NIOSH Investigation of Gilster Mary Lee
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Technical Assistance to Missouri Department of Health

Interim Report

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SUMMARY

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. At the request of the Missouri Department of Health, staff of the National Institute for Occupational Safety and Health have investigated exposures and health outcomes at the company. Industrial hygiene assessments divided the plant into four work areas based on anticipated exposure levels to dust and volatile organic chemicals from artificial butter flavorings. Respirable dust concentrations from salt dumping operations were about 10-fold higher in the area in which flavorings were mixed compared to the office and outdoor work areas. Diacetyl, the predominant ketone in the plant, was present in concentrations 17 times higher in the mixing area compared to the microwave packaging area, 100 times higher compared to the warehouse and polyethylene packaging area, and 1000 times higher compared to the office and outdoor areas.

In late October 2000, 117 current workers (87%) participated in health questionnaire interviews, spirometry, diffusing capacity, and chest x-rays. Plant employees had 2.6 times the rates of chronic cough and shortness of breath compared to national data, adjusted for smoking and age group; younger employees who had never smoked had rates about five times higher than expected from national rates. Overall, plant employees had 3.3 times the rate of obstructive spirometry abnormalities compared to national adjusted rates; never smokers had 10.8 times the national expected rate. Worker reports of physician-diagnosed asthma and chronic bronchitis were about twice as frequent as expected from national data, with a 3.3-fold excess of chronic bronchitis in never smokers. Microwave popcorn production workers had statistically higher rates of regular trouble with breathing and unusual fatigue, compared with workers in two lower exposure groups. Strong exposure-response relationships existed between quartile of estimated cumulative exposures to diacetyl and respirable dust and frequency and degree of airway obstruction.

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. We recommend extensive primary, secondary, and tertiary prevention efforts for all current and former workers.

ABBREVIATIONS

CFU	Colony forming units
DLCO	Diffusion capacity of lung to carbon monoxide
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
MMAD	Mass median aerodynamic diameter
MEK	Methyl ethyl ketone
NIOSH	National Institute for Occupational Safety and Health
NHANES III	National Health and Nutrition Examination Survey III
OSHA	Occupational Safety and Health Administration
PEL	Permissible exposure limit
p	Probability
ppm	Parts per million
STD	Standard deviation
TWA	Time-weighted average
VOC	Volatile organic compound

BACKGROUND

In May 2000, nine former workers at a factory that mixes and packages microwave popcorn were reported to the Missouri Department of Health by an occupational medicine physician to have bronchiolitis obliterans, a severe lung disease characterized by fixed airflow obstruction. Four of these workers were placed on a lung transplant list. Many of the workers had no history of smoking. On the basis of these cases, the Missouri Department of Health (MDOH) requested technical assistance from the Centers for Disease Control and Prevention's National Institute for Occupational Safety and Health (NIOSH) in August of 2000 to determine whether exposures at the popcorn plant contributed to the disease and whether other former and current workers had developed this illness.

In August and September of 2000, NIOSH investigators made site visits to the plant and conducted initial investigations of the environmental conditions and health concerns. These investigations consisted of interviews with current and former workers, inspection of the plant and processes, review of company environmental records, and some preliminary sampling for contaminants in air and bulk materials. Index cases among former workers in this plant had been diagnosed during the period of 1992-2000, and none reported an incident of presumed overexposure that preceded their symptoms. Among diagnosed cases, duration of employment before symptom onset ranged from 3 months to 3 years. Five of the diagnosed cases worked as mixers for flavoring agents of microwave popcorn, but four had only worked on the microwave popcorn packaging lines. In nearly all cases, chronic and progressive shortness of breath, persistent cough, and unusual fatigue preceded the diagnosis by several months to several years. However, several affected individuals described other symptoms, such as phlegm, wheezing, episodes of mild fever, and generalized aches. One mixer reported severe skin dermatitis. Most diagnosed cases had fixed airflow obstruction, resulting in low forced expiratory volume (FEV_1) (14% of predicted in one case) and air trapping (increased residual volume and total lung capacity), normal chest x-rays, and normal diffusing capacity. Pulmonary function testing in the early stages of the disease was unavailable, and mis-diagnosis and referral to specialized centers for final diagnosis were common. In almost every diagnosed case, the symptoms slowly improved when the affected worker stopped working at the popcorn plant, but lung function remained abnormal.

From October 30 to November 3, 2000, NIOSH conducted a medical survey of current plant workers. In November 2000, NIOSH conducted quantitative industrial hygiene surveys. Respirator training and fit testing were provided for workers in the microwave production mixing area which had the highest flavoring and particulate exposures. Animal exposure studies were also begun at NIOSH. In December 2000, NIOSH provided notification letters to all participants in the medical survey for test results including spirometry, chest x-rays, and diffusing capacity tests. NIOSH supported state and county health department efforts to vaccinate workers against influenza and pneumonia. On the basis of preliminary clinical findings, NIOSH issued interim control recommendations in December 2000 for respirator use by all workers in the microwave production area, pending the implementation of engineering controls. In January 2001, NIOSH staff assisted the company with the planning and selection of new engineering controls. Before and after industrial hygiene measurements on January 18-19 showed that the initial engineering control changes recommended by NIOSH were effective in reducing concentrations of organic vapors in plant air.

In March 2001, NIOSH met with company officials and consultants and with the Missouri Department of Health to review the preliminary survey results from this evaluation and to discuss future actions. Following this meeting, the company invited NIOSH to perform recommended longitudinal medical and environmental follow-up studies at the plant over an 18-month interval. These surveys were initiated the first week in April. NIOSH also prepared a fact sheet for plant workers describing NIOSH's efforts, preliminary findings, and future plans. This fact sheet was distributed to plant workers prior to the April surveys.

Investigation of this outbreak is continuing through longitudinal medical and environmental follow-up studies at the plant, animal exposure studies, and evaluation of other microwave popcorn plants. This interim report provides a summary of the findings available to date from this study.

PROCESS DESCRIPTION

Gilster Mary Lee packages popcorn for both national and international distribution under private label. The plant has been in operation since 1983, formerly as Jasper Popcorn Company and as Gilster Mary Lee Corporation since 1999. The plant produces packaged popcorn kernels and since 1986, microwave popcorn.

The plant receives whole kernel corn largely from grain silos in Missouri and Nebraska. Three to four hybrid varieties are processed; genetically engineered corn is not processed at the plant. The popcorn arrives by truck and is air cleaned after unloading. An organo-phosphate insecticide is applied, and the corn is transferred by conveyor to plant silos. The corn is typically stored in the silos for 2 months or less prior to processing. From the silo, the corn is processed by screening and by air cleaning on a gravity table. A magnet is used to remove any metal objects in the corn. A worker (outside processing job category) oversees this operation. Following this processing, the popcorn is sent to either the *microwave packaging area* or the *polyethylene packaging area.*

In the polyethylene area, the corn is directly packaged in polyethylene bags by machine on the polyethylene line, with no flavorings or food additives. Typically three workers (packers and stackers) operate the polyethylene line with one supervisor present. There is one polyethylene packaging line at this plant, and it is typically operated daily for two shifts. After packaging, the bags are boxed, stacked, wrapped in plastic, and transported to the warehouse by fork lift.

A majority of the corn processed at this plant is packaged in the microwave production area, which encompasses a mixing room and packaging lines to produce microwave bags containing popcorn and flavorings. These flavorings include soybean oil, salt, artificial butter flavorings and coloring agents. The flavoring agents are batch mixed in the mixing room, which opens onto the large room with seven packaging lines. The mixing room has a salt dump station, which augers salt into a heated tank of oil to which other flavorings were added by raising the lid. Typically one worker, the mixer, operates the mixing room per shift. Following mixing, the flavorings mixture is piped as a liquid to holding tanks above the microwave popcorn packaging lines. These tanks are maintained at a temperature above 108 degrees Fahrenheit to keep the flavorings mixture from solidifying. On the line operations, the popcorn and flavorings are automatically added to the popcorn bags by a bartell machine; one worker, the machine operator, oversees this process. After the popcorn and flavorings have been added, the bags of popcorn are sealed, labeled and automatically enclosed in a plastic wrap on the packaging line. The bags of popcorn are next placed into boxes for distribution to market. Two different packing stations are operated on each line, and small boxes are placed in larger boxes in the packaging operations. Approximately three workers per line complete the packaging operations. Following packaging, the boxes of microwave popcorn are stacked on pallets and enclosed in plastic wrap. One worker is typically involved in stacking operations for one or two of the seven lines. The microwave area typically operates three shifts per day and five-seven days per week depending upon the season.

After the boxes of popcorn are stack-wrapped on pallets, they are transported from the microwave area to a large warehouse by workers operating fork lifts. These workers also load the product onto trucks in the warehouse loading dock. The plant has quality control operations for both the microwave popcorn and polyethylene products. Maintenance personnel keep the lines operating. Management and clerical workers are located in an office physically removed from the microwave packaging area.

The plant has general dilution ventilation, although prior to this evaluation, these systems were not operated in the winter when ambient temperatures were low. In the summer of 1999, a local exhaust ventilation system was added to the microwave mixing room to control salt dumping operations. Roof air intake systems were also added to the microwave area in the summer of 1999. In January 2001, axial dilution ventilation wall fans, continuous use of the local exhaust ventilation fan on the salt dump station in the microwave mixing room, and closing of the large door to the microwave mixing room were initiated to better contain and exhaust contaminants generated during mixing and production operations.

OBJECTIVES

In response to this technical assistance request from the Missouri Department of Health, the following objectives were the focus of this project:

1. Investigate the occurrence of possible occupational respiratory illness and symptoms among the popcorn plant employees via the use of respiratory questionnaires, spirometry, chest X-ray, and carbon monoxide diffusion capacity.

2. Identify processes or agents associated with respiratory disease. Based on the sentinel (index) cases and information from NIOSH walk-through surveys, respiratory exposures from flavors, individual organic chemicals, and salt dust were selected as a focus of these evaluations.

3. Determine exposure controls and prevention methods needed based on any identified associations between exposures and respiratory effects or based on worker over-exposures by existing occupational exposure standards.

4. Recommend preventive health actions for the company, health department, local physicians, and workers.

5. Evaluate the effectiveness of interventions in preventing respiratory disease.

6. Disseminate the results and recommendations to encourage prevention strategies in similar work environments nationwide.

METHODS

Environmental assessment. Industrial hygiene sampling measured contaminants generated by the production of popcorn and microwave popcorn with both full-shift, personal and area samples, and for some gases, partial shift and grab samples (Table 1). We sampled during four separate visits: a preliminary walk-through survey (August), a qualitative environmental survey (September), a cross-sectional industrial hygiene survey (November), and a follow-up industrial hygiene survey (January).

The walk-through survey provided the opportunity to become familiar with the plant processes and materials and to assess potential process contaminants for later evaluation. During the subsequent semiquantitative environmental survey, we conducted area sampling for airborne total dusts, total endotoxins, and organic vapors. We collected bulk samples of corn and soybean oil for microbiological analysis. The sampling results from this survey helped to refine the potential analytes for the subsequent quantitative industrial hygiene survey. Diacetyl, a ketone with butter flavor characteristics, was the predominant volatile organic compound. The cross-sectional industrial hygiene survey included personal sampling for respirable dusts and qualitative organic vapors in air. We conducted area sampling for a number of analytes including airborne total and respirable dusts (using both high and low volume sampling), particle size distributions, volatile organic compounds in air, ketones (diacetyl, acetoin, nonanone, and methyl ethyl ketone), acetylaldehyde, and acetic acid. We measured temperature and relative humidity. Environmental analytes collected during the January follow-up included personal and area sampling for ketones.

Medical survey. Company management distributed announcements of the NIOSH survey, and company staff scheduled current employees who volunteered to participate in the survey during their work shift. Trained NIOSH interviewers administered a questionnaire in a NIOSH trailer located onsite. The questionnaire consisted of a subset of standardized questions on demographic information, respiratory symptoms, and tobacco use (Ferris, 1978); details of current and past duties, work exposures, and practices at the microwave popcorn plant; previous work history; health history; additional acute and chronic respiratory, irritant, and constitutional symptoms; and respirator use (Table 2). The questionnaire also recorded duration and changes of symptoms away from the work environment; change of job, duties, or work area due to breathing problems; physician diagnoses pertinent to the outbreak; and subjective classification of work environment changes after ventilation was added in mid-1999. Symptoms and job history data were updated on an interviewer-administered, computer-assisted follow-up questionnaire in April 2001, including subjective assessment of the work environment after ventilation changes in January 2001. Qualified technicians performed pulmonary function tests and obtained chest x-rays, which were taken as objective health outcome measures.

Spirometry. We used a dry rolling-seal spirometer interfaced to a personal computer to record at least 3 maximal expiratory maneuvers. Testing procedures conformed to the American Thoracic Society's recommendations for spirometry (ATS, 1995). We selected the largest forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) for analysis. We calculated predicted values and lower limits of normal using reference values (Hankinson, 1999) generated from the third National Health and Nutrition Examination Survey (NHANES III). Test results were compared to the lower limit of normal values to identify participants with abnormal spirometry patterns of obstruction and restriction (ATS, 1991). We defined obstruction as a FEV_1/FVC% below the lower limit of normal and assessed reversibility with bronchodilator, using a 12%/200 milliliter FEV_1 improvement criterion. We defined restriction as a low FVC and normal FEV_1/FVC%.

DLCO. We used commercial systems purchased from Jaeger and Medical Graphics to measure the carbon monoxide diffusion capacity of the lung (DLCO), which reflects the ease with which a gas passes across the lung tissue and into the bloodstream. Using standard guidelines for performing the test (ATS, 1995), we compared DLCO results to reference values determined from a sample of non-smoking adults from the state of Michigan (Miller, 1983) and defined them as abnormal if the observed DLCO was less than the calculated lower limit of normal.

Chest x-rays. We took posterior-anterior chest x-rays on a full-size (14 x 17 inch) film. Two NIOSH-certified B Readers (physicians trained and certified in the classification of chest x-rays for the pneumoconioses) independently classified the films according to the current international classification system for pneumoconiosis (ILO, 1980), without knowledge of the participant's age, occupation, symptoms, smoking history, or pulmonary function abnormalities.

Statistical analyses. We used a double entry verification technique on responses from participants and used program modules provided by the SAS Institute, Inc. (SAS, 1990) for all statistical analyses. Outcome measures, exposure measures, and confounders were defined both before and after examination of the data. We calculated averages, standard deviations (STD), and prevalence estimates. We used chi-square and Fisher's exact methods to test categorical data and Student's t test and Pearson's correlation to evaluate continuous data. We considered probability (p) values less than 0.05 to represent associations unlikely to be due by chance.

Exposure estimates. We divided the worker population into four groups based on anticipated exposure levels: office and outdoor workers (the "control" or internal reference group with expected very low exposures); warehouse, polyethylene, maintenance, and quality control workers (with low exposures); microwave packaging workers (moderate exposures); and mixers (high exposures). In each of the work groups, we averaged the measurements for jobs sampled within that area as a representative measure of current exposure. We assessed relations between current exposure group and health outcome. To protect confidentiality of worker symptoms and pulmonary function abnormalities in the three mixers, we aggregated their results for presentation here with the remainder in microwave production.

We estimated cumulative exposures for each participant by summing the products of time worked in each of the four exposure groups and mean exposure for that group. To assess exposure-response relations for respirable dust and for diacetyl, we ranked participants by estimated cumulative exposures, divided them into quartiles, and compared rates of health outcomes among quartiles of the cumulative exposure metrics.

RESULTS

Environmental Assessment, September 2000

In the initial semi-quantitative sampling in September 2000, the area total dust concentration from the microwave mixing room was the highest at 0.73 mg/m^3. The total dust concentration from the microwave machine operator area on line 1 was 0.2 mg/m^3, and the concentration from the microwave packaging area for line 1 was 0.15 mg/m^3. Scanning electron micrographs of the salt used in the microwave popcorn flavoring mixture suggest that much of the salt has a physical diameter below 10 micrometers and, consequently, would contain a substantial respirable fraction (Figure 1A). Scanning electron microscopic evaluation of airborne samples collected on glass slides, when the lid of a flavoring holding tank was lifted, suggested the presence of salt and oil particles in plant air (Figure 1B).

Qualitative sampling for volatile organic compounds (VOCs) in the air detected over 100 different VOCs in the microwave processing area (Figure 2); the predominant compounds identified in the microwave mixing room included the ketones diacetyl, methyl ethyl ketone (MEK), acetoin, and 2-nonanone, and acetic acid.

The endotoxin concentration from the microwave mixing room was low at 56 EU/m^3. The concentration from the line 1 machine operator location was 58 EU/m^3 and from the line 1 packaging area, 26 EU/m^3. Concentrations of fungi and bacteria were below detectable limits [< 2 colony forming units (CFUs) per milliliter] in the bulk sample of soybean oil and in the bulk samples of popcorn obtained following cleaning processes (< 7 CFU/gram). While some spores were detected in plant air, they were not common. There is no Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for endotoxins or culturable fungi and bacteria (CFR, 1998). NIOSH review of company sampling records for aflatoxin in bulk corn in the year 2000 indicated that the samples were all below detectable limits by thin layer chromatography at the University of Missouri. Plant management reported that aflatoxins had not been detected in any of the corn samples submitted for analysis in previous years. There is no OSHA PEL for aflatoxins (CFR, 1998).

Industrial Hygiene Survey, November 2000

Dust. Total dust concentrations [full-shift, time-weighted averages (TWAs)] from the 55 area samples ranged from below detectable concentrations (< 0.007 mg/m^3) to a high of 1.0 mg/m^3, with a mean concentration of 0.24 mg/m^3 (STD 0.19 mg/m^3). The non-combustible fraction of five high volume airborne total dust samples ranged from approximately 15 to 30 percent by weight (average 21%). Microscopic examination of the non-combustible fraction showed generally higher salt content in the mixing room samples.

The 140 TWA respirable dust samples had a mean of 0.13 mg/m^3 (STD 0.11 mg/m^3), and the personal and area samples had similar means and standard deviations. The average total and respirable dust concentrations were highest in the microwave areas (Figure 3), with the highest mean concentrations in the mixing room. In mixing, the mean respirable dust concentration of seven personal samples was 0.38 mg/m^3 (STD 0.22 mg/m^3). These respirable and total dust concentrations are below the existing OSHA PEL for particulates not otherwise regulated including total dusts (15 mg/m^3) and respirable dusts (5 mg/m^3); however, these standards may not be appropriate to protect plant workers considering the respiratory disease at this plant (CFR, 1998).

Particle size distributions from cascade impactors in the microwave mixing room were unimodal, with mass median aerodynamic diameters (MMADs) ranging from 2.3 to 5 micrometers, expressed as geometric means (Table 3). The nine particle size distributions from the microwave machine operators, packers, and stackers locations had a MMAD of 2.5 or less; most of the samples appeared unimodal. The polyethylene packaging lines and the warehouse had larger particle size distributions with MMADs ranging from 5 to 8.5 micrometers (Figures 4-5).

Ketones and other organic compounds. Thermal desorption tube samples indicated that several ketone compounds (diacetyl, acetoin, nonanone, and MEK) were the predominant hydrocarbons in the microwave popcorn production area (Table 4). The 53 area samples for diacetyl ranged from below detectable limits to 98 parts per million (ppm) parts air by volume, with a mean of 8.1 ppm (STD 18.5 ppm). Acetoin concentrations were lower (mean 1.0 ppm). Only five of the 52 nonanone samples had quantifiable levels with the highest concentration being 0.06 ppm. The two samples analyzed for MEK had concentrations of 3.1 and 4.7 ppm. The OSHA PEL for MEK is 200 ppm as a TWA. The average ketone concentrations were highest in the microwave mixing room (Figure 6B), where the 10 area samples had a mean diacetyl concentration of 37.8 ppm (STD 27.6 ppm) and a mean acetoin concentration of 4.1 ppm (STD 4.1 ppm). Diacetyl was also detected in areas outside of microwave production, including the polyethylene line area, warehouse, and office areas (Figure 6A); however, most of the samples from these locations were below quantifiable levels.

Acetic acid was detected in samples from the microwave mixing and packaging, maintenance, and quality control areas. The area airborne TWA acetic acid concentrations on 49 samples from these areas ranged from below detectable limits (< 0.04 ppm) to a high of 12.4 ppm, with a mean concentration of 1.4 ppm (STD 2.3 ppm). The highest acetic acid concentrations were measured in the mixing area, with a mean of 5.5 ppm (STD 3.2 ppm) from eight samples. This was the only area with a TWA concentration in excess of 10 ppm, the OSHA PEL for acetic acid (CFR, 1998). In the microwave packaging area, 24 samples had a mean of 2.7 ppm (STD 2.7).

Acetaldehyde concentrations were low, ranging from below detectable limits (approximately 0.007 ppm) to 0.1 ppm. The OSHA PEL for acetaldehyde is 200 ppm as a TWA (CFR, 1998).

Summary exposures by work area. Average current exposure levels by work area for dust and diacetyl are summarized in Table 5, indicating that mixing area employees had 1000-fold exposures to diacetyl compared to office and outside workers, 100-fold exposures compared to polyethylene packaging, warehouse, maintenance, and quality control workers, and about 17-fold compared to other microwave production workers. The gradient of exposure for respirable dust was less than 10-fold between least and most exposed groups.

Medical Survey Results

Worker characteristics. Of approximately 135 employees working at the plant in late October 2000, 117 (87%) completed a questionnaire (Table 6). The median age of the respondents was 36 years (range: 18-67). Most (91%) were white, five were Hispanic, two were black, two were Native American, and one a Pacific Islander. The majority were current or former cigarette smokers. The night workforce was younger and had shorter tenure in the plant. Length of employment ranged from 1 month to 17 years, 7 months, with a median of 4 years, 5 months. All employees worked full-time at 36-50 hours per week, with a median of 40 hours.

Sixty-eight percent of workers currently worked in microwave popcorn production, including mixing and packaging areas (Table 6). Eight workers reported having changed their jobs because of breathing difficulties; two associated their breathing difficulties with the polyethylene production area and six with the microwave production area. Of the six in microwave popcorn production, four were either mixers or training to be mixers when they made a job change. Seven of the eight reported that their breathing improved after their job change.

Cumulative exposures for diacetyl ranged from 0 to 110 ppm-years. The cut points for the four quartiles of cumulative diacetyl exposure were 0.5, 5, and 11 ppm-years. For respirable dust, cumulative exposures ranged from 0 to 2.1 mg-years/m^3, with quartile cut points of 0.05, 0.4, and

0.9 mg-years/m^3. A statistically significant correlation existed between individual cumulative diacetyl and cumulative respirable dust exposures (Pearson's correlation = 0.60, N = 117). A significant correlation existed between the two exposures for 79 workers in microwave packaging and mixing room areas (Pearson's correlation = 0.67).

Of 116 employees with spirometry tests, 73.3% had normal spirometry; 8.6% had a low vital capacity (restriction); 9.5% had airway obstruction; and another 8.6% had airway obstruction and a low vital capacity. Of those 18.1% with airflow obstruction, three had severe abnormalities with FEV_1 less than 40% predicted. Only two workers with airway obstruction had a significant response to the inhaled bronchodilator. Of those 10 employees with pure restriction, the vital capacity was borderline to mildly low in 9, and all had a body mass index of more than 24 kg/m^2, suggesting that their restriction may be due, in part, to their being overweight. Of 116 employees who performed testing for DLCO, 106 had interpretable tests. Only seven (6%) had a low DLCO test result; six of the seven had normal spirometry and the seventh had airway obstruction and a low vital capacity.

Chest radiographs on 115 participants showed no small (1/0 criterion) or large opacities consistent with pneumoconiosis and no cor pulmonale. Two films showed radiologic emphysema (one of which had bullae); one film had saber sheath tracheal narrowing attributed to chronic obstructive pulmonary disease (COPD) or tracheal stenosis; and one film had focal upper zone scarring and left base atelectasis. Four x-rays had abnormalities requiring follow-up, including solitary pulmonary nodules or asymmetric pleural thickening.

Symptom rates compared to national data. We compared the respiratory symptoms and physician-diagnosed respiratory diseases reported by the current employees to expected responses to the same or similar questions from a recent national survey (NHANES III). The prevalence of chronic cough, shortness of breath, and wheezing apart from colds among the current work force were 2.6, 2.6, and 3.0 times higher than expected, as reflected in observed/expected prevalence ratios (Table 7). Except for wheezing in the last 12 months, the prevalence ratios were higher in never smokers and younger employees (17-39 year olds).

Lung disease diagnosis rates compared to national data. The prevalences of self-reported physician-diagnosed asthma, chronic bronchitis, and hayfever among the current workforce were 1.8, 2.1, and 1.2 times higher than expected (Table 8). The prevalence of chronic bronchitis in older and younger never smokers were 2.3 and 5 times higher than expected, respectively.

Abnormal lung function compared to national data. The number of employees with airflow obstruction by smoking status and in relation to expected rates from the national data (NHANES III) is given in Table 8. The prevalence of obstruction increased by age group in both smokers and never smokers, and the excess over national rates was particularly apparent for never smokers. The observed/expected prevalence ratios for never smokers were 11.4 for workers above 40 years old and 8.3 for those under 40 years old. Overall, current employees had 3.3 times the rate of airway obstruction, when compared to the national population sample.

Symptom prevalence by work area. Responses to questions regarding respiratory and systemic symptoms and physician-diagnosed diseases are summarized by current work area in Table 9. Workers in microwave production (including mixers) tended to report chronic cough, chronic wheezing, attacks of wheezing, chest tightness, and shortness of breath with exertion more frequently than the workers in the other two categories. They differed statistically from the other two exposure groups in reporting regular trouble with their breathing. About two-thirds of the microwave production workers and half of the polyethylene packaging, warehouse, maintenance, and quality control workers reported one or more respiratory or systemic symptoms, compared to 2 of 7 (29%) workers in the office and outdoor areas. When we only counted employees with incident symptoms and diagnoses which started after hire, rates of respiratory symptoms and physician diagnoses in microwave production workers were similar to those in the warehouse and polyethylene areas, but tended to be higher than in the small group of office and outdoor workers (Table 10).

About half (46%) of the microwave production workers reported one or more systemic symptoms compared to 23% in the polyethylene/warehouse areas and none in the office and outside area. The predominant systemic symptom was unusual fatigue, with only 13% and 10% of the microwave production workers reporting night sweats and flu-like achiness, respectively. When comparisons of symptoms with onset since employment were made, systemic symptoms and skin problems (but not respiratory symptoms) were in statistically significant excess among microwave production workers in comparison to the other groups (Table 10). Episodes of acute bronchitis were not correlated with work area. Similarly, physician diagnoses of asthma, emphysema, and chronic bronchitis did not differ in prevalence by work area.

Mucous membrane irritation symptoms were more common in moderate to high exposure work areas. About 72% of the microwave production workers reported work-related irritation to their eyes, nose, or throat, compared to 58% in the polyethylene packaging, warehouse, maintenance, and quality control exposure areas and 3 of 7 (43%) in the least exposed office and outdoor workers. Onset of skin rashes and skin problems after hire were also clustered in microwave production, and twice as many reported skin problems compared to those with lower exposures.

Spirometry results by cumulative exposure. Employees with obstructive abnormalities clustered among those with higher exposures using either the diacetyl or respirable dust cumulative exposure metric (Figures 7 and 8). For diacetyl exposure quartiles, the rates of obstructive spirometry were 6.9%, 14.3%, 23.3%, and 27.6% with increasing cumulative exposure. The rate in the highest quartile of exposure differed statistically from that in the lowest quartile; there was a statistically significant trend ($p = .01$). For respirable dust quartiles, the rates of obstructive spirometry were 0%, 10.3%, 40%, and 20.7% with increasing cumulative exposure. As the quartiles of exposure increased (lowest to highest), there was a significant increase in the rate of obstructive spirometry ($p = .002$). The proportion of employees with abnormal spirometry increased by quartile of increasing exposure from 13.8% in the office and outdoor group to 25%, 30%, and 37.9% in the highest diacetyl cumulative exposure quartile. For cumulative respirable dust quartiles, the proportion of employees with abnormal spirometry increased from 3.6% in the lowest exposure quartile to 20.7%, 46.7%, and 34.5%.

Quartiles of increasing cumulative exposure to diacetyl had decreasing average percent predicted FEV_1 (which is corrected for age, gender, and height), a good measure of the severity of both restrictive and obstructive spirometry outcomes. Using the lowest diacetyl exposure quartile as the reference group, average percent predicted FEV_1 fell by 5.5%, 10.5%, and 14.2% in the second, third, and fourth quartiles, respectively (Figure 9A). Similar trends were seen when using respirable dust cumulative exposure quartiles (Figure 9B).

Associations between the outcome measures. Workers with airway obstruction had more incident chronic cough, chronic wheeze, attacks of wheezing, chest tightness, and shortness of breath with onset after hire compared to workers who had no airways obstruction (Table 11). On the other hand, about a quarter of those with obstructive abnormalities did not report onset of any of these symptoms after hire. Workers with airway obstruction did not have higher prevalence of systemic symptoms and skin problems with onset after hire compared to workers without airway obstruction.

Those participants with airway obstruction by spirometry were more likely to have a diagnosis of attacks of bronchitis, chronic bronchitis, asthma, pneumonia, and emphysema since employment (Table 11). Among those with physician-diagnosed attacks of bronchitis since employment, the number of attacks ranged up to 22 (median 4). Although those with airflow obstruction were much more likely to have reported a doctor diagnosis of chronic bronchitis or asthma after hire, only 13 of the 21 (62%) had a physician diagnosis that would account for obstructive impairment (asthma, emphysema, and chronic bronchitis).

Employees with pure restriction on spirometry were largely asymptomatic and were not clustered in the microwave production area. There were no significant associations between a low DLCO and airway obstruction or work area.

Initial Engineering Interventions

Ventilation changes in the microwave production area would not likely affect office, outdoor, and polyethylene packaging workers. Warehouse, maintenance, and quality control workers have work areas which open into the microwave packaging area, but might not notice effects of ventilation interventions in the microwave packaging area. In the late October-November survey, 17/79 (22%) of the workers currently in microwave packaging and mixing operations reported that the addition of ventilation in the summer of 1999 had improved the work environment; an additional 33% reported that the environment had stayed the same; and the remainder (46%) didn't know. Of the 42 microwave packaging and mixing operations workers who participated in both October 2000 and April 2001 surveys, 26% reported improvement in the work environment following the January engineering interventions; 50% reported it had not changed; and 21% did not know.

On January 18, 2001, before the increase in ventilation, closing the mixing room door, and continuous exhaust of the salt dump operation in the mixing room, ketone concentrations were similar to those documented for particular jobs and areas in November 2000 (Table12). Following these initial engineering interventions on January 19, 2001, the mean diacetyl concentration fell about 3 to 12-fold for specific personal and area sampling pairs in microwave production, with the least effect on the personal samples for mixers. Total organic vapor concentrations, assessed with 15-minute TWAs and peak concentrations, fell markedly for mixing and microwave popcorn production line jobs between January 18 and January 19 with the institution of controls (Figure 10).

Comparison of spirometry results for the 64 workers tested in the late October survey and April follow-up documented four participants with declines in FEV_1 of 10% or more, ranging to 27% in a newly symptomatic worker in the fall of 2000 whose spirometry had then been normal.

DISCUSSION

Nature of the disease. Bronchiolitis obliterans, which occurred in some former workers from this plant, is a rare lung disease with inflammation of the small airways (King, 1998). Known work-related causes include inhalation of nitrogen dioxide, silo gases, ammonia, chlorine, hydrogen fluoride, ozone, phosgene, fly ash, and sulfur dioxide. In occupational settings, an incident of overexposure often results in severe initial symptoms of pulmonary edema, followed by seeming recovery and development of bronchiolitis obliterans weeks later. Bronchiolitis obliterans has also been reported in cases of hypersensitivity pneumonitis in work settings with aerosols of micro-organisms or chemicals to which workers become sensitized. Apart from work-related exposures, most bronchiolitis obliterans cases are diagnosed in the months following bone marrow or lung transplants. In these evolving cases, the disease may progress from the mild (subclinical) stage to the severe stage within a few months. In the early (mild) stage, there are no symptoms. In the severe stage, bronchiolitis obliterans causes shortness of breath upon mild to moderate exertion. The respiratory symptoms in the moderate and severe stages are common to many types of lung disease.

When the development of bronchiolitis obliterans is insidious (as in post-transplant patients), lung function test abnormalities begin during the mild stage and become progressively abnormal during the moderate and severe stages. The lung function test results show airways obstruction (a low FEV_1/FVC and a low FEV_1) which does not improve with use of an inhaled bronchodilator (such as albuterol), and in the moderate to severe stages, hyperinflation of the residual volume may occur. The DLCO is normal, but oxygen desaturation may occur during exercise. The chest x-ray is normal, but a high resolution lung computerized tomography exam may show inhomogeneity of aeration in the moderate to severe stages.

The diagnosis of bronchiolitis obliterans is suspected when the clinical history includes one of the known causes, more common lung diseases are ruled out, and the above pattern of lung function abnormalities is present. The diagnosis of bronchiolitis obliterans is then confirmed by the histological examination of lung tissue obtained during an open lung biopsy.

The treatment of bronchiolitis obliterans arising from chemical inhalation injury is generally ineffective in curing the disease and limited to treatment of symptoms. The clinical features of the index cases are similar to those of "constrictive" bronchiolitis, which occurs with chemical causes. Only a minority of cases, such as those arising in hypersensitivity pneumonitis cases or those with organizing pneumonia (proliferative bronchiolitis), respond to oral corticosteroids or other strong anti-inflammatory medications, most of which have serious side-effects.

Three outcomes. The above discussion suggests that there are three lung disease outcomes which can be measured: 1) respiratory symptoms, 2) abnormal lung function, and 3) a physician diagnosis of lung disease. This NIOSH investigation measured all three of these outcomes during the fall 2000 examination of the current employees of the Jasper popcorn plant. We compared the abnormality rates for these three outcomes to national data (an external control group) and to relatively unexposed employees at the plant (an internal control group).

Excessive rates when compared to national data. Excellent up-to-date data on the rates of 1) respiratory symptoms, 2) lung function (spirometry) abnormalities, and 3) physician-diagnosed common lung diseases from a sample of the population of the United States are available from the NHANES III study. NIOSH employees provided the spirometers and helped to obtain and analyze the NHANES III data. The most important factors which are known to affect the abnormality rates of these 3 outcomes are age, gender, and smoking status. Therefore, we stratified our comparisons to take these factors into consideration. Smoking status (current or former) is slightly under-estimated when self-reported, but this applies equally for both the NHANES III study and this investigation. By design, the identical standardized respiratory symptom and disease questions used by the NHANES III were also used for this investigation (Table 2), which allows direct comparisons of response rates.

Excessive symptoms. The most common respiratory symptoms are cough, phlegm, wheezing, and shortness of breath. Both never smokers and smokers in both age groups from the plant reported higher rates of respiratory symptoms (observed) than the national data (expected) (Table 7). The observed/expected ratios (excessive rates) for respiratory symptoms were larger in the younger never-smokers than in the smoking employees and older employees. For three of the symptoms, the younger never-smoking employees had about 4 to 5 times the expected rate of symptoms. This excess of respiratory symptoms is not specific for any single type of lung disease, but strongly suggests that at least some of the employees at the plant are experiencing some type of lung disease more frequently than the national population sample

Excessive lung function abnormality rates. The most common pattern of lung function abnormality is limitation of forced exhaled airflow, diagnosed by the spirometry test where the FEV_1/FVC and the FEV_1 are found to be low. Airway obstruction is the most common pattern because asthma and chronic obstructive pulmonary disease, which includes emphysema and chronic bronchitis due to cigarette smoking, are obstructive lung diseases. Since about 1 of every 5 adult smokers over age 45 develop chronic obstructive pulmonary disease, it is important to stratify comparisons of lung function abnormality rates by smoking status. Predicted (expected) values for spirometry results are corrected for height, age, gender, and race. The same predicted equations (from the healthy subset of NHANES III participants) were used to determine spirometry abnormality rates for both the national data and the employees in this plant.

Young never-smoking employees had about 8 times the expected rate of airways obstruction, while the older never-smoking employees had over 11 times more airways obstruction than the national rate (Table 8). The older smokers were also 3.3 times more likely to have airways obstruction than the national rate for this age group of smokers. These results suggest that employees at the plant have obstructive lung disease much more frequently than the national population sample.

Excessive respiratory disease diagnoses. The most common types of chronic obstructive airway diseases in the United States are asthma, chronic bronchitis, and emphysema. We also asked about hayfever (allergic rhinitis) because it is common, associated with asthma, and not due to smoking or occupational exposures. Plant employees had about twice the national rates for a physician diagnosis of asthma and for chronic bronchitis, but about the same rates of hayfever. The emphysema rates were too low in both the employees and the national data for this age group for meaningful comparisons.

Exposure-response relations within the plant. Internal comparisons of relatively exposed versus relatively unexposed employees at a given plant are also important, since they are not subject to any biases between this investigation and national studies, and they may establish an exposure-response relationship between the degree of the exposure and the risk or severity of the health outcomes. In studies of occupational diseases, the presence of an exposure-response relationship suggests that the exposure index is causally related to the health outcome or is a marker for the causative exposure.

Since the microwave popcorn company did not have exposures previously known to cause bronchiolitis obliterans, the distribution of health effects among the workforce and in relation to possible (previously unrecognized) causes provides clues to what has caused the cluster of bronchiolitis obliterans cases in former workers and the excess respiratory disease in this workforce. The findings of this investigation indicate that the causative exposure is long-standing in the plant, since the earliest case among former workers dated to 1992. The exposure continued past the fall survey, since a few workers were apparently newly affected between the beginning of November 2000 and the beginning of April 2001. This endemic pattern of disease occurrence argues for a hazard which is present frequently and perhaps continually.

The greatest hazard was for mixers, as reflected in their over-representation among the former worker cases. However, severe index cases occurred among others in microwave packaging, which shared high risk of symptoms, in comparison to workers in the warehouse, polyethylene line, offices, and outdoors. The current exposures to ketones, other volatile organic compounds, and respirable dust were all greatest in microwave popcorn production and were particularly high for mixers. Estimated cumulative exposures were correlated with chronic lung function effects, reflected both in rates of obstructive and abnormal spirometry abnormalities and in average decreases in FEV_1 for the higher cumulative exposure quartiles. The exposure-response relationship between diacetyl cumulative exposure and pulmonary function was unequivocal, suggesting that diacetyl may be the cause or a marker for a cause of respiratory disease in this workforce. Cumulative respirable dust was also associated with respiratory outcomes, although the highest quartile of exposure did not have the lowest average percent predicted FEV_1 nor the highest rate of FEV_1 abnormalities. Since diacetyl, other volatile organic compounds, and respirable dust measurements by job area were correlated (as were the diacetyl and respirable dust cumulative exposure indices), any of them may be a marker for the causative agent or agents in the mixing and microwave popcorn production areas.

Our understanding of the cause will be enhanced by ongoing animal respiratory toxicology studies. To date, BBA butter flavoring, which contains diacetyl and many volatile organic compounds, has caused damage to epithelial lining of the rat respiratory system in animal experiments. These preliminary animal findings suggest that diacetyl exposure or another flavoring component is a biologically plausible cause of the excess human respiratory effects in the popcorn plant. Animal exposures to respirable salt have not yet been conducted at NIOSH. Support for the flavoring-as-cause hypothesis exists in a NIOSH Health Hazard Evaluation in a company mixing flavorings in corn starch for the baking industry (NIOSH, 1986). This company had two young workers who developed bronchiolitis obliterans, one of whom reported his suspicion of "cinnabutter" as a cause. In addition to animal studies, investigations of workers in other microwave popcorn plants and in the flavoring industry may help establish the risk of particular suspected agents and their exposure-response relations.

Clinical characteristics of the excess work-related lung disease. The bronchiolitis obliterans diagnosis of many of the former worker index cases depended upon extensive clinical tests that are not available in a plant investigation setting. The pattern of cough and shortness of breath with exertion, coupled with the finding of airway obstruction that did not change with bronchodilator, normal chest x-rays, and normal diffusing capacity, is consistent with bronchiolitis obliterans as the most likely explanation for the excess respiratory disease in the plant population and its association with exposures arising in the mixing room of microwave popcorn production. The clinical picture is not that of occupational asthma, emphysema, or interstitial lung disease.

This investigation provides evidence that some workers with airway obstruction do not report symptoms; conversely, the prevalence of symptoms far exceeds the rates of obstructive airways abnormalities. This may be a result of an insensitive definition of abnormal, in the absence of baseline spirometry data at the beginning of employment. Whether symptomatic workers are at higher risk for developing airways obstruction remains to be determined by longitudinal followup. The clinical course of many of the former worker cases suggests that the pulmonary function impairment is irreversible, despite exposure cessation. The association of cumulative exposure metrics with pulmonary function impairment is consistent with a long term effect. Whether the current workers with abnormalities will improve with reduction of exposure is impossible to know without careful followup. In the face of this uncertainty, affected workers and their physicians need to be told the findings of this investigation so that they can make decisions about acceptable risks and continued exposure.

Although some of the most severe cases among former workers had suffered systemic symptoms and skin problems, only respiratory symptoms appeared associated with the lung abnormalities among the current workforce. On the other hand, work-related excesses of skin problems and systemic symptoms were evident in microwave production processes. These may be independent outcomes of the same or different exposures or reflect effects at earlier stages of disease.

In summary, we found excessive rates of 1) respiratory symptoms, 2) lung function abnormality (airway obstruction), and 3) physician-diagnosed asthma and chronic bronchitis in the plant employees. We found an exposure-response relationship between plant areas with differing current exposures and symptoms. Indices of cumulative exposure to both particulates and diacetyl vapor were related to obstructive lung function outcomes in plant employees. The survey findings are best explained by the occurrence of work-related bronchiolitis obliterans in this microwave popcorn plant in relation to exposures arising in the mixing room but widely disseminated to varying extents through other areas of the plant.

Implications for screening and surveillance for bronchiolitis obliterans. The severity of bronchiolitis obliterans in some of the index cases makes prevention of the disease in exposed employees critically important. The excessive rates of both respiratory symptoms and impaired lung function (airway obstruction) in the current employees suggest that some of the current employees have mild to moderate bronchiolitis obliterans. This disease may progress to severe disabling disease (as in the index cases) if their past workplace exposures were to continue.

All levels of disease prevention are important in this situation: 1) primary, 2) secondary, and 3) tertiary. Primary prevention at the plant has already begun, by identifying the major sources of particulates and organic vapors, and lowering employee exposures to these sources. The first step of secondary prevention has also begun, the identification of employees who have subclinical disease (airway obstruction, but without respiratory symptoms). These screening exams should be repeated at regular intervals to identify incident (additional new) cases of airway obstruction. The next steps should be to prevent further hazardous workplace exposures in these affected employees; to prevent further lung disease by promoting smoking cessation for those who are current smokers; and to assess the effectiveness of preventive interventions by repeating the respiratory questions and spirometry tests at intervals determined by the findings.

Tertiary prevention is the treatment of established disease. Employees who have any respiratory symptoms or airway obstruction should be referred to a physician for a diagnostic work-up and appropriate treatment. Those with moderate to severe airway obstruction should be referred even if they don't report any respiratory symptoms.

Surveillance is the detection of abnormal rates of disease in *groups* of persons (in contrast to screening of individuals to see if they have disease). The severity of this outbreak of work-related obstructive lung disease suggests that surveillance be initiated for the entire plant to ensure the effectiveness of the primary prevention efforts. If new cases arise, the causative exposure is continuing either because controls are inadequate or because we have overlooked a causative source or agent. Only by surveillance will we determine the quantitative risk of particular exposure levels. No occupational exposure standards exist for the likely cause(s) of this outbreak, and the standard for particulates not otherwise regulated is inappropriate, given the severity of the demonstrated disease. The excess level of symptoms in the microwave production area, apart from mixing, suggests that exposures measured there in November were too high. Even the warehouse, quality control, maintenance, and polyethylene groups had higher symptom rates than the lowest exposure comparison workers from outdoor and office locations. The April follow-up indicated that new cases of obstructive abnormalities had arisen since November, but we do not know whether these cases occurred as a result of continuing higher exposures before January 19 or whether the engineering controls are still inadequate in protecting workers from lung disease. On the basis of this investigation, we recommend surveillance of exposures and workforce health at other plants with similar workplace exposures.

Why not just use physician diagnoses to find new cases? It took many years for community physicians to suspect that work-place exposures might be responsible for the employees they saw with severe airways obstruction. The symptoms were non-specific and could be due to any serious chronic lung disease. The fixed airways obstruction seen on spirometry testing was probably attributed in individual cases to smoking-related chronic bronchitis or emphysema (COPD) or "airway remodelling" due to long-term untreated asthma. More than a third of employees with obstructive airways disease did not receive a physician diagnosis which might explain their condition. DLCO tests were not used to exclude the diagnosis of COPD. Standard chest x-rays were largely normal. Since bronchiolitis obliterans is a rare disease, most clinicians did not consider this diagnosis, and this food production industry had not been previously recognized as having this type of lung hazard. Most index cases did not report a tight temporal association between being at work and increased symptoms. In the circumstance of a new exposure-disease association, recognition of a disease cluster and findings in the entire workforce can lay the basis for attributing respiratory disease in individuals to the workplace. The disease was severe and probably not reversible when employees waited to seek medical attention until they experienced shortness of breath with mild to moderate exercise. These factors suggest that screening or surveillance for new cases of bronchiolitis obliterans should not depend on waiting for diagnoses from community physicians.

Limitations of this investigation. The cross-sectional survey was limited since both exposure and outcome were measured simultaneously. Measured exposures may not reflect historical exposures, particularly for respirable dust, since exhausting of salt dumping operations occurred in the summer of 1999. On the other hand, exposures to volatile organic compounds, such as diacetyl, may not have been much affected by past ventilation interventions. In these analyses, we assigned workers and jobs to four assumed exposure groups, which we demonstrated had different average exposures; nevertheless, individual exposure may be misclassified by these assumptions, leading to biased estimates of current and cumulative exposures. An example is the quality control workers, who were grouped *a priori* with warehouse and polyethylene workers; later diacetyl and respirable dust measurements show that they would more appropriately be grouped with microwave packaging workers. Such misclassification of exposure may reduce the probability of recognizing a true effect.

Another consequence of cross-sectional surveys is underestimation of the health outcomes associated with exposures due to the healthy worker effect. In this plant, nine former workers left employment because of lung disease, thereby leaving a healthier workforce which does not show the true burden of disease. Eight of the current workforce changed assignments due to respiratory problems. To the extent they moved to lower exposure areas, these workers are counted as having developed health effects in their current assignments, which may be inaccurate. Our indices of cumulative exposure are one way to correct for this limitation.

Despite an 87% participation rate, this cross-sectional survey was limited by the reduced statistical power to make internal comparisons, especially between minimally-exposed and highly-exposed groups. Because of this, we have presented data even when statistically significant differences were not demonstrated. Since some ill employees left the workplace due to respiratory symptoms, our statistical power to detect association between workplace exposures and respiratory outcomes was reduced. This may account for our observation that neither current nor cumulative exposure indices were related in a statistically significant way to rates of physician-diagnosed lung diseases which were commonly given to ill employees.

The worker surveys from October and April include additional data not presented here, as analyses are ongoing. Although we took into account major confounders, such as age, gender, and smoking, this interim report does not address prior occupational history, for example. Planned analyses include multivariate modelling. The respiratory abnormality excesses reported here are so large that we do not expect our major conclusions to change. Rather than delay public health action, we seek to get this interim information in the hands of employers, who can reduce exposures and implement surveillance, and of workers, who can protect themselves by using respiratory protection, good work practices, and medical screening and followup.

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Table 1 . Industrial hygiene sampling methods, November 2000 - January 2001, Missouri popcorn plant.

Analytes	Media/sampler	Flow (lpm)	Analytical methods
Total dust in air	37 mm PVC Filter, Open Face Filter Cassette	3.0	Gravimetric analysis by NIOSH Method 500 (NIOSH, 1994)
Respirable dust in air	37 mm PVC Filter, BGI Cyclone	4.2	Gravimetric analysis by NIOSH Method 500 (NIOSH, 1994)
High volume total dust	37 mm PVC Filter, Open Face Filter Cassette	28.2	Filter ashing and gravimetric analysis (NIOSH, 1994)
High volume respirable dust	37 mm PVC Filter, Open Face Filter Cassette	9.0	Gravimetric analysis by NIOSH Method 500 (NIOSH, 1994)
Total endotoxin in air	37 mm PVC Filter, Open Face Filter Cassette	3.0	Kinetic Limulus Amebocyte Lysate Test (BioWhittaker: Kinetic-QCL, Limulus Amebocyte Lysate 192 Test Kit, 2000)
Particle size distributions	Six stage cascade impactor	2.0	Gravimetric analysis (NIOSH, 1994; Hinds, 1982)
Volatile organic compounds in air	Thermal Desorption Tube	0.03 to 0.05	Gas chromatography / mass spectrometry by NIOSH Method 2549 (NIOSH, 1994)
	Photoionization meter	–	Direct reading instrument (ACGIH, 1995)
Ketone compounds in air	Anasorb tube	0.03	Gas chromatography by NIOSH method 2557 (NIOSH, 1994)
Acetaldehyde in air	Sorbent tube (silica gel treated with 2,4 dinitrophenylhydrazine)	0.025	High performance liquid chromatography (HPLC) by NIOSH method 2016 (NIOSH, 1994)
Acetic acid in air	Long term diffusion tubes	–	Direct reading results by colorimetric methods (ACGIH, 1995; Leichnitz, 1989)
Culturable fungi & bacteria in corn & soybean oil	Nutrient agar	–	Enumeration of bacteria and fungi by dilution plating (ACGIH, 1999)
Temperature and % relative humidity	Psychrometer	–	Direct reading meter (ACGIH, 1995)

Table 2. Questions used to define symptoms and diagnoses, October 2000 - April 2001, Missouri popcorn plant.

Health condition	Question
Chronic cough	ATS-DLD* 7E. Do you usually cough on most days for 3 consecutive months or more during the year?
Wheeze	Have you ever had wheezing or whistling when you did not have a cold?
Wheezing attacks	ATS-DLD* 11AC. Have you ever had 2 or more attacks of wheezing that have make you feel short of breath?
Chest tightness	During the last 12 months, have you woken up with a feeling of chest tightness?
Shortness of breath	ATS-DLD* 13B. Are you troubled by shortness of breath walking with people of your own age on level ground?
Trouble breathing	I have regular trouble with my breathing but it always gets completely better or my breathing is never quite right.
Fever	While working at the plant have you had weekly or daily fever?
Chills	While working at the plant have you had weekly or daily chills?
Night-sweats	While working at the plant have you had weekly or daily night-sweats?
Flu-like achiness	While working at the plant have you had weekly or daily flu-like achiness?
Fatigue	While working at the plant have you had weekly or daily unusual tiredness or fatigue?
Mucous membrane irritation	Is there any exposure in your work environment that you find irritating to your eyes, nose, or throat?
Asthma	ATS-DLD* 20C. Have you ever had asthma confirmed by a doctor?
Chronic bronchitis	ATS-DLD* 18C. Have you ever had chronic bronchitis confirmed by a doctor?
Emphysema	ATS-DLD* 19C. Have you ever had emphysema confirmed by a doctor?
Atopy (allergic)	Have you ever had hay-fever or eczema confirmed by a doctor?
Attacks of bronchitis	ATS-DLD* 17.1B. Since you began working at the plant, have you ever had attacks of bronchitis confirmed by a doctor?
Pneumonia	ATS-DLD* 17.2B. Since you began working at the plant, have you ever had pneumonia confirmed by a doctor?
Skin problem	Since working at the plant, have you developed any new skin rash or skin problems?

* Corresponding questions in the American Thoracic Society - Division of Lung Diseases (ATS-DLD) standardized questionnaire (Ferris, 1978).

Table 3. Geometric mean and geometric standard deviation of particle size distributions (µm) by location, November 2000, Missouri popcorn plant.

Location (line)	Unimodal sample (µm)		Bimodal sample (µm) [1]	
	GM*	GSD*	GM	GSD
Mixing room	2.5	2.9	–	–
Mixing room	2.3	2.4	–	–
Mixing room	2.4	2.5	–	–
Mixing room	5	3	–	–
Upper deck	1.2	2.5	–	–
Machine operator (1)	1.9	4	–	–
Machine operator (1)	1.2	2.1	12	2.2
Machine operator (7)	2.3	3.5	–	–
Packing (1)	1.5	3.5	–	–
Packing	1.2	1.6	7.5	2
Packing (1&2)	2	3.5	–	–
Stacking (1)	2.5	2.9	–	–
Stacking (5)	1.3	2.2	–	–
Quality control	0.2	2.1	3	2.5
Polyethylene line- packing	8.5	2.7	–	–
Polyethylene line	5	1.7	–	–
Polyethylene line - machine operator	6	2.5	–	–
Warehouse	6.7	2.1	–	–

[1]Bimodal particle size distributions are those with two distinct, major size fractions contributing to the overall distribution.

* GM=Geometric Mean; GSD=Geometric Standard Deviation

Table 4. Predominant volatile organic compounds by area, November 2000, Missouri popcorn plant.

Predominant compounds*	Location											
	Microwave											
	mixing	upper-deck	machine operators	packing	stacking	supervisor	Quality control	Warehouse	Polyethylene line, machine operator	Polyethylene line, packing	Office worker	Outside processing
Diacetyl (2 , 3-butanedione)	X	X	X	X	X	X	X	X	X	X	X	
Methyl ethyl ketone (2-butanone)	X	X	X	X	X	X	X	X	X	X	X	
p -Dichlorobenzene			X	X	X	X	X		X	X	X	X
Limonene			X	X	X	X	X		X			X
C_7 aliphatic hydrocarbons	X	X	X	X	X			X				
Heptane	X	X	X	X	X		X	X				
Ethyl acetate	X		X	X	X							
2-Nonanone	X											
M. W. 154, $C_{10}H_{18}O$ compound	X											
Acetoin (3-hydroxy-2-butanone)	X	X										
Nonanal	X											
Acetic acid	X											
Acetoin dimers	X											
Isopentane			X									
Pentane			X									
1-Butoxy-2-propanol			X	X	X				X	X		
Trichloroethylene				X		X						
1-Methoxy-2-propanol				X	X							
Dimethyl benzenediol					X					X		

Predominant compounds*	Location											
	Microwave						Quality control	Warehouse	Polyethylene line, machine operator	Polyethylene line, packing	Office worker	Outside processing
	mixing	upper-deck	machine operators	packing	stacking	supervisor						
Acetaldehyde					X			X				
Methanol					X			X				
Butyl cellosolve (2-butoxy ethanol)		X			X							
1-Propoxy-2-propanol									X			
Decamethylcyclopentasiloxane									X	X	X	
Propyl acetate									X			
3-Buten-2-one										X		
Isobutane					X			X				
2-Ethyl-1-hexanol								X				
Acetophenone								X				
α-α-Dimethyl benzenemethanol								X				

* By gas chromatography/mass spectrometry on thermal desorption tubes.

Table 5. Mean exposure levels by work area, November 2000, Missouri popcorn plant.

Exposure work areas	Level of exposure					
	Diacetyl		Respirable dust		Total dust	
	N	Mean (ppm)	N	Mean (mg/m^3)	N	Mean (mg/m^3)
Office and outside - very low exposure	10	0.03	23	0.05	11	0.13
Polyethylene packaging area, warehouse, maintenance, and quality control - low exposure	9	0.35	25	0.09	9	0.14
Microwave packaging area - moderate exposure	22	1.88	72	0.12	24	0.20
Mixing room - high exposure	12	32.27	18	0.34	11	0.53

Table 6. Characteristics of 117 workers, October 2000, Missouri popcorn plant.

Characteristic	Category	Frequency	Percent
Age group	< 20 years	5	4
	20-29 years	35	30
	30-39 years	26	22
	40-49 years	25	21
	50-59 years	21	18
	60-69 years	5	4
Gender	Male	56	48
Race	White	107	91
Smoking status	Current smoker	47	40
	Former smoker	17	15
	Never smoker	52	45
Work shift	First shift (morning)	59	50
	Second shift (afternoon)	30	26
	Third shift (night)	28	24
Work area	Office and outside	7	6
	Polyethylene packaging area, warehouse, maintenance, and quality control	31	26
	Microwave packaging area	76	65
	Mixing room	3	3

Table 7. Respiratory symptoms, by smoking status and age, among current workforce compared to expected numbers from the national NHANES III survey, October 2000, Missouri popcorn plant.

Symptoms	Age group	Smokers					Never smokers					All employees				
		N	Expected %*	Expected E**	Obs.†	O/E††	N	Expected %	Expected E	Obs.	O/E	N	Expected %	Expected E	Obs.	O/E
Chronic cough	17 - 39	40	13.0	5.2	15	2.9	26	2.3	0.6	3	5.0	66	7.5	5.0	18	3.6
	40 - 69	25	14.3	3.6	6	1.7	26	6.3	1.6	4	2.5	51	11.2	5.7	10	1.8
	Total	65	13.7	8.9	21	2.4	52	3.8	2.0	7	3.5	117	9.2	10.8	28	2.6
Shortness of breath	17 - 39	38	22.6	8.6	23	2.7	26	9.0	2.3	11	4.8	64	15.7	10.0	34	3.4
	40 - 69	24	30.3	7.3	13	1.8	24	20.6	4.9	14	2.9	48	26.5	12.7	27	2.1
	Total	62	26.5	16.4	36	2.2	50	13.5	6.8	25	3.7	112	20.6	23.1	61	2.6
Wheezing or whistling in chest in last 12 months †††	17 - 39	40	26.1	10.4	16	1.5	26	11.0	2.9	4	1.4	66	18.4	12.1	20	1.7
	40 - 69	24	21.7	5.2	10	1.9	26	10.9	2.8	6	2.1	50	17.6	8.8	16	1.8
	Total	64	23.9	15.3	26	1.7	52	11.0	5.7	10	1.8	116	18.0	20.9	36	1.7
Wheezing apart from colds	17 - 39	40	16.3	6.5	18	2.8	26	6.2	1.6	6	3.8	66	11.2	7.4	24	3.2
	40 - 69	25	16.6	4.2	11	2.6	26	7.6	2.0	7	3.5	51	13.7	7.0	18	2.6
	Total	65	16.4	10.7	29	2.7	52	6.8	3.5	13	3.7	117	12.0	14.0	42	3.0

* Estimated percent expected from the national NHANES III survey.
** Expected number (E) = %(Expected) x Total N.
† Observed number reported from questionnaire.
†† Observed to expected ratio, indicating excess prevalence of condition.
††† NIOSH question specified wheezing or whistling in chest, during the last 12 months when you did not have a cold.

Table 8. Self-reported physician diagnoses and obstructive spirometry abnormalities, by smoking status and age among current workforce compared to expected numbers from the national NHANES III survey, October 2000, Missouri popcorn plant.

Health condition	Age Group	Smokers					Never smokers					All employees				
		N	Expected %*	Expected E**	Obs.†	O/E††	N	Expected %	Expected E	Obs.	O/E	N	Expected %	Expected E	Obs.	O/E
Asthma	17 - 39	40	8.9	3.6	6	1.7	26	6.6	1.7	2	1.2	66	7.8	5.1	8	1.6
	40 - 69	25	8.5	2.1	4	1.9	26	7.4	1.9	5	2.6	51	8.1	4.1	9	2.2
	Total	65	8.7	5.7	10	1.8	52	6.9	3.6	7	1.9	117	7.9	9.2	17	1.8
Chronic bronchitis	17 - 39	40	7.0	2.8	5	1.8	26	2.3	0.6	3	5.0	66	4.6	3.0	8	2.7
	40 - 69	25	8.7	2.2	3	1.4	26	5.1	1.3	3	2.3	51	7.3	3.7	6	1.6
	Total	65	7.8	5.1	8	1.6	52	3.4	1.8	6	3.3	117	5.8	6.8	14	2.1
Hayfever	17 - 39	40	11.6	4.6	6	1.3	26	13.5	3.5	3	0.9	66	12.6	8.3	9	1.1
	40 - 69	25	11.3	2.8	4	1.4	26	14.9	3.9	4	1.0	51	12.7	6.5	8	1.2
	Total	65	11.4	7.4	10	1.4	52	14.0	7.3	7	1.0	117	12.6	14.7	17	1.2
Obstructive spirometry abnormalities	17 - 39	39	3.8	1.5	0	0.0	26	2.3	0.6	5	8.3	65	3.0	2.0	5	2.5
	40 - 69	25	12.1	3.0	8	2.7	26	2.7	0.7	8	11.4	51	8.5	4.3	16	3.7
	Total	64	8.0	5.1	8	1.6	52	2.4	1.2	13	10.8	116	5.5	6.4	21	3.3

* Estimated percent expected from the national NHANES III survey.
** Expected number (E) = %(Expected) x Total N.
† Observed number reported from questionnaire.
†† Observed to expected ratio, indicating excess prevalence of condition.

Table 9. Symptom and physician diagnosis prevalence by current work area, November 2000, Missouri popcorn plant.

Health condition	Office and outside (N=7)		Polyethylene packaging, warehouse, maintenance, and quality control (N=31)		Microwave packaging and mixing (N=79)	
Respiratory symptoms	N	%	N	%	N	%
Chronic cough	1	14	6	19	21	27
Chronic wheeze	1	14	10	32	31	39
Attacks of wheezing	1	14	5	16	19	24
Chest tightness	1	14	8	26	23	29
Shortness of breath	1	14	8	26	22	30[a]
Regular trouble with breathing	0	0	7	23	30	38*
Systemic symptoms						
Fever	0	0	0	0	1	1
Chills	0	0	0	0	3	4
Night sweats	0	0	0	0	10	13*
Flu-like achiness	0	0	0	0	8	10*
Unusual fatigue	0	0	7	23	31	39*
Other symptoms						
Mucous membrane irritation	3	43	18	58	55	72[b]*
Skin irritation	1	14	4	13	29	37*
Doctor diagnoses						
Bronchitis attacks	1	14	9	29	14	18
Chronic bronchitis	0	0	3	10	11	14
Emphysema	0	0	2	6	2	3
Asthma	1	14	5	16	11	14
Pneumonia	1	14	8	26	13	16

[a] N=74 respondents.
[b] N=76 respondents.
* Statistical significant trend ($p < .05$).

Table 10. Symptom onset and physician diagnoses after hire by current work area, November 2000, Missouri popcorn plant.

Health condition	Office and outside (N=7)		Polyethylene packaging, warehouse, maintenance, and quality control (N=31)		Microwave packaging and mixing (N=79)	
Respiratory symptoms	**N**	**%**	**N**	**%**	**N**	**%**
Chronic cough	0	0	5	16	13	16
Chronic wheeze	0	0	5	16	19	24
Attacks of wheezing	0	0	3	10	9	11
Chest tightness	1	14	7	22	20	26
Shortness of breath	0	0	5	16	13	17
Systemic symptoms	0	0	5	17	32	41*
Other symptoms						
Skin problem	1	14	4	13	26	33*
Atopy	0	0	2	6	7	9
Doctor diagnoses						
Chronic bronchitis	0	0	2	6	4	5
Emphysema	0	0	1	3	2	3
Asthma	0	0	2	6	5	6

*Statistically significant trend ($p < .05$).

Table 11. Percent prevalence of symptoms and physician diagnoses with onset after hire by airway obstruction, November 2000, Missouri popcorn plant.

Health condition	Obstruction (N=21)		No obstruction (N=95)	
Respiratory symptoms	**N**	**%**	**N**	**%**
Chronic cough	7	33*	11	12
Chronic wheeze	10	48*	14	15[a]
Attacks of wheezing	6	29*	6	6
Chest tightness	10	48*	18	19[a]
Shortness of breath	7	33*	11	12[a]
One or more respiratory symptoms	16	76	53	56
Systemic symptoms	7	33	30	32[b]
Other symptoms				
Skin problem	4	19	27	28
Doctor diagnoses				
Chronic bronchitis	5	24*	1	1[a]
Asthma	5	24*	2	2
Emphysema	3	14*	0	0
Bronchitis attacks	11	52*	12	13
Pneumonia	10	48*	12	13

* Statistically significant difference ($p < .05$)

[a] N=94 respondents.

[b] N=93 respondents.

Table 12. Diacetyl and acetoin concentrations, January 2001, Missouri popcorn plant.

	Diacetyl (ppm)*		Acetoin (ppm)	
Sample type/location	**January 18 †**	**January 19 ††**	**January 18**	**January 19**
Area - microwave mixer	86.9	9.7	11.7	2.01
Personal - microwave mixer	13.7	4.26	2.81	0.60
Personal - microwave machine operator	2.74	0.41	0.34	0.13
Personal - microwave machine operator	1.70	0.19	0.20	0.04
Area - microwave machine operator	3.04	0.53	0.38	0.12
Personal-microwave packer	2.98	0.29	0.42	0.04
Area - microwave packer	3.04	0.27	0.32	0.12
Personal - quality control	2.76	0.24	0.38	0.05
Area - microwave upper deck	3.26	0.59	0.38	0.12
Average	13.4	1.83	1.88	0.36
Standard deviation	27.8	3.23	3.76	0.64

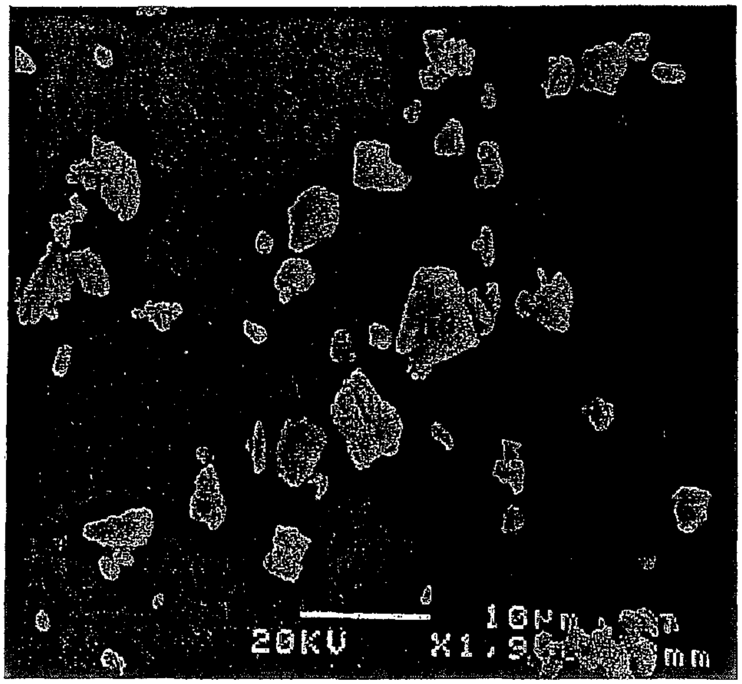
† Sampling on January 18th was done with minimal dilution ventilation.

†† Sampling on January 19th was done with the microwave mixing room under negative pressure and with the wall dilution ventilation fans operating (the initial engineering interventions).

* ppm - parts per million parts air by volume.

Figure 1. Scanning electron microscopy of airborne particles, November 2000, Missouri popcorn plant.

A) Salt particles collected on a filter from aerosolizing bulk salt sample in NIOSH laboratory;



B) Oil and salt on glass slide set in holding-tank to assay airborne aerosol.

Figure 2. Organic vapors by gas chromatography/mass spectrometry in the mixing room, November 2000, Missouri popcorn plant.

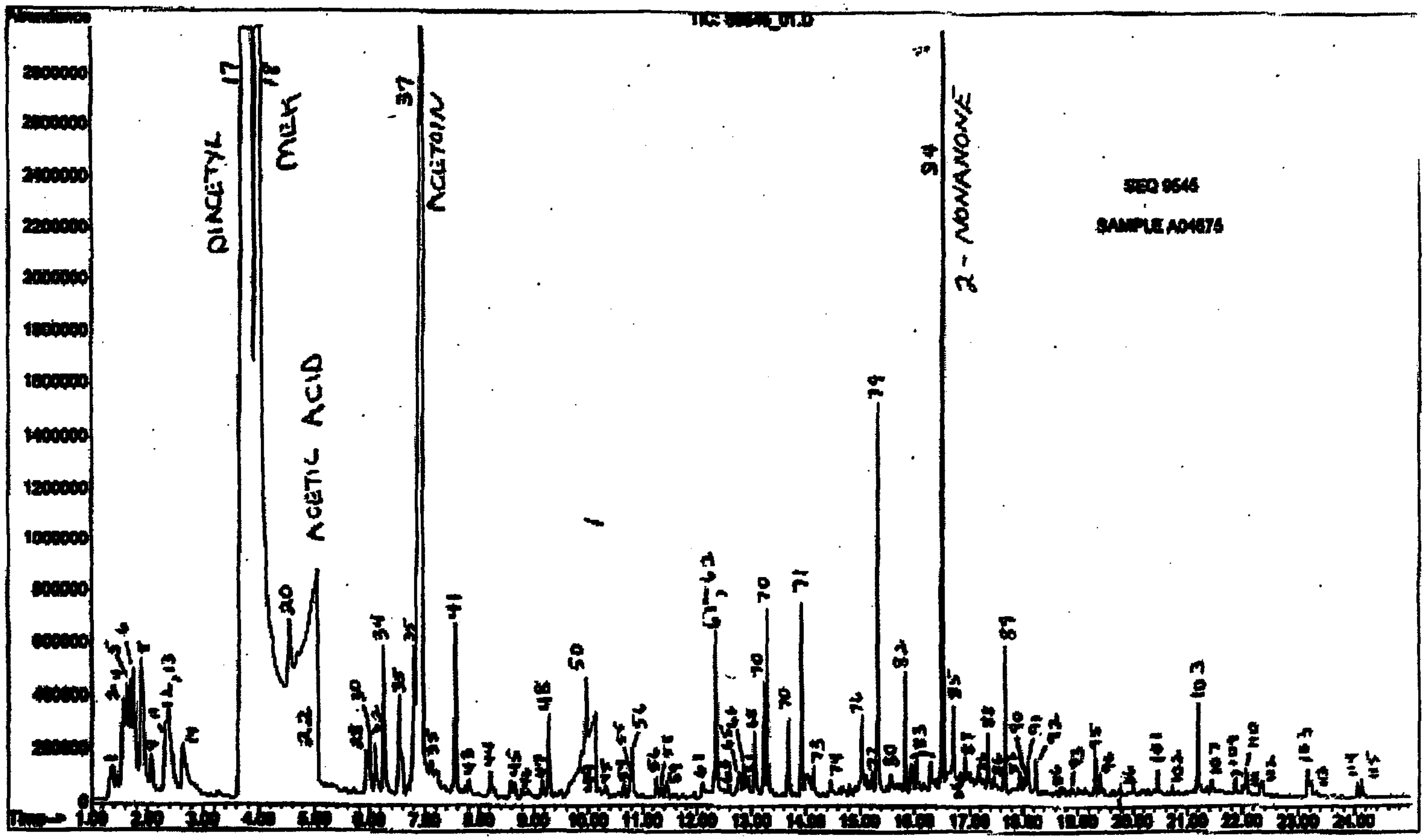


Figure 3. Average total and respirable dust concentrations by job and area, November 2000, Missouri popcorn plant.

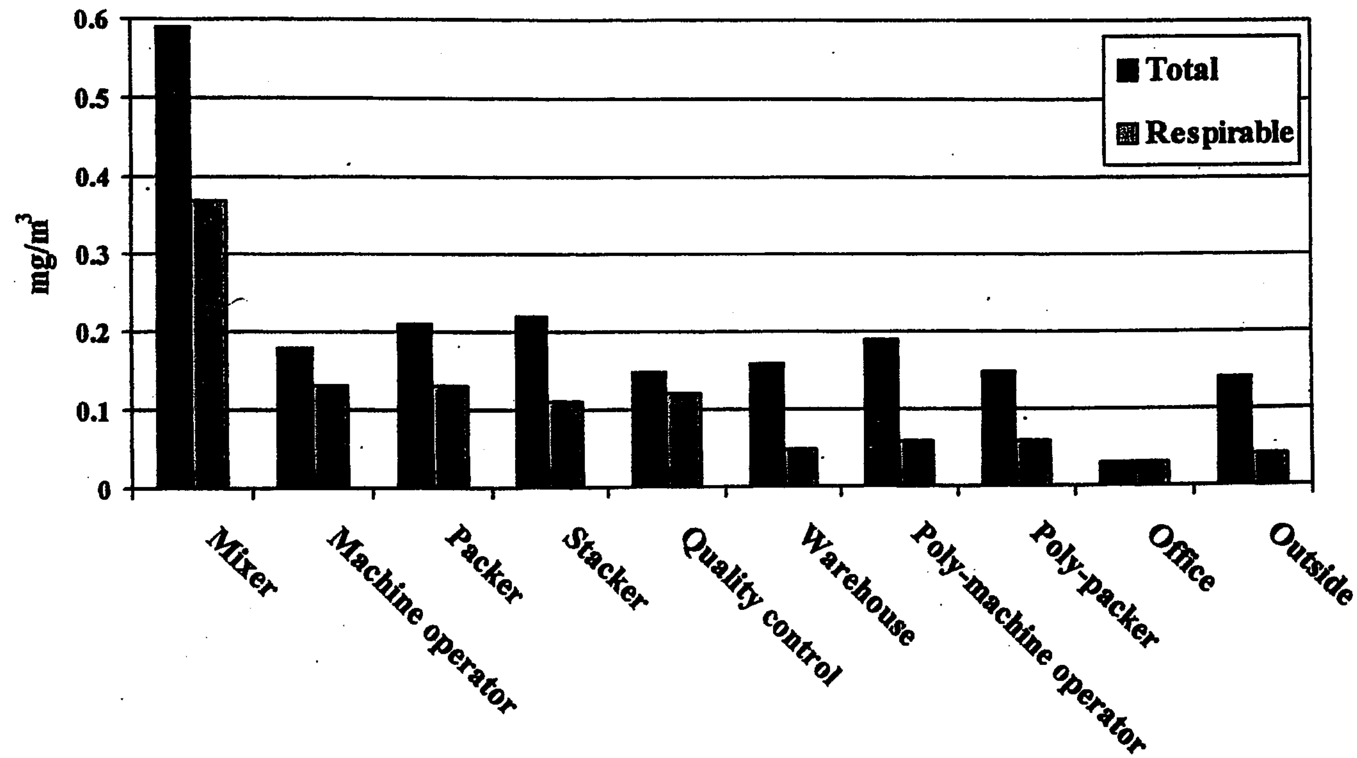


Figure 4. Particle size distributions from A) microwave mixing, B) microwave machine operators, C) microwave packing, and D) microwave stacking, November 2000, Missouri popcorn plant.

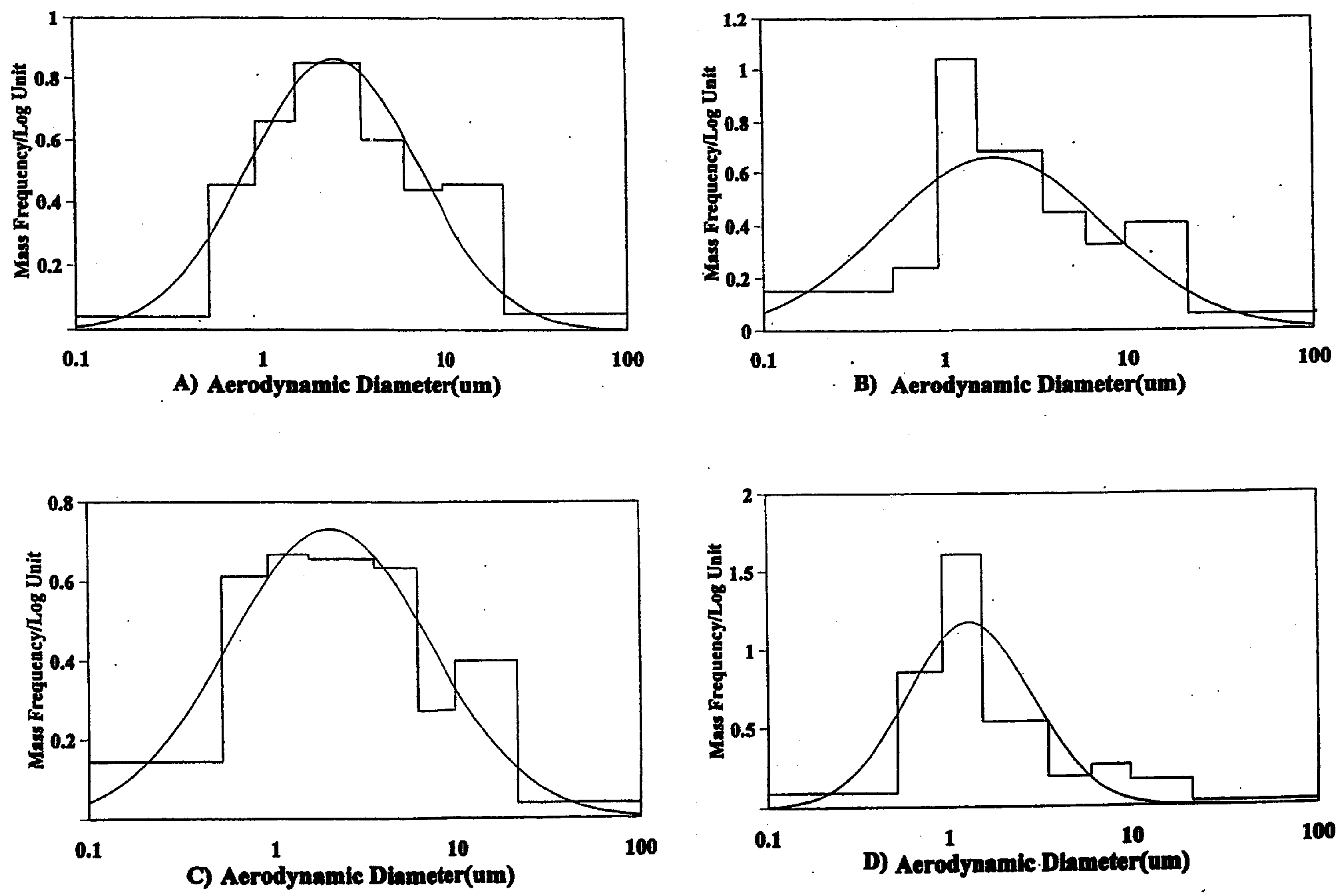


Figure 5. Particle size distributions from A) polyethylene line and B) warehouse, November 2000, Missouri popcorn plant.

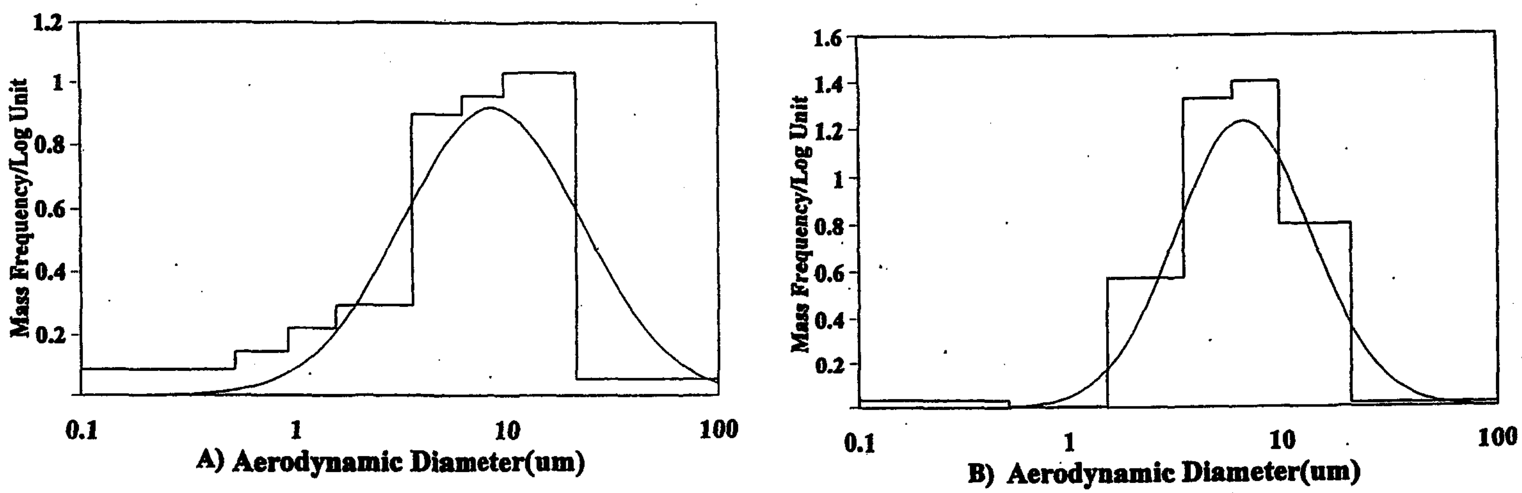


Figure 6. Average diacetyl and acetoin concentrations by non-microwave area (A), and by microwave area (B), November 2000, Missouri popcorn plant. Note the large difference in vertical scale between the two graphs (0.1 vs 4.0 ppm interrupted to a high of 38 ppm).

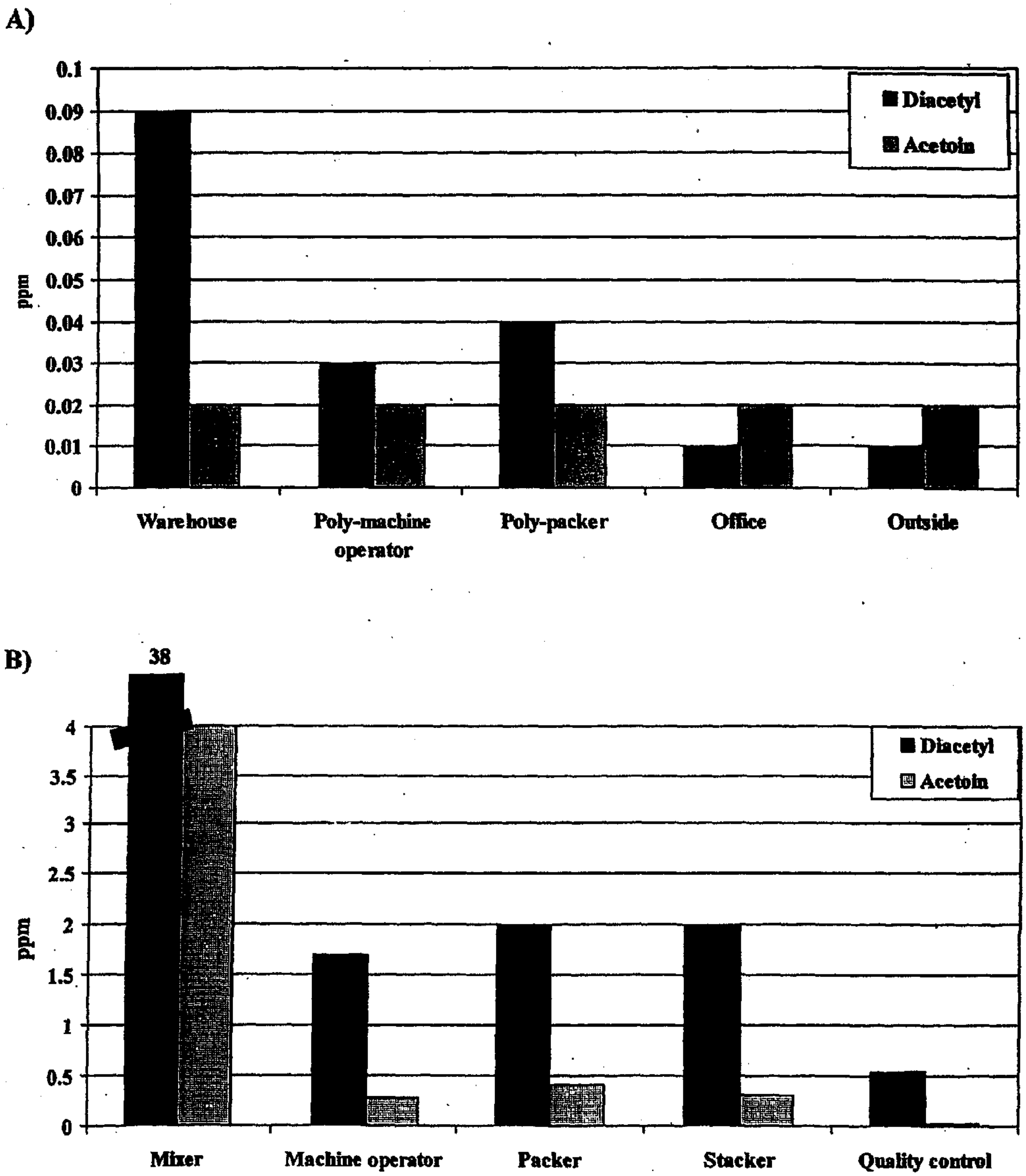


Figure 7. Distribution of workers with obstructive spirometry abnormalities by quartile of cumulative exposure to diacetyl (ppm-years), November 2000, Missouri popcorn plant. Stars indicate workers with obstruction; dots indicate workers without obstructive abnormality.

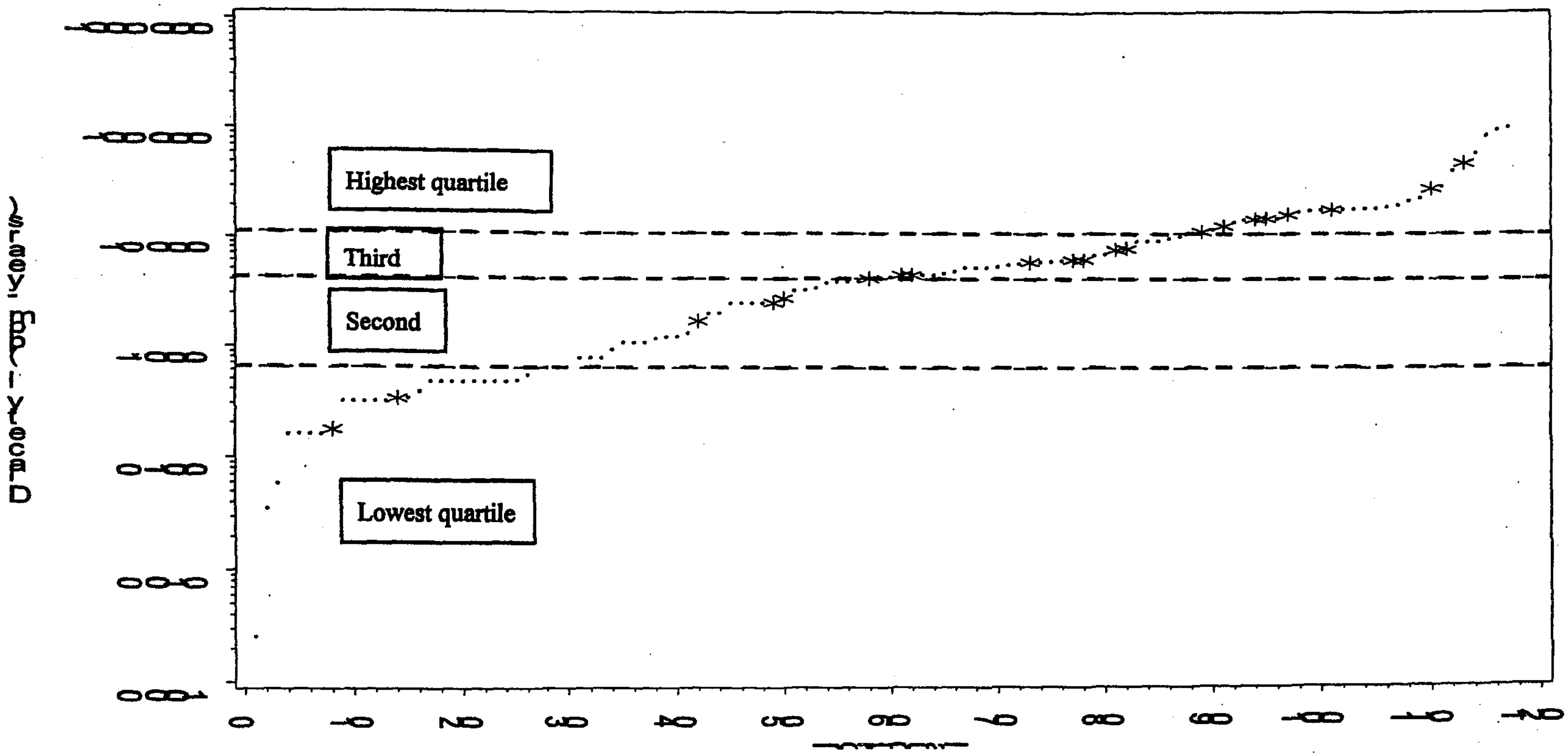


Figure 8. Distribution of workers with obstructive spirometry abnormalities by quartile of cumulative exposure to respirable dust (mg-years/m^3), November 2000, Missouri popcorn plant. Stars indicate workers with obstruction; dots indicate workers without obstructive abnormality.

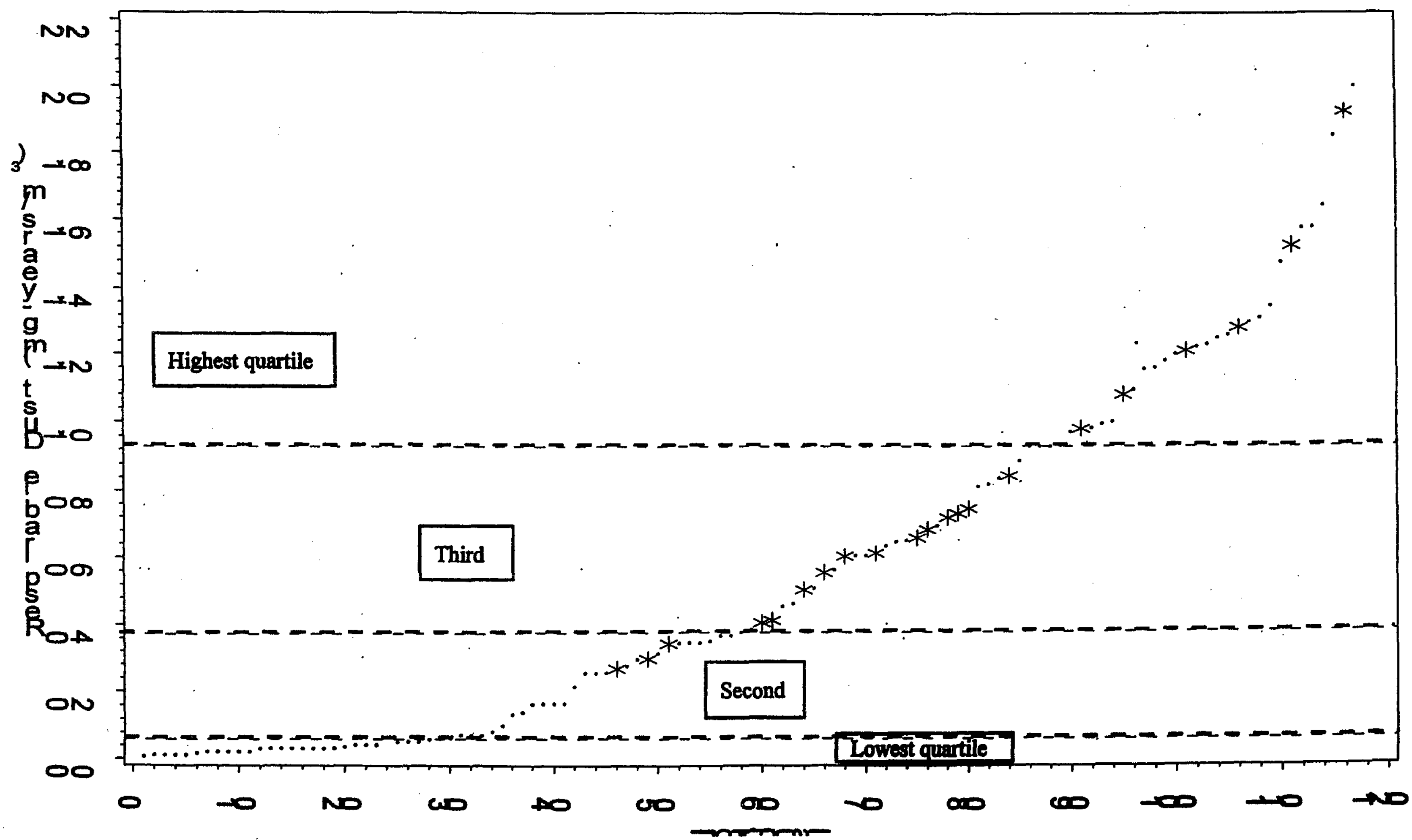
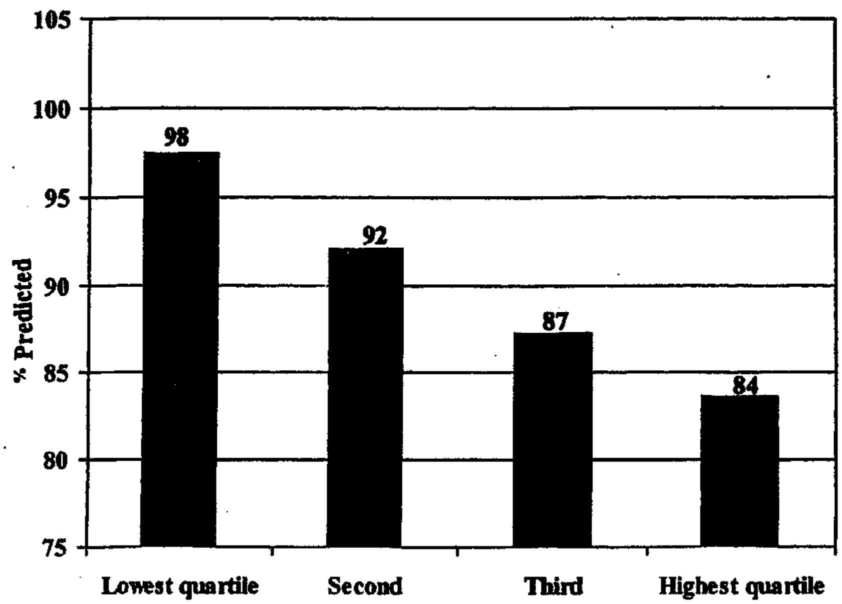


Figure 9. Average percent predicted FEV_1 by quartile of cumulative exposure to diacetyl (A) and respirable dust (B), November 2000, Missouri popcorn plant.

A)



B)

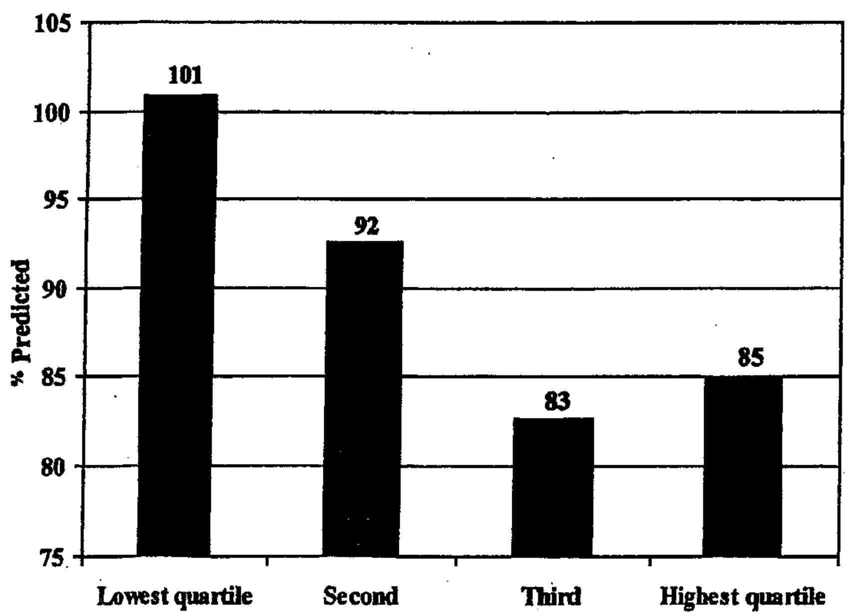


Figure 10. Relative peak and mean organic vapor concentrations (by photoionization detector) by microwave production area, on January 18, 2001 (before the initial engineering interventions) and January 19, 2001 (after interventions), Missouri popcorn plant.