many diacetyl-using processes as feasible in one day, the reported area diacetyl levels are likely higher than those that would occur on a normal work day at many of the flavor production facilities.

Our findings from personal samples in flavor manufacturing workers showed higher mean diacetyl exposure levels than the personal exposure levels reported in popcorn facilities where cases of BO have occurred.[2] However, the duration of diacetyl exposure appears to be much shorter for flavor workers than for popcorn production workers. Durations of 1 to 2 hr are typical for most diacetyl-using processes in flavor facilities, and these processes are often not conducted on a daily basis. A number of flavor facilities reported using diacetyl less often than monthly. Because of this difference in frequency and duration of diacetyl use, the 8-hr TWA levels in flavor facilities are likely to be substantially lower than those at microwave popcorn facilities.

We found a median calculated 8-hr TWA exposure for powder operations, which appear to be the areas of highest exposure at most flavor facilities, of 0.32 ppm (Table V). The calculated 8-hr median TWAs for other operations are near or below the current LOD (0.01 ppm). Our findings suggest that whereas short-term exposures at flavor facilities may be similar to those at microwave popcorn plants, exposures to diacetyl over an 8-hr work shift may be much lower for flavor workers.

In contrast with a previous investigation reporting diacetyl emissions from liquids as being 64 times higher than those from powders,[9] we found higher personal diacetyl exposures from powder operations compared with liquid compounding operations ($p < 0.003$). The mean diacetyl level in liquid compounding was 2.00 ppm, or, excluding one outlier of 60 ppm, 1.09 ppm. In comparison, mean diacetyl levels for powder operations were 4.24 ppm. These findings are similar to those reported at a single flavoring plant[14] where mean diacetyl levels for the powder operation were 10 times higher compared with liquid compounding.

We found maximum diacetyl levels during powder product mixing and packaging as high as 525 ppm. Previous investigation in one flavor facility showed that workers in liquid production reported fewer symptoms and had fewer findings of airways obstruction than did employees in the powder area.[14] In a report of seven possible cases of BO in workers at several California flavor facilities, all had worked with powdered flavorings.[15]

Our study of 16 flavor manufacturing facilities confirms that the highest diacetyl exposures are likely to occur in powder operations. In addition, exposures for powder operations may be underestimated, since the measurement method may not account for exposure resulting from inhaled particles coated with diacetyl. In fact, some powder formulations contain encapsulated diacetyl that may, when inhaled, become biologically available to the worker. Due to this evidence suggesting higher risk and higher exposures, efforts should be particularly directed toward controlling diacetyl exposures during powdered flavor mixing and packaging operations.

Although production processes in flavor manufacturing share many features in common, there is variability among flavor companies in the numbers of employees, types of flavors produced, frequency and quantity of diacetyl used, availability of engineering controls, and degree of automation of production. These differences may explain the variability in ranges of exposures among companies. Nevertheless, as outlined in our description of the flavor production process, there are ample opportunities for worker exposure to potentially hazardous chemicals.

Recently, questions have been raised about the reliability of published methods for analyzing diacetyl exposure concentrations based on personal and area air samples.[8] Our findings are similar to those reported at multiple microwave popcorn plants and at other flavor manufacturing facilities, suggesting that results are comparable. More work needs to be done to assess effects of humidity and other factors that may affect diacetyl measurements, particularly given the importance of developing regulatory standards for diacetyl-using industries. Moreover, the reliability and reproducibility of real-time monitoring methods to assess peak exposures to diacetyl should be further evaluated, as there is increasing concern that peak exposures to diacetyl may be important in conferring risk for disease in production workers.

CONCLUSIONS

Results of exposure monitoring in 16 flavor companies show that peak airborne levels of diacetyl may be similar to reported levels in other diacetyl-using industries where cases of fixed obstructive lung disease have occurred. Our findings suggest that powder operations result in the highest exposures in flavor production areas. Compared with the microwave popcorn industry, there is wide variability in frequency and duration of use of diacetyl among flavor companies, with likely lower 8-hr TWA exposures overall. Further investigation of peak, 8-hr, and cumulative exposures and their association with risk for obstructive lung disease is necessary to develop regulatory standards that protect worker health.

REFERENCES

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

2. **Kanwal, R., G. Kullman, C. Piacitelli, et al.:** Evaluation of flavorings-related lung disease risk at six microwave popcorn plants. *J. Occup. Environ. Med. 48(2)*:149–157 (2006).
3. **Pakdeeto, A., N. Naranong, and S. Tanasupawat:** Diacetyl of lactic acid bacteria from milk and fermented foods in Thailand. *J. Gen. Appl. Microbiol. 49*:301–307 (2003).
4. **Gavin, C., M.C. Williams, and J.B. Hallagan:** *Poundage and Technical Effects Update Survey, 2005*. Washington, D.C.: The Flavor and Extract Manufacturers Association of the United States, 2008.
5. **Hubbs, A.F., L.A. Battelli, W.T. Goldsmith, et al.:** Necrosis of nasal and airway epithelium in rats inhaling vapors of artificial butter cflavoring. *Toxicol. Appl. Pharm. 185*:128–135 (2002).
6. **Hubbs, A.F., L.A. Battelli, R.R. Mercer, et al.:** Inhalation toxicity of the flavoring agent, diacetyl (2,3-butanedione), in the upper respiratory tract of rats. *Toxicol. Sci. 78 (Suppl 1)*:438–439 (2004).
7. **Flavor and Extract Manufacturers Association of the United States (FEMA):** *Respiratory Health and Safety in the Flavor Manufacturing Workplace*. Washington, D.C.: FEMA, 2004.
8. **National Institute for Occupational Safety and Health (NIOSH):** Diacetyl. In *NIOSH Manual of Analytical Methods (NMAM),* 4th ed., 3rd suppl. P.C. Schlecht and P.F. O'Conner (eds.) Pub no. 2003-154. Cincinnati, Ohio: Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, NIOSH, 2003.
9. **Boylstein, R., C. Piacitelli, A. Grote, R. Kanwal, G. Kullman, and K. Kreiss:** Diacetyl emissions and airborne dust from butter flavorings used in microwave popcorn production. *J. Occup. Environ. Hyg. 3*:530–535 (2006).
10. **Kullman, G., R. Boylstein, W. Jones, C. Piacitelli, S. Pendergrass, and K. Kreiss:** Characterization of respiratory exposures at a microwave popcorn plant with cases of bronchiolitis obliterans. *J. Occup. Environ. Hyg. 2*:169–178 (2005).
11. **Akpinar-Elci, M., W.D. Travis, D.A. Lynch, and K. Kreiss:** Bronchiolitis obliterans syndrome in popcorn production plant workers. *Eur. Respir. J. 24*:298–302 (2004).
12. **National Institute of Occupational Safety and Health (NIOSH):** *Health Hazard Evaluation at Gilster-Mary Lee Corporation, Jasper, Missouri* by R. Kanwal, G. Kullman, K. Fedan, and K. Kreiss (HETA 2000-0401-2991). Cincinnati, Ohio: Department of Health and Human Services, Centers for Disease Control and Prevention, NIOSH, 2006.
13. **Akpinar-Elci, M., K.J. Stemple, O. Cinar Elci, R.A. Dweik, K. Kreiss, and P.L. Enright:** Exhaled nitric oxide measurement in workers in a microwave popcorn production plant. *Int. J. Occup. Environ. Health 12*:106–110 (2006).
14. **National Institute for Occupational Safety and Health (NIOSH):** *Report on Severe Fixed Obstructive Lung Disease in Workers at a Flavoring Manufacturing Plant, Carmi Flavor and Fragrance Co., Inc., Commerce California* by R. Kanwal and G. Kullman (HETA 2006-0303-3043). Cincinnati, Ohio: Department of Health and Human Services, Centers for Disease Control and Prevention, NIOSH, 2007.
15. **Materna, B., J. Quint, S. Payne, et al.:** Fixed obstructive lung disease among workers in the flavor-manufacturing industry – California, 2004–2007. *MMWR 56(16)*:389–393 (2007).
16. **Van Rooy, G.B.G.J., J.M. Rooyackers, M. Prokop, R. Houba, and D.J.J. Heederik:** Bronchiolitis obliterans syndrome in chemical workers producing diacetyl for food flavorings. *Am. J. Respir. Crit. Care. Med. 176*:498–504 (2007).