Report on an Investigation of Asthma and Respiratory Symptoms among Workers at a Soy Processing Plant

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NIOSH *National Institute for Occupational Safety and Health*

The employer shall post a copy of this report for a period of 30 calendar days at or near the workplace(s) of affected employees. The employer shall take steps to insure that the posted determinations are not altered, defaced, or covered by other material during such period. [37 FR 23640, November 7, 1972, as amended at 45 FR 2653, January 14, 1980].

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ABBREVIATIONS

ACGIH	American Conference of Governmental Industrial Hygienists
ATS	American Thoracic Society
BCA	bicinchoninic acid
BCIP	bromo-chloro-indolyl phosphate
BD	bronchodilator
BHR	bronchial hyperresponsiveness
BRFSS	Behavioral Risk Factor Surveillance System
BSA	bovine serum albumin
°C	degrees Celsius
cm	centimeter
CP4-EPSPS	5-enolpyruvylshikimate-3-phosphate synthase from Agrobacterium sp. strain CP4
ECRHS	European Community Respiratory Health Survey
ELISA	enzyme-linked immunosorbent assay
EU/m^3	endotoxin units per cubic meter of air
°F	degrees Fahrenheit
FEIA	fluoroenzyme immunoassay
FEV_1	forced expiratory volume in the first second of exhalation
FVC	forced vital capacity
GM	geometric mean
GSD	geometric standard deviation
H_2O_2	hydrogen peroxide
HEPA	high-efficiency particulate air
HHE	Health Hazard Evaluation
hr	hour
HRP	horseradish peroxidase
IgE	immunoglobulin E
IgG	immunoglobulin G
kDa	kilodalton
kU/l	kilounits per liter
l	liters
LLN	lower limit of normal
lpm	liters per minute
mA	milliamps
MCT	methacholine challenge test
mg/m^3	milligrams per cubic meter of air
mg/l	milligrams per liter
mg/ml	milligrams per milliliter
mm	millimeters
MMAD	mass median aerodynamic diameter
N	normal
NBT	nitroblue tetrazolium
ng/m^3	nanograms per cubic meter of air

ng/ml	nanograms per milliliter
NHANES III	Third National Health and Nutrition Examination Survey
NIOSH	National Institute for Occupational Safety and Health
nm	nanometers
NMAM	NIOSH Manual of Analytical Methods
N95	filters at least 95% of airborne particles. Not resistant to oil.
N99	filters at least 99% of airborne particles. Not resistant to oil.
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAPR	powered air-purifying respirator
PBS	phosphate buffered saline
PBS-T	phosphate-buffered saline with Tween®
PC	provocative concentration
PEL	permissible exposure limit
PNOR	particulates not otherwise regulated
PNOS	particulates not otherwise specified
PNPP	p-nitrophenyl phosphate
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
PR	prevalence ratio
PTFE	polytetrafluoroethylene
rpm	revolutions per minute
REL	recommended exposure limit
SAPP	sodium acid pyrophosphate
SDS-PAGE	sodium dodecyl sulfate-polyacrylamide gel electrophoresis
SE-St	standard soy extract
STD	standard deviation
TLV	threshold limit value
TMB	tetramethylbenzidine
TWA	time-weighted average
µg	micrograms
µg/ml	micrograms per milliliter
µl	microliter
µm	micrometer
V	volt
VOC	volatile organic compound
w/v	weight per volume

Highlights of the NIOSH Health Hazard Evaluation

The National Institute for Occupational Safety and Health (NIOSH) received a confidential request to conduct a Health Hazard Evaluation (HHE) at the Solae Company in Memphis, TN. Workers reported breathing difficulty and asthma that they attributed to workplace exposures, including soy and mold.

What NIOSH Did:

- Observed workers during routine activities.
- Measured dust and soy antigen concentrations in the air throughout the plant.
- Interviewed 147 current workers about their health and job histories.
- Assessed 140 current workers' lung function using several breathing tests.
- Conducted skin allergy testing for 132 workers and blood allergy testing for 135 workers.
- Provided information for reducing workers' exposures to potentially hazardous materials.

What NIOSH Found:

- Some dust concentrations in the air exceeded current occupational exposure standards.
- Curd operators and unloading workers had the highest soy antigen exposures and office and warehouse workers had the lowest soy antigen exposures.
- Solae workers had a higher than expected prevalence of physician-diagnosed asthma, sinusitis, and wheeze (a symptom of asthma) compared to the U.S. adult population.
- Among workers with adult-onset asthma, the rate of diagnosis was five times higher after employment at the Solae plant than before employment.
- Asthma and asthma-like symptoms were more common in workers who responded to soy on the blood test but not more common in workers who responded to soy on the skin test.
- Sinusitis, nasal allergies, and rash were more common in workers who reported having seen or smelled mold in the workplace in the previous 12 months.
- Production workers were more likely to report work-related asthma-like symptoms than non-production workers.
- Airways obstruction on spirometry and reports of work-related asthma-like symptoms were associated with peak dust concentrations.
- Some workers with respiratory exposures, including

NIOSH investigators found that respiratory problems among workers at Solae were more common than expected and were associated with: immune response to soy; working in production jobs; peak dust concentrations; and workplace mold. Based on these findings, the NIOSH investigators recommend: (1) reducing worker exposures to soy and other dusts by engineering controls and personal protective equipment; and (2) encouraging workers to promptly report symptoms to their supervisor and their personal physician or other healthcare provider.

temporary and contract workers, were not included in the company's respiratory protection program.

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What Solae Company Managers Can Do:

- Examine opportunities for further use of engineering controls, versus personal respiratory protection, to reduce worker exposures to dusts.
- Enforce the use of respiratory protection in plant areas, sub-areas, and jobs identified as having higher dust concentrations (measured as peaks and time-weighted averages).
- Include in the plant's respiratory protection program all workers (permanent, temporary, and contract workers) who have respiratory exposures.
- Encourage workers to report new or worsening respiratory symptoms to their supervisor and to their personal physician or other healthcare provider.
- Provide personal respiratory protection for all workers with work-related asthma; if ineffective, relocate these workers to lower exposure areas such as the warehouse or office locations.

What Solae Workers Can Do:

- Wear appropriate respiratory protection where and when instructed.
- Report any new or worsening respiratory symptoms to your supervisor and your personal physician or other healthcare provider.
- Workers with symptoms should provide their personal physician or other healthcare provider with a copy of this Highlights section of the HHE report.

Summary

NIOSH investigators conducted industrial hygiene and medical evaluations at the Solae plant in Memphis, TN. Some dust concentrations in the air exceeded current occupational exposure standards. Solae workers had higher than expected prevalences of physician-diagnosed asthma, sinusitis, and wheeze (a symptom of asthma) compared to the U.S. adult population. Among workers with adult-onset asthma, the rate of diagnosis was five times higher after employment at the Solae plant than before employment at the plant. All asthma outcomes were significantly associated with immune response to soy, as measured by soy-specific IgE. Sinusitis, nasal allergies, and rash were more common in workers who reported having seen or smelled mold in the workplace. Airways obstruction on spirometry and increased reports of work-related asthma-like symptoms were associated with peak concentrations of dust. Worker exposures to soy and other dusts should be reduced using engineering controls and personal protective equipment, and workers should promptly report symptoms to their supervisor and personal physician or other healthcare provider.

On December 12, 2006, the National Institute for Occupational Safety and Health (NIOSH) received a confidential Health Hazard Evaluation (HHE) request from workers at the Solae Company's plant in Memphis, TN. The requesters described respiratory symptoms and diagnoses, including sinus congestion and asthma, which they attributed to the workplace. They noted exposure to soy materials, lime (calcium oxide (CaO)), microbial contaminants such as mold, and insects.

NIOSH investigators conducted telephone interviews with workers, a union representative, treating physicians, and company management and safety officials. On March 6, 2007, NIOSH investigators visited the plant to observe the process, measure concentrations of airborne dust, collect bulk samples of soy materials, and interview workers about their symptoms and exposures. They later conducted an industrial hygiene survey (July 9–13 and July 30–August 3, 2007). NIOSH investigators collected personal and area air samples from different plant areas, sub-areas, and jobs during the survey. They collected: personal (breathing-zone) air samples for inhalable dust and inhalable soy antigen; personal (breathing-zone) and area air measurements for airborne dust of respirable and thoracic size fractions using a real-time sampler; and area air samples for inhalable dust, inhalable soy antigen, total dust, total endotoxin, selected metals, and particle size distributions. They also collected bulk samples of soy materials from different sub-areas of the plant. From July 23–August 2, 2007, NIOSH investigators also conducted a medical survey of current workers at the plant; it consisted of an interviewer-administered questionnaire; lung function testing, including spirometry, bronchodilator, and methacholine challenge testing; and skin and blood allergy testing.

Inhalable dust exposures were highest for the autopack operator, unloading switch operator, and sanitation job categories. Some of the samples from these job categories, as well as from starch dumping, exceeded the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for total dust as particulate not otherwise regulated (PNOR) and the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (TLV®) for inhalable dust. The task of starch dumping, which produced the highest dust concentrations measured (21.7 mg/m^3), was typically done by workers from several different job categories outside their normal shift work, using respiratory protection.

Detectable soy antigen air concentrations were measured in all plant areas and sub-areas; the highest geometric mean inhalable soy antigen area concentration was in the flake processing room (308,000 ng/m^3). Job categories with the highest geometric mean soy antigen concentration as measured by personal samples included the unloading switch operator (27,540 ng/m^3), curd operator (25,960 ng/m^3), and unloading lead (14,360 ng/m^3). Currently, there are no occupational exposure standards or guidelines specifically for soybean dusts, though the more general PNOR standard does apply to soybean dusts.

The highest endotoxin concentration, 217 EU/m^3, was measured in the flake processing room; all other endotoxin concentrations were below 50 EU/m^3. Calcium was detected in 5 of 67 total dust air samples; if the calcium in these samples was all present as lime (CaO), the highest corresponding lime concentration in air would have been approximately 0.52 mg/m^3, a level well below the existing OSHA standard for lime dust.

Of the 281 workers currently employed at the plant by the Solae Company, 147(52%) consented to participate in the medical survey and completed the questionnaire. Participation rates varied by worker classification, ranging from 66 of 94 (70%) production workers to 42 of 114 (37%) non-production workers. NIOSH staff conducted lung function testing for 140 of these workers, skin allergy testing for 132, and blood allergy testing for 135.

Participating workers at the Solae plant in Memphis had higher than expected prevalences of physician-diagnosed asthma, sinusitis, and wheeze (a symptom of asthma) compared to the U.S. adult population. The prevalences of current and ever physician-diagnosed asthma for participating males were higher than expected based on a survey of the state of Tennessee, but these differences did not reach statistical significance. Among participants with adult-onset, physician-diagnosed asthma, most were diagnosed after hire at Solae. The incidence rate was five times greater after hire than before hire, consistent with a temporal relationship of occupational exposures preceding asthma diagnosis. Compared to non-production workers, production workers were more likely to report asthma-like symptoms that improve away from work. Work-related asthma-like symptoms were also associated with peak dust concentrations. Compared to workers exposed to lower peak concentrations, participants exposed to higher peak

concentrations of dust were more likely to report work-related asthma-like symptoms. Additionally, workers who reported seeing or smelling mold in the workplace were more likely to report work-related sinusitis, nasal allergies, and rash compared to workers not reporting this exposure.

Fourteen participants (10%) had airways obstruction on spirometry (six borderline and eight mild or worse severity). Eleven (8%) had spirometry results indicating a restrictive pattern. One had both airways obstruction and restriction. Two had a clinically significant response to bronchodilator and 12, including eight without airways obstruction on spirometry, had evidence of bronchial hyperresponsiveness on methacholine challenge testing.

The prevalence of positive immunoglobulin E (IgE) to soy among Solae workers was five times greater than the prevalence among a group of comparison workers who were not occupationally exposed to soy, suggesting that immune recognition of soy among Solae workers resulted from occupational exposures. All asthma outcomes were significantly associated with immune response to soy, as measured by soy-specific IgE levels in the blood but not as measured by the skin prick test for soybean allergy.

Concentrations of soy antigen and dust exposure were process-related. Compared to workers exposed to lower peak concentrations, those exposed to higher peak dust concentrations (measured by real-time sampling) were more likely to have spirometry indicating airways obstruction and to report work-related asthma-like symptoms. In addition, level of immunoglobulin G (IgG) to soy was associated with inhalable soy antigen level and work classification. Time-weighted-average inhalable soy antigen and dust concentrations were not associated with asthma outcomes in analyses involving all participants.

Keywords: Occupational asthma, symptoms, airways obstruction, soy protein, IgE

INTRODUCTION

On December 12, 2006, the National Institute for Occupational Safety and Health (NIOSH) received a confidential Health Hazard Evaluation (HHE) request from workers at the Solae Company's plant in Memphis, TN. The requesters described respiratory symptoms and diagnoses, including sinus congestion and asthma, which they attributed to the workplace. They noted exposure to soy materials, lime (calcium oxide (CaO)), microbial contaminants such as mold, and insects.

Soy is a known cause of food allergy and is considered one of eight major compounds responsible for 90% of IgE-mediated food allergy in childhood [Allen et al. 2006; L'Hocine and Boye 2007]. At least 16 soy proteins have been identified as food allergens, some of which have immune cross-reactivity with proteins from other members of the legume family, such as peanut. In addition, recent studies have demonstrated cross-reactivity between a soy food allergen and birch pollen allergens [Kleine-Tebbe et al. 2002; Mittag et al. 2004].

Environmental exposure to soy also has been associated with sensitization and respiratory illness in some community settings. In the 1980s, epidemics of asthma occurred in the Spanish city of Barcelona. Investigators identified the unloading of soybeans from ships in the harbor as highly associated with asthma epidemic days, on which visits to the emergency room for asthma were unusually high and clustered on an hourly basis [Antó et al. 1989]. Furthermore, asthmatic patients presenting on epidemic days were far more likely to have IgE antibodies to soybean dust than asthma patients presenting on non-epidemic days [Sunyer et al. 1989]. Several low-molecular-weight proteins (7–8 kDa) concentrated in the soybean hull were implicated [Gonzalez et al. 1994; Codina et al. 1997]. Ultimately, the epidemics were halted after soybean silos in the harbor were fitted with filters, providing further evidence of a causal relationship [Picado 1992]. Soy has since been associated with previously unexplained epidemics of asthma in New Orleans in the 1950s and 1960s, via a retrospective study that found a strong association between the presence of soy-containing vessels in the harbor and visits to the emergency room for asthma [White et al. 1997].

There is some evidence to suggest that occupational exposure to soy also may lead to sensitization and respiratory illness. The first report of work-related asthma associated with soy described five soy mill workers with asthma-like symptoms and positive skin

scratch tests to various soy products [Duke 1934]. A NIOSH HHE investigation at a facility where raw soybeans were processed to oil and meal found a high prevalence of asthma-like symptoms among the 50 evaluated workers, but a specific immunological link to soy was not made [NIOSH 1987].

Two subsequent smaller studies examined the relationship between respiratory symptoms and soy-specific immune responses among soy mill and control workers [Zuskin et al. 1991; Roodt and Rees 1995]. In both studies, respiratory symptoms were more common in soy workers than controls. In one of the studies, soy workers were more likely to have positive results on soy-specific allergy tests [Roodt and Rees 1995]. However, neither study demonstrated an association between symptoms and soy-specific immunity.

A study of asthma among bakers did demonstrate an association between symptoms and soy-specific IgE [Baur et al. 1998]. When bakers were categorized by presence (n=142) or absence (n=45) of respiratory symptoms, 11 (8%) symptomatic bakers had a positive skin response to soy compared to one (2%) asymptomatic baker and 35 (25%) symptomatic bakers had soy-specific IgE compared to three (7%) asymptomatic bakers; the latter finding was statistically significant. However, similar associations were noted for other allergens to which the bakers were exposed, such as wheat and rye flours, complicating interpretation of the study's findings.

A report of four bakers and confectioners with work-related respiratory symptoms examined the relationship between soy flour and hull antigens and occupational asthma [Quirce et al. 2000]. The authors found that all participants had positive skin test responses to both prepared and commercial soy extracts. Three (75%) had positive soy-flour-specific IgE, but only one reacted to a hull-antigen extract. Methacholine and soy-flour inhalation challenges were positive in all cases. In general, the hull extract contained mainly low-moleclular-weight polypeptides, while the flour extract had higher-molecular-weight proteins (18–51 kDa). The participants' sera reacted mainly with the latter proteins.

Thus, while some soy proteins have been identified as allergens and soy-exposed workers appear to be at increased risk of respiratory symptoms, studies of soy-exposed workers to date have not found a consistent association between soy allergy and respiratory illness. Furthermore, the potential etiologic roles played by flour and hull antigens in occupational settings have not been clearly elucidated.

In addition to soy, requestors described several other exposures—specifically, mold, mites, cockroaches, and bacteria in storage bins—that could be relevant to respiratory symptoms and asthma at the plant. Exposure to mold or other dampness-related agents in damp indoor environments is associated with respiratory symptoms, including nasal and throat symptoms, cough, wheeze, and exacerbation of asthma in sensitized asthmatic individuals [IOM 2004]. In addition, more recent evidence suggests that such exposures can cause asthma [Jaakkola et al. 2005; Cox-Ganser et al. 2005]. Mite exposure has also been found to both cause asthma and exacerbate preexisting asthma [IOM 2000]. In addition, cockroach exposure may cause asthma in some populations and also has been found to exacerbate preexisting asthma [IOM 2000]. Endotoxin, a component of some bacteria, also has been linked to asthma, including occupational asthma, and other chronic respiratory effects [Bardana 2008; Wang et al. 2005].

While the Occupational Safety and Health Administration (OSHA) does not specify a permissible exposure limit (PEL) for soy, mold, mite, cockroach antigens, or endotoxin in the air, the PEL for total dust is 15 mg/m^3 and for respirable dust is 5 mg/m^3. Respirable dust refers to the fraction of airborne dust that is capable of depositing in the gas-exchanging (i.e., alveolar) portion of the lungs. Inhalable dust refers to the fraction of airborne dust that can be inhaled and deposited anywhere along the respiratory tract. Respirable dust is thus a fraction of inhalable dust.

Plant and Process Description

The Solae Company, an alliance between DuPont and Bunge Limited, processes soy flakes into soy products for both human and animal consumption. The plant receives de-oiled, de-hulled crushed soy flakes by railcar for further processing into soy powder products. Workers in the unloading area empty the soy from railcars into storage bins. The soy flakes are then processed in several flake processing sites of the plant. Following processing, the soy product goes to a wet-in process where water is added to create a soy slurry.

The soy slurry goes to one of several separate production operations. The basic processing steps are the same for each of the production operations. These production operations are all automated and each operation has a control room that provides

computer control and oversight of the entire production process. Production leads oversee all production processes.

For each of the production operations, the soy slurry goes first to a curd sub-area where soy proteins are extracted, concentrated, and washed. Soy proteins are concentrated in the slurry to approximately 91%. Chill tanks are used next to adjust the concentration of solids, pH, and mineral content of the soy slurry. The curd operator oversees these plant processes.

In the next step, the concentrated soy slurry is sent by high-pressure pumps to be sprayed into the top of a gas-heated spray-drying tower for flash drying. Each tower is several stories in height and the sprayed slurry dries as it falls by gravity. At the bottom of the tower, the soy powder is collected using several different techniques. A spray dryer operator oversees the spray-drying process.

The dried soy powder is automatically transferred from the spray-drying towers to the autopackaging sub-area. In autopackaging, the soy powder is put into 44- or 1,000-pound bags by the autopack operator using an automated bagging machine, which fills and seals each bag of soy powder. During this process, other specialty ingredients (e.g., minerals) may also be added depending on final product specifications. An autopack assistant is also present. Following this process, the bags of soy powder are stacked on a pallet and then wrapped in plastic. The finished product is stored in a warehouse located about a mile from the production lines.

In the curd process, a portion of the soy slurry is separated out as waste product. This material predominantly consists of solids containing lower soy protein content that is used for animal feed. The waste material is sent to a separate drying tower, the feed dryer. A feed dryer operator oversees this process.

Additional product additives may include lime (calcium oxide (CaO)), sodium sulfite, sodium acid pyrophosphate (SAPP), sodium hydroxide, or potassium iodate.

The soy plant also has laboratory operations for quality control. There are on-site maintenance operations and a maintenance shop. Sanitation operators are active throughout the plant. Their tasks involve cleaning by shoveling, sweeping, brushing, and vacuuming soy or other process materials. The production plants have in-

wall vacuum systems; they do not clean by blowing dust with compressed air. The plant also has several different offices located throughout the facility.

The production plants use both general dilution and local exhaust ventilation. General dilution ventilation, accomplished primarily by roof exhaust systems, is common in most plant areas. Local exhaust ventilation is used for dust control on the soy packaging lines.

The plant has a written respiratory protection program in place. At the time of our survey, maintenance workers, material handlers (railcar unloading workers), and production employees whose jobs involve the handling of certain chemicals were included in the company's respiratory protection program. This program includes the elements required by OSHA; the initial respirator training is classroom-based training provided on-site with on-line annual refresher training. Respirators are provided for contract and temporary employees; however, these workers were not included in the respiratory protection program or provided respirator training.

Additional occupational health and safety training is provided to workers through an on-line program managed by an outside contractor.

NIOSH investigators conducted telephone interviews with workers, a union representative, treating physicians, and company management and safety officials and also reviewed medical records prior to visiting the plant. During the initial plant visit on March 6, 2007, NIOSH investigators observed the process, measured airborne particle concentrations using a real-time dust monitor (*Personal* DataRam®, models *p*DR-1000An/1200 [Thermo Electron Corporation, Franklin, MA]), collected bulk samples of soy materials, and interviewed workers who currently or previously held positions in sanitation about job duties and symptoms.

On this initial visit, we observed peak dust concentrations as high as approximately 100 milligrams per cubic meter of air (mg/m^3) during shoveling activities by sanitation operators. We also noted that some workers' respirators were not being worn properly and discussed our observations with workers and management. Furthermore, we noted temporary and contract employees were not included in the company's respiratory protection program. In addition, we found that respiratory and dermatological symptoms were common among interviewed workers and that some workers attributed their symptoms to exposures at the plant. On the basis of these initial findings, we planned more comprehensive industrial hygiene and medical surveys. We described these surveys in presentations to workers during the week of July 9, 2007.

Industrial Hygiene Survey

NIOSH investigators conducted an industrial hygiene survey at the plant from July 9–13 and July 30–August 3, 2007. We sampled on one second shift and nine first shifts. We collected full-shift, time-weighted average (TWA) personal and area air samples from different plant areas, sub-areas, and jobs and measured temperature and relative humidity. Air samples included personal-breathing-zone (PBZ) air samples for inhalable dust and inhalable soy antigen, PBZ and area dust exposures using a real-time sampler, and area air samples (for total and inhalable dust, total, inhalable, and respirable soy antigen, total endotoxin, selected metals, and particle size distributions). The optical configuration for the real-time sampler responds to particles in the size range from 0.1 to 10 micrometers, roughly corresponding to standard gravimetric measures of respirable and thoracic dust fractions. We also collected bulk samples of soy materials, including genetically-modified soy, from different plant areas. Table 1 lists these sampling methods. For statistical analyses, samples below

detectable limits were assigned a value of one-half of the minimum detectable concentration.

The inhalable dust and inhalable soy antigen air samples were the primary personal exposure indices for this survey. We collected these full-shift TWA samples using the IOM Personal Sampler (SKC, Inc., Eighty Four, PA) containing polytetrafluoroethylene (PTFE) membrane filters with a 2-micrometer pore size and a sampling flow rate of 2.0 liters per minute (lpm). These samples were analyzed gravimetrically according to the NIOSH Manual of Analytical Methods (NMAM) 500 [NIOSH 1994] and by enzyme-linked immunosorbent assay (ELISA) for soy protein antigen concentration. Protein extracts from bulk pre-processed soy flakes served as a reference standard for the ELISA. Details on these laboratory methods are presented in Appendix A.

Medical Survey

NIOSH investigators conducted a medical survey July 23–August 2, 2007. We invited all current workers at the plant to give written informed consent for a 15-minute interviewer-administered questionnaire, lung function testing, and allergy testing. Following the survey, we mailed reports to each participant at his or her home address. The reports explained individual lung function and allergy testing results and provided recommendations for follow-up of abnormalities.

The questionnaire (Appendix B) consisted of questions from the European Community Respiratory Health Survey (ECRHS) [Grassi et al. 2003] and the American Thoracic Society (ATS) adult respiratory questionnaire (ATS-DLD-78) [Ferris 1978], supplemented by questions specific to the survey at the Solae plant. It addressed respiratory and dermatological symptoms, asthma and other diagnoses, smoking history, workplace exposures to mold, occupational history at the soy plant, and demographic information.

Lung function testing consisted of spirometry, followed by bronchodilator (BD) or methacholine challenge testing (MCT). A NIOSH technician administered spirometry tests using a dry rolling-seal spirometer interfaced to a personal computer following ATS guidelines [Miller et al. 2005]. We compared spirometry results to reference values generated from third National Health and Nutrition Examination Survey (NHANES III) data

[Hankinson et al. 1999]. Each participating worker's largest forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) were selected for analysis. We classified participants as having airways obstruction if they had a ratio of FEV_1/FVC below the lower limit of normal with a normal FVC. FEV_1 determined the severity of airways obstruction, which ranged from borderline (FEV_1 above the lower limit of normal but below the predicted value) to very severe (FEV_1 <35% of predicted). We defined restriction as a normal FEV_1/FVC ratio with FVC below the lower limit of normal. We classified participants with both FEV_1/FVC ratio and FVC below the lower limit of normal as having mixed obstructive and restrictive abnormalities.

If the participant's FEV_1 was less than 1.5 L or 70% of predicted, BD was administered to determine reversibility, using two puffs of a beta-agonist. We defined reversibility as an FEV_1 increase of at least 12% and 200 ml after bronchodilator administration [Pellegrino et al. 2005]. If the participant's FEV_1 was greater than or equal to 1.5 L or 70% of predicted, MCT was used to examine bronchial hyperresponsiveness (BHR). Although not specific for asthma, people with current asthma symptoms often have BHR [ATS 2000]. ATS guidelines for administering MCT [ATS 2000] were followed to determine the provocative concentration (PC) of methacholine that causes an interpolated 20% decline in FEV_1 from baseline (i.e., the PC_{20}). We classified participants as having BHR if they had a PC20 of 16.0 mg/ml or less. Severity of BHR ranged from borderline (PC_{20} of 4.1 to 16.0 mg/ml) to definite (PC_{20} of ≤ 4.0 mg/ml) [ATS 2000].

We conducted tests of the immune system reflecting allergy (IgE antibody) and exposure (IgG antibody). Allergy testing consisted of skin prick testing and measurement of total and specific IgE levels in blood. For skin prick testing, we applied to the skin the following commercially available extracts using the Greer*Pick*™ system (Greer Laboratories, Lenoir, NC, USA): soy, birch mix, cat hair, cockroach mix, eastern 10 tree mix, house dust mite mix (*Dermatophagoides farinae* and *D. pteronyssinus*), ragweed mix, and 9 southern grass mix. We included birch mix to address possible immunological cross-reactivity between soy and birch antigens [Mittag et al. 2004]. The panel of extracts included a negative control (the diluent) and a positive control (histamine). For each extract, we determined the mean diameter of the wheal reaction (average of length and width) at 15 minutes. We defined a positive response as a mean diameter at least 3 mm larger than the negative

control and at least 25% of the size of the positive control.

For IgE and IgG levels, we collected 20 ml of venous blood from each participating worker. We analyzed blood samples for total IgE by fluoroenzymeimmunoassay (FEIA) using an ImmunoCAP® 100 (Phadia AB, Uppsala, Sweden). Total IgE was considered to be elevated when the titer exceeded 100 kU/L. Specific IgE levels were measured using ImmunoCAP for soy (f14), peanut (f13), and storage mite (d71) (Phadia AB, Uppsala, Sweden). Specific IgE was considered positive when titers exceeded 0.35 kU/L. Peanut was included to address possible immunological cross-reactivity between soy and peanut antigens [Ballmer-Weber and Vieth 2008]. Storage mite was included as storage mites can be found in grain products and have been associated with asthma [van Hage-Hamsten and Johansson 1998]. Peanut and storage mite were not included in skin prick testing due to risk of anaphylaxis (peanut) and lack of commercially available extract (storage mite). Specific IgG levels were measured using ImmunoCAP for soy (Gf14).

Using these same methods, we determined levels of specific IgE and IgG for soy in de-identified sera from a population of 50 healthcare workers not occupationally exposed to soy [Zeiss et al. 2003].

We used IgE inhibition assays to determine the relative soy allergen content of bulk samples of pre-processed soy flakes and soy powder found in the autopackaging sub-areas. In addition, to characterize antigens and allergens in terms of molecular weight and to compare patterns of reactivity to soy proteins among various bulk soy samples, we performed IgG and IgE immunoblot analyses.

Details on these laboratory methods are presented in Appendix A.

Statistical Methods

We used the lung function tests and the questionnaire responses to define health conditions which included airways obstruction (including those with mixed abnormalities), BHR, current asthma, post-hire asthma, asthma-like symptoms, work-related asthma-like symptoms, work-related sinusitis, work-related nasal allergies, work-related rash, and work-related cough. We defined current asthma as physician-diagnosed asthma that was still present. We defined post-hire asthma as physician-diagnosed asthma that was diagnosed after the date of hire at the soy plant or that recurred after the date

of hire at the soy plant, following at least one year without asthma. We defined asthma-like symptoms as at least one of the following: wheezing or whistling in the chest in the past 12 months; waking up with a feeling of tightness in the chest in the past 12 months; an attack of asthma in the past 12 months; or currently taking any medicine for asthma [Grassi et al. 2003]. Work-related health conditions were those reported to improve away from work.

We investigated what might explain participants' health conditions (outcome variables) using the questionnaire responses, immune testing, and information from the industrial hygiene survey. We looked for associations between health conditions and the following explanatory variables: current work classification (see below); employment tenure at the plant; history of ever working at the plant as the employee of a contract company; having seen or smelled mold in the workplace in the past 12 months; positive response to individual allergens on skin testing; having changed jobs within the plant due to breathing difficulties; elevated total IgE; positive IgE to soy; positive IgE to storage mite; positive IgE to peanut; positive IgG to soy; age, race (black or another race); gender; smoking status (current, former, or never); and atopy (defined as history of nasal allergies and/or eczema). An alternative definition of atopy, using response to the panel of allergens on skin prick testing, was more weakly associated with asthma outcomes and was not used in final statistical models. We additionally examined the following explanatory variables: inhalable dust, inhalable soy antigen, and peak dust concentrations (see below).

We conducted industrial hygiene sampling on 20 jobs and report these results in the industrial hygiene section. To explore epidemiologic associations in this relatively small population, we combined these jobs into 12 broad job titles and three work classifications (Table 2). For example, the three unloading positions were combined to create one broad job title of "unloading." On the basis of our understanding of the process and jobs, we categorized current work classification as production, production support, or non-production. Production workers included autopack operators, autopack assistants, curd operators, feed dryer operators, production leads, and spray dryer operators. Production support workers included maintenance workers sanitation crew members, and unloading area workers. Non-production workers included laboratory technicians, office-based employees, and warehouse workers.

On the basis of current job and distribution tertiles of air sampling results grouped by the 12 broad job titles, we assigned participants to low, medium, and high exposure categories for inhalable dust, inhalable soy antigen, and peak dust concentrations (Table 2). For inhalable dust and for inhalable soy antigen, we based these classifications on geometric mean results; classifications were similar when based on arithmetic mean and maximum concentrations. For peak dust, we based these classifications on the highest peak concentrations determined by personal and area real-time sampling.

We used descriptive statistics to investigate the distribution of demographic and clinical variables. We calculated prevalence ratios (PR) of respiratory symptoms and diagnoses from comparisons with data obtained from the U.S. adult population from NHANES III [DHHS 1996] using indirect standardization for race (white or black), sex, age (17–39 years or 40-69 years), and cigarette smoking status (ever or never), and with more recent data for Tennessee from the Behavioral Risk Factor Surveillance System (BRFSS) [CDC 2007] using standardization for sex. We calculated the incidence density rate ratios for pre-hire asthma diagnosis at age 16 or older and for post-hire asthma diagnosis. We assessed the validity of self-reported asthma categories by comparing the results of spirometry and MCT for workers with and without each of the asthma outcomes using contingency tables. We calculated the PR of soy-specific IgE positivity from comparisons with the prevalence observed in a population of non-occupationally exposed healthcare workers [Zeiss et al. 2003]. Mean soy-specific IgG levels in participants and the population of healthcare workers were compared using Student's t-test. We used logistic regression to examine associations between the health outcomes and potential explanatory variables. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using the likelihood ratio test. Given the limited number of participants with a particular outcome, when more than one explanatory variable was associated with an outcome of interest, we used stratification and the Cochran-Mantel-Haenszel test to further examine associations.

We used linear regression to examine associations between FEV1 and potential explanatory variables, adjusted for age, race, gender, and height. We explored associations between measures of immune response to soy and estimates of exposure using logistic regression for the categorical variables and linear regression for the

continuous variables. IgG values were not normally distributed and were therefore log-transformed for inclusion in the models. We used contingency tables to examine immunological cross-reactivity against soy and birch and peanut antigens and to explore frequency distributions by exposure category. Analyses were done using SAS® software version 9.1 and JMP® versions 5.1 and 7.0 [SAS Institute Inc., Cary, NC].

INDUSTRIAL HYGIENE SURVEY

Inhalable Dust and Inhalable Soy Antigen Air Concentrations

Area sampling results Table 3 summarizes concentrations from area inhalable dust and inhalable soy antigen samples by plant area. The areas with the highest geometric mean (GM) concentrations of inhalable dust were from sanitation—the M34 spray dryer bottom (9.83 mg/m^3) and unloading (1.15 mg/m^3) sub-areas. The unloading area had the highest GM concentration of soy antigen (111,600 nanograms per cubic meter of air (ng/m^3), followed by sanitation—the M34 spray dryer bottom (6,225 ng/m^3). Table 4 summarizes concentrations from area inhalable dust and inhalable soy antigen samples by plant sub-area. The sub-areas with the highest GM concentrations of inhalable dust were the flake processing (27.1 mg/m^3), M34 spray dryer bottom (8.48 mg/m^3 during sanitation activities), track 5 garage (2.18 mg/m^3), and feed drying (1.83 mg/m^3) sub-areas. The feed drying and M34 spray dryer bottom sub-areas both had some individual inhalable dust concentrations that exceeded 10 mg/m^3. The sub-areas with the highest GM concentrations of soy antigen were the flake processing (308,000 ng/m^3), track 5 garage (256,100 ng/m^3), and curd (48,670 ng/m^3) sub-areas.

Figure 1 presents the inhalable dust and inhalable soy antigen sampling results from area samples by plant sub-area. Dusts from the track 1 and 5 garages and the curd sub-area had the highest soy antigen content as indicated in Table 4. Airborne dust from the warehouse, office, laboratory, and storeroom areas had the lowest soy antigen content (Table 3).

The overall Spearman correlation coefficient for the 70 paired inhalable dust and soy antigen area concentrations was 0.710 ($p<0.001$). While corresponding correlation coefficients for data from individual areas were not statistically significant, those for two sub-areas were statistically significant—autopackaging ($r=0.74$, $n=11$, $p<0.01$) and curd ($r=0.89$, $n=7$, $p<0.01$).

Personal sampling results Table 5 presents the mean personal exposures to inhalable dust and inhalable soy antigen samples by job category. The highest GM concentration of inhalable dust was measured among the workers involved in starch dumping (21.7 mg/m^3). This was typically a partial-shift activity and completed

by workers in several job categories outside their regular shift work, so it was treated as a separate personal exposure event. The autopack operators had the next highest GM inhalable dust exposure (1.60 mg/m^3). Jobs with GM concentrations of inhalable dust of about 1 mg/m^3 include unloading switch operator (0.996 mg/m^3), sanitation operator (0.971 mg/m^3), analytical laboratory worker (0.974 mg/m^3), autopack area lead (0.937 mg/m^3), and curd operator (0.806 mg/m^3). As with the area samples, the highest GM concentration of soy antigen was seen in the unloading area; the unloading switch operator job category had a soy antigen exposure of 27,540 ng/m^3. The curd operator had the next highest soy antigen exposure (25,960 ng/m^3), followed by the unloading lead (14,360 ng/m^3). The highest soy antigen concentrations were seen among job categories handling the raw de-hulled, de-oiled soy flakes prior to the processing operations. The analytical laboratory worker, plant lead, and sanitation operator had soy antigen exposures higher than most plant process workers except for curd operators.

Figure 2 presents the personal inhalable dust and inhalable soy antigen exposures by job category. Consistent with area sampling results, inhalable dusts from the curd and unloading operator personal samples had the highest soy antigen content as indicated in Table 5. The lowest soy antigen content was seen in the personal inhalable dust samples from workers involved in starch dumping; warehouse workers also had relatively low soy antigen content, as did microbiological laboratory and autopack workers.

The overall Spearman correlation coefficient for all 178 paired personal inhalable dust soy antigen concentrations was 0.35 ($p<0.001$). Among samples restricted to specific job categories, statistically significant correlation was seen for autopack operator ($r=0.55$, $n=19$, $p<0.05$), sanitation operator ($r=0.63$, $n=16$, $p<0.01$), unloading lead ($r=1.0$, $n=6$, $p<0.001$), unloading operator ($r=0.90$, $n=5$, $p<0.05$), autopack lead ($r=1.0$, $n=3$, $p<0.001$), analytical laboratory worker ($r=1.0$, $n=3$, $p<0.001$), and warehouse lead ($r=1.0$, $n=3$, $p<0.001$).

Individual sampled workers in several different jobs had personal inhalable dust concentrations exceeding the ACGIH TLV for inhalable particulates not otherwise specified (PNOS) of 10 mg/m^3 as a full-shift TWA. These included autopack operator (3 samples from the M32 and M33 areas), sanitation operator (2 samples), and unloading switch operator (1 sample). Five of these 6 samples

also exceeded the OSHA PEL for Particulates Not Otherwise Regulated (PNOR) of 15 mg/m^3 (total dust) as a full-shift TWA. Additionally, 5 of the 7 partial-shift personal samples from workers involved in starch dumping were high by comparison to this OSHA PEL. Workers involved in starch dumping used a respirator; however, this task was typically done as overtime, resulting in additional exposure beyond the worker's normal shift.

The GM inhalable dust concentrations by current work classification were: 0.77 mg/m^3 for production, 0.60 mg/m^3 for production support, and 0.29 mg/m^3 for non-production. The mean inhalable soy antigen concentrations by current work classification were: 2,782 ng/m^3 for production, 2,991 ng/m^3 for production support, and 235 ng/m^3 for non-production.

Real-time Measurement of Dust Concentrations

Table 6 provides a summary of real-time measurements of airborne dust, including TWA, minimum, and maximum concentrations, and the number of concentration peaks by concentration category. Forty-seven real-time area samples were collected; the highest peak dust concentration (44.2 mg/m^3) was measured July 9 in the M34 feed drying sub-area, where 10 other dust peaks also exceeded 10 mg/m^3. The M32 autopackaging sub-area had a peak dust concentration of 23.5 mg/m^3 and two other peaks that also exceeded 10 mg/m^3. M33 flake processing had a peak concentration of 12.1 mg/m^3 and three other dust peaks that also exceeded 10 mg/m^3. The track 5 garage had a peak concentration of 23.0 mg/m^3. Among sub-areas that had no real-time area sample peaks exceeding 10 mg/m^3, curd and M34 spray dryer bottom each had several peak dust concentrations exceeding 5 mg/m^3.

Table 6 also shows results from the 24 real-time personal dust measurements. The M34 feed dryer operator sampled on August 1 had the highest peak dust exposure at 22.8 mg/m^3 and seven other peaks that also exceeded 10 mg/m^3. (In contrast, the highest peak concentration for the M34 feed dryer operator sampled two days later was 7.37 mg/m^3 and the highest peak concentration for the M34 feed dryer operator sampled two days earlier was 1.37 mg/m^3). The M33 autopack assistant had a peak dust exposure of 17.7 mg/m^3 and four other peaks that also exceeded 10 mg/m^3. The M34 autopack assistant sampled on August 3 had a peak dust exposure of 15.7 mg/m^3 and one other peak that also exceeded 10 mg/m^3. The M34 starch dumping worker had a single peak dust exposure

exceeding 10 mg/m^3 (15.7 mg/m^3) and the M35 starch dumping worker had a peak concentration just below 10 mg/m^3.

From personal and area samples, job categories with exposure peaks exceeding 10 mg/m^3 during this survey were unloading, feed dryer, and autopack; sanitation operators had peak exposures equal to or exceeding 10 mg/m^3 measured during the walk-through survey (data not shown). Starch dumping also produced high peak dust concentrations approximating and exceeding 10 mg/m^3. The feed dryer operator, autopack assistant, and workers involved in starch dumping each had several peak dust concentrations exceeding 5 mg/m^3. Figure 3 provides a graphical display of these 24 personal samples.

Total Dust and Total Endotoxin Air Concentrations

Table 7 presents TWA total dust and total endotoxin concentrations from area samples by plant area. The highest total dust and endotoxin concentrations were measured in the M33 flake processing room (40.6 mg/m^3 total dust and 217 endotoxin units per cubic meter of air (EU/m^3)). From all other plant areas, total dust concentrations were less than 10 mg/m^3 and endotoxin concentrations were less than 50 EU/m^3.

Particle Size Distributions of Airborne Dust

Table 8 presents mass distributions of airborne dust for different plant areas and sub-areas as percentages of total airborne particulate in the respirable, thoracic, and inhalable fractions. Respirable refers to dusts that are small enough to deposit in the gas exchange (i.e., alveolar) regions of the lung. The sample collected from the M34 control room had the largest fraction of airborne dust in the respirable size range, approximately 57%. The two samples from the laboratory location averaged approximately 51% of airborne particulate in the respirable fraction. The curd sub-area and office areas had respirable fractions of 36% and 38% respectively. The averages of the two unloading area samples and the three M34 spray dryer bottom samples (the latter during sanitation activities) had the smallest fractions of airborne dust in the respirable range, approximately 6% and 2%, respectively. The thoracic fraction of an airborne particulate represents that portion that can deposit anywhere in the lung, including the alveolar region and lung airways.
Inhalable particulates are those that can be deposited in

any portion of the respiratory tract, including the nose and throat, as well as the lung. Those areas/sub-areas with a larger respirable fraction commonly also had a larger inhalable dust fraction including the M34 control room (approximately 87%), the laboratory areas (approximately 85%), the curd sub-areas (approximately 81%), and the office areas (approximately 80%).

Metal Concentrations in Air

Twelve of 67 area TWA air samples had quantifiable metal/element concentrations; these included calcium, magnesium, manganese, phosphorus, and potassium (data not shown). Magnesium and potassium were the most abundant. The highest concentration, 0.66 mg/m^3 magnesium, was measured in the M33 flake processing room. This room, the M34/M35 feed dryers, and the M32 autopackaging sub-area had the highest metal concentrations. Calcium (Ca) was present at quantifiable concentrations in 5 of 67 samples; the highest calcium concentration was 0.4 mg/m^3 in the M33 flake processing room.

MEDICAL SURVEY

Participation

Of the 281 workers employed at the plant by the Solae Company in July 2007, 147 (52%) consented to participate in the medical survey and completed the questionnaire. Although additional workers at the plant employed by contract companies were invited to participate, they declined to do so. Participation rates varied by work classification and ranged from 70% in production to 37% in non-production (Table 9). Most of the 147 participants had spirometry (n=140; 95%), BD or MCT (n=109; 74%), skin prick testing (n=132; 90%), and blood IgE testing (n=135; 92%). Table 10 details demographic characteristics of the participants.

Questionnaire Responses

Table 11 details selected health information collected from participants by questionnaire. Twenty (14%) reported ever being diagnosed with asthma by a physician. Thirteen (9%) reported current asthma, 11 (7%) of whom met the definition of post-hire asthma. Fifty-four (37%) reported having had one or more of the asthma-like symptoms in the previous 12 months and 18 (12%) reported having work-related asthma-like symptoms in the previous

12 months. In addition, 31 (21%) reported work-related sinusitis in the previous 12 months, 12 (8%) reported work-related nasal allergies, 15 (10%) reported work-related rash in the previous 12 months, and 11 (8%) reported work-related cough.

A total of 36 participants (24%) indicated having health problems that they believed were related to working at Solae. Specific work-related health problems cited included skin problems, cough, sinus problems, asthma, and other respiratory problems. Six (4%) reported having changed jobs at the plant due to breathing difficulties. A total of 54 (37%) met the questionnaire criteria for atopy.

Fifty-seven (39%) participants reported seeing or smelling mold in the past 12 months. Mold was reported in spray dryer (M33 and M32 towers were specifically noted), feed dryer, curd, storage bin, and warehouse locations.

Comparison of Post-hire to Pre-hire Asthma Incidence Of the 10 participants who reported being diagnosed with current or former asthma after age 16, 8 (80%) were diagnosed after hire at Solae. The pre-hire incidence density rate was 0.8 cases per 1,000 person-years of observation and the post-hire incidence density rate was 4.9 cases per 1,000 person-years of observation. The post-hire to pre-hire incidence density rate ratio was 6.0 (95% CI: 1.4, 41.1).

Comparison to National and State Prevalence As shown in Table 12, the overall prevalences of respiratory symptoms and diagnoses, including wheeze, sinusitis, and physician-diagnosed asthma, were significantly higher among participating workers than expected from NHANES III data. The overall prevalences of ever and current physician-diagnosed asthma among participating workers were both about twice what would be expected based on national survey data, though only the former was statically significant. When stratified by sex, prevalences of both ever and current physician-diagnosed asthma were both higher than expected for each sex, though the findings were only significant for males. The overall prevalences of ever and current physician-diagnosed asthma among participating workers were not significantly different than what would be expected based on a BRFSS survey of the Tennessee adult population. When stratified by sex, the prevalences of ever and current physician-diagnosed asthma were elevated only in males, but even these did not reach statistical significance.

Pulmonary Function Testing

Results of lung function testing are shown in Table 13. Of the 140 participants who participated in spirometry testing, 136 (97%) had interpretable results. Fourteen (10%) had results indicating airways obstruction without restriction (6 borderline, 8 mild or greater severity); 11 (8%) had results indicating a restrictive impairment without obstruction; and one (1%) had results indicating a mixed pattern of obstruction and restriction. Among the seven participants who had BD testing, four had interpretable BD results; two (one with airways obstruction and the other with a low FEV_1) showed reversibility. Among the 102 participants who had MCT testing, all had interpretable results; 12 had BHR (8 borderline, 4 definite), including eight (8%) without airways obstruction. In total, objective evidence indicating FEV_1 reversibility or BHR was found in 14 participants (13%).

Asthma outcomes, as defined by questionnaire responses, were associated with obstruction and BHR determined by pulmonary function tests. Participants reporting current asthma were more likely to have spirometry indicating airways obstruction than those not reporting current asthma ($p<0.001$). Participants reporting asthma-like symptoms were more likely to have spirometry indicating airways obstruction than those not reporting these symptoms ($p<0.05$). Participants reporting post-hire onset asthma were more likely to have BHR on MCT ($p<0.01$) than those without post-hire onset asthma. Participants reporting work-related asthma-like symptoms were more likely to have BHR ($p<0.01$) compared to those without work-related asthma-like symptoms.

Immunological Testing

Table 14 details the results of immunological skin testing. Fifty-seven (43%) of the 132 participants who underwent skin prick testing had one or more positive responses to the tested allergens. Nine (7%) had a positive response to soybean.

All 135 participants who underwent blood testing had detectable IgG to soy (mean concentration = 97.9 mg/L, range: 0.5–2,100). Among the 50 comparison healthcare workers not known to be occupationally exposed to soy, 27 (54%) had detectable IgG to soy (mean concentration = 1.47 mg/L, range: 0.01–10). The mean detectable concentration of IgG to soy was significantly higher among the Solae workers ($p<0.001$).

Among the Solae workers, we observed a significant association between soy-specific IgG level and inhalable soy antigen. Workers in the high soy antigen exposure group had higher mean concentration of IgG to soy than those in both the medium ($p<0.05$) and low ($p<0.001$) soy antigen exposure groups. Similarly, workers in the medium soy antigen exposure group had higher IgG to soy than those in the low soy antigen exposure group ($p<0.05$). Similar trends were observed for work classification. Production workers had higher mean concentration of IgG to soy than those in both the medium ($p<0.001$) and low ($p<0.001$) soy antigen exposure groups.

Table 15 presents the IgE results. Fifty-five (41%) had total IgE levels that were elevated. Soy-specific IgE positivity was found in 28 (21%) of participants, including five (56%) of the nine participants with a positive skin test response to soy. Among the 50 comparison healthcare workers not known to be occupationally exposed to soy, two (4%) were positive for soy-specific IgE. The prevalence of soy-specific IgE positivity was significantly higher among Solae workers than among the comparison population (PR=5.2, 95% CI: 1.3, 21).

Among those positive for soy-specific IgE, the odds of having positive peanut-specific IgE were 22 times greater than among those without soy-specific IgE positivity (OR=22.1, 95% CI: 7.85, 69.1). Participants with positive soy-specific IgE results were also more likely to have a positive SPT response to soybean (OR=5.94, 95% CI: 1.45, 25.9); eastern 10 tree mix (OR=5.62, 95% CI: 1.93, 16.7); and 9 southern grass mix (OR=3.21, 95% CI: 1.30, 8.05).

We found no significant positive associations between measures of immune response to soy (skin prick or IgE) and inhalable soy antigen concentration or work classification. Specifically, the prevalence of soy-specific IgE positivity did not vary significantly by work classification: production (20%), production support (24%); and non-production (18%). However, among non-production workers, the prevalence of positive IgE to soy ranged from 0% for warehouse workers to 29% for laboratory workers.

Risk Factors for Asthma Outcomes

Table 16 details results of univariate analyses relating to asthma and asthma-like symptoms. Compared to other participants, participants positive for soy-specific IgE were significantly more

likely to report current asthma, post-hire asthma, asthma-like symptoms, or work-related asthma-like symptoms (ORs = 3.66, 4.43, 3.18, and 5.86, respectively). Compared to participants not reporting atopy, participants reporting atopy were more likely to report post-hire asthma and asthma-like symptoms (ORs = 5.22 and 2.78, respectively). When stratified by atopy, soy-specific IgE positivity remained significantly ($p<0.05$) associated with post-hire asthma and asthma-like symptoms. Participants with a positive skin prick response to birch mix were significantly more likely to report current asthma than participants with a negative skin prick response to birch mix (OR=8.29). When stratified by response to birch mix, the association between soy-specific IgE positivity and current asthma remained significant ($p=0.05$).

Work-related asthma-like symptoms were associated with increasing category of peak dust exposure. Compared to those in the low-exposure category, work-related asthma-like symptoms were more likely to be reported by participants in the high- and medium-exposure categories (OR = 9.37 and 6.96, respectively). Work-related asthma-like symptoms were also associated with current work classification; participants in production were more likely than non-production workers to report work-related asthma-like symptoms (OR=9.11). Within non-production, the prevalence of work-related asthma-like symptoms was 0% for warehouse workers and for office workers. When stratified by soy-specific IgE positivity, the association of work-related asthma-like symptoms with current work classification remained significant ($p<0.05$). No other explanatory variables, including smoking status, inhalable dust concentrations, or soy antigen concentrations, were associated with asthma or asthma-like symptoms.

When examined by categorical level of exposure to inhalable soy antigen, the prevalence of soy-specific IgE positivity was lowest for workers in the high soy antigen exposure group ($p<0.01$). A similar trend was seen for work-related asthma-like symptoms but the association was not statistically significant (Figure 4).

Risk Factors for Other Health Outcomes

Table 17 details results of univariate analyses relating to other health outcomes. Participants who reported atopy were significantly more likely to report sinus problems than those not reporting this condition (OR=4.17). Compared to workers who reported no workplace mold exposure, participants who reported

having seen or smelled mold in the workplace in the previous 12 months were significantly more likely to report sinus problems, nasal allergies, or skin problems (ORs = 2.68, 2.15, and 3.79, respectively). Participants who had ever worked in production were significantly more likely to report cough than those who had never worked in production (OR=4.18). Cough was also significantly associated with category of exposure to inhalable soy antigen: the odds of workers with medium exposure to report cough were more than tripled compared to those with low exposure (OR=3.13). Nasal allergies were inversely associated with concentration of inhalable soy antigen; participants with medium soy antigen exposure were significantly less likely to report nasal allergies than those with low soy antigen exposure (OR=0.34). Finally, compared to other participants, those with a positive skin test response to grass were significantly more likely to report nasal allergies (OR=5.40). None of the other potential explanatory variables were significantly associated with these other health outcomes.

Table 18 details results of univariate analyses relating to other work-related health outcomes. When analyses were limited to work-related outcomes, workplace mold exposure remained significantly associated with sinus problems (OR=5.66), nasal allergies (OR=3.51), and skin problems (OR=3.62). Production support workers were significantly more likely to report work-related nasal allergies than non-production workers (OR=7.45). Tenure at Solae was inversely associated with work-related skin problems: participants with the longest tenure at the plant were significantly less likely to report work-related rash compared to those with the shortest tenure at the plant (OR=0.12). Participants in the high exposure category for peak dust concentration were significantly more likely to report work-related rash than those in the low exposure category (OR=5.29). Even after stratifying by workplace mold exposure, this association remained significant ($p<0.05$). With the exception of skin response to birch extract, none of the other potential explanatory variables were significantly associated with these other work-related outcomes.

Not shown in any of the preceding tables, participants who reported having changed jobs at Solae due to breathing problems were more likely to have positive IgE to soy (OR=17.7, 95% CI: 2.48, 354).

Risk Factors for Pulmonary Function Testing Outcomes

Participants exposed to high peak concentrations of dust were significantly more likely to have spirometry indicating airways obstruction than participants exposed to low peak concentrations (OR=8.49, 95% CI: 1.41, 163). Even after stratifying by current asthma diagnosis, this association remained significant ($p<0.05$). A similar trend was observed for participants in the medium exposure category, but this association did not reach statistical significance (OR=4.90, 95% CI: 0.79, 94.5). Participants who had ever worked in production were also significantly more likely to have spirometry indicating airways obstruction compared to those who had never worked in production (OR=7.60, 95% CI: 1.44, 140). Participants who had a positive skin test to cat hair allergen were significantly more likely to have spirometry indicating airways obstruction compared to those with a negative test result for this allergen (OR=5.62, 95% CI: 1.06, 25.0). None of the other potential explanatory variables were significantly associated with pulmonary function outcomes. (Estimates for the preceding associations between airways obstruction on spirometry and various risk factors were comparable when analyses defined airways obstruction to exclude borderline obstruction.)

Analyses of Soy Protein and Immune Reactivity

The total protein contents of the pre-processed soy flakes and the processed soy powder collected in the autopackaging sub-area were similar, varying by only 12%. Using sera pooled from 13 Solae workers positive for soy-specific IgE, soy allergen inhibition assays demonstrated that the level of soy allergen was higher in the pre-processed soy flakes than in the soy powder on a per mass basis. The soy powders averaged 56% reduction in IgE reactivity (Table 19).

As shown in Figure 5, soy protein analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) showed generally similar protein profiles for all four extracts; additional subtle high-molecular-weight bands were evident on the original stained gels. The Western blot analysis clearly showed that the three soy powder extracts had additional high-molecular weight antigens not seen in the soy flakes extract (Figure 5).

Sera of 16 workers with positive ImmunoCAP to soy were tested in IgE immunoblots. There was no unique pattern of IgE reactivity.

Rather, immunoblot analyses demonstrated reaction to multiple soy proteins of various molecular weights that differed among the 16 workers' sera. The most commonly reactive proteins were a doublet at a molecular weight of about 75 kDa and a protein band at about 30 kDa. Preliminary sequence analysis indicates these proteins to be the soy storage proteins (proteins that store the seed's energy) beta conglycinin (75 kDa) and glycinin (30 kDa).

Our analysis of the genetically-modified soy powder confirmed the presence of 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) from Agrobacterium sp. strain CP4 (also referred to as CP4-EPSPS) in the genetically-modified soy powder but not the unmodified soy powder. Additionally, we did not find IgE or IgG antibodies to the CP4-EPSPS in any of the workers' sera that were tested.

Compared to a nationally representative sample of the U.S. adult population [DHHS 1996], we found that workers who participated in the NIOSH survey at the Solae plant in Memphis had significantly higher than expected prevalences of physician-diagnosed asthma, wheeze (a symptom of asthma), and sinusitis. The prevalences of current and ever physician-diagnosed asthma among surveyed Solae workers were more similar to corresponding rates for the state of Tennessee, but the Tennessee rates can be questioned because they are from a telephone survey with a response rate of only 30-50% [CDC 2007]. Elevated rates of respiratory problems among workers at the Solae plant do not, by themselves, necessarily indicate a workplace cause, as respiratory problems can be provoked by other shared exposures that are independent of work, such as outdoor allergens or local air pollution. However, the associations we observed between health outcomes and workplace factors do point to an occupational cause as discussed in more detail below.

We found evidence that asthma and asthma-like symptoms among Solae workers were related to workplace exposures at the plant. Most participating Solae workers with adult-onset, physician-diagnosed asthma had been diagnosed after hire. The asthma incidence rate was six times higher after employment at the Solae plant than before employment at the Solae plant, suggesting that risk of developing adult-onset asthma after coming to work at Solae was six times higher than it had been prior to employment at the plant. In other words, some exposure during employment at Solae likely caused asthma. While these data only represent the experience of participating workers, they indicate a temporal relationship between occupational exposures and asthma diagnosis, which is necessary (but not sufficient) evidence for establishing a causal relationship.

Compared to workers in non-production jobs, workers in production and production support jobs were significantly more likely to report work-related asthma-like symptoms. Moreover, Solae workers exposed to high or medium peak dust concentrations were more likely to report work-related asthma-like symptoms than workers exposed to low peak concentrations. We also found that obstruction on spirometry and BHR on MCT were significantly associated with asthma outcomes defined by questionnaire responses, supporting our use of questionnaire responses to identify respiratory health outcomes. Such use of questionnaire responses is common [Toren et al. 1993; Braun-

Fahrländer et al. 1997].

The prevalence of soy-specific IgE positivity among Solae workers was five times greater than the prevalence among a group of comparison workers who did not work at a soy plant, and the mean level of soy-specific IgG was significantly higher among Solae workers than among the comparison workers. These immunological results indicate specific immune recognition of soy among Solae workers, resulting from their occupational exposures. In fact, all Solae workers had detectable IgG to soy compared to just half of the control population, and soy-specific IgE positivity was present in 21% of Solae workers compared to only 4% of the comparison workers.

Among the participating Solae workers, all asthma outcomes were significantly associated with allergy to soy, as measured by soy-specific IgE. Workers with positive IgE to soy on blood testing were more likely to have current asthma, post-hire asthma, asthma-like symptoms, and work-related asthma-like symptoms. Atopy, an allergic condition that can predispose to asthma, was also associated with asthma outcomes among participating Solae workers, but these associations between asthma outcomes and positive IgE to soy were observed not only among workers with atopy (as defined by questionnaire responses), but also among workers without atopy. There was a strong association between soy-specific IgE and peanut-specific IgE, a finding consistent with previously published documentation of soy and peanut cross-reactivity [Kleine-Tebbe et al. 2002; Mittag et al. 2004]. However, we found that asthma symptoms among the participating Solae workers were not associated with immune reactivity to peanut allergens, indicating that the association we found between asthma symptoms and soy reactivity was not confounded by immunological cross-reactivity to peanut. While current asthma was associated with skin response to birch, the association between asthma and soy-specific IgE remained significant even when this was taken into account.

Associations between respiratory symptoms and occupational exposures to soy have been reported by others [Zuskin et al. 1991; Roodt and Rees 1995]. However, unlike our evaluation at the Solae plant, neither of these previous studies of soy mill workers demonstrated an association between symptoms and soy-specific immunity. A study of bakers that did find such an association also implicated other allergens [Baur et al. 1998], limiting conclusions

about the role of soy allergy. In contrast, results of our evaluation at the Solae plant strongly support a specific role of immunity to soy in work-related asthma.

Pre-processed soy flakes were used as the reference standard to determine soy antigen exposure. Western blot analysis of the soy powder and pre-processed soy flakes did not detect additional protein antigen bands unique to the soy powder. Thus, the use of the pre-processed soy flakes as a reference standard in the determination of inhalable soy antigen concentrations appears to allow for an accurate characterization of exposures to soy antigen. Moreover, the soy allergen inhibition assays demonstrated that the soy allergen level was higher in the pre-processed soy flakes than the soy powder, further strengthening the use of the pre-processed soy flakes as the reference standard.

Workers at the Solae plant in Memphis are exposed to airborne dusts containing soy antigen from the processing of de-hulled, flaked soybeans. We found that these soy antigens are high-molecular-weight antigens, as contrasted to the lower-molecular-weight soy antigens reported in the asthma outbreaks that occurred in Barcelona, where whole soybeans including soybean hulls were handled [Gomez-Olles et al. 2007]. The low-molecular-weight soy antigen concentrations in community air samples from Barcelona on days when soybeans were unloaded (temporally consistent with the concurrent community asthma outbreak) ranged from 10 to 10,590 ng/m^3, with a GM of 324 ng/m^3 [Antó et al. 1989; Antó et al. 1993]. At Solae, using higher-molecular-weight soy antigen from processed soy flakes, concentrations measured in the personal inhalable dust samples were higher, ranging from below detectable levels (less than approximately 10 ng/m^3) to 3,500,000 ng/m^3. These were occupational measures, as contrasted to the community measures reported from Spain. Installation of filtration devices on the Barcelona soybean silos reduced the GM concentrations of soy antigen from 324 to 25 ng/m^3 and reports of asthma among the exposed community were also reduced.

There has been only limited assessment of occupational exposures to soy dust and antigen at soybean processing plants. Results ranging from 50 to 2,580 ng/m^3 in three South African soybean processing plants were measured using a polyclonal antibody-based immunoassay specific for soy trypsin inhibitor as a measure of soy protein [Spies et al. 2008]. At the Solae plant, job categories with the highest exposures to soy antigen (all exceeding 3,000

ng/m^3) included curd operators, production leads, all unloading job categories, and sanitation operators. Many workers start employment in sanitation, and therefore receive high and possibly more sensitizing exposures to dust and soy antigen early in their tenure at the plant. Due to the infrequent use of respirators by workers at the Solae plant, it seems reasonable to think that past respirator use would have done little to substantially attenuate these exposures.

The immunoblot analysis demonstrated that individual participants with soy-specific IgE reacted in different ways to multiple different soy antigens, most commonly to two known soy storage proteins. These two antigens were in the higher-molecular-weight range, suggesting that soy allergy among Solae participants is distinct from that of allergy to low-molecular-weight hull antigens observed in community epidemics of asthma in Spain [Gonzalez et al. 1994; Codina et al. 1997]. This finding is consistent with the fact that soy beans are de-hulled before processing at Solae, which would be expected to result in very limited, if any, exposure to hull antigens at the plant. Because exposures to soy antigens differ between environmental and occupational exposures and little is known about immune responses and adverse health effects among workers exposed to soy flakes, more study is warranted of workers exposed to soy flakes. Different workers responded immunologically to different soy proteins, which may account for variations in clinical symptoms, diagnoses, and exposure-response relationships. Differing immunological responses might affect the interpretation of standard allergy tests in the clinical setting, as these tests may not contain all of the implicated proteins [Herian et al. 1992]. Notably, we found no evidence of detectable immune reactivity to the additional protein (CP4- EPSPS) in the genetically modified soy powder, consistent with previously published findings [Kim et al. 2006].

The commercial availability of a test for IgE to soy raises the possibility of routine monitoring of soy-exposed workers for immune response to soy. However, the scientific basis for monitoring of immune response among soy workers is still being developed, and at this time it is not clear how information gained from such monitoring could be used to reduce risk. While blood test results aggregated by plant work areas or locations might prove useful for indicating where additional exposure controls may be warranted, taking any action based solely on an individual worker's immune response is not supported by our findings. While we

found significant associations between asthma outcomes and positive IgE to soy, many workers with positive IgE to soy did not have physician-diagnosed current asthma (23 of 28, or 82%) or asthma-like symptoms (11 of 28, or 39%). Determining whether those workers are at higher risk for development of asthma with continued soy exposure would require a prospective study. In the absence of such data, relying on the immune response to soy alone to make decisions about job assignments of individual workers could unfairly discriminate against some workers. It is also important to note that we found that some workers who reported work-related asthma-like symptoms did not have positive IgE to soy and that production work was associated with increased prevalence, independent of immune response to soy. Thus, relying on the immune response to soy alone to determine whether an individual worker's asthma symptoms are related to workplace exposures would fail to identify some cases of possible work-related asthma among workers at the Solae plant.

We also found evidence that health outcomes other than asthma had an occupational component, distinct from the risk factors identified for asthma. Workers who reported seeing or smelling mold in the workplace were more likely to report work-related sinusitis or sinus problems, nasal allergies, and rash or skin problems. Rash and skin problems have been reported in persons exposed to mold and respiratory symptoms are known to be associated with exposure to mold [IOM 2004]. However, it is important to note these symptoms are not specific to mold exposure. It is possible that workers who had seen or smelled mold were exposed to other agents that may have caused these symptoms.

We found associations between airborne dust exposure and other symptoms among Solae workers. Participants exposed to high peak dust concentrations were more likely to report work-related rash than those with low peak concentrations. Additionally, the odds of reporting cough among participants who had ever worked in production were four-fold the corresponding odds among those who had never worked in production.

At the Solae plant, worker exposures to inhalable dust varied by job category, with GM exposures ranging from 0.15 mg/m^3 (warehouse lead) to 1.60 mg/m^3 (autopack operator). Workers involved in the periodic, partial-shift task of starch dumping had a higher GM inhalable dust exposure of 21.7 mg/m^3. Excluding starch dumping, these TWA inhalable dust exposures are in a

range consistent with those reported from other plants processing whole soybeans [NIOSH 1987; Spies et al. 2008]. Workers in the high-exposure category for TWA inhalable dust exposure included curd, sanitation operators, and autopack operators and assistants. Based on full-shift personal sampling results, some workers in these job categories had exposures exceeding the OSHA PEL of 15 mg/m^3 for PNOR as total dust (5 samples) and/or the ACGIH TLV of 10 mg/m^3 for inhalable PNOS (6 samples) [29 CFR 1910.1000 (1977); ACGIH 2008]. This finding of excessive dust exposure is consistent with sampling results from other soybean processing plants [NIOSH 1987; Spies et al. 2008]. Of note, these PNOR and PNOS values are designed for application to particulates that have low toxicity and they are not designed to protect workers from immune sensitization or asthma. The Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (Federal Republic of Germany) recommends a lower general threshold limit value of 4 mg/m^3 for inhalable dust [DFG 2008]. The ACGIH has a lower TLV for grain dusts of 4 mg/m^3 based on critical effects of irritation, bronchitis, and pulmonary function effects; however, as currently worded, that TLV is explicitly intended only for oat, wheat, and barley grains. ACGIH has an even lower TLV for inhalable flour dust of 0.5 mg/m^3 based not only on irritation and lung function effects, but also on asthma [ACGIH 2008].

While limiting TWA exposures is an important way to prevent occupational respiratory diseases, high short-term (peak) concentrations may also be a risk factor, especially for respiratory disease including asthma. In fact, we found that Solae workers exposed to high or medium peak dust concentrations were more likely to have airways obstruction and to report work-related asthma-like symptoms than workers exposed to low peak concentrations. Studies of workers exposed to diisocyanate have found associations between peak exposures and respiratory effects including asthma [Klees and Ott 2000; Leroyer et al. 1998]. At Solae, job categories with the highest peak dust concentrations (i.e., with peak concentrations exceeding 10 mg/m^3) were generally those job categories with the highest TWA exposures and workers in office and warehouse jobs had the lowest exposures in terms of peak dust and TWA inhalable dust concentrations, consistent with recent findings from a study of bakery workers [Meijster et al. 2008]. Despite this association, we found that peak concentrations were a better predictor than mean concentrations of airways obstruction among Solae workers. Based in part on

this finding, peak exposures should be considered in addition to the more traditional mean concentrations when assessing risk and intervening to prevent adverse health effects among workers at the Solae plant.

Most health outcomes observed among Solae workers were not significantly associated with inhalable soy antigen concentration or inhalable dust concentration. Moreover, we found that workers exposed to higher concentrations of inhalable soy antigen were no more likely to have positive IgE to soy than workers exposed to lower concentrations. One explanation for this observation may be that sensitization and symptoms are provoked by relatively low concentrations of inhalable soy antigen. The fact that none of the participating warehouse or office workers, who had some of the lowest soy antigen and dust exposures, had work-related asthma-like symptoms, suggests that there is a threshold for symptoms that exceeds their exposures.

While we examined multiple estimates of exposure, including averages and peaks, we did not assess cumulative exposures in our analyses (due to the challenges of missing data and variations in job titles and exposures over time). However, when we examined job tenure, a surrogate for cumulative exposure, we found that it was not associated with respiratory outcomes. IgG level, which is thought to be determined by degree of exposure, was associated with our estimates of soy exposure and supported our methods. The fact that IgG level (in contrast to IgE level) was not associated with health outcomes emphasizes the contribution of factors beyond exposure (e.g., individual susceptibility) to disease manifestation.

The lack of an observed association between soy-specific IgE and exposure may reflect a healthy worker effect [Li and Sung 1999]. The healthy worker effect occurs when workers who develop work-related symptoms or disease transfer within a plant from a particular work area or leave a plant entirely. Workers remaining behind in that particular work area or plant are generally less susceptible and may appear healthier than the general population or workers in other work areas of the plant. Given that positive IgE to soy was associated with asthma and asthma-like symptoms, workers with positive IgE to soy may tend to avoid exposure to higher inhalable soy antigen concentrations through attrition (leaving employment) or transfer within the plant to plant locations with lower inhalable soy antigen concentrations. Indeed,

the fact that only 7% of the surveyed workers with positive IgE to soy were in the high-exposure category for inhalable soy antigen (which constituted about 27% of all participants) is consistent with a healthy worker effect. Investigations of wheat allergy among bakery workers have found lower prevalences of health outcomes among higher exposure groups in cross-sectional studies, but not in longitudinal studies, which are less prone to the healthy worker effect [Jacobs et al. 2008]. Further evidence for a possible healthy worker effect in the Solae plant is the inverse relationship we observed job tenure and work-related rash. This observation that workers with many years of Solae employment are less likely to report rash may be the result of workers tending to leave employment if they develop work-related rash.

Endotoxin, a component of the cell wall of Gram-negative bacteria, has been linked to asthma, including occupational asthma, and other chronic respiratory effects [Bardana 2008; Wang et al. 2005]. There are no OSHA, ACGIH, or NIOSH exposure standards or guidelines specific for endotoxin. However, several exposure limits have been proposed based on research from various occupational settings. Based largely on a study of the effect on lung function of cotton dust exposures [Castellan et al. 1987], an endotoxin exposure limit of 50 EU/m^3 (inhalable dust) has been proposed in Europe [Heederik and Douwes 1997]. The endotoxin measurements from the Solae plant were done on total dust samples rather than inhalable dust samples, but most were well below this guideline and, in fact, less than 10 EU/m^3. It is of note that endotoxin-related respiratory effects are still possible for workers exposed to endotoxin at concentrations below the guideline cited above, particularly given evidence that exposure to endotoxin can increase the response to allergens among sensitized workers [Bardana 2008].

Some workers reported concerns about exposure to lime, which is used as an additive at this soy plant. Lime, a known mucous membrane, skin, and respiratory irritant, is a chemical compound of calcium bound with oxygen (CaO). Based on TWA air samples for calcium, we did not detect elevated concentrations of airborne lime in this workplace, though higher short-term, task specific exposures for some job tasks may have occurred.

One limitation of our evaluation at the Solae plant was that exposure measurements were limited to a two-week period during the summer and these measures may not have been representative

of year-round exposures due to effects of season, production schedules, or work practices. Ventilation practices may be different during winter operating conditions, or production schedules may vary due to differences in seasonal demand; any such differences may have influenced our measured and assigned exposure levels. Also, while we focused on airborne exposures in our analyses, it is possible that other routes of exposure may determine or contribute to sensitization to soy. For instance, ingestion or dermal exposures may be relevant for some work-related lung diseases [Redlich and Herrick 2008], but were not included in our evaluation. Additionally, we emphasized recent symptoms and current job and thus may have failed to identify important contributing factors that occurred previously.

As with any observational study of current workers, any symptomatic workers who left employment prior to our survey would not have been included our study. Also, symptomatic and asymptomatic current workers could have differentially participated. The low overall participation rate (52%) and the non-participation of temporary or contract workers (individuals often assigned to jobs, such as sanitation, with higher dust exposures) support this possibility. However, when current work classification was considered, participation was relatively high among production workers (70%), who would be expected to be at greatest risk of work-related respiratory illness. Moreover, while the 147 Solae workers who participated constitute the largest known group of soy workers to be evaluated for respiratory illness [NIOSH 1987; Zuskin et al. 1991; Roodt and Rees 1995], the small number of workers in sub-groups, such as particular job or diagnostic categories, may have precluded some analyses and limited our ability to find more evidence that adverse health outcomes among Solae workers are attributable to work exposures.

Conclusions

In summary, we found that respiratory symptoms and diagnoses were common among Solae workers who participated in our medical survey; that most participants with adult-onset physician-diagnosed asthma were diagnosed after hire at Solae; and that adult incidence rate of adult-onset asthma was greater after hire at the Solae plant than before hire. Immune response to soy antigens, as measured by soy-specific IgG and IgE, was greater for participants than for a comparison group of workers not occupationally exposed to soy. Asthma outcomes were significantly associated with levels of soy-specific IgE in workers' blood, and work-related asthma-like symptoms and airways obstruction on spirometry were associated with peak dust concentrations. Asthma outcomes were not associated with current measures of inhalable soy antigen concentration or inhalable dust concentration, possibly due to a low exposure threshold for sensitization or symptoms and/or a healthy worker effect. Participants with soy-specific IgE reacted to a variety of soy antigens, most commonly higher-molecular-weight antigens distinct from the low-molecular-weight antigens seen in community epidemic asthma related to soy hull antigens. Work-related sinusitis, nasal allergies, and rash were significantly associated with self-reported workplace exposure to mold. Overall, evidence from this HHE indicates that workplace conditions contributed to respiratory problems among workers at Solae.

RECOMMENDATIONS

Based on our findings, we recommend the actions listed below to create a more healthful work place at the Solae plant. We encourage Solae management to use these recommendations to develop an action plan based, if possible, on the "hierarchy of controls" approach. This approach groups actions by their likely effectiveness in reducing or removing hazards. In most cases, the preferred approach is to eliminate hazardous materials and install engineering controls to reduce exposure or shield employees. Until such controls are in place, or if they are not effective or feasible, administrative measures and/or personal protective equipment may be needed.

1) Engineering controls:

- Consider opportunities for additional engineering controls to reduce worker exposures to dusts in various plant locations:

    - Autopackaging: Because personal dust exposures in these rooms were among the highest at the plant, consider additional ventilation and enclosure controls in autopackaging.

    - Laboratory: Perform all laboratory tests involving the handling of soy product/dusts under a laboratory exhaust hood. Bulk samples retrieved from various plant locations for laboratory testing should be stored in a hood or in a way to minimize the potential for dust from these samples to become airborne in the laboratory.

    - Starch Dumping: Because starch dumping produced some of the highest dust concentrations, this activity should be controlled with additional ventilation and enclosures (following our survey, Solae management reported that such control systems had been added). Additional dust sampling is recommended to evaluate worker exposures with these new systems in operation.

    - Unloading Garages: Consider installation of enclosures with local exhaust ventilation systems in the soy unloading areas.

- Flake Processing Rooms: Consider the addition of enclosure and ventilation controls.

- All Plant Areas: Consider additional engineering controls to ensure that soy dusts and other process effluents are contained at the source and not disseminated to other plant locations such as office areas. Specifically, consider the use of flexible-duct exhaust ventilation systems positioned to reduce worker exposures during the collection of bulk samples from various plant process locations.

- Consider engaging an experienced industrial ventilation engineer in the design and installation of the above-recommended engineering controls.

2) Respiratory protection:

Include all workers with respiratory exposures to soy dusts (such as workers in the sanitation, unloading, maintenance, laboratory, and plant production departments) in the plant's respiratory protection program.

- Enforce the use of respiratory protection in plant locations or jobs identified as having higher dust concentrations (such as flake processing, starch dumping, storage bin, feed and spray dryers, unloading garages, and autopackaging); enforce the use of respiratory protection in jobs identified as having higher dust exposure (such as autopack operators, unloading operators, curd operators, sanitation operators, and starch dumping).
- Temporary and contract workers, including sanitation operators, who work in plant areas with higher dust concentrations need to be included in the respiratory protection program. The Tennessee Occupational Safety and Health Division (TOSHA) requires that, in the absence of a formal contract between the job-site employer and contract company addressing respiratory protection, it is the responsibility of the job-site employer to assure that all workers on site are properly trained and instructed on the use of respiratory protection and included in the job site employer's respiratory protection program (personal

communication, TOSHA).

- Sanitation operators with potential exposures to microbial growth, such as mold reported in various plant locations, should be included in the respiratory protection program and instructed on the proper use of PPE, as use of PPE has been shown to reduce respiratory symptoms in mold-exposed individuals [Cummings et al. 2008].
- The minimum level of protection for soy, starch, or lime dusts should be a N95 filtering-facepiece respirator. Half- and full-facepiece respirators with N99 filters may provide a more consistent seal and hence a higher level of protection.
- A formal respiratory protection program that adheres to the requirements of the OSHA Respiratory Protection Standard (29 CFR 1910.134) is required. The program administrator for the program must have adequate training and experience to run it and regularly evaluate its effectiveness. The respiratory protection program must include a written policy, change schedule for respirator cartridges, pre-use medical evaluation, pre-use and annual fit-testing and training, and the establishment and implementation of procedures for proper respirator use (such as prohibiting use with facial hair, ensuring user seal check and inspection of respirators prior to each use, and ensuring proper storage of respirators to protect respirators from damage, contamination, dust, sunlight, and extreme temperatures). Details on the Respiratory Protection Standard are available on the OSHA website (www.osha.gov/SLTC/respiratoryprotection/index.html) and on the TOSHA website (www.tennessee.gov/labor-wfd/tosha.html). Guidance at these sites should be followed to ensure that Solae's respiratory protection program is consistent with OSHA requirements.

- Workers with work-related asthma should be provided with the option of using respiratory protection. (The use of respiratory protection may be useful. Previous studies of other allergens have demonstrated that filtering facepiece respirators and powered air purifying respirators (PAPRs) reduce allergen load by 90% or more [Renstrom et al. 2002; Renstrom et al. 2006]; PAPRs with a protection factor of 1000 (i.e., tight-fitting full-face PAPRs) would be expected to be even more protective). If respiratory protection is not effective, or not medically advised, workers diagnosed with work-related asthma should be relocated away from

further exposure to the provocative agent. While our air sampling found detectable concentrations of soy antigen in all work areas at Solae, the office and warehouse areas had some of the lowest measurements, and workers in these areas did not report work-related asthma-like symptoms. These observations suggest that individual workers affected by asthma and soy allergy in other areas may benefit from relocation to the warehouse or office areas. However, individuals with allergic asthma may continue to react to very small amounts of substances to which they are allergic. Thus, an individualized approach may be required, depending upon medical findings, serial evaluations of effectiveness of respiratory protection, and recommendations of the affected worker's physician.

3) Medical surveillance:

Given the concerns noted in the Discussion section about monitoring soy-specific IgE among workers, we recommend an emphasis on symptom reporting.

- Workers should report any new or worsening respiratory symptoms to their supervisor and personal physician or other healthcare provider.
- Workers with symptoms should provide their personal physician or other healthcare provider with a copy of the Highlights section of this HHE report.
- If workers are tested for allergy to soy, we recommend the use of the blood test instead of, or in addition to, the skin test, given the observed associations between asthma outcomes and positive IgE to soy (but not between asthma outcomes and skin test response to soy). However, given that IgE testing did not identify all Solae participants with work-related asthma outcomes, allergy testing should be used as an adjunct to other diagnostic modalities, and not as a means of ruling out work-related asthma in workers who are occupationally exposed to soy.

4) Work practices:

Use the following best work practices to minimize worker exposure to dust, soy antigen, and mold, whenever possible:

- Clean spills of soy materials promptly to minimize fugitive dust emissions. Where possible, use a vacuum with a high-

efficiency particulate air (HEPA) filter, instead of shoveling, brushing, or sweeping, to clean spills. Wear respirators and eye and skin protection when cleaning up spills. (See respiratory protection recommendation above and eye and skin protection recommendation below).

- Clean areas of visible microbial growth, including mold. Place special emphasis on locations where workers reported visible mold growth or mold odors, including the spray drying towers (the M33 and M32 towers were specifically noted), the storage bins, and curd, warehouse, and feed dryer sub-areas. Guidelines for cleaning mold-damaged materials can be found at the following website: (http://www.nyc.gov/html/doh/html/epi/moldrpt1.shtml).
- Train employees on how to properly use exhaust hoods currently in place and any that are installed in the future.

5) Eye and skin protection:

- Provide workers with eye protection and protective clothing and gloves to limit contact with soy dusts/additives during production and clean-up activities. If safety goggles or glasses are utilized for eye protection, they should be either unvented or indirectly vented.
- Workers cleaning adhered soy dusts from the sides of silos should also use PPE, including gloves, protective clothing that covers exposed skin, head/hair cover, eye protection, and respiratory protection (as previously described above in the respiratory protection recommendation).

6) Administrative controls:

- Limit entry into high-dust exposure plant locations, such as flake processing and starch dumping, to essential workers. Minimize the time workers are required to spend in locations where dust is generated. Use signs to alert workers to high-dust locations and remind them to avoid these locations or use respiratory protection.

7) Other issues:

The following recommendation is based on observations made at the plant but not elsewhere addressed in this report.

- Evaluate the potential for heat stress among workers in plant production, production support, and sanitation jobs.

Special focus should be on workers who spend time around the spray and feed dryer locations during hot, humid days. Additionally, the use of respirators and other PPE can create additional demands on workers, increasing the potential for heat stress, and should be considered in the evaluation.

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Table 1. Industrial Hygiene Sampling Methods

Analyte	Media / Sampler	Flow Rate (lpm)	Analytical Methods
Airborne inhalable dust and inhalable soy antigen	Polytetrafluoroethylene (PTFE) membrane filters with a 2-micrometer pore size used in an IOM Personal Sampler (SKC).	2.0	Gravimetric analysis according to NIOSH Manual of Analytical Methods (NMAM) 500 [NIOSH 1994, ACGIH 2001]. Soy protein analysis by enzyme-linked immunosorbent assay (ELISA) using rabbit anti-soy protein (Sigma-Aldrich) [Gomez-Olles et al. 2007].
Airborne total and respirable soy antigen*	NIOSH BC Mark 7 2-stage sampler with a 37-mm PTFE filter in non-conductive cassette.	3.5	Soy protein analysis by ELISA using rabbit anti-soy protein (Sigma-Aldrich) [Gomez-Olles et al. 2007].
Airborne total dust and total endotoxins	37-mm polycarbonate (PC) filter in filter cassette (open-face).	2.0	Gravimetric analysis according to NMAM 500 [NIOSH 1994]. Endotoxin analysis according to kinetic Limulus assay [Milton et al. 1992].
Airborne total dust with analysis for calcium/metals	37-mm filter cassette (open face).	2.0	Gravimetric analyses according to NMAM 500 and NMAM 7300 [NIOSH 1994].
Airborne particle size distributions	Eight-stage cascade impactor with grease-coated Mylar® media for all stages and polyvinyl chloride (PVC) media for the back-up filter.	2.0	Gravimetric analysis by NMAM 500 [NIOSH 1994].
Real-time measurement of airborne dust	Photometric meter, DataRAM, models *p*DR-1000An/1200 (Thermo Electron Corporation, Franklin, MA). Some units were operated as active samplers and equipped with respirable cyclone, 37-mm PTFE filter in cassette (open-faced).	-- 4.0	Direct-reading instrument set for one-minute logging intervals [ACGIH 2001]. Active direct-reading instrument [ACGIH 2001].
Bulk soy samples for soy antigen	Sterile pyrogen-free polypropylene containers.		Soy protein analysis by ELISA using rabbit anti-soy protein (Sigma-Aldrich) [Gomez-Olles et al. 2007].
Temperature and relative humidity	Electronic psychrometer.		Direct-reading meter [ACGIH 2001].

* Samples taken for methods development efforts; results not presented in this HHE report.

Table 2. Exposure Categories for Inhalable Soy Antigen Concentration, Inhalable Dust Concentration, and Peak Dust Concentration by Work Classification and Broad Job Title

Work Classification	Broad Job Title	Exposure Categories*: Inhalable Soy Antigen	Exposure Categories*: Inhalable Dust	Exposure Categories*: Peak Dust
Production	Autopack operators	Medium	High	High
	Autopack assistants	Low	High	High
	Curd operators	High	High	Medium
	Feed dryer operators	Medium	Medium	High
	Production leads	High	Medium	Medium
	Spray dryer operators	Medium	Low	Medium
Production support	Maintenance workers	Low	Low	Medium
	Sanitation operators	High	High	High
	Unloading operators	High	Medium	High
Non-production	Laboratory technicians	Medium	Medium	Low
	Office staff	Low	Low	Low
	Warehouse workers	Low	Low	Low

*Soy Antigen categories: Low=24–804 ng/m^3; Medium=959–2,297 ng/m^3; High=2,634–25,957 ng/m^3.
Inhalable Dust categories: Low=0.17–0.54 mg/m^3; Medium 0.58–0.73 mg/m^3; High=0.75–1.6 mg/m^3.
Peak Dust categories: Low=no peak >1 mg/m^3; Medium=maximum peak ≥1mg/m^3 but <10 mg/m^3; High=maximum peak ≥10 mg/m^3.

Table 3. Means and Ranges for Area Inhalable Soy Antigen and Inhalable Dust Concentrations*, and Mean Soy Antigen Content of Inhalable Dust, by Plant Area

Area	N	Analyte	GM	GSD	Mean	SD	Minimum	Maximum	Soy Antigen Content of Inhalable Dust (ng/mg)
M32	6	**Soy Antigen**	**2,959**	**10.70**	**3,3270**	**75,680**	**163.4**	**187,700**	**18,400**
		Dust	0.822	4.79	2.03	2.99	0.092	7.97	
M33	14	**Soy Antigen**	**3,040**	**29.61**	**67,980**	**132,900**	**ND**	**408,600**	**53,900**
		Dust	0.398	11.0	3.89	8.07	0.015	27.1	
M34	16	**Soy Antigen**	**1,427**	**7.777**	**5,607**	**6,597**	**56.45**	**16,420**	**20,500**
		Dust	0.396	5.31	1.73	3.84	0.022	14.9	
M35	12	**Soy Antigen**	**1,674**	**31.45**	**53,230**	**107,100**	**ND**	**358,300**	**30,200**
		Dust	0.372	6.76	1.70	4.43	0.012	12.1	
M34 spray dryer bottom**	2	**Soy Antigen**	**6,225**	**1.344**	**6,361**	**1,855**	**5,050**	**7,673**	**633**
		Dust	9.83	1.28	9.98	2.46	8.24	11.7	
Unloading	3	**Soy Antigen**	**111,600**	**4.375**	**187,300**	**168,100**	**21,220**	**357,300**	**102,000**
		Dust	1.15	3.47	1.80	1.83	0.321	3.84	
Laboratory	2	**Soy Antigen**	**79.29**	**5.376**	**142.3**	**167.1**	**24.14**	**260.5**	**1,090**
		Dust	0.082	2.72	0.103	0.089	0.040	0.170	
Maintenance	2	**Soy Antigen**	**541.8**	**1.342**	**553.6**	**160.5**	**440.1**	**667.0**	**3,770**
		Dust	0.151	1.16	0.151	0.022	0.136	0.167	
Warehouse	2	**Soy Antigen**	**41.54**	**1.949**	**46.25**	**28.76**	**25.91**	**66.58**	**160**
		Dust	0.284	1.05	0.284	0.014	0.275	0.294	
Storeroom	1	**Soy Antigen**	**100.8**	**--**	**100.8**	**--**	**--**	**--**	**1,060**
		Dust	0.095	--	0.095	--	--	--	
Office	10	**Soy Antigen**	**20.54**	**3.057**	**44.89**	**79.70**	**ND**	**265.1**	**914**
		Dust	0.076	1.81	0.087	0.042	0.020	0.152	

*Concentrations in nanograms per cubic meter of air (ng/m^3) for inhalable soy antigen and milligrams per cubic meter of air (mg/m^3) for inhalable dust.
** Area measurements obtained during sanitation activities.
N – Number of samples; GM – geometric mean; GSD – geometric standard deviation; SD – standard deviation.
ND – below detectable limits for soy antigen in air, approximately 10 ng/m^3 depending on sample volume. Eight area samples were below detectable limits for soy antigen.

Table 4. Means and Ranges for Area Inhalable Soy Antigen and Inhalable Dust Concentrations*, and Mean Soy Antigen Content of Inhalable Dust, by Plant Sub-Area[1]

Sub-area	N	Analyte	GM	GSD	Mean	SD	Minimum	Maximum	Mean Soy Antigen Content of Inhalable Dust (ng/mg)
Track 1 Garage	1	**Soy Antigen**	**21,220**	--	**21,220**	--	--	--	**66,100**
		Dust	0.321	--	0.321	--	--	--	
Track 5 Garage	2	**Soy Antigen**	**256,100**	**1.602**	**270,400**	**122,800**	**183,500**	**357,300**	**121,000**
		Dust	2.18	2.22	2.54	1.84	1.24	3.84	
Flake Processing	1	**Soy Antigen**	**308,000**	--	**308,000**	--	--	--	**11,300**
		Dust	27.1	--	27.1	--	--	--	
Control Room	8	**Soy Antigen**	**358.7**	**6.229**	**2,200**	**4,989**	**56.45**	**14,410**	**11,000**
		Dust	0.095	2.06	0.116	0.076	0.022	0.284	
Curd	7	**Soy Antigen**	**48,670**	**4.640**	**119,400**	**150,000**	**8,921**	**408,600**	**105,000**
		Dust	0.625	2.49	0.882	0.740	0.252	1.91	
Spray drying	9	**Soy Antigen**	**511.9**	**5.843**	**1,625**	**2,718**	**30.61**	**8,626**	**11,100**
		Dust	0.107	4.38	0.211	0.201	0.012	0.623	
M34 Spray dryer bottom	3	**Soy Antigen**	**5,882**	**1.260**	**5,992**	**1,459**	**5,050**	**7,673**	**700**
		Dust	8.48	1.36	8.76	2.74	6.31	11.7	
Feed drying	10	**Soy Antigen**	**23,420**	**4.629**	**68,700**	**112,300**	**2,231**	**358,300**	**53,100**
		Dust	1.83	7.42	5.73	6.46	0.088	16.7	
Autopackaging	11	**Soy Antigen**	**233.5**	**6.852**	**1,009**	**2,181**	**ND**	**7,486**	**721**
		Dust	0.500	5.01	1.36	2.28	0.022	7.97	
Autopackaging Warehouse	1	**Soy Antigen**	**143.8**	--	**143.8**	--	--	--	**1,200**
		Dust	0.120	--	0.120	--	--	--	
		=	=	=	=	=	=	=	
Laboratory, Analytical	1	**Soy Antigen**	**260.5**	--	**260.5**	--	--	--	**1,600**
		Dust	0.170	--	0.170	--	--	--	
Laboratory, Micro	1	**Soy Antigen**	**24.14**	--	**24.14**	--	--	--	**600**
		Dust	0.040	--	0.040	--	--	--	
Office, Front	2	**Soy Antigen**	**27.14**	**3.889**	**40.65**	**42.80**	**ND**	**70.91**	**1,050**
		Dust	0.092	1.55	0.096	0.041	0.067	0.125	
Office, Engineering	1	**Soy Antigen**	**ND**	--	**ND**	--	--	--	--
		Dust	0.057	--	0.057	--	--	--	
Office, Purchasing	1	**Soy Antigen**	**ND**	--	**ND**	--	--	--	--
		Dust	0.081	--	0.081	--	--	--	
Plant Office, South	3	**Soy Antigen**	**13.09**	**1.539**	**13.98**	**6.530**	**ND**	**21.52**	**288**
		Dust	0.054	2.37	0.066	0.042	0.020	0.103	
Plant Office, North	1	**Soy Antigen**	**265.1**	--	**265.1**	--	--	--	**1,750**
		Dust	0.152	--	0.152	--	--	--	
Office, Process Tech Trail	1	**Soy Antigen**	**30.38**	--	**30.38**	--	--	--	**564**
		Dust	0.054	--	0.054	--	--	--	
Office, Unloading	1	**Soy Antigen**	**ND**	--	**ND**	--	--	--	--
		Dust	0.139	--	0.139	--	--	--	

NOTE: Some sub-area designations used in this table do not correspond in a one-to-one relationship with area designations used in Table 3. A sub-area designation can encompass parts of several different designated areas.
*Concentrations in nanograms per cubic meter of air (ng/m^3) for inhalable soy antigen and milligrams per cubic meter of air (mg/m^3) for inhalable dust.
N – Number of samples; GM – geometric mean; GSD – geometric standard deviation; Mean – arithmetic mean; SD – standard deviation.
ND – below detectable limits for soy antigen in air, approximately 10 ng/m^3 depending on sample volume. Eight area samples were below detectable limits for soy antigen.

TABLES (CONTINUED)

Table 5. Means and Ranges for Personal Inhalable Soy Antigen and Inhalable Dust Concentrations*, and Mean Soy Antigen Content of Inhalable Dust, by Job Title

Job Title	N	Analyte	GM	GSD	Mean	STD	Minimum	Maximum	Mean Soy Antigen Content of Inhalable Dust (ng/mg)
Plant lead	9	**Soy Antigen**	**4,175**	**5.841**	**16,540**	**36,040**	**175.8**	**112,300**	**26,000**
		Dust	0.492	3.51	1.45	3.15	0.163	9.82	
Curd operator	20	**Soy Antigen**	**25,960**	**4.673**	**57,000**	**70,600**	**393.0**	**269,800**	**48,600**
		Dust	0.806	2.89	1.19	0.924	0.050	3.64	
Spray dryer operator	20	**Soy Antigen**	**1,853**	**2.780**	**3,073**	**3,675**	**242.1**	**14,590**	**6,120**
		Dust	0.539	2.12	0.771	1.01	0.167	4.82	
Feed dryer operator	13	**Soy Antigen**	**2,297**	**2.139**	**2,861**	**1,890**	**386.8**	**8,125**	**5,030**
		Dust	0.583	2.37	0.863	1.05	0.148	4.22	
Autopack area lead	3	**Soy Antigen**	**1,783**	**3.365**	**2,707**	**2,609**	**498.8**	**5,585**	**2,090**
		Dust	0.937	5.30	2.18	2.99	0.208	5.62	
Autopack operator	19	**Soy Antigen**	**959.0**	**2.767**	**1,657**	**1,965**	**185.8**	**6,095**	**930**
		Dust	1.60	3.64	4.45	9.15	0.261	39.0	
Autopack assistant	13	**Soy Antigen**	**804.4**	**2.214**	**1,078**	**970.4**	**180.0**	**3,934**	**1,510**
		Dust	0.745	1.89	0.891	0.536	0.303	1.75	
Sanitation lead	2	**Soy Antigen**	**835.7**	**7.096**	**1,775**	**2,214**	**209.1**	**3,340**	**4520**
		Dust	0.363	1.14	0.364	0.047	0.331	0.397	
Sanitation operator	16	**Soy Antigen**	**3042**	**25.65**	**378,100**	**1,035,000**	**ND**	**3,538,000**	**17,200**
		Dust	0.971	4.54	5.29	13.2	0.252	48.8	
Unloading lead	6	**Soy Antigen**	**14,360**	**4.384**	**27,800**	**28,640**	**1,178**	**66,720**	**38,600**
		Dust	0.478	1.91	0.565	0.342	0.204	1.07	
Unloading operator	5	**Soy Antigen**	**5,992**	**3.772**	**13,250**	**20,550**	**1,347**	**49,860**	**18,200**
		Dust	0.488	1.53	0.525	0.231	0.283	0.897	
Unloading switch operator	6	**Soy Antigen**	**27,540**	**4.834**	**102,600**	**205,200**	**6,268**	**520,400**	**32,100**
		Dust	0.996	5.21	5.10	11.2	0.373	28.0	
Office worker	9	**Soy Antigen**	**396.4**	**9.367**	**1,226**	**1,305**	**ND**	**3,932**	**8,290**
		Dust	0.171	1.33	0.178	0.052	0.111	0.275	
Warehouse lead	3	**Soy Antigen**	**15.71**	**2.263**	**19.98**	**17.63**	**ND**	**40.34**	**109**
		Dust	0.147	2.24	0.185	0.159	0.083	0.368	
Warehouseman	4	**Soy Antigen**	**33.64**	**2.683**	**45.86**	**35.75**	**ND**	**89.47**	**117**
		Dust	0.475	1.41	0.498	0.186	0.346	0.764	
Maintenance worker	12	**Soy Antigen**	**407.4**	**7.864**	**1,227**	**1,377**	**ND**	**4,323**	**5,110**
		Dust	0.331	1.52	0.359	0.149	0.175	0.656	
Lab (analytical) worker	3	**Soy Antigen**	**4,389**	**2.510**	**5,625**	**4,291**	**1,642**	**10,170**	**4,720**
		Dust	0.974	3.01	1.46	1.55	0.372	3.24	
Lab (microbiology) worker	4	**Soy Antigen**	**511.9**	**3.555**	**857.2**	**900.2**	**107.2**	**2,131**	**1,760**
		Dust	0.584	3.76	1.07	1.24	0.150	2.85	
Storeroom clerk	3	**Soy Antigen**	**186.4**	**3.730**	**280.6**	**213.9**	**41.06**	**452.4**	**1,700**
		Dust	0.170	1.41	0.177	0.064	0.132	0.251	
Starch dumping	7	**Soy Antigen**	**199.9**	**5.548**	**495.5**	**527.6**	**ND**	**1,315**	**46.1**
		Dust	21.7	3.04	31.9	23.3	3.00	60.2	
Other	1	**Soy Antigen**	**ND**	**--**	**ND**	**--**	**--**	**--**	--
		Dust	0.286	--	0.286	--	--	--	

* Concentrations in nanograms per cubic meter of air (ng/m^3) for inhalable soy antigen and milligrams per cubic meter of air (mg/m^3) for inhalable dust.
N – Number of samples; GM – geometric mean; GSD – geometric standard deviation; SD – standard deviation.
ND – below detectable limits for soy antigen in air, approximately 10 ng/m^3 depending on sample volume. Twelve personal samples were below detectable limits for soy antigen.

Table 6. Real-time Dust Concentrations and Number of Concentration Peaks by Sampling Area, and Sub-area or Job Title

Sub-area or Job Title	Area	Date	Concentration (mg/m^3) TWA	Concentration (mg/m^3) Min.*	Concentration (mg/m^3) Max.*	# Peaks > 1 mg/m^3	# Peaks > 5 mg/m^3	# Peaks > 10 mg/m^3
Area Samples								
Control room	M32	10-Jul	0.029	ND	0.308	0	0	0
	M33	09-Jul	0.070	0.037	0.127	0	0	0
Curd	M32	11-Jul	0.139	0.413	5.75	244	7	0
	M33	09-Jul	1.64	0.148	2.68	1682	0	0
	M34	09-Jul	0.155	0.025	0.520	0	0	0
		12-Jul	0.212	0.032	0.392	0	0	0
		13-Jul	0.664	0.345	0.882	0	0	0
	M35	11-Jul	0.546	0.406	0.731	0	0	0
Spray drying	M32	10-Jul	0.062	0.021	0.237	0	0	0
	M33	09-Jul	0.003	ND	0.008	0	0	0
		12-Jul	0.001	ND	0.057	0	0	0
	M34	10-Jul	0.354	0.324	1.07	1	0	0
	M35	09-Jul	0.007	ND	0.954	0	0	0
		11-Jul	0.398	0.335	3.08	4	0	0
Feed drying	M33	09-Jul	0.052	0.032	0.196	0	0	0
		12-Jul	0.328	0.075	0.774	0	0	0
		13-Jul	0.162	0.025	0.439	0	0	0
	M34	09-Jul	1.71	0.364	44.2	48	19	11
		11-Jul	0.063	0.022	0.280	0	0	0
	M35	10-Jul	0.061	0.025	0.336	0	0	0
		12-Jul	0.156	ND	0.442	0	0	0
		13-Jul	0.787	0.333	1.83	50	0	0
Autopackaging	M32	10-Jul	0.096	ND	0.780	0	0	0
		11-Jul	0.441	0.009	23.5	19	6	3
	M33	09-Jul	0.051	ND	0.230	0	0	0
		13-Jul	0.062	0.021	0.237	0	0	0
	M34	09-Jul	0.144	0.010	0.338	0	0	0
	M35	10-Jul	0.070	0.021	0.143	0	0	0
		12-Jul	0.095	0.048	0.417	0	0	0
Track 1 garage	Unloading	12-Jul	0.091	0.031	1.47	2	0	0
Track 5 garage	Unloading	10-Jul	0.201	ND	23.0	15	3	1
		13-Jul	0.019	0.008	0.048	0	0	0
Flake processing	M33	12-Jul	1.17	0.008	12.1	136	15	4
In-shop	Maintenance	11-Jul	0.069	0.042	0.360	0	0	0
		13-Jul	0.119	0.074	1.97	2	0	0
Analytical	Laboratory	10-Jul	0.019	0.001	0.061	0	0	0
Micro	Laboratory	12-Jul	0.000	ND	0.009	0	0	0
Office, engineering	Office	10-Jul	0.001	ND	0.014	0	0	0
Office, front	Office	13-Jul	0.005	ND	0.035	0	0	0
Plant office, North	Office	11-Jul	0.043	0.007	0.090	0	0	0
Office pro. tech trail	Office	12-Jul	0.332	0.324	0.349	0	0	0
Office, unloading	Office	10-Jul	0.015	0.003	0.080	0	0	0
Spray dryer bottom	M34	12-Jul	0.565	0.025	9.30	37	4	0
		13-Jul	0.084	0.023	2.11	2	0	0

Table 6 cont.

Warehouse	Main Warehouse	11-Jul	0.053	0.017	0.206	0	0	0
		13-Jul	0.030	ND	0.116	0	0	0
	M35	13-Jul	0.059	0.043	0.113	0	0	0
Personal Samples								
Curd operator	M34	31-Jul	0.180	0.014	2.28	4	0	0
		03-Aug	0.068	0.006	0.496	0	0	0
	M35	13-Jul	0.159	0.064	4.20	7	0	0
Spray dryer operator	M34	11-Jul	0.398	0.335	3.08	4	0	0
Feed dryer operator	M31	02-Aug	0.068	0.024	1.26	1	0	0
	M33	13-Jul	0.161	ND	3.82	13	0	0
	M34	30-Jul	0.114	0.053	1.37	1	0	0
		01-Aug	0.741	0.098	22.8	35	16	8
		03-Aug	0.381	0.019	7.37	19	2	0
Autopack operator	M33	12-Jul	0.216	0.058	4.27	4	0	0
	M34	30-Jul	0.397	ND	2.80	35	0	0
		31-Jul	0.180	0.014	2.28	4	0	0
		01-Aug	0.403	0.006	1.01	1	0	0
Autopack assistant	M33	30-Jul	0.680	0.007,	17.7	42	17	5
	M34	01-Aug	0.137	ND	0.780	0	0	0
		02-Aug	0.158	0.008	0.814	0	0	0
		03-Aug	0.523	0.025	15.8	19	4	2
	M35	12-Jul	0.095	0.048	0.471	0	0	0
Operator	Sanitation	11-Jul	0.275	0.005	3.75	22	0	0
		12-Jul	0.091	0.031	1.47	2	0	0
		13-Jul	0.084	0.023	2.11	2	0	0
Maintenance worker	Out of Shop	01-Aug	0.174	0.037	0.766	0	0	0
Starch dumping	M34	31-Jul	1.03	0.097	15.1	98	11	1
	M35	30-Jul	0.869	0.131	9.45	57	2	0

* Minimum and maximum values of all one-minute data logging intervals for each sample.
Abreviations: mg/m3 – milligrams per cubic meter of air; TWA – time-weighted average concentration; ND – Not detected.
- 09-Jul samples collected on 2nd shift samples; all other samples collected on 1st shift.
- The optical configuration for the real-time sampler responds to particles in the size range from 0.1 to 10 micrometers, roughly corresponding to standard gravimetric measures of respirable and thoracic dust fractions.

Table 7. Means and Ranges for Area Total Dust and Total Endotoxin Concentrations* by Plant Area

Area	N	Analyte	GM	GSD	Mean	SD	Minimum	Maximum
M32	6	**Endotoxin**	**1.11**	**4.00**	**2.48**	**3.58**	**0.261**	**9.55**
		Dust	0.264	4.55	0.575	0.643	0.046	1.39
M33	14	**Endotoxin**	**0.969**	**21.5**	**21.4**	**57.4**	**ND**	**217**
		Dust	0.281	6.54	3.27	10.7	0.045	40.6
M34	13	**Endotoxin**	**1.03**	**8.77**	**7.23**	**14.5**	**ND**	**49.5**
		Dust	0.251	4.12	0.788	1.62	0.049	5.93
M35	13	**Endotoxin**	**0.390**	**11.0**	**3.04**	**6.01**	**ND**	**21.0**
		Dust	0.200	5.75	0.981	2.08	0.030	7.12
M34 spray dryer bottom**	2	**Endotoxin**	**1.35**	**1.43**	**1.39**	**0.485**	**1.05**	**1.73**
		Dust	4.55	1.86	5.00	2.91	2.94	7.05
Unloading	3	**Endotoxin**	**1.31**	**3.66**	**2.13**	**2.23**	**0.348**	**4.64**
		Dust	0.326	7.01	0.960	1.40	0.054	2.57
Laboratory	2	**Endotoxin**	**0.259**	**8.49**	**0.616**	**0.790**	**0.057**	**1.17**
		Dust	0.031	1.66	0.033	0.016	0.022	0.045
Maintenance	2	**Endotoxin**	**0.549**	**1.38**	**0.564**	**0.180**	**0.436**	**0.691**
		Dust	0.066	2.01	0.074	0.048	0.040	0.108
Warehouse	2	**Endotoxin**	**0.506**	**1.37**	**0.519**	**0.162**	**0.404**	**0.633**
		Dust	0.060	1.03	0.060	0.002	0.059	0.062
Storeroom	1	**Endotoxin**	**0.632**	**--**	**0.632**	**--**	--	--
		Dust	0.037	--	0.037	--	--	--
Office	8	**Endotoxin**	**0.257**	**2.86**	**0.410**	**0.453**	**0.046**	**1.44**
		Dust	0.029	1.27	0.030	0.007	0.022	0.040

*Concentrations in endotoxin units per cubic meter of air (EU/m^3) for endotoxins and milligrams per cubic meter of air (mg/m^3) for total dust.
** Area measurements obtained during sanitation activities.
N – Number of samples; GM – geometric mean; GSD – geometric standard deviation; SD – standard deviation.
ND – below detectable limits for endotoxin in air, approximately 0.05 EU/m^3 depending on sample volume. Nine endotoxin samples were below detectable limits.

Table 8. Mass Distribution of Airborne Dust by Particle Size Fraction*

Area/Sub-Area/Job	Area/Sub-Area	Date	% Respirable	% Thoracic	% Inhalable
Curd	M33	9-Jul	41.74	69.06	84.29
	M34	10-Jul	32.69	50.61	78.74
		12-Jul	46.88	64.41	84.08
	M35	9-Jul	22.74	44.62	76.37
Curd Averages			36.0	57.2	80.9
Spray Dryer	M33	9-Jul	14.37	21.24	67.05
	M34	9-Jul	22.79	48.4	77.30
		10-Jul	26.89	48.03	77.51
	M35	11-Jul	41.74	57.03	80.73
Spray Dryer Averages			26.5	43.7	75.5
Feed Dryer	M33	9-Jul	16.40	26.44	69.85
		12-Jul	2.442	6.813	61.22
	M34	11-Jul	42.77	62.41	82.99
	M35	12-Jul	12.27	42.09	75.99
		13-Jul	23.23	55.10	78.52
Feed Dryer Averages			19.4	38.6	73.7
Autopackaging	M32	10-Jul	8.092	22.49	67.83
	M34	9-Jul	12.42	33.98	72.42
		11-Jul	25.55	46.45	77.47
		13-Jul	14.10	33.83	72.72
	M35	12-Jul	14.35	30.06	71.30
Autopackaging Averages			25.5	33.4	72.3
Unloading	Track 5 Garage	10-Jul	8.063	30.04	71.11
	Track 5 Garage	13-Jul	3.647	28.70	70.72
Unloading Averages			5.90	29.4	71.0
Laboratories	Analytical Lab	10-Jul	49.24	63.34	83.86
	Microbiological Lab	12-Jul	52.15	70.4	86.68
Laboratory Averages			50.7	66.9	***85.3***
Offices	North Office	11-Jul	37.02	50.79	78.62
	Unloading Office	10-Jul	38.83	54.88	80.56
Office Averages			37.9	52.8	79.6
Sanitation	M34 Spray Dryer Bottom	11-Jul	3.289	19.80	67.02
		12-Jul	1.549	15.51	65.63
		13-Jul	1.612	12.64	63.94
Sanitation Work Averages			2.15	16.0	65.5
Warehouses	Main Warehouse	11-Jul	25.86	47.58	77.08
		13-Jul	24.36	41.64	74.85
Warehouse Averages			25.1	44.6	76.0
Other	Maintenance, in-shop	11-Jul	31.20	48.71	77.83
	M34 Control Room	13-Jul	57.49	73.82	87.25

*expressed as percentages of total airborne dust mass

Table 9. Participation in Medical Survey by Current Work Classification

Work Classification	Employees at time of survey	Participants
	(N)	n (%)
Production Curd operator Spray dryer operator Feed dryer operator Autopack operator Autopack assistant Production leads	94	66 (70)
Production support Unloading operator Sanitation operator Maintenance operator	73	39 (53)
Non-production Warehouse worker Laboratory technician Office staff	114	42 (37)
Total	281	147 (52)

Table 10. Characteristics of Medical Survey Participants (n=147)

Variable	
Mean age, years (range)	45 (19, 66)
Mean tenure employed at Solae, years (range)	5 (<1, 32)
Mean number of jobs at Solae (range)	3 (1, 14)
Males (%)	118 (80)
Black, non-Hispanics (%)	99 (67)
White, non-Hispanics (%)	47 (32)
Current smokers (%)	33 (22)
Former smokers (%)	36 (24)

Table 11. Self-reported Symptoms and Diagnoses Among Medical Survey Participants (N=147)

Symptom or Diagnosis	Participants n (%)
Ever asthma (physician-diagnosed)	20 (14)
Current asthma (physician-diagnosed)	13 (9)
Post-hire asthma (physician-diagnosed)	11 (7)
Asthma-like symptoms in the past 12 months	54 (37)
Asthma-like symptoms in the past 12 months among those without physician-diagnosed asthma (N=127)	36 (28)
Work-related asthma-like symptoms in the past 12 months	18 (12)
Wheeze in the past 12 months	43 (29)
Wheeze without a cold in the past 12 months	23 (16)
Sinusitis in the past 12 months	88 (60)
Work-related sinusitis in the past 12 months	31 (21)
Nasal allergies	49 (33)
Work-related nasal allergies	12 (8)
Rash in the past 12 months	33 (22)
Work-related rash in the past 12 months	15 (10)
Cough	24 (16)
Work-related cough	11 (8)
Ever eczema (physician-diagnosed)	8 (5)

Table 12. Comparison of Respiratory Symptoms and Diagnoses among Medical Survey Participants to U.S. Adult Population (NHANES III) and Tennessee Adult Population (2007 BRFSS) Data.

Diagnosis or Symptom	Observed	Expected	Prevalence Ratio	95% CI
NHANES III				
•Ever asthma (physician-diagnosed)				
Male	16	8.63	**1.9***	**1.1, 3.0***
Female	4	2.43	1.6	0.6, 4.2
Overall	20	11.1	**1.8***	**1.2, 2.8***
•Current asthma (physician-diagnosed)				
Male	11	5.94	**1.9***	**1.0, 3.3***
Female	2	1.79	1.1	0.3, 4.1
Overall	13	7.73	1.7	1.0, 2.9
•Sinusitis in the past 12 months	88	44.1	**2.0***	**1.6, 2.5***
•Wheeze in the past 12 months	43	20.8	**2.1***	**1.5, 2.8***
•Wheeze without a cold in the past 12 months	23	14	**1.6***	**1.1, 2.5***
•Obstruction	15	13.3	1.1	0.6, 1.9
•Restriction	11	9.43	1.2	0.7, 2.1
BRFSS				
•Ever asthma (physician-diagnosed)				
Male	16	12.0	1.3	0.8, 2.2
Female	4	4.23	0.9	0.4, 2.4
Overall	20	16.3	1.2	0.8, 1.9
•Current asthma (physician-diagnosed)				
Male	11	7.55	1.5	0.8, 2.6
Female	2	3.13	0.6	0.2, 2.3
Overall	13	10.7	1.2	0.7, 2.1

* Asterisked/bolded prevalence ratios and confidence intervals indicate statistical significance.

Table 13. Pulmonary Function Test Results

Spirometry (N=136)	
Mean FEV_1 % predicted (range)	96 (48, 136)
Mean FVC % predicted (range)	99 (53, 135)
Mean FEV_1/FVC % (range)	78 (43, 96)
Obstruction (without restriction), n (%)	14 (10)*
Restriction (without obstruction), n (%)	11 (8)
Mixed obstruction and restriction, n (%)	1 (1)
Bronchodilator Response (N=4)	
FEV_1 reversibility, n %	2 (50)
Methacholine Challenge Testing (N=102)	
Bronchial hyperresponsiveness (BHR), n %	12 (12)**

*includes 6 participants with borderline obstruction
**includes 8 participants with borderline BHR

Table 14. Allergy Skin Test Results (N=132)

Variable	Positive*	
	n	(%)
Birch mix	9	(7)
Cat hair	11	(8)
Cockroach mix	14	(11)
House dust mite mix	22	(17)
9 southern grass mix	40	(30)
Ragweed mix	24	(18)
Soy	9	(7)
Eastern 10 tree mix	19	(14)
One or more positive results	57	(43)

*positive response defined as a mean wheal diameter at least 3 mm larger than the negative control and at least 25% of the positive control

Table 15. Total and Specific Allergy Blood Test Results (N=135)

Variable	Positive* n (%)
Total IgE	55 (41)
Peanut IgE	24 (18)
Soybean IgE	28 (21)
Storage mite IgE	14 (10)

* Total IgE considered positive when concentration exceeds 100 kU/L. Specific IgE considered positive when concentration exceeds 0.35 kU/L.

Table 16. Risk Factors for Asthma and Asthma-like Symptoms (N=147)

Factor **£**	Odds Ratios (95% CIs)+ Current Asthma Yes=13	Odds Ratios (95% CIs)+ Post-hire Asthma Yes=11	Odds Ratios (95% CIs)+ Asthma-like Symptoms Yes=54	Odds Ratios (95% CIs)+ Work-related asthma–like symptoms Yes=18
Positive IgE to soy				
Yes	**3.66 (1.00, 13.2)***	**4.43 (1.15, 17.2)***	**3.18 (1.36, 7.70)***	**5.86 (2.01, 17.6)***
No	1.0	1.0	1.0	1.0
Atopy				
Yes	3.06 (0.97, 10.6)	**5.22 (1.43, 24.7)***	**2.78 (1.39, 5.64)***	1.44 (0.52, 3.91)
No	1.0	1.0	1.0	1.0
Current work classification				
Production	0.45 (0.09, 2.16)	0.45 (0.09, 2.16)	0.76 (0.34, 1.72)	**9.11 (1.69, 169)***
Production support	1.73 (0.45, 7.25)	1.09 (0.24, 4.91)	1.26 (0.52, 3.07)	6.03 (0.91, 118)
Non-production	1.0	1.0	1.0	1.0
Peak dust exposure				
High	0.46 (0.06, 2.52)	0.23 (0.01, 1.61)	0.63 (0.25, 1.56)	**9.37 (1.61, 178)***
Medium	1.21 (0.34, 4.88)	1.02 (0.27, 4.21)	1.17 (0.53, 2.64)	**6.96 (1.23, 131)***
Low	1.0	1.0	1.0	1.0
Skin response to birch				
Yes	**8.29 (1.51, 39.5)***	5.57 (0.73, 30.0)	1.60 (0.38, 6.36)	2.22 (0.31, 10.4)
No	1.0	1.0	1.0	1.0

+ Unadjusted odds ratios and 95% likelihood confidence limits; reference category identified by odds ratio of 1.0.
* Asterisked/bolded odds ratios and confidence intervals indicate statistical significance.
- N may be less than 147 for some models due to missing data.
- **£** Race/ethnicity, gender, age, smoking status, soy IgG level, elevated total IgE, peanut IgE positivity, storage mite IgE positivity, positive skin response to other tested extracts (soybean, cat hair, cockroach mix, eastern 10 tree mix, house dust mite mix, ragweed mix, and 9 southern grass mix), mold exposure, Solae job tenure, history of ever working as a contractor, inhalable soy antigen level, and inhalable dust level were not significantly associated with asthma outcomes in univariate analysis.

Table 17. Risk Factors for Other Health Outcomes (N=147)

Factor £	Odds Ratios (95% CIs)+ Sinusitis or Sinus Problems Yes=88	Odds Ratios (95% CIs)+ Nasal Allergies Yes=49	Odds Ratios (95% CIs)+ Rash or Skin Problems Yes=33	Odds Ratios (95% CIs)+ Cough Yes=24
Self-reported atopy				
Yes	**4.17 (1.97, 9.42)***	**	1.88 (0.85, 4.15)	0.84 (0.32, 2.06)
No	1.0	1.0	1.0	1.0
Saw or smelled mold at work				
Yes	**2.68 (1.32, 5.62)***	**2.15 (1.07, 4.36)***	**3.79 (1.71, 8.76)***	0.76 (0.29, 1.86)
No	1.0	1.0	1.0	1.0
Ever production				
Yes	0.71 (0.34, 1.43)	0.53 (0.26, 1.09)	0.71 (0.32, 1.61)	**4.18 (1.35, 18.39)***
No	1.0	1.0	1.0	1.0
Inhalable soy antigen level				
High	1.40 (0.62, 3.29)	0.43 (0.17, 1.01)	1.34 (0.50, 3.56)	2.18 (0.67, 7.33)
Medium	0.99 (0.46, 2.17)	**0.34 (0.14, 0.79)***	1.58 (0.63, 3.96)	**3.13 (1.09, 9.80)***
Low	1.0	1.0	1.0	1.0
Grass skin allergy				
Yes	1.53 (0.71, 3.41)	**5.40 (2.45, 12.3)***	1.28 (0.54, 2.96)	2.14 (0.79, 5.67)
No	1.0	1.0	1.0	1.0

+ Unadjusted odds ratios and 95% likelihood confidence limits; reference category identified by odds ratio of 1.0.
* Asterisked/bolded odds ratios and confidence intervals indicate statistical significance.
** Not calculated: definition of self-reported atopy included nasal allergies.
- N may be less than 147 for some models due to missing data.
- **£** Race/ethnicity, gender, age, smoking status, soy IgG level, elevated total IgE, soy IgE positivity, peanut IgE positivity, storage mite IgE positivity, positive skin response to other tested extracts (soybean, birch mix, cat hair, cockroach mix, eastern 10 tree mix, house dust mite mix, and ragweed mix), Solae job tenure, history of ever working as a contractor, current work classification, peak dust exposure, and inhalable dust level were not significantly associated with other health outcomes in univariate analysis.

Table 18. Risk Factors for Other Work-Related Health Outcomes (N=147)

Factor ₤	Odds Ratios (95% CIs)+ Sinusitis or Sinus Problems Yes=31	Odds Ratios (95% CIs)+ Nasal Allergies Yes=12	Odds Ratios (95% CIs)+ Rash or Skin Problems Yes=15
Saw or smelled mold at work			
Yes	**5.66 (2.44, 14.1)***	**3.51 (1.05, 13.7)***	**3.62 (1.21, 12.2)***
No	1.0	1.0	1.0
Current work classification			
Production	2.18 (0.77, 7.17)	3.36 (0.52, 65.6)	2.76 (0.65, 18.9)
Production support	2.91 (0.94, 10.1)	**7.45 (1.19, 144)***	2.94 (0.59, 21.5)
Non-production	1.0	1.0	1.0
Solae tenure tertile (days)			
High (> 3,987)	0.80 (0.27, 2.31)	0.53 (0.10, 2.32)	**0.12 (0.01, 0.69)***
Medium (2,100 to 3,987)	1.51 (0.59, 4.04)	0.68 (0.16, 2.75)	0.87 (0.27, 2.74)
Low (< 2,100)	1.0	1.0	1.0
Peak dust exposure			
High	2.86 (0.95, 9.83)	1.08 (0.26, 4.01)	**5.29 (1.26, 36.3)***
Medium	2.16 (0.75, 7.17)	0.64 (0.09, 2.94)	1.38 (0.26, 10.3)
Low	1.0	1.0	1.0
Skin response to birch			
Yes	1.70 (0.34, 6.88)	**6.33 (1.19, 28.7)***	0.97 (0.05, 5.91)
No	1.0	1.0	1.0

+ Unadjusted odds ratio and 95% likelihood confidence limits; reference category identified by odds ratio of 1.0.
* Asterisked/bolded odds ratios and confidence intervals indicate statistical significance.
- N may be less than 147 for some models due to missing data.
- **₤** Race/ethnicity, gender, age, smoking status, soy IgG level, elevated total IgE, soy IgE positivity, peanut IgE positivity, storage mite IgE positivity, positive skin response to other tested extracts (soybean, cat hair, cockroach mix, eastern 10 tree mix, house dust mite mix, ragweed mix, and 9 southern grass mix), history of ever working as a contractor, inhalable soy antigen level, and inhalable dust level were not significantly associated with other work-related health outcomes in univariate analysis.

Table 19. IgE Inhibition Analysis of Allergen Content from Products at Solae

Sample	Allergen Concentration (Arbitrary units)	Allergen reduction (% of pre-processed flakes)
Pre-processed soy flakes	2600	--
Soy powder (M33)	1050	60%
Soy powder (M35)	1276	51%
Soy powder (M34)	1151	56%

Figure 1. Geometric Mean Inhalable Dust and Inhalable Soy Antigen Concentrations from Area Samples by Plant Sub-area

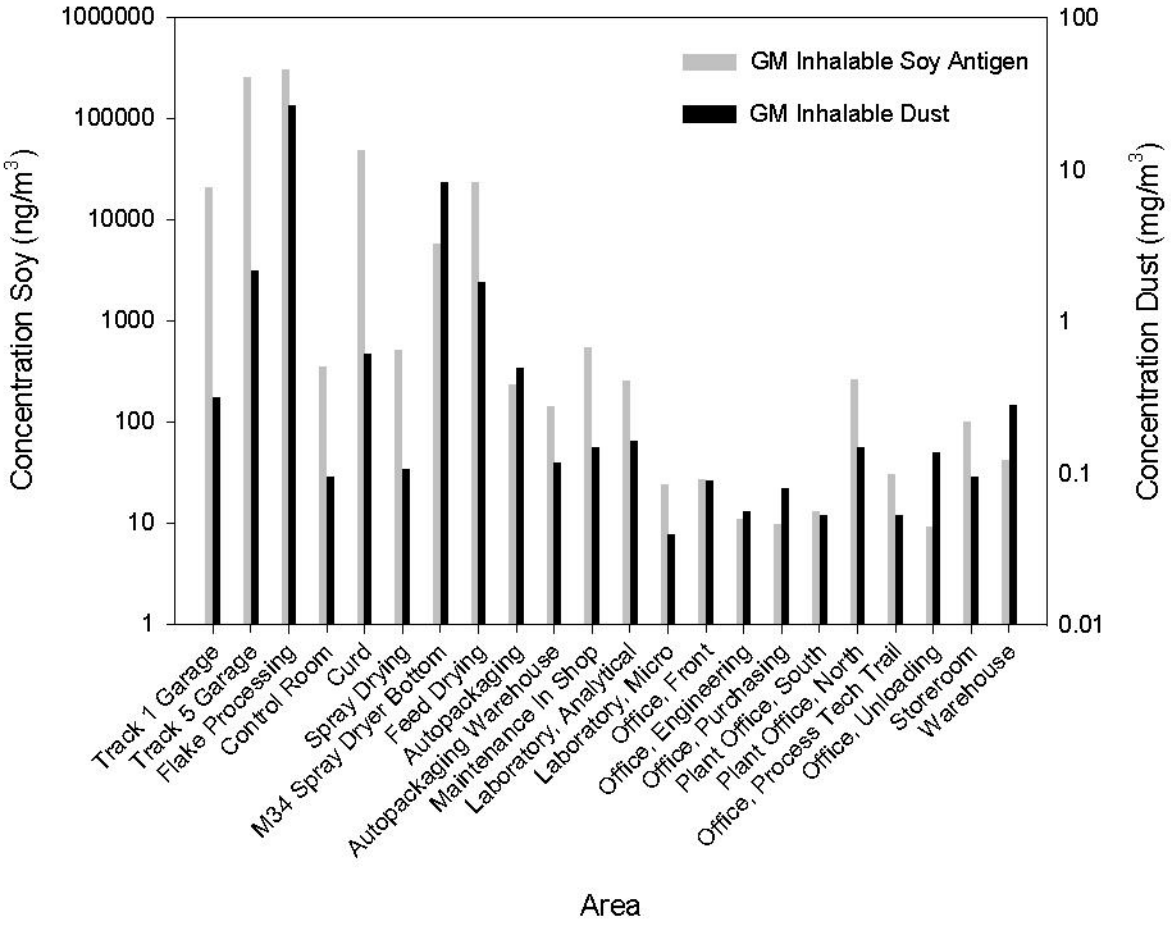


Figure 2. Geometric Mean Personal Inhalable Dust and Inhalable Soy Antigen Exposures by Job Title

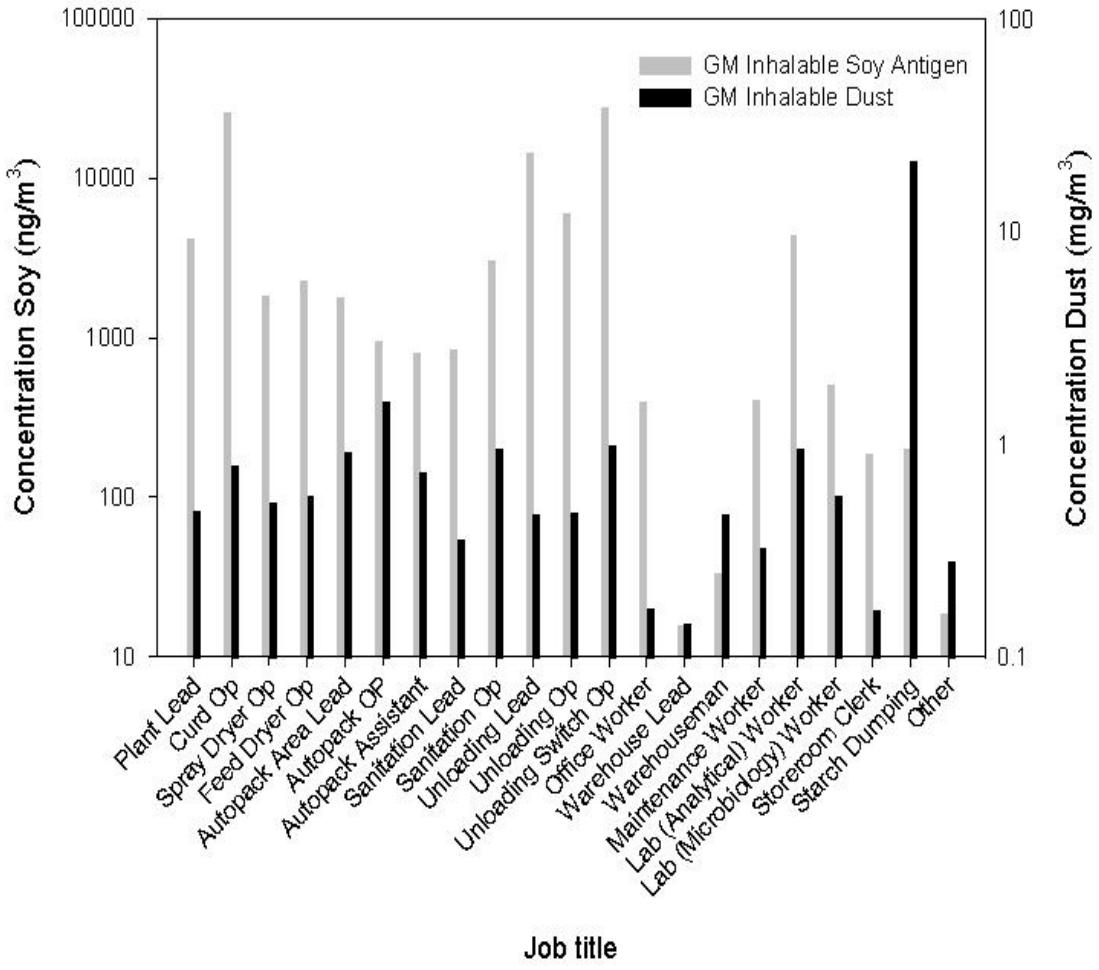
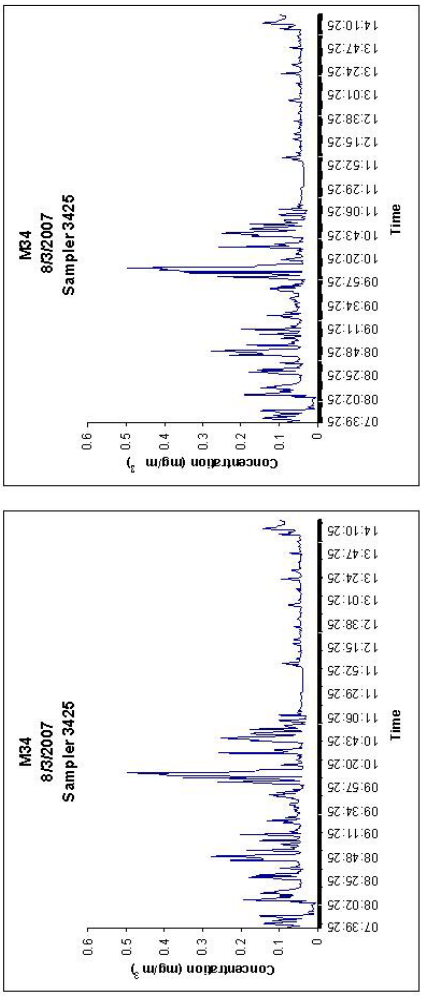
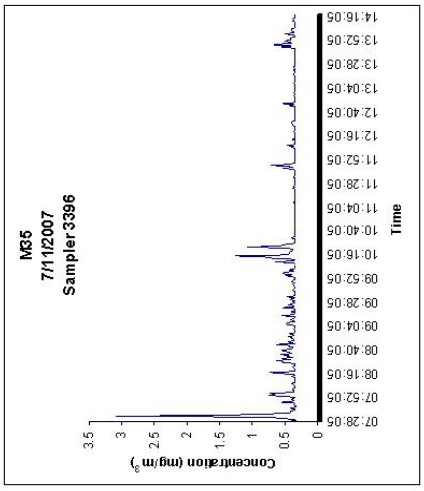


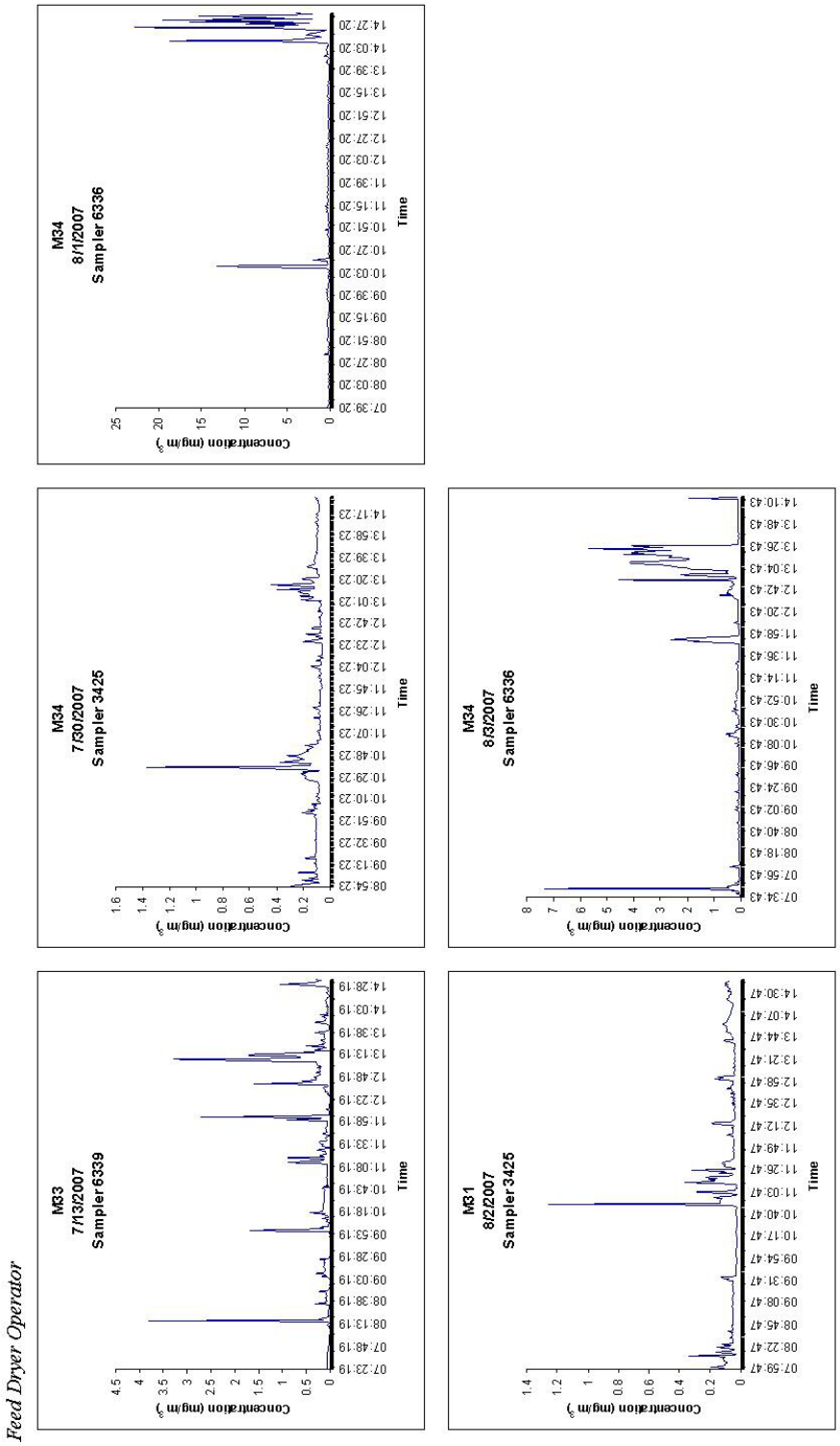
Figure 3. Real-time Respirable Dust Exposures from Personal Samples by Job Category

Curd Operator

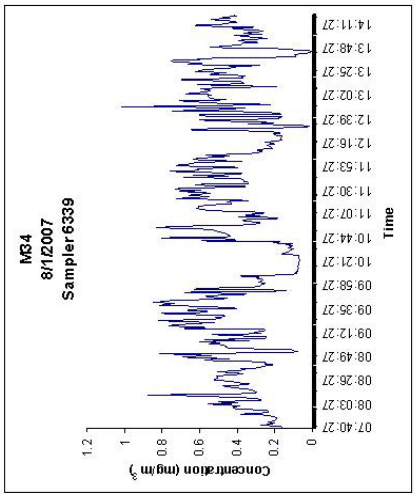


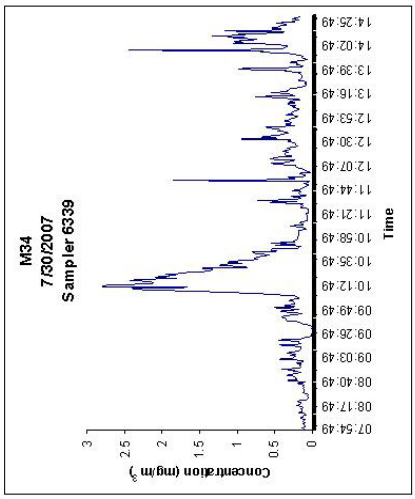
Spray Dryer Operator



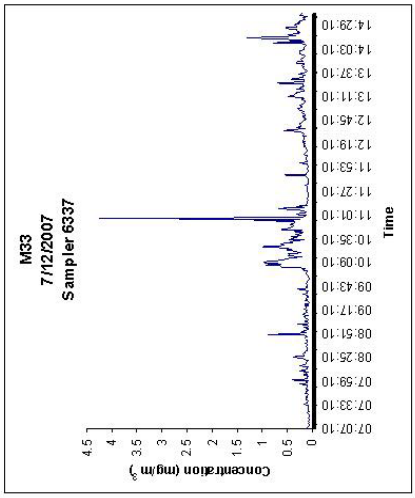


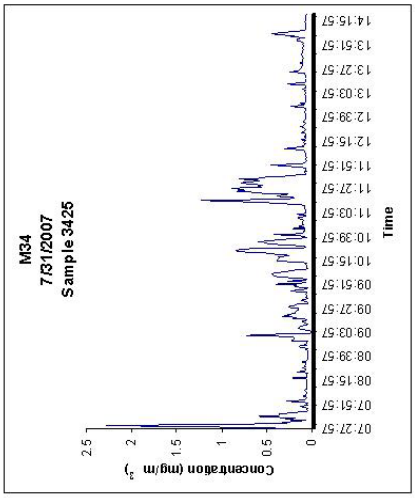
Feed Dryer Operator

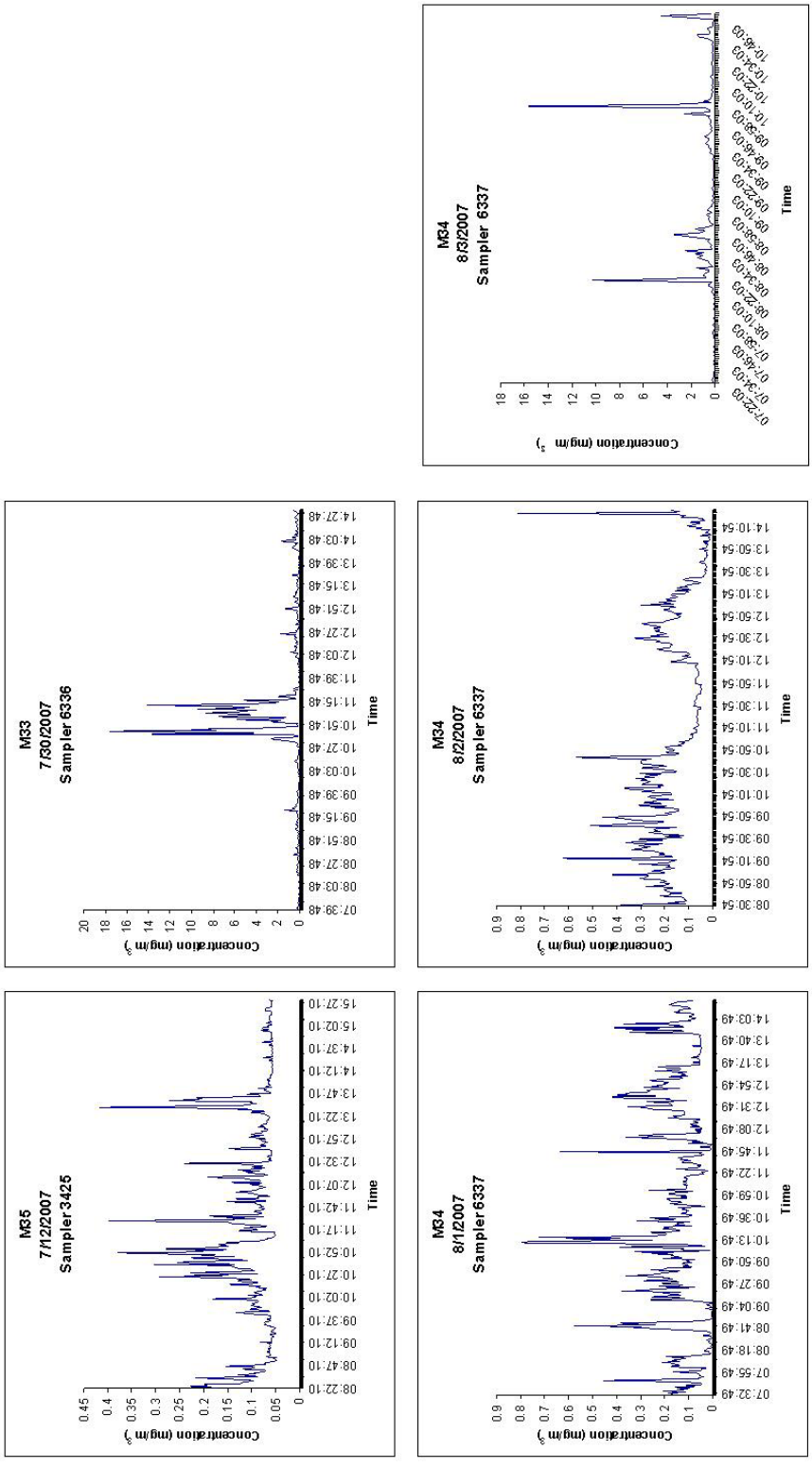




Autopack Operator






M35
7/12/2007
Sampler 3425
Concentration (mg/m³)
Time
M33
7/30/2007
Sampler 6336
Concentration (mg/m³)
Time
M34
8/2/2007
Sampler 6337
Concentration (mg/m³)
Time
M34
8/1/2007
Sampler 6337
Concentration (mg/m³)
Time
M34
8/3/2007
Sampler 6337
Concentration (mg/m³)
Time
Autopack Assistant

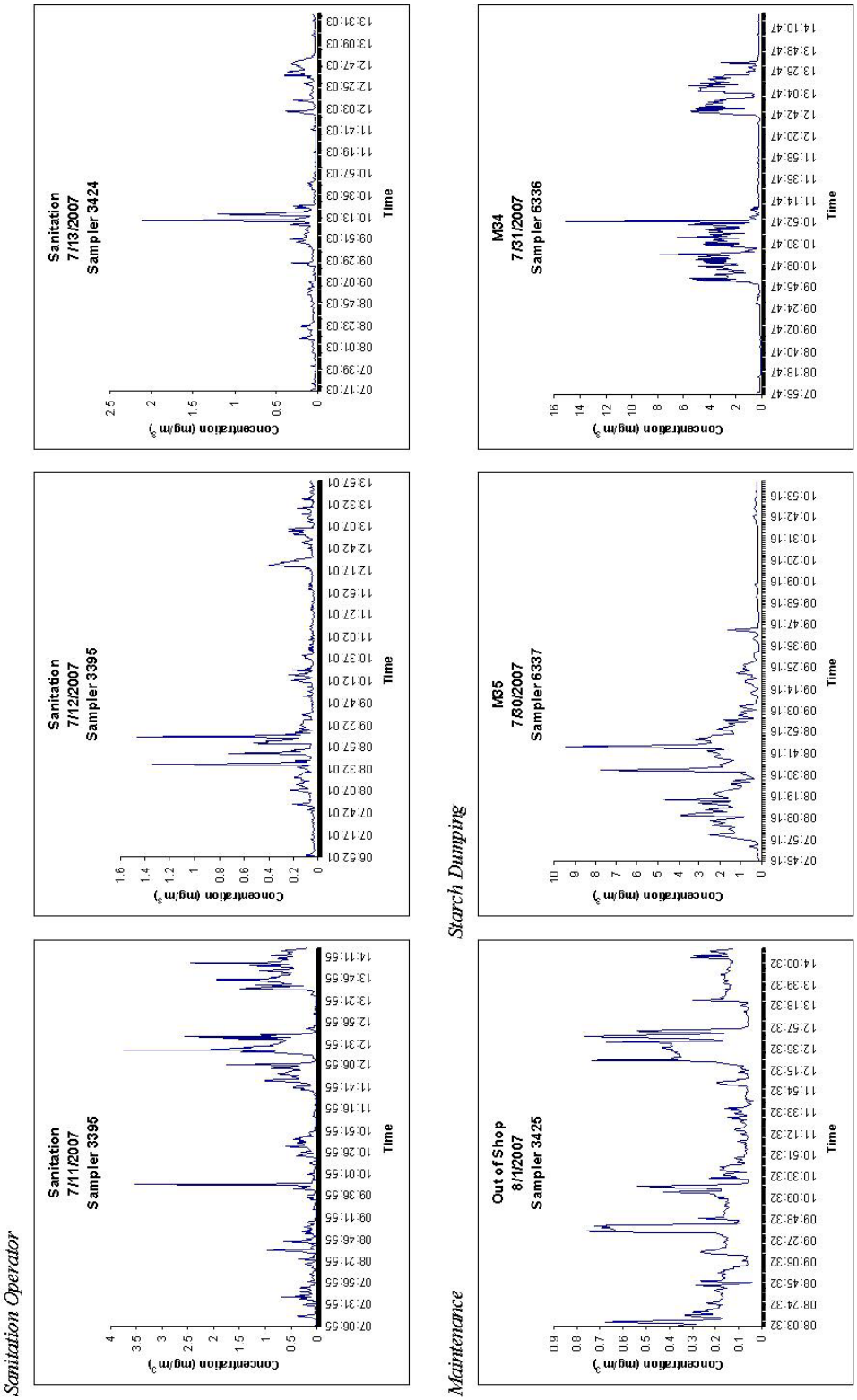

Sanitation Operator
Starch Dumping
Maintenance
Sanitation
7/11/2007
Sampler 3395
Concentration (mg/m³)
Time
Sanitation
7/12/2007
Sampler 3395
Concentration (mg/m³)
Time
Sanitation
7/13/2007
Sampler 3424
Concentration (mg/m³)
Time
M35
7/30/2007
Sampler 6337
Concentration (mg/m³)
Time
M34
7/31/2007
Sampler 6336
Concentration (mg/m³)
Time
Out of Shop
8/1/2007
Sampler 3425
Concentration (mg/m³)
Time

Figure 4. Prevalences of Positive IgE to Soy and of Work-related Asthma-like Symptoms, by Category of Exposure to Inhalable Soy Antigen

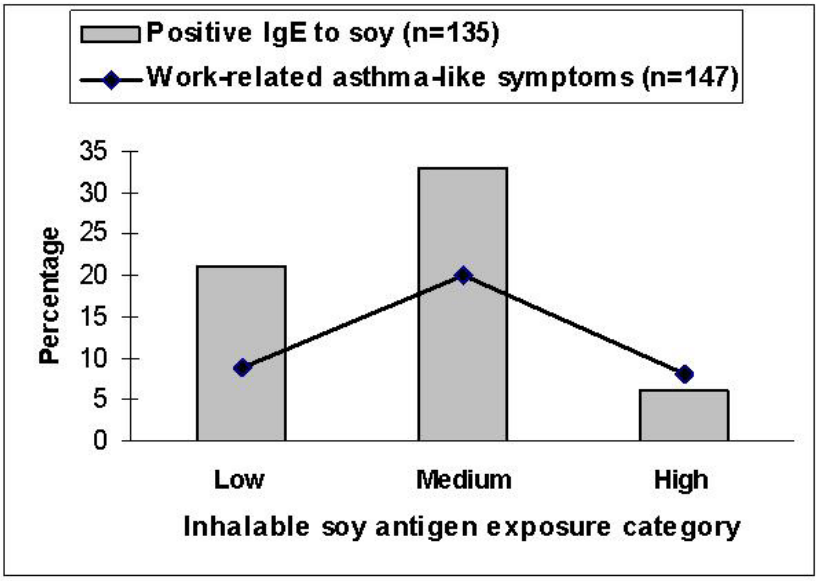
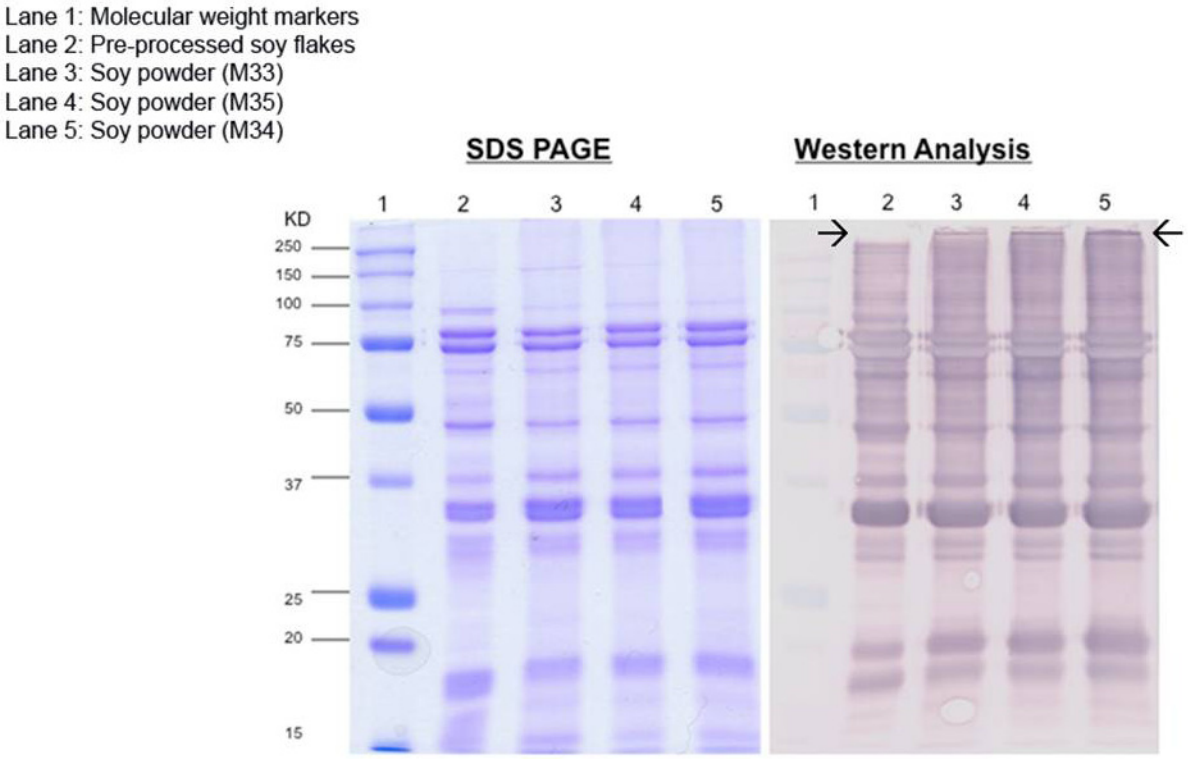


Figure 5. IgG Immunoblot Analysis of Soy Proteins found at Solae Using SDS-PAGE and Western Blot*



*Arrows indicate additional high-molecular-weight bands observed in the soy powders (lanes 3–5) but not in the pre-processed soy flakes (lane 2). Though not evident from the scanned images of the SDS-PAGE gels shown in this figure, the original SDS-PAGE gels showed corresponding subtle increased staining for the soy powder extracts compared to the soy flakes extract.

Immunological Methods

Soy Protein Extraction: Personal inhalable air samples were analyzed using enzyme-linked immunosorbent assay (ELISA). Filters were removed from the head housing of the IOM sampler and placed in a 1.5 ml polypropylene microfuge tube. Filters were extracted in 1 ml of phosphate buffered saline with Tween® (PBS-T) for 2 hrs at 4°C on an orbital shaker. Aliquots of the extract were centrifuged at 10,000 rpm for 5 minutes and stored at 4°C for immediate use or at -20°C for longer storage. Protein extracts from bulk pre-processed soy flakes were prepared as a reference standard by extracting 10% w/v in PBS for 4 hrs at 4°C under constant agitation. The protein concentration of the reference solution was determined according to the bicinchoninic acid (BCA) method (Pierce Chemical Co, Rockford, IL). The standard soy extract (SE-St) was diluted in PBS to make a 1 mg/ml stock reference solution, aliquoted, and stored at -20°C.

Soy Antigen ELISA Assay: ELISA assay plates (Nunc MaxiSorb, #442-404, Fischer Scientific, Pittsburgh, PA) were coated with soy antigen by placing 100 µl of standard soy extract ((SE-St) (1 µg/ml in carbonate buffer)) in all wells of the plates and incubating in a moist chamber overnight at room temperature. Extracts or SE-St (0.5 mg/ml) were serially diluted in duplicate into the wells of a blocked non-protein binding plate and incubated with a 1/2000 dilution of rabbit polyclonal anti-soy protein antibody (Sigma # S2519, LOT 046K4775, Sigma-Aldrich, Inc., St. Louis, MO). After incubation at room temperature for 1 hr with constant shaking, samples were then transferred to the blocked SE-St-coated assay plate and incubated for 1 hr at 37°C. Plates were washed 3 times in PBS-T and incubated with 100 µl of a horseradish peroxidase (HRP)-labeled goat anti-rabbit IgG (Sigma # A-0545, Sigma-Aldrich, Inc., St. Louis, MO) for 1 hr at 37° C. After the plate was washed 3 times, a colored reaction product was produced by the addition of o-phenylenediamine (1mg/ml containing 0.1% H_2O_2). The reaction was stopped after 20 minutes by adding 50 µl of 4 N sulfuric acid per well and quantified by reading the optical density at 490 nm. The concentration of soy antigen in the extract was determined by comparing the optical density of the unknowns with that of the SE-St reference standard and expressed as mass protein/ml of extract. The inhibition assay had a linear working range between 8 and 500 ng/ml and a limit of quantification of 16 ng/ml. When available, the mean values of 3 consecutive dilutions, but a minimum of 2 dilutions for each extract were used to calculate antigenic protein levels.

Soy Allergen Assay: IgE inhibition assays were conducted using pooled sera from participants with a positive ImmunoCAP® to soy. Equal volumes of pooled sera and soy extracts were mixed prior to addition to the soybean (F1) disc and ImmunoCAP analysis. Inhibition with serial dilutions of the bulk soy flake extract (see above, in "Soy Protein Extraction") was used to construct a standard inhibition curve and allergen levels in unknowns were determined by comparison to the soy flake standard extract using an assignment of 2600 Arbitrary Units.

SDS-PAGE/Immunoblot Analysis of Soy Protein: Immunoblot analysis was performed to characterize allergens in soy samples using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and Western blots. Soy extracts (5 µg/lane) were separated on a 10% Tris-HCl gel (Bio-Rad, Hercules, CA) under denaturing conditions and transferred to a nitrocellulose membrane (0.2 µm, BioRad, Hercules, CA). For some experiments requiring 2 dimensional analysis, isoelectric focusing of soy protein prior

to SDS-PAGE analysis was performed using 7 cm Immobiline™ DryStrip gels pH 4-7 (GE Healthcare, Piscataway, NJ) at 3500V for 2.5 hrs and 200V for 1 hr. Focused gel strips were then equilibrated for 30 minutes at room temperature in SDS equilibration buffer followed by SDS-PAGE. Pre-stained broad-range markers (BioRad, Hercules, CA) were used for molecular mass determinations. Membranes were blocked with 3% bovine serum albumin (BSA) in PBS for 1 hr and incubated for 1.5 hrs with a 1/10 or 1/100 dilution of human sera. For allergen detection, the blots were reacted for 1 hr with a 1/1000 dilution of monoclonal human IgE (clone GE1, Sigma-Aldrich, Inc., St. Louis, MO) and then for one hr with a 1/15000 dilution of AP-conjugated anti-mouse IgG H + L (Promega Corp, Madison, WI). For antigen detection, after incubation with a 1/100 dilution of human sera the blots were reacted with AP-conjugated monoclonal antibody to human IgG1 (Clone GG-5, Sigma-Aldrich, Inc., St. Louis, MO). In both cases, immunoreactive proteins were visualized using nitroblue tetrazolium and bromo-chloro-indolyl phosphate (NBT/BCIP, Roche Diagnostics, Indianapolis, IN). For identification of 5-enolpyruvylshikimate-3-phosphate synthase from Agrobacterium sp. strain CP4 (CP4-EPSPS), blocked membranes were incubated for 4 hrs with a 1/20 dilution of HRP-conjugated anti-CP4 antibody (QuantiPlate™ Kit for Roundup Ready® Soybean and Soy Flour, Envirologix, Portland, ME). Membranes were then washed 3 times with PBS-T and immuno-reactive proteins visualized using the 1-Component Tetramethylbenzidine (TMB) Membrane Peroxidase Substrate (KPL, Gaithersburg, MD). Color was allowed to develop for a maximum of five minutes.

Genetically Modified Soy ELISA Assay: For quantitative detection of CP4-EPSPS, extracts of dust from the Solae plant were analyzed with the QuantiPlate Kit for Roundup Ready Soybean and Soy Flour in accordance to the manufacturer's instructions (Envirologix, Portland, ME). Briefly, soy protein extracts were diluted 1:10 and 1:50 in the provided wash buffer. Following the addition of the Roundup Ready Enzyme Conjugate to the pre-coated Quantiplate, 50 µl of diluted sample extracts were added to respective wells. Contents were briefly mixed and incubated at ambient temperature for 45 minutes. After incubation, sample wells were washed in triplicate with wash buffer prior to the addition of 100 µl of substrate. Samples were then incubated for 15 minutes at ambient temperature followed by the addition of 100 µl of Stop Solution. Spectrophotometric measurement was performed at 450 nm within 30 minutes of the addition of the Stop Solution.

CP4-EPSPS Antibody Analysis: Sera from Solae employees were analyzed for immunoglobulin G (IgG) or immunoglobulin E (IgE) reactivity to CP4-EPSPS using a modified protocol of the Quantiplate Kit (Envirologix, Portland, ME). Briefly, 100 µl of genetically modified soy protein extracts were added to antiCP4-EPSPS pre-coated Quantiplates and incubated at ambient temperature for 1 hr. Wells were next washed 4 times with PBS-T, blocked with 100 µl 3% BSA for 30 minutes and subsequently incubated one hr with 50 µl of subject serum. Wells were then washed and incubated 1 hr at ambient temperature with 100 µl of AP-conjugated anti-human IgG (Sigma-Aldrich, Inc., St. Louis, MO) or anti-human IgE (Sigma-Aldrich, Inc., St. Louis, MO). After washing, antibody reactivity was revealed using 200 µl of p-nitrophenyl phosphate (PNPP) substrate (Sigma-Aldrich, Inc., St. Louis, MO) following incubation at ambient temperature for 30 minutes. The reaction was stopped by the addition of 50 µl of 4 N sulfuric acid per well and the optical density measured at 405 nm.

Appendix B

SOLAE COMPANY WORKER QUESTIONNAIRE

Today's Date: __ __ / __ __ / __ __ __ __
(Month) (Day) (Year)

Section I: Identification and Demographic Information

Your Name:______________________________ _____________________________ ___
(Last name) (First name) (MI)

Your Mailing Address:

____
(Number, Street, and/or Rural Route)

____________________________________ ______ ______________
(City) (State) (Zip Code)

Your Home Telephone Number: ( ) _______ - __________

If you move, is there someone who would know how to contact you?

Contact's Name:__________________________ _____________________________ ___
(Last name) (First name) (MI)

Contact's Relationship to you:____________________

Contact's Mailing Address:

____
(Number, Street, and/or Rural Route)

____________________________________ ______ ______________
(City) (State) (Zip Code)

Contact's Telephone Number: ( ) _______ - __________

~~~~~~
~~

1. Date of Birth: __ __ / __ __ / __ __ __ __
(Month) (Day) (Year)
~~~~~~

Appendix B

2. Sex: 1.____ Male 2. ____ Female

3. Are you Spanish, Hispanic, or Latino? 1. ___ Yes 2. ___ No

4. Check one or more of the following categories to describe your race:

5. ___ White
3. ___ Black or African-American
2. ___ Asian
1. ___ American Indian or Alaska Native
4. ___ Native Hawaiian or Other Pacific Islander

Appendix B
Section II. Health Information

I'm now going to ask you some questions about your health.

5. Have you had wheezing or whistling in your chest at any time in the last 12 months? 0. ___ No 1. ___ Yes

If Yes:

5a. Have you been at all breathless when the wheezing noise was present? 0. ___ No 1. ___ Yes

5b. Have you had this wheezing or whistling when you did not have a cold? 0. ___ No 1. ___ Yes

5c. When you are away from Solae on days off or on vacation, is this wheezing or whistling:

1. _____ The same 2. _____ Worse 3. _____ Better

6. Have you woken up with a feeling of tightness in your chest at any time in the last 12 months? 0. ___ No 1. ___ Yes

If Yes:

6a. When you are away from Solae on days off or on vacation, is this problem:

1. _____ The Same 2. _____ Worse 3. _____ Better

7. Have you been woken by an attack of shortness of breath at any time in the last 12 months? 0. ___ No 1. ___ Yes

If Yes:

7a. When you are away from Solae on days off or on vacation, is this problem:

1. _____ The Same 2. _____ Worse 3. _____ Better

8. Have you had an attack of asthma in the last 12 months? 0. ___ No 1. ___ Yes

If Yes:

8a. When you are away from Solae on days off or on vacation, are your attacks of asthma:

1. _____ The same 2. _____ Worse 3. _____ Better

9. Are you currently taking any medicine (including inhalers, aerosols, or tablets) for asthma? 0. ___ No 1. ___ Yes

If Yes:

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9a. When you are away from Solae on days off or on vacation, do you take the medicine for asthma:

1. ____ The Same 2. ____ More often 3. ____ Less often

10. During the past 12 months have you had sinusitis or sinus problems? 0. ___ No 1. ___ Yes

IF YES:

10a. Was it confirmed by a doctor? 0. ___ No 1. ___ Yes

10b. When you are away from Solae on days off or on vacation, is your sinusitis:

1. ____ The same 2. ____ Worse 3. ____ Better

11. During the past 12 months have you had bronchitis? 0. ___ No 1. ___ Yes

12. During the past 12 months have you had a flu-like illness with aches and pains, fever, chills, and night sweats? 0. ___ No 1. ___ Yes

If Yes:

12a. When you are away from Solae on days off or on vacation, is this flu-like illness:

1. ____ The same 2. ____ Worse 3. ____ Better

13. During the past 12 months have you had any skin rash or skin problems? 0. ___ No 1. ___ Yes

IF YES

13a. Which of the following describes your skin problem? (check all that apply)

i. red, inflamed skin	0. ___ No	1. ___ Yes
ii. hives	0. ___ No	1. ___ Yes
iii. dry or itchy skin	0. ___ No	1. ___ Yes
iv. peeling skin	0. ___ No	1. ___ Yes

13b. Which of the following areas of your body were affected by your skin problem? (check all that apply)

i. your face	0. ___ No	1. ___ Yes
ii. your neck	0. ___ No	1. ___ Yes
iii. your arms	0. ___ No	1. ___ Yes
iv. your hands	0. ___ No	1. ___ Yes
v. other areas?	0. ___ No	1. ___ Yes

vi. Specify other areas _____

13c. When you are away from Solae on days off or on vacation, are these skin problems:

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1._____The same 2. _____ Worse 3._____Better

14. Do you usually have a cough? 0. ___ No 1. ___ Yes

IF YES:

14a. When you are away from Solae on days off or on vacation, is this cough:

1._____The same 2. _____ Worse 3._____ Better

15. Has a doctor ever told you that you had asthma? 0. ___ No 1. ___ Yes

IF YES:

15a. In what month and year were you first told that you had asthma? _____ month _____year
(option: childhood)

15b. Do you still have asthma? 0. ___ No 1. ___ Yes

15c. Did your asthma ever go away for at least a year, only to come back again?
0. ___ No 1. ___ Yes 9. ___ Don't know

If Yes to 15c, ask 15d:

15d. In what month and year did your asthma come back? _____ month _____year

16. Do you have any nasal allergies including hay fever? 0. ___ No 1. ___ Yes

IF YES:

16a. When you are away from Solae on days off or on vacation, are your nasal allergies:

1._____ The same 2. _____ Worse 3._____ Better

17. Has a doctor ever told you that you have eczema? 0. ___ No 1. ___ Yes

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Section III. Work Information

18. Did you ever work for Solae as a contract worker? (Contract worker refers to workers hired by another company who work on site at the Solae plant.) 0. ___ No 1. ___ Yes

19. Please list all the jobs you have worked at the Solae Company.

	Job Title (pull-down)	Start Month/Year	End Month/Year	Major Work Areas (pull-down)
19a.				
19b.				
19c.				
19d.				
19e.				
19f.				
19g.				

20. In the last 12 months, have you worked in areas where you either saw or smelled mold? 0. ___ No 1. ___ Yes

If Yes:

20a. List areas where you saw or smelled mold:

_____

21. Do you have health problems that you believe may be related to working at Solae? 0. ___ No 1. ___ Yes

IF YES:

21a. Describe these health problems:

_____

21b. What do you think caused these health problems?

_____

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22. Have you ever had to change your job, job duties, or work area at Solae because of breathing difficulties? 0. ___ No 1. ___ Yes

IF YES:

22a. In what month and year did you change your job, job duties, or work area?
__ __/__ __ __ __
Month Year

22b. What were your job duties before the change?

_____

22c. What was your work area before the change?

_____

22d. What were your job duties after the change?

_____

22e. What was your work area after the change?

_____

22f. Did your breathing difficulties get better after the change? 0. ___ No 1. ___ Yes

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Section IV. Tobacco Use Information

23.	Have you ever smoked cigarettes? (NO means less than 20 packs of cigarettes or 12 oz. of tobacco in a lifetime or less than 1 cigarette a day for a year.)	0. ___ No 1. ___ Yes

IF YES:

23a.	How old were you when you first started regularly smoking cigarettes?	_____ Years old
23b.	Do you now smoke cigarettes (as of 1 month ago)?	0. ___ No 1. ___ Yes

If no to 23b, then ask 23c:

23c.	If you stopped smoking cigarettes completely, how old were you when you stopped?	_____ Years old
23d.	Over the entire time that you smoked, what is the average number of cigarettes that you smoked per day?	_____ Cigarettes per day

Acknowledgements and Availability of Report

The Respiratory Disease Hazard Evaluation and Technical Assistance Program (RDHETAP) of NIOSH conducts field investigations of possible health hazards in the workplace. These investigations are conducted under the authority of Section 20(a)(6) of the Occupational Safety and Health (OSH) Act of 1970, 29 U.S.C. 669(a)(6), or Section 501(a)(11) of the Federal Mine Safety and Health Act of 1977, 30 U.S.C. 951(a)(11), which authorizes the Secretary of Health and Human Services, following a written request from any employers or authorized representative of employees, to determine whether any substance normally found in the place of employment has potentially toxic effects in such concentrations as used or found. RDHETAP also provides, upon request, technical and consultative assistance to federal, state, and local agencies; labor; industry; and other groups or individuals to control occupational health hazards and to prevent related trauma and disease.

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Copies of this report have been sent to the president of the Bakery, Confectionery, Tobacco Workers, and Grain Millers Union, Local 393, management representatives at the Solae Company, requesters, Tennessee Department of Health, and the OSHA Regional Office. This report is not copyrighted and may be freely reproduced. The report may be viewed and printed from the following internet address: http://www.cdc.gov/niosh/hhe. Copies may be purchased from the National Technical Information Service (NTIS) at 5825 Port Royal Road, Springfield, Virginia 22161.

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