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E.S.I. MEATS, INC.
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I. SUMMARY

In January 1987, the National Institute for Occupational Safety and Health (NIOSH) received a request to evaluate respiratory symptoms among meat processing workers at E.S.I. Meats, Inc., in Bristol, Indiana. The workers reported experiencing wheezing and shortness of breath related to exposure to the proteolytic enzyme meat tenderizer papain.

To assess worker exposure to papain, personal breathing-zone (PBZ) and general area (GA) samples were collected using conventional air monitoring equipment. The samples were analyzed specifically for papain utilizing a very sensitive (low nanogram) radioimmunoassay procedure. Papain was detected in all twenty PBZ samples, with concentrations ranging from 0.22 to 1.7 ug/m^3, and in all GA samples located in the compounding room and in the meat processing department. The highest concentrations (1.0 to 2.1 ug/m^3) were measured at the liquid sprayers on each of the steak lines where papain tenderizer was used. Lower levels (0.02 to 0.22 ug/m^3) were measured at other meat processing lines, indicating that the papain aerosol generated by the sprayers was dispersed throughout the department, exposing workers on other conveyor lines.

There are no exposure standards specific for proteolytic enzyme tenderizers. Employees' exposures to papain were above the ACGIH ceiling TLV of 0.06 ug/m^3 established for subtilisins, which are proteolytic enzymes used in detergents. This exposure limit was used in the interpretation of the papain data; the comparative biological and antigenic potencies of subtilisins and papain were assumed to be similar.

Three hundred fifty-seven workers completed a questionnaire to determine the presence of symptoms suggestive of occupational asthma. Fifty-one symptomatic workers, and 45 without symptoms, completed a medical survey including a questionnaire, pulmonary function tests, peak expiratory flow rate determinations (PEFR), skin-prick tests, radioallergosorbent tests (RAST), and measurement of serum immunoglobulin E (IgE). Twenty-nine employees were determined to have either possible or definite IgE mediated tenderizer-related occupational asthma (TROA), based upon questionnaire responses compatible with occupational asthma, immunologic evidence of allergy to tenderizers, and PEFR measurements suggestive of work-related bronchial lability. The prevalence of definite or possible occupational asthma at this plant was 12% among tenderizer-exposed workers.

On the basis of these data, NIOSH investigators have determined that a health hazard existed among employees of E.S.I. Meats, Inc., Bristol, Indiana, from occupational exposure to proteolytic enzyme meat tenderizers. Recommendations to reduce exposures to enzymes, care for affected workers, and prevent further illness are made in Section IX of this report.

KEYWORDS: SIC 2013 (Sausages and other prepared meat products), proteolytic enzymes, papain, bromelain, ficin, occupational asthma

II. INTRODUCTION

In January, 1986, the National Institute for Occupational Safety and Health (NIOSH) received a request from three employees at E.S.I. Meats, Inc. to investigate respiratory symptoms among workers exposed to meat tenderizers. An initial site visit and walkthrough were conducted by NIOSH personnel on February 5, 1987. A one-page questionnaire was administered to 357 E.S.I. employees on April 2-3, 1987. Based on the results of this survey, a combined medical/industrial hygiene survey was undertaken on July 6-10, 1987. Each participant in the medical study was notified of the results of his/her medical testing on February 1, 1988. Interim reports were mailed to E.S.I. and the requestors in February and April 1988.

III. BACKGROUND

E.S.I. Meats, Inc. is a meat portioning plant. Three proteolytic enzyme meat tenderizers derived from tropical fruits, papain, bromelain, and ficin, are used as components of spice mixtures that are sprayed on some steaks prior to packing.

E.S.I. employees interviewed prior to the initial site visit reported that numerous workers believed they had asthma related to exposure to these enzymes.

A review of E.S.I. records by NIOSH revealed the following:

E.S.I.'s OSHA 200 log for 1984 has an entry noting reactive airways disease in a worker, requiring 22 missed work days, beginning in late May.

In response to a complaint, Indiana OSHA conducted a site visit on October 24, 1984. The site visit report described a hazard caused by enzyme tenderizers in the mixing and processing areas.

A report dated August 26, 1986 to E.S.I. by their insurance carrier described papain as a cause of asthma, and recommended enclosing tenderizer application areas to reduce worker exposure to the enzymes.

A second report by the insurance company, dated October 9, 1986, reported the results of an industrial hygiene survey of the plant to measure airborne tenderizer levels. The survey found "excessive" levels of airborne enzyme, and "strongly recommended" that the company take steps to reduce worker exposure to tenderizers.

IV. PROCESS DESCRIPTION

Large frozen cuts of beef are received by truck, and then prepared into steaks, ground beef, and other meat products. Approximately 31 million pounds of meat are processed each year. The company started operations at a facility in Goshen, Indiana in 1969. They moved to the current facility in 1980; most of the workers from the Goshen plant continued to work at the Bristol plant.

At the time of our survey, approximately 475 workers were employed at this facility, of which about 435 were production workers and 40 were office (management/clerical) workers. The majority of the production workers were divided among meat processing line workers, quality assurance personnel, sanitation/maintenance workers, dock workers, and truck drivers. Meat is processed daily on the first and second shifts. The third shift is used for sanitation and equipment maintenance.

The plant uses a number of proprietary spice mixtures, which are formulated by suppliers according to customer specifications. Some of the spice mixtures contain proteolytic enzyme tenderizer(s). Most (>95%) of these steaks are tenderized with papain; a small percentage (<5%) are tenderized with seasonings containing an enzyme blend of bromelain and ficin. Aside from the enzymes, seasonings may contain salt, dextrose, monosodium glutamate, hydrolyzed vegetable protein, and spices.

Seasoning mixtures are received as a dry powder in 35 or 45 lb. bags which are stored and formulated into solution in a 42' x 12' compounding room. One worker (quality technician) per shift is responsible for formulating the liquid seasoning solutions. It is a batch operation and involves the manual dumping of seasonings containing papain into mixing tanks containing water. The only protective equipment worn was that required by the USDA (lab coat, hair net and plastic hat). Disposable dust respirators and gloves were available, but usually not worn. The mix tanks were not equipped with local exhaust ventilation. On the average, 15 to 20 bags of enzyme-containing seasonings are dumped each shift, usually 3 bags at a time, according to manufacturer's dilution specifications. In addition, "booster packs" (up to 1.5 lbs. of enzyme concentrate (papain and salt only)) are added to the seasoning solution, on an as needed basis, to maintain the enzyme at an acceptable activity level. When integrated over the shift, the bag dumping task, and thus the compounder's exposure, lasted no more than an hour per shift. Once prepared, the liquid seasonings are piped from this room to the main meat processing department, where they are applied to the steaks.

The meat processing department is a 15,000 ft^2 open room, maintained at 45-50 degrees Fahrenheit, where several meat product conveyor lines (i.e., ground beef, tenderized steak, sirloin tip, and choice steak) are situated parallel to one another.

The papain-tenderized steak lines are located between the ground beef lines and the sirloin tip and choice steak lines. At the time of our study, papain was used on three lines, two rib-eye and one T-bone. Each of these lines was similar in operation and staffing requirements. At the beginning of each line three workers are responsible for one of the following tasks: removing meat from boxes, operating automatic shaping or slicing machines, or weighing steaks for quality control purposes. While on the conveyor line, the steaks are mechanically tenderized, then sprayed with the spice solution containing papain. The spice solution was applied to the steaks using multiple coarse jet spray nozzles, which are positioned over and under the screen conveyor. The sprayers are covered with a removable metal hood to reduce off-spray. The treated steaks are then placed into plastic bags by approximately eight baggers. The only protective equipment worn by the packers, aside from the USDA-required ensemble, was vinyl gloves, which were worn by some workers on the hand nearest the conveyor. At the end of the conveyor line, 2 to 3 workers are involved in boxing, palletizing, and transfer operations.

Neither pre-employment nor periodic medical examinations are performed. A local hospital is used for emergency care. No medical records are maintained on site.

V. METHODS

A. ENVIRONMENTAL

1. Sample collection

A total of forty samples, 20 personal breathing-zone (PBZ) and 20 general area (GA), were collected to assess airborne concentrations of papain. The sampling protocol was designed to evaluate those workers with the greatest potential for exposure to papain. Personal PBZ samples were collected for the following job classifications: the quality technician, who was responsible for adding dry spice formulations containing papain to mix tanks containing water, and the steak packers who were responsible for bagging rib-eye and T-bone steaks, which had been sprayed with liquid spice mixtures containing papain.

The GA air samples were collected from selected production and nonproduction areas. Production area air samples were placed at the following sites: directly above the mix tank inside the compounding room, directly outside the compounding room, on the liquid tenderizer sprayers for each of the three steak lines where tenderizers were used, and on three other meat lines where papain was not used. Nonproduction area samples were collected from one site, the north office area.

Air samples were collected on 37 mm mixed cellulose ester (MCE) filters connected to battery-operated sampling pumps calibrated at 2.0 to 2.5 liters per minute (Lpm). Sampling trains were calibrated daily. Proper air flow rate and sample integrity were checked periodically during the work shift. Field blanks were prepared and submitted with the other filters. Samples were stored in a freezer at 5 degrees Centigrade until they were analyzed.

2. Sample analysis

Filter samples were analyzed for papain using a two-site immunoradiometric assay (TSIRA) developed by researchers at the Allergy Research Laboratory, Mayo Clinic/Foundation. This immunochemical technique involved two components: A) extraction of papain from the filter samples and B) assay of papain by TSIRA.

a. Extraction of papain from filters:

A two-step extraction procedure was used to prepare the field samples for assay. First, the field samples (37 mm MCE filters) were placed into separate test tubes containing 3 milliliters (mL) acetone. The tubes were vortexed, dissolving the filter but not insoluble papain (if present in the samples). The solutions were then filtered under vacuum onto polytetrafluoroethylene (PTFE) filters. The PTFE filters, used to trap the papain, were

placed into vials. One half ml phosphate buffer was added to the vials containing the PTFE filter and vortexed, solubulizing the papain for assay.

b. Assay by TSIRA:

The two-site immunoradiometric assay required the use of two key immuno-reagents: pure papain enzyme, and hyperimmune rabbit anti-papain serum. The purified papain was used to prepare the reference standards and to isolate immunoglobulin G (IgG) from the rabbit serum. The rabbit serum was the source of IgG, the papain-specific antibody used to bind the papain in the reference and field samples.

The rabbit serum, containing papain antibodies (as well as other proteins) was added to a column containing purified papain covalently linked to Sepharose resin. As the serum passed through the column, IgG antibodies to papain complexed with the papain antigen. Other (unbound) proteins in the serum were subsequently washed away. Papain antibodies were eluted from the column using a glycine buffer solution, and concentrated. An aliquot of the concentrate was radioiodinated with iodine-125 for the radioimmunoassay.

The assay was performed in Immulon wells. An excess of the purified IgG was added to the wells, adsorbing to its surface. Reference standards, internal standards, and unknowns (field samples) were added to separate wells. After incubation, the wells were washed and the radioiodinated antibody added. After a second incubation period the wells were washed again and counted. The bound radioactivity is proportional to the amount of papain in the samples. The concentration of papain in the unknowns was calculated from a standard curve of counts versus the papain reference standards.

The sensitivity of this assay was such that 0.32 ng was reliably measured. When considering the minimum air volume for any one sample collected during this evaluation (794 liters), this assay was capable of measuring concentrations of papain as low as 0.4 ng per cubic meter of air.

B. MEDICAL

On April 2-3, 1987, we administered a questionnaire to every available employee at the plant, to identify workers with three symptom complexes suggestive of occupational asthma. These were (1) wheezing, (2) shortness of breath or difficulty breathing, and/or (3) chest tightness or pain, occurring within the past month, and occurring less frequently or not at all on days away from work. We invited to participate in the follow-up case-control study (July 6-10, 1987), all respondents who reported two of the three symptom complexes listed above, plus an equal number of respondents chosen at random from among those with none of these chest symptoms. In the case-control study:

1. Pulmonary function testing was performed after at least 2-3 hours at work, using an Ohio Medical model 822 dry rolling seal spirometer, attached to a Spirotech 220B dedicated

computer. Procedures conformed to the American Thoracic Society's criteria for screening spirometry.[1] Predicted values were calculated using the Knudson equation.[2] Predicted values for Blacks were determined by multiplying the value predicted by the Knudson equation by 0.85.[3] If there was evidence of an abnormality on spirometric examination, the participant was requested to return the following day, pre-shift, for another pulmonary function test. Required as evidence of pulmonary test abnormality was an FVC less than 80% of predicted, or an FEV1/FVC ratio less than 0.7. [4]

2. Peak expiratory flow rates (PEFR) were measured serially, using Wright's portable mini-peak flow meters for one week, every three hours while awake, and during the night if awakened for any reason. Three exhalations were recorded each time, and the maximum of the three was accepted as the PEFR determination. Any wheezing, shortness of breath, chest tightness or cough experienced at the time of a PEFR determination was supposed to be reported on the peak flow record. A participant was considered to have significant bronchial lability if the difference between the minimum and the maximum PEFR on at least one day exceeded 20% of the day's maximum PEFR.[5]

3. Skin-prick tests were administered, and serum specific-IgE levels were measured by the radioallergosorbent test (RAST) method. The skin test panel included commercial (pharmaceutical grade) papain, bromelain, and ficin; "factory" papain, bromelain, and ficin from the E.S.I. plant; three spices used in E.S.I.'s tenderizing mixtures; and chymopapain, a proteolytic enzyme similar to papain. The RAST panel included chymopapain, factory papain, commercial papain, bromelain, and ficin. Saline and histamine solutions were applied as negative and positive controls. A skin test was considered positive if the wheal (swelling) diameter measured at least 3 mm greater than the saline control. RAST results were expressed as counts per minute of I^{125}-labeled IgE bound to allergen-coated disks, and were considered positive if the test serum count was more than 3 standard deviations above of the mean of that for non-exposed laboratory controls. Total serum IgE level was measured by radioimmunassay (normal range 10-125 IU per milliliter where IU equals 2.3 milligrams).

4. Skin-prick tests were administered to a panel of common airborne allergens, including bluegrass, ragweed, alternaria, grass, cat hair, and mite.

5. A supervised self-administered questionnaire was provided that addressed medical and work history, and the presence of other possible risk factors for asthma.

We developed the following epidemiologic case definitions for tenderizer-related occupational asthma (TROA).

1. We classified a participant as having <u>definite</u> TROA if he or she fulfilled all three of the following criteria.

   a. Respiratory symptoms temporally be related to work, as reported on the initial questionnaire.

b. Symptomatic, significant bronchial lability temporally related to work. The criteria for significant bronchial lability are described above (section V.B.2.). The bronchial lability was considered to be symptomatic if the participant reported wheezing, shortness of breath, chest tightness or cough as his or her peak expiratory flow rate reached the minimum for the day. The bronchial lability was considered work-related if (a) the difference between the maximum and minimum exceeded 20 percent on at least one work day, and was less than 20 percent on all non-work days; or (b) if there was an obvious U-shaped appearance to the PEFR determination on a workday. The U-shaped appearance suggests that the PEFR had fallen in response to work exposures and had risen towards the maximum upon cessation of exposure.

c. At least one positive skin test or RAST to a tenderizer or chymopapain.

2. We classified a participant as having <u>possible</u> TROA if he or she fulfilled (a) and (b) above but had no positive skin test or RAST to tenderizers or chymopapain. Alternately, a participant was classified as having possible occupational asthma if he or she had respiratory symptoms believed to be related to work and at least one positive skin test or RAST to tenderizer, but no evidence of significant symptomatic bronchial lability.

VI. <u>EVALUATION CRITERIA</u>

A. Environmental

As a guide to the evaluation of the hazards posed by workplace exposures, NIOSH field staff employ environmental evaluation criteria for assessment of a number of chemical and physical agents. These criteria are intended to suggest levels of exposure to which most workers may be exposed up to 10 hours per day, 40 hours per week for a working lifetime without experiencing adverse health effects. It is, however, important to note that not all workers will be protected from adverse health effects if their exposures are maintained below these levels. A small percentage may experience adverse health effects because of individual susceptibility, a pre-existing medical condition, and/or a hypersensitivity (allergy). In addition, some hazardous substances may act in combination with other workplace exposures, the general environment, or with medications or personal habits of the worker to produce health effects even if the occupational exposures are controlled at the level set by the evaluation criterion. These combined effects are often not considered in the evaluation criteria. Also, some substances are absorbed by direct contact with the skin and mucous membranes, and thus potentially increase the overall exposure. Finally, evaluation criteria may change over the years as new information on the toxic effects of an agent become available.

The primary sources of environmental evaluation criteria for the workplace are: 1) NIOSH Recommended Exposure Limits (RELs),[6] 2) the American Conference of Governmental Industrial Hygienists' (ACGIH) Threshold Limit Values (TLV's),[7] and 3) the U.S. Department of Labor, Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PELs).[8] Often, the NIOSH RELs and ACGIH TLV's are lower than the corresponding OSHA PELs. Both NIOSH RELs and ACGIH TLV's usually are based on more recent information than are the OSHA standards. The OSHA PELs also may be required to take into account the feasibility of controlling exposures in various industries where the agents are used; the

NIOSH RELs, by contrast, are based primarily on concerns relating to the prevention of occupational disease. In evaluating the exposure levels and the recommendations for reducing these levels found in this report, it should be noted that industry is legally required to meet only those levels specified by an OSHA standard.

A time-weighted average (TWA) exposure refers to the average airborne concentration of a substance during a normal 8- to 10-hour workday. Some substances have recommended short-term exposure limits or ceiling values which are intended to supplement the TWA where there are recognized toxic effects from high short-term exposures.

B. Papain

In addition to its use in the meat processing industry, papain is used extensively worldwide as an ingredient in a number of industrial and consumer products. In the pharmaceutical and cosmetics industry it is used in antiinflammatory agents, veterinary compounds, and cleaners for soft contact lenses. Papain is formulated with spices in spice mills. In the baking industry it is used as a dough enhancer. It is used as a clarifying and chillproofing agent in the manufacture of beer. In scientific research papain is used to induce emphysema in rodents, and it is a component in a reagent used in immunoglobulin analysis. Papain is also used in the tanning industry to condition leather goods.

There are no environmental exposure criteria specific for papain. However, ACGIH recommends a TLV of 0.06 micrograms per cubic meter of air (ug/m^3) as a ceiling concentration for proteolytic enzymes known as subtilisins.[7]

Papain and subtilisins have both been shown to cause allergic respiratory sensitization among exposed workers.[9-13]

Subtilisins are derived from Bacillus subtilis or closely related bacteria, and are used extensively in the laundry detergent industry. They are well characterized proteins, with a molecular weight similar to papain. The ACGIH TLV is considered sufficiently low to prevent respiratory sensitization among detergent workers exposed to subtilisins.[9] Although the comparative biological potencies of subtilisins and papain are not precisely known, current thinking indicates that they are likely to be similar. Accordingly, in this study the ACGIH TLV was used in the interpretation of the environmental papain concentrations.

VII. RESULTS

A. Environmental

Papain was detected in all twenty personal PBZ samples, with concentrations ranging from 0.22 to 1.7 ug/m^3 (Table 1). All of these samples exceeded the ACGIH TLV of 0.06 ug/m^3 for proteolytic (subtilisins) enzymes. The two PBZ samples from the quality technician had papain concentrations of 0.45 and 0.60 ug/m^3. These two samples were collected over the entire work shift and not just during the bag dumping operation per se, which represented this worker's only source of exposure to papain. Therefore, the reported concentrations,

although accurately reflecting an 8-hour TWA, underestimate the short-term papain exposures directly attributable to the dumping operation.

The eighteen PBZ samples collected from the steak packers ranged from 0.22 to 1.7 ug/m^3 (Table 1). The three highest exposures were measured on packers on the T-bone line. On the average, packers on this steak line were exposed to higher concentrations of papain than packers on the rib-eye lines, although the ranges of exposures between the T-bone and rib-eye lines were very similar.

Results of the general area air monitoring showed that papain was detected in the compounding room and at all sampled locations in the main processing department (Table 2). Two samples located above the mix tank in the compounding room had papain concentrations of 1.4 and 1.7 ug/m^3. As with the personal samples, these samples were collected over the entire work shift and not just during the bag dumping operation per se. Therefore, reported concentrations, although accurately reflecting an 8-hour TWA, underestimate the airborne papain levels directly attributable to the bag dumping operation. Papain was not detected in 2 air samples located outside the compounding room, indicating that once aerosolized, papain appears to be confined to this room.

Of the 12 air samples that were collected at 6 sites in the main processing room, the highest papain concentrations were measured at the liquid (tenderizer) sprayers on the T-bone and rib-eye conveyor lines. Papain concentrations for 6 samples ranged from 1.0 to 2.1 ug/m^3. At three other meat lines, papain concentrations for 5 samples (one sample was lost in analysis) ranged from 0.02 to 0.22 ug/m^3. The presence of measurable papain at these latter 3 sites indicate that workers on other meat processing lines (who were not monitored) are also exposed to papain, but at lower levels.

In two areas where papain was not used (pre-processing and front office), papain concentrations in three of 4 air samples were nondetectable, with a trace (0.002 ug/m^3) being detected in one sample from the pre-processing area.

B. Medical

1. Screening Questionnaire

Of the 475 production and non-production employees, 357 (75%) completed the screening questionnaire. Sixty-nine (19%) of these 357 reported symptoms consistent with our epidemiologic case definitions of occupational asthma, and are referred to as symptomatic workers, or suspect asthma cases in the sections that follow. These 69, plus 69 workers without symptoms (controls), were invited to participate in the medical follow-up survey.

2. Medical Follow-up Survey

Of 138 workers invited, 96 (70%) completed at least one component of the survey. Results for each component are described below.

a. Pulmonary Function Testing

Ninety-three participants had pulmonary function tests. All but 4 (4%) had normal results. Two of these 4 had "obstructive" spirometric patterns during the work day. Repeat studies, performed pre-shift, were essentially unchanged. The third had a normal initial study, but returned the following day after several hours on the production floor, reporting severe wheezing and shortness of breath. Pulmonary exam at that time revealed severe, diffuse wheezing in both lungs. A repeat pulmonary function test showed a "restrictive" pattern. The fourth had a "restrictive" pattern during the work day. Repeat pre-shift studies were unchanged.

b. Peak Expiratory Flow Rate (PEFR) Measurements

Ninety-two participants completed peak flow determinations on at least one day. Seventy-four (80%) completed measurements on enough (at least 3) days to determine whether they had significant bronchial lability. Eleven (15%) of these 74 produced peak flow patterns showing significant bronchial lability. Analysis of these patterns showed that 8 of these 11 had work-related bronchial lability. The other 3 produced patterns of bronchial lability that could not be clearly attributed to work.

c. Skin-prick Tests

Ninety-one participants had skin-prick tests. Thirty-one (34%) reacted to at least one of the papain, bromelain or ficin preparations. Nineteen (21%) exhibited cutaneous reactivity to papain; 21 (23%) to purified bromelain; and 14 (15%) to purified ficin. Concurrent cutaneous sensitization to 2 or more enzymes was found in 15 (48%) of the 31 enzyme reactive workers.

Nine (10%) of the participants exhibited positive skin tests to 2 or more common allergens.

d. Blood Tests

Eighty-five participants provided blood samples for radioallergosorbent tests (RAST) and determination of serum immunoglobulin E (IgE) concentration.

RAST

Twenty-two (26%) exhibited significant RAST reactivity to at least one of the enzyme preparations. Seventeen (20%) had a positive RAST test to chymopapain; 17 (20%) to one of the papain preparation; 3 (16%) to bromelain; and 3 (20%) to ficin. Concurrent RAST reactivity to 2 or more enzyme preparations was found in 8 (36%) of the 22 RAST- positive workers.

IgE

Ten (12%) had elevated serum concentrations of IgE.

e. Questionnaire

Ninety-six participants completed the questionnaire. Results are incorporated in the analysis sections below.

3. Analysis of Follow-up Survey

a. Asthma Diagnosis

Using the diagnostic criteria for tenderizer-related occupational asthma (TROA) described in the Methods section, we classified six participants as having definite TROA and 23 participants as having possible TROA.

b. Exposure to Tenderizers

We divided the 96 workers into two papain exposure categories, based on our observations of production processes, interviews with workers, and the industrial hygiene measurements of airborne papain (Table 3). Of the 96 participants, 77 (80%) worked in jobs with a high likelihood of exposure to tenderizers. Nineteen (20%) worked in areas with low or no likelihood of exposure to papain. Of the 29 individuals classified as having either definite or possible tenderizer-related occupational asthma, all but one worked in an exposure area. The relationship between papain exposure and occupational asthma is statistically significant (Odds ratio 10.3, $p<.01$, Table 4)

c. IgE

Thirteen percent (6/47) of the workers who had symptoms suggestive of occupational asthma on the initial questionnaire, and 10% (4/38) of those without symptoms, had elevated serum levels of IgE. Table 5 compares the IgE level of two groups: workers with symptoms suggestive of asthma who did not fit the diagnostic criteria for possible or definite TROA, and those with these symptoms who did fit the TROA criteria. Workers with TROA were more likely to have elevated IgE than symptomatic workers without TROA. ($p=0.03$).

d. PFTs

"Obstructive"

Of the two workers with "obstructive" patterns, one had abnormal chest anatomy because of prior surgery, and did not have symptoms of asthma.

The second had symptoms, but negative skin tests. PEFR determinations showed variability up to 15%, but did not fit the diagnostic criteria for significant bronchial lability. Blood tests were refused.

"Restrictive"

Of the two participants with "restrictive" patterns, the first reported no symptoms of asthma, but questionnaire responses revealed a history of hay fever, excema (a rash), and seasonal rhinitis (runny nose). Skin-prick tests and RASTs for tenderizers were positive. PEFR determinations showed variability of 19% on a work day (criterion for significant bronchial lability was 20%). The lack of reported symptoms precluded the diagnosis of occupational asthma.

The second, who had an additional, abnormal, PFT during an episode of wheezing at work, had positive skin-prick tests and RASTs for tenderizers, and significant symptomatic bronchial lability on PEFR measurements. This worker fit the criteria for definite TROA.

e. RAST and Skin-prick Tests

RAST

Twenty-three percent (11/47) of workers with symptoms suggestive of work-related asthma on the initial questionnaire, and 28% (11/38) of asymptomatic workers had at least one positive RAST. This difference was not statistically significant.

Skin-prick Tests

Forty-one percent (20/49) of workers with symptoms suggestive of work-related asthma on the initial questionnaire, and 26% (11/42) of asymptomatic workers, had at least one positive skin test to a tenderizing enzyme preparation. This difference was not statistically significant, but both rates are substantially higher than the 1% rate of cutaneous reactivity to papain found in a population of atopic persons without occupational exposure to enzymes.[14]

f. Risk Factors

We examined several risk factors for asthma and their relationship to respiratory symptoms and the diagnosis of possible or definite occupational asthma.

1. Atopy

Atopic individuals have frequent allergic reactions to common airborne allergens, such as those included in the skin-prick test panel. Table 6 compares the atopic status of two groups: workers with symptoms suggestive of asthma who did not fit the diagnostic criteria for definite or possible tenderizer-related occupational asthma (TROA), and those with

these symptoms who did fit the criteria for TROA. Workers with asthma were more likely to be atopic than symptomatic workers without asthma. ($p<.01$)

Table 7 compares the atopic status of two different groups: all those with symptoms, regardless of their asthma diagnosis, and those without symptoms (the control group). The proportion of atopic individuals was higher in the symptomatic worker group, but the difference between the groups was not statistically significant ($p = .06$).

2. Tobacco Use

The prevalence of cigarette use among symptomatic workers classified as definite or possible TROA was 52%. The prevalence among symptomatic workers not diagnosed with asthma was 45%. The difference between these two groups was not statistically significant.

3. Cold Air

We asked workers whether they had a job that required moving in and out of freezers. Forty-one percent of both symptomatic worker groups (those diagnosed with TROA, and those not diagnosed with TROA) answered yes.

4. Allergic symptoms

Table 8 presents the prevalence of eczema (a skin condition), and seasonal rhinitis (runny nose) in the two groups of workers with respiratory symptoms (those diagnosed with TROA, and those not). The prevalence of each symptom was not significantly different between the two groups.

5. Others

a. Chymopapain

Chymopapain is a pharmaceutical product used to treat spinal disk disease. No participants reported having been treated with this product.

b. Prevenzyme

Prevenzyme is a papain-containing pharmaceutical product used in the treatment of certain gastrointestinal disorders. One participant, an asymptomatic worker with no positive skin or blood tests, reported having been treated with this product.

c. Fast Food

Some fast food products are treated with tenderizers, and may be a potential source of papain exposure for consumers. Table 9 compares the fast food consumption of the two symptomatic worker groups (with and without TROA). The proportions in the two consumption categories are not significantly different.

d. Childhood and Seasonal Asthma

Seasonal and childhood asthma were each reported by 3% of workers with TROA, and by none and 5% respectively, of participants without TROA. The differences between the groups with and without TROA are not significant.

e. Contact Lenses

Papain is a component of some contact lens cleaning products. Suspect asthma cases (with work-related symptoms on the initial questionnaire) and controls (without work-related symptoms) did not differ significantly in their use of contact lenses. Sixty-four percent of the cases using contact lenses (7/11), and 17% of controls using lenses (1/6), reported symptoms (one or more of: cough, chest tightness, wheezing, shortness of breath, runny or stuffy nose, diarrhea, abdominal cramps, vomiting, or itchy or swollen eyes) after cleaning their lenses with papain-containing cleaning tablets. Five (63%) of 8 with TROA, and two (25%) of 8 of those without TROA, reported such symptoms after cleaning contact lenses with papain-containing products. [Neither of these differences was statistically significant ($p = 0.09$ and $p = 0.16$) respectively, Fisher's exact test, 1-tailed)].

VIII. DISCUSSION AND CONCLUSIONS

The original intent of this hazard evaluation was to attempt to determine whether worker exposure to tenderizers at E.S.I. Meats was associated with occupational asthma.

We have demonstrated that IgE mediated tenderizer-related occupational asthma is occurring among workers at E.S.I. The prevalence of possible or definite TROA among the E.S.I. workforce available for our study is at least 8% (29/357), and the prevalence among tenderizer-exposed workers is at least 12% (29/233). Since some non-participants might also have had TROA, the actual prevalence could be higher. The prevalence among symptomatic workers is 58% (29/50).

Individuals diagnosed with possible or definite TROA were significantly more likely to be exposed to tenderizers, have elevated serum levels of IgE, and be atopic. We did not establish associations between TROA and tobacco use, freezing air exposure, eczema or seasonal rhinitis, or exposure to pharmaceutical papain.

Immunologic sensitivity to tenderizers in the absence of reported symptoms, observed in 11 participants, may be a predictor of the development of asthma with continued exposure. Some of these individuals may already

have sub-clinical asthma, that is, bronchial constriction caused by tenderizers that is not severe enough to cause symptoms. This is suggested by several asymptomatic participants with evidence of immunologic sensitivity, whose PEFR determinations demonstrated bronchial lability just below the criterion for significance used in this study. These questions can only be answered by further study of these people.

The environmental monitoring results showed that papain becomes aerosolized during compounding (bag dumping) and liquid spray application operations. These results also show that all workers monitored (i.e., compounder and the steak baggers) on the T-bone and rib-eye lines using tenderizer were exposed to excessive levels of papain when compared to the ACGIH TLV for subtilisins. Although no air samples were collected from other workers on the steak lines using papain or on workers on the other meat processing lines, results of the general area monitoring suggest that these workers are also exposed to papain, but probably at lower levels than those measured for the packers.

IX. RECOMMENDATIONS

A. Environmental

1. Engineering Controls

Worker exposure to proteolytic enzymes (papain, bromelain, ficin) should be reduced as low as feasible to prevent sensitization of additional E.S.I. employees and to diminish symptoms in those already sensitized. This can be best accomplished through use of engineering controls. Specifically:

a. The mix tanks in the compounding room should be equipped with local exhaust ventilation (LEV) designed to maintain a capture velocity of at least 150 feet per minute at the worker. This design will minimize dust concentrations in the workers' breathing-zone when dry tenderizer is added to the tanks.

b. The liquid sprayers on the T-bone and rib eye lines should be equipped with local exhaust ventilation. Exposure to airborne tenderizer would be minimized by establishing negative pressure air flow into the sprayer hood. The sprayer hoods should be more fully enclosed to prevent splattering of the liquid spice solution.

2. Personal Protective Equipment

Appropriate respiratory protection should be used until effective engineering controls are implemented.

a. As indicated in our letter dated August 19, 1987, compounders should wear high efficiency particulate respirators. With an appropriate LEV system in place the use of respiratory protection may no longer be necessary.

b. Workers should avoid all skin contact with the spice solutions or meat that has been treated with the spice solutions. Every employee who must come in contact with the spice solutions should wear impervious polyethylene gloves.

B. Medical

1. Workers should be clearly informed of the hazards of working with proteolytic enzymes. The association of tenderizer-related asthma with other allergies (atopy) should be discussed with current employees and with new workers prior to placement.

2. Every worker with asthma related to workplace exposure to tenderizers should be offered a work assignment that would minimize tenderizer exposure. Each of these workers should be assessed and treated by a physician knowledgeable in the management of occupational asthma. Drugs that prevent asthmatic attacks should be considered an adjunct to, not a substitute for, minimizing potential exposure to the substances that cause the attacks.

3. Each worker who develops episodic respiratory symptoms should be evaluated by a physician for work-related asthma.

C. Industry-wide

Manufacturers and suppliers of tenderizers should inform constituents of the potential for developing respiratory and dermal allergies by including current health effects information regarding proteolytic enzymes on Material Safety Data Sheets (MSDS) and on packages of raw materials. They should state that enzyme tenderizers (papain, bromelain, ficin) may produce respiratory and skin sensitization (allergies) in exposed workers. Irritation was the only health effect listed on several of the MSDS's and package labels we reviewed.

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XI. ACKNOWLEDGMENTS

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XII. DISTRIBUTION AND AVAILABILITY OF REPORT

Copies of this report are currently available upon request from NIOSH, Division of Standards Development and Technology Transfer, Publications Dissemination Section, 4676 Columbia Parkway, Cincinnati, Ohio 45226. After 90 days, the report will be available through the National Technical Information Service (NTIS), 5285 Port Royal, Springfield, Virginia 22161. Information regarding its availability through NTIS can be obtained from the NIOSH Publications Office at the Cincinnati address. Copies of this report have been sent to:

1. E.S.I. Meats, Inc., Bristol, Indiana
2. OSHA, Region V
3. U.S. Department of Agriculture, Washington, D.C.
4. Bureau of Local Health Services, Indiana State Board of Health
5. Indiana OSHA

For the purpose of informing affected employees, copies of this report shall be posted by the employer in a prominent place accessible to the employees for a period of 30 calendar days.

Table 1

Full-Shift Personal Breathing-Zone Papain Exposures

ESI Meats, Inc.
Bristol, Indiana
HETA 87-112

July 7-8, 1987

Date	Sample Description	Sample Time (min)	Sample Volume (L)	Papain Concentration (ug/m^3)
7-7-87	Quality Technician	342	843	0.45
7-8-87	Quality Technician	397	794	0.60
7-7-87	Packer, T-bone line	356	868	1.4
7-8-87	Packer, T-bone line	497	994	1.7
7-7-87	Packer, T-bone line	461	1075	0.64
7-8-87	Packer, T-bone line	501	1002	0.24
7-7-87	Packer, T-bone line	455	1064	1.5
7-8-87	Packer, T-bone line	485	970	0.45
7-7-87	Packer, rib-eye line 1	461	1081	1.1
7-8-87	Packer, rib-eye line 1	496	990	0.37
7-7-87	Packer, rib-eye line 1	443	1014	0.37
7-8-87	Packer, rib-eye line 1	456	912	0.37
7-7-87	Packer, rib-eye line 1	443	1038	0.33
7-8-87	Packer, rib-eye line 1	487	970	0.29
7-7-87	Packer, rib-eye line 2	444	1040	0.96
7-8-87	Packer, rib-eye line 2	454	906	0.77
7-7-87	Packer, rib-eye line 2	434	1016	0.54
7-8-87	Packer, rib-eye line 2	445	890	0.38
7-7-87	Packer, rib-eye line 2	442	1035	1.3
7-8-87	Packer, rib-eye line 2	472	942	0.22

Evaluation Criteria for subtilisins (ACGIH TLV, 1988): 0.06 (ceiling)

Table 2
General Area Papain Concentrations
ESI Meats, Inc.
Bristol, Indiana
HETA 87-112
July 7-8, 1987

Date	Sample Description	Sample Time (min)	Sample Volume (L)	Papain Concentration (ug/m^3)
7-7-87	Compounding Rm, above mix tank	452	1059	1.4
7-8-87	Compounding Rm, above mix tank	400	800	1.7
7-7-87	Corridor, directly outside compounding room	440	1030	ND
7-8-87	Corridor, directly outside compounding room	532	1064	ND
7-7-87	T-bone line, on sprayer	500	1168	2.1
7-8-87	T-bone line, on sprayer	523	1046	1.0
7-7-87	Rib-eye line 2, on sprayer	476	1092	1.2
7-8-87	Rib-eye line 2, on sprayer	516	1034	1.1
7-7-87	Rib-eye line 1, on sprayer	479	1118	1.1
7-8-87	Rib-eye line 1, on sprayer	518	1036	1.2
7-7-87	Nitrogen freeze tunnel	442	1036	0.02
7-8-87	Nitrogen freeze tunnel	525	1050	0.02
7-7-87	Eagle scale platform	444	1041	0.22
7-8-87	Eagle scale platform	512	1024	0.19
7-7-87	Choice 2 line	452	1059	Sample Lost
7-8-87	Choice 2 line	510	1022	0.08
7-7-87	Preprocessing Room	427	997	0.002
7-8-87	Preprocessing Room	528	1056	ND
7-7-87	Office	434	1023	ND
7-8-87	Office	503	1004	ND

Evaluation Criteria for subtilisins (ACGIH TLV, 1988): 0.06 (ceiling)

TABLE 3

JOB GROUPINGS INCLUDED IN PAPAIN EXPOSURE GROUPS

No Exposure (19 workers)		Exposure (77 workers)	
	# of workers		# of workers
Front Office	7	Choice 3 line	6
Warehouse	6	Choice 2 line	15
Sanitation	2	Choice 1 line	27
Cafeteria	2	Rib-eye line	12
Maintenance	2	T-bone line	9
		Quality/Laboratory	3
		Ground Beef	5

TABLE 4

PAPAIN EXPOSURE AND ASTHMA(*) DIAGNOSIS AMONG ALL PARTICIPANTS

	Diagnosis	
	asthma	no asthma
Exposure		
high	28	49
low	1	18

Odds Ratio = 10.3, 95% Confidence Limits: 1.44, 444 ($p<.01$)

* possible or definite tenderizer-related occupational asthma

TABLE 5

ELEVATED IgE AMONG SYMPTOMATIC WORKERS WITH AND WITHOUT TROA

	TROA	
	yes	no
Elevated IgE		
yes	6	0
no	23	20

Odds rates undefined; p = 0.03 (Fisher's exact test, 1-tailed)

TABLE 6

ATOPIC STATUS AND ASTHMA(*) DIAGNOSIS AMONG SYMPTOMATIC WORKERS

	Diagnosis	
	asthma	no asthma
Atopic(**)		
yes	8	0
no	21	20

Odds rates undefined; p = 0.01 (Fisher's exact test, 1-tailed)

* possible or definite tenderizer-related occupational asthma

** cutaneous reactivity to at least two airborne allergens

TABLE 7

ATOPIC STATUS AND SYMPTOMS SUGGESTIVE OF ASTHMA

	asthma symptoms	
	yes	no
Atopic(**)		
yes	22	11
no	27	31

Odds ratio = 2.3, 95% confidence interval: 0.9, 6.2 (p = .06)

** cutaneous reactivity to at least two airborne allergens

TABLE 8

PREVALENCE OF ECZEMA AND SEASONAL RHINITIS AMONG SYMPTOMATIC WORKERS WITH AND WITHOUT TENDERIZER-RELATED ASTHMA

	with TROA	without TROA
eczema	7%	10%
seasonal rhinitis	45%	31%

TABLE 9

FAST FOOD CONSUMPTION AMONG SYMPTOMATIC WORKERS
WITH AND WITHOUT TENDERIZER-RELATED ASTHMA

	with TROA	without TROA
less than once per week	24%	18%
more than once per week	76%	82%