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I.   SUMMARY

In June 1987, the National Institute for Occupational Safety and Health received a request from the International Chemical Workers Union to evaluate respiratory symptoms among workers in an ethical narcotics manufacturing building at the Penick Corporation, Newark, New Jersey.

In February 1988, 39 workers participated in an initial medical survey to determine the prevalence of asthma and respiratory complaints. Five workers demonstrated cross-shift decrements in one-second forced expiratory volume (FEV1) of greater than 10%. Serial peak flow measurements revealed evidence of airway hyperactivity in 10 workers during the work week. The overall self-reported prevalence of new-onset, physician-diagnosed asthma at the time of the initial survey was 10/39 (26%). Twenty of 35 workers demonstrated serologic evidence of morphine 6-hemisuccinate-human serum albumin (M6HSA)-specific IgG. No specific IgE to opiates was detected.

Industrial hygiene monitoring detected substantial exposures to alkaloid dusts throughout the building. Detectable amounts of airborne alkaloid dust were measured at all operations evaluated in this study. The exposure levels varied greatly, depending upon the moisture content of the material being handled. Furthermore, the mean concentration of alkaloids during the short-term dry powder handling operations (mean time = 22 minutes) was 4,823 ug/m^3, whereas the mean concentration of alkaloids during the short-term damp powder operations (mean = 19 minutes) was 210 ug/m^3. Higher levels of alkaloids were measured during the handling of dry material, as illustrated by the concentration, 23,564 ug/m^3, in a short-term sample collected during the hand scooping of dry codeine powder.

Environmental air samples collected for organic solvents detected over-exposures to toluene, butanol, methanol, and ethanol, during short-term episodic jobs. These jobs required the employees to come into close contact with the operating process. Full-shift organic solvent exposures were dependent upon the number of times the employee came into contact with the process.

During a follow-up survey conducted in December 1988, 32 current employees in the narcotic production area participated in a study of immunologic parameters including opiate skin tests, measurement of serum immunoglobulins and specific IgG and IgE to morphine, assessment of lymphocyte subtypes, and mitogen stimulation assays. A significant decrease in M6HSA IgG antibody levels was noted in 21 workers who submitted blood specimens during both test periods. Quantitative skin prick testing with opiates revealed that narcotic production workers had greater reactivity to most of the compounds than either of two referent groups: Penick employees from other areas, and an outside group without known opiate exposure.

On the basis of these data, NIOSH investigators have concluded that employees at the Penick Corporation developed asthma from occupational exposure to narcotic dusts. Recommendations to reduce exposure to narcotic dusts and solvents, and to evaluate workers with suspected work-related illnesses are found in Section IX of this report.

Keywords: SIC 2833 (Medicinal Chemicals and Botanical Products), 2834 (Pharmaceutical Preparations), occupational asthma, morphine, atopy, narcotic dusts, immunology.

II.   INTRODUCTION

In June 1987, the National Institute for Occupational Safety and Health received a request from the International Chemical Workers Union to evaluate symptoms of headache, nausea, and respiratory symptoms among workers employed in the narcotics manufacturing building at Penick Corporation, Newark, New Jersey. An initial site visit was performed in August 1987, and an initial medical and environmental survey took place during the week of February 5, 1988. The preliminary data and reports in the medical literature about the potential health hazards associated with occupational exposure to narcotic dusts prompted a return visit to the plant in December 1988, to gain additional information about the possible immunological mechanisms for the reported symptoms. The union and company were notified of the medical results of the two surveys in letters of April 11, 1988 and March 31, 1989. Participants were notified of their own test results in letters dated May 10, 1988 and July 12, 1989. Preliminary industrial hygiene results were included in letters dated October 16, 1987, and May 25, 1988. Recommendations to control narcotic dust exposure were presented to the union and company on November 7, 1988.

III.   BACKGROUND

The starting material for the commercial production of morphine is the sap of the opium poppy, Papaver somniferum. The sap is obtained by incising the unripe seed pods, which contain a latex-like substance containing over 20 alkaloids. These alkaloids include two basic classes, the phenanthrenes, of which morphine is one example, and the enzylosoquinones, from which the vasodilator papaverine is obtained. Thebaine, a non-narcotic structurally complex substance, is also found in the raw material and is an important structural intermediate for the production of other compounds.

Gum opium is composed of approximately 10-13% morphine, about 2-3.5% codeine, and 1-2% thebaine by weight.[1] In an effort to avoid diversion of the raw materials to the illegal narcotics trade, some countries, most notably Turkey, have developed large processing facilities which obviate the necessity of the hand-incision stage of the process. The material is then slightly dehydrated to form a concentrated form of a dark rich material known as poppy straw concentrate. This material, containing approximately 70% pure morphine by weight, is then shipped for further manufacturing.

The Penick Corporation is one of only three facilities in the United States that produces morphine, codeine, synthetic, and semisynthetic narcotics from the raw materials gum opium and poppy straw concentrate. Penick manufactures the end product narcotics from either gum opium or poppy straw concentrate, which undergoes a series of distillations, chemical extractions with common solvents, precipitations, and centrifugations to obtain the specific alkaloid of interest. The end products are dried to remove moisture and are then milled to appropriate size. The materials are then analyzed for purity, weighed to assess yield and to avoid diversion, and then packaged and shipped to the final destination. No compounding or tableting takes place in this plant. Material handling includes automated and manual operations. The production process consists of batch operations which are accomplished in reaction vessels typically fitted with agitators for mixing and hatchways for making additions. The transfer of process solutions between vessels is accomplished by mechanical pumping or is gravity fed via closed piping, or occasionally by bulk drumming of liquid. Once the solid alkaloids have precipitated from solution, they are handled manually. Exposure to solid alkaloid materials and solvents occurs during work involving solids isolation, drying, blending, milling, and manually transferring between containers. Worker exposure to alkaloid materials can also occur during lab analysis, quality control, final processing, and packaging operations.

Because of security concerns, no natural ventilation via open windows is allowed in the narcotic production. Control of organic vapor is accomplished by mechanical dilution ventilation from both localized forced air exhaust and supply systems and from general area systems throughout the production area. The general production areas receive 100% outside fresh air. Design air flow capacities based on room air changes per hour (RCH) for the general production areas range from 12.2 to 30.8 RCH. Storage vaults have dedicated exhaust ventilation. Exhaust fans are switched on by personnel entering the vault room.

The production of narcotic pharmaceuticals began at the Penick Corporation Newark site in 1951. CPC International Inc. purchased the Penick plant in 1968, and continued ownership until March 1988, when CPC sold the plant to Mayfair Pharmaceutical Inc. In addition to narcotic production, the Penick Corporation also operates a fermentation facility for production of pharmaceutical and biotechnology products, and a production facility for bismuth salts at the Newark plant site. Plant population is less than 200 people, who are divided between the various functions carried on at the site. All production and maintenance workers are members of the International Chemical Workers Union (ICWU) Local 153. The majority of the production workers are divided into shift crews that rotate throughout the work week. There is a small number of day shift only workers who handle specific operations that do not require around the clock manning. A staff of production supervisors works in each of the operating departments, and accountability personnel in addition to the other supervisory staff also work in the narcotics department. There is a joint union-management safety and health committee in the plant which meets regularly.

IV.   METHODS

A. Environmental

During the site visits, observations were made of the various tasks, use of exposure control methods, and potential sources of exposure. Material safety data sheets were reviewed to determine a profile of chemical use and to identify potential health hazards. Environmental measurements were obtained to evaluate employees' exposures to chemicals and to assess the performance of the ventilation systems. Management and employees were interviewed on the use of personal protective equipment, plant operations, and potential sources of exposure. The use of personal protective equipment and its proper selection, size, availability, and effectiveness was noted.

Based on the information collected on the initial site visit, the environmental evaluation consisted of two phases. Phase #1 consisted of collecting instantaneous readings during episodic employee exposures to organic solvents and alkaloid dust using direct-reading instrumentation. Phase #2 consisted of collecting full-shift and short-term personal breathing zone (PBZ) samples for organic solvents and alkaloid dusts.

During phase #1, environmental exposures were estimated using direct-reading instrumentation at various locations throughout the process. Organic solvent levels were recorded using both direct reading colorimetric Drager gas detector tubes and a Foxboro Miran 1B portable ambient air infrared analyzer. Alkaloid dust concentrations were recorded using the GCA Mini-RAM aerosol monitor. In addition, a qualitative and quantitative assessment of the ventilation system was conducted for comparison with the original design specifications. The qualitative assessment was conducted using smoke tubes and observing the general air patterns throughout the building. Quantitative measurements were made throughout the system with an Alnor thermo-anemometer and bolometer.

During phase #2, full-shift and short-term air samples were collected for evaluating workers' exposures to organic solvents and alkaloid dusts. Personal breathing zone samples were collected from workers in each job category on each of the three shifts. In addition, area samples were collected to assess the potential for microbial contamination as a source for the respiratory problems.

Personal breathing zone samples for organic solvents were collected by drawing air through a sorbent tube attached via tygon tubing to a battery-operated pump which was pre-calibrated to a desired flow rate. The following sampling and analytical methods were utilized for each individual analyte: methanol, NIOSH method #2000 using a 1000-milligram (mg) silica gel tube; ethanol, NIOSH method #1400 using a 600-mg charcoal tube; and toluene, butanol, and dimethylaniline (DMA), OSHA method #7 using 150-mg charcoal tubes. To guard against breakthrough of the sample media, each sorbent tube was replaced half-way through the shift. Analysis of the media was conducted by the NJDOH Environmental Health Laboratory using gas chromatography according to each of the aforementioned analytical methods.

Personal breathing zone samples for alkaloid dusts were collected by drawing air through a 37-mm glass fiber filter attached via tygon tubing to a battery powered pump at a flow rate of either 2.5 or 4.0 liters per minute (lpm). Each sample was analyzed for codeine and morphine using a high-pressure liquid chromatograph (HPLC). The sampling and analytical methods were adopted from those used by Merck and Company, Incorporated, of Rahway, New Jersey (where alkaloid production had occurred until approximately 1983).[2] Standards were first prepared by spiking known amounts of analytes onto glass fiber filters. Samples and standards were then desorbed in 4.0 ml of mobile phase (0.01 M sodium pentane sulfonate in 22/78 acetonitrile/water) for 30 minutes with sonication. The resulting sample and standard solutions were injected into the HPLC system using a 0.01 M sodium pentane sulfonate in 22/78 acetonitrile and water. 150 microliters (ul) of the sample were injected at a flow rate of 1.2 ml/minute and analyzed at a wavelength of 254 nanometers (nm). The limit of detection (LOD) for codeine was 4.0 ug/sample. The LOD for morphine was 5.0 ug/sample.

All environmental monitoring results for chemicals in narcotic area were requested from the Company. These data were reviewed to establish the exposure history for the workers in this study.

Area air samples for microbial contamination were collected by drawing air through midget impingers with distilled water as the collection media, attached via tygon tubing to environmental sampling pumps operating at a flow rate of 2.5 lpm. Bulk samples were also collected from the liquid surface of a processing vessel where floating material was present. Each impinger sample was rinsed out with distilled water and serial dilutions of 1:50, 1:500, and 1:5000 were prepared. The samples were plated onto an S D Agar with penicillin and streptomycin and incubated at 30 degrees Celsius. The plates were counted at 24, 48, and 72 hours. The air samples were evaluated for the identification and enumeration of fungi. The bulk samples were evaluated for the identification of predominate fungi present.

B. Medical: Initial Study (February 1988)

1. Questionnaire

During the week of February 8, 1988, a physician from the investigating team individually administered a questionnaire to all available employees who were willing to participate. The questionnaire was designed to ascertain the prevalence of respiratory symptoms and medical diagnoses among the work force.

2. Pulmonary Function Testing

Pulmonary function testing was performed before and after each work-shift on Monday, Wednesday, and Friday of the work week. In addition, pre- and post-shift testing was offered on Tuesday to accommodate several workers who did not report for testing on Monday. Individuals were encouraged to complete three sets of pre- and post-shift tests.

Pulmonary function testing was completed 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.[3] When possible, participants had the testing performed by the same technician on the same testing device.

3. Peak expiratory flow rates (PEFR)

PEFRs were measured serially for one week, using mini-Wright's portable peak flow meters. Participants were asked to record peak flow every 3 hours while awake, and during the night if awakened for any reason. Individuals reported each morning to one of the examining stations to turn in the results from the previous day. This was done to assess the efficacy of the reporting and to prevent individuals from recording values which might be influenced by the knowledge of the previous day's results. Three exhalations were recorded each time, and the maximum of the three was accepted as the PEFR. A participant was considered to have significant bronchial lability if the difference between the minimum and maximum PEFR on at least 1 day exceeded 20% of the day's maximum PEFR.

4. Urine Solvents and Metabolites

Participants submitted pre- and post-shift urine specimens for analysis of hippuric acid (a metabolite of toluene), methanol, formic acid (a metabolite of methanol), and creatinine (used to standardize concentrations of the other substances).

5. Immunologic Tests

Serum obtained from participants was analyzed for specific IgE to gum opium using the radioallergosorbent test (RAST). Serum was also analyzed for specific IgG and IgE to morphine-6-hemisuccinate-human serum albumin (M6HSA) conjugate using an enzyme linked immunosorbent assay (ELISA). Determination of specific IgE to the M6HSA was also performed using RAST. Screening for specific IgG was done at 1:10 dilutions. Purity of the antigen (M6HSA) was assessed using gas chromatography/mass spectroscopy. Results were considered positive if the optical density of the participants' sera exceeded 2.5 times the mean of the laboratory control sera.

C. Medical: Follow-up Study (December 1988)

1. Participant Selection

All participants from the February 1988 study were invited to participate in the second phase of the medical study (December 1988). In addition, we asked the management and union to help us identify workers who had not been previously employed in the narcotic production area to serve as a referent population. Workers were given a brief screening questionnaire to identify individuals with asthma, disorders of the immune system, or other medical conditions that might affect the interpretation of results. Workers were also asked about the use of prescription narcotic medications in the past.

2. Blood Tests

   Blood specimens were analyzed by a local commercial laboratory for standard hematologic parameters (complete blood count with differential) and serum immunoglobulins (total IgE, IgM, IgG, and IgA).

3. Serum Opiates

   Twenty-three individuals returned consent forms in September 1988 to permit the serum obtained in February 1988 to be analyzed for the presence of opiate compounds. The purpose of this test was to detect any opiates in the blood that might interfere with the antibody testing. Specimens were analyzed using a radioimmunoassay method that has a limit of detection of 9 nanograms/ml blood but can suffer interference ("false positives") from over-the-counter medicine and certain foodstuffs, such as poppy seeds.

4. Lymphocyte Surface Markers

   The percentages and numbers of individual white blood cells (lymphocyte subtypes) were determined using a fluorescent-activated cell sorter (FACS). These lymphocytes were analyzed for total T-cells, total T-helper lymphocytes, total T-suppressor lymphocytes, total B-cells, and total natural killer cells (using two markers). Results were analyzed by determining the mean value of results in each study group. Differences between mean values were determined using a Student's t-test.

5. Lymphocyte Proliferation Tests

   The ability of lymphocytes to proliferate in response to three concentrations of three different lectins was analyzed using a protocol obtained from the National Institutes of Health. The mean value, expressed as disintegrations per minute (dpm), of each set of results was compared between study groups.

6. Immunological Tests

   Sera from participants were tested for three types of antibodies to a M6HSA compound prepared from morphine base supplied by Penick. The sera were tested for the presence of 1) IgG to M6HSA, 2) IgE to M6HSA, and 3) specific IgG4 to M6HSA. To ensure comparability between samples taken in February 1988 and December 1988, specimens from both time periods were analyzed simultaneously. Specimens with insufficient amounts of sera were excluded. A test was considered positive if the measurements of an antibody in a worker's serum exceeded 2.5 times the mean of the laboratory control sera. Differences in total specific IgG between the February 1988 exposed group, December 1988 exposed group, and the December 1988 unexposed group were analyzed with the Kruskal-Wallis statistical test. A Wilcoxon test for paired observations was used to investigate differences in ELISA absorbance ratios for individual workers who provided sera at both testing periods.

7. Skin Tests

   Skin prick testing was performed using a battery of nine common aeroallergens (blue grass, elm, red oak, orchard grass, cat, alternaria, hormodendrum, dust mite, and ragweed). Phosphate buffered saline (PBS) was used as a negative control and histamine (10 mg/ml) was used as a positive control. A test was considered positive if the largest diameter of the measured wheal (hive) was at least 4 mm. A person was considered atopic if there were at least two positive skin tests to common allergens.

The dichotomous outcome variables (reaction/no reaction) were compared using a chi-square test or a Fisher's exact test, as appropriate.

Quantitative skin prick testing was performed using a series of opiates obtained from the company. Compounds tested during this evaluation included codeine phosphate, morphine sulphate, thebaine, oxycodone, M6HSA, hydrocodone, didrate, gum opium, and two protein extracts from the gum opium (designated as Opium A and Opium B). Testing was performed using decremental serial ten-fold dilutions of each test compound. Skin test concentrations for all compounds ranged from 10 mg/ml to 10^{-3} mg/ml. A prick test was reported as positive if the largest wheal diameter measured at least 4 mm. If two dilutions produced an identical 4-mm wheal, the result was recorded as positive at the higher dilution. An individual who had a wheal greater than 4 mm in diameter, but who did not have a skin prick test performed at the next lower concentration, was considered to have missing values.

There are no published data on skin prick responses to opiates. Codeine and morphine are often used as positive controls in intradermal skin testing because of their ability to release histamine directly from mast cells. Results are therefore expressed in several ways. The small number (8) of individuals available at the plant as a referent population limited the study's ability to evaluate potential differences in sensitivity to the opiates. Instead, a local medical center provided data on the results of identically performed skin prick test of 17 individuals in the Cincinnati area without known exposure to opiates. These individuals received a limited battery of opiate skin prick tests and were not tested for the common aeroallergens.

Results were coded either as a positive reaction or no reaction. To assess group differences with respect to the lowest concentration producing a positive reaction, mean sensitivity scores were assigned as follows: 6 = no reaction, 5 = lowest positive reaction at 10 mg/ml, 4 = lowest positive reaction at 1 mg/ml, 3 = lowest positive reaction at 0.1 mg/ml, 2 = lowest positive reaction at 0.01 mg/ml, and 1 = lowest positive reaction at 0.001 mg/ml. Therefore, the lower a person's score, the more sensitive he/she is to the allergen being tested. The mean scores were compared between groups using the Kruskal-Wallis non-parametric analysis of variance.

The percentage of positive reactors in each group was compared using a 2X3 contingency table and a chi-square test.

V.   EVALUATION CRITERIA

A. Environmental Criteria

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 Criteria Documents and recommended exposure limits (RELs)[4], 2) the American Conference of Governmental Industrial Hygienists' (ACGIH) Threshold Limit Values (TLVs)[5], and 3) the U.S. Department of Labor (OSHA) occupational health standards.[6] Often, the NIOSH RELs and ACGIH TLVs are lower than the corresponding OSHA standards. The OSHA standards 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 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 (STELs) or ceiling values which are intended to supplement the TWA where there are recognized toxic effects from high short-term exposures.

B. Solvents

Individual exposure criteria for n-butyl alcohol, dimethylaniline, ethyl alcohol, methyl alcohol, and toluene, are as follows:

Compound	OSHA (PEL)	ACGIH (TLV)	NIOSH (REL)
	[------------concentration in PPM------------]		
n-Butyl alcohol	50 (C,S)	50 (C,S)	N/A
Dimethylaniline	5 (TWA,S) 10 (STEL)	5 (TWA,S) 10 (STEL)	N/A
Ethyl alcohol	1000 (TWA)	1000 (TWA)	N/A
Methyl alcohol	200 (TWA,S) 250 (STEL)	200 (TWA,S) 250 (STEL)	200 (TWA) 800 (C)
Toluene	100 (TWA) 150 (STEL)	100 (TWA) 150 (STEL)	100 (TWA) 200 (C) 10 min

Key

PPM	= parts per million
C	= the employee's ceiling exposure which should not be exceeded during any part of the work day
TWA	= the eight- or ten-hour time-weighted average exposure
STEL	= the 15-minute time-weighted average exposure
S	= skin absorption is possible
N/A	= not available

Because most solvents are central nervous system depressants, simultaneous exposure to more than one of them may produce an additive effect even when exposure to each individual solvent is at or below its recommended limit. In mixed solvent exposures, acceptable levels as defined by OSHA are calculated by using the following formula:

$$C1/PEL1 + C2/PEL2 + ... + Cn/PELn = \text{Composite Concentration}$$

Where C = concentration of the individual solvent
Where PEL = permissible exposure limit for that solvent.

Exposure is considered to be below the mixed solvent concentration when the composite concentration is less than 1.0.

C. Alkaloids

There is presently no established exposure criterion set for occupational exposures to alkaloid dust. One previous manufacturer in the United States established exposure levels based on the pharmacological effect of sedation;[7] these levels, however, may not be adequate to prevent allergic or idiosyncratic reactions to opiates. These reference exposure levels are presented here because they are the only ones available. They have not been evaluated by NIOSH and should not be construed as NIOSH recommendations.

	8-hour TWA	1-hour STEL
codeine	500 ug/m^3	4000 ug/m^3
morphine	100 ug/m^3	1000 ug/m^3

The air sampling results of this study provide an estimate of exposure via the inhalation route. It should be noted, however, that dermal adsorption and ingestion are also potential pathways for morphine and codeine to be adsorbed into the body. These routes of exposure were not measured, and thus cannot be accounted for in assessment of total dose.

D. Microorganisms

Increasing attention is being focused upon the potential for immunologic response, after repeated inhalation, to a variety of organic materials. Cases of hypersensitivity pneumonitis have been documented in individuals exposed, in the occupational environment, to fungi, thermophilic actinomycetes, as well as animal proteins. Current research on the cause of respiratory illness associated with exposure to microorganisms has not yet developed any dose response relationships. The sensitizing potential of airborne microorganisms to a susceptible individual may also play an important role in the development of respiratory illness.

VI. RESULTS

A. Environmental

1. Solvents

Table 1 presents the results of the 36 PBZ short-term organic vapor samples that were collected during seven different production operations. Substantial exposures to individual solvents were measured during each of the six solids separating digout operations, ranging from 37 to 625 parts per million (ppm) for toluene, 271 to 1300 ppm for butanol, and 3200 to 9000 ppm for ethanol. Toluene exposure during handling of tar cake, dumping of reactor solids, and the accidental spillage of process liquor were found to be greater than the STEL of 150 ppm. In addition, substantial exposures were measured during the opening of various reactor vessels, ranging from 145 to 1030 ppm for butanol and 400 to 2000 ppm for methanol. Finally, substantial exposures to ethanol were measured during the mixing of various solutions in open vats, ranging from 2000 to 4000 ppm. Negative pressure respirators (either half or full face) equipped with organic vapor/acid gas cartridges were worn by the employees during these operations.

Table 2 presents the results of twenty personal breathing zone full-shift samples for individual solvents. The TWAs for each individual solvent, as well as the mixed composite concentrations, were less than the evaluation criteria for all of the samples collected, except for the two deterring operators. An overexposure to toluene, averaging 123 ppm was measured on the deterring operators.

2. Alkaloids

Table 3 presents the 27 personal breathing zone short-term exposures to codeine and morphine collected during seven different handling operations. Substantial airborne exposures were measured during those operations which required the handling of dry alkaloid powder, including powder scooping, blender loading and unloading, and dryer unloading. The highest levels of codeine [23,564 micrograms per cubic meter (ug/m^3)] and morphine (10,523 ug/m^3) were collected during the transfer of dry powder using hand scooping techniques. Codeine levels measured during the loading and unloading of the blenders ranged in concentration from 2,074 to 8,652 ug/m^3. Codeine levels measured during the manual dumping of material from the dryers ranged from 72 to 3,723 ug/m^3.

Table 4 presents the results of the 12 full-shift samples for codeine and morphine collected during the finishing, milling, and packaging of codeine powder. Detectable amounts of codeine were measured at each of the job positions sampled, whereas only one of the 12 samples collected for morphine had a detectable amount. Air levels of codeine measured in the product finishing room ranged from 32 to 183 ug/m^3. Air levels measured during the milling of codeine ranged from 364 to 594 ug/m^3. An air level of codeine measured during the packaging of codeine into drums for shipment was found to be 1,572 ug/m^3.

3. Microbial

Each of the area air samples collected in the production areas was negative for fungal growth. The bulk samples collected on the first floor around the macerator and press area identified Aspergillus flavus and niger, and Penicillium, Mucor, Rhodotorula, and Geotrichum species; and Candida krusei.

4. Ventilation

General:

Table 5 presents a summary of the measured capacities of the general ventilation system. On the average, the supply and exhaust capacities measured throughout the production areas in the narcotic manufacturing facility were found to be 41 and 60% of the system design, respectively.

Table 6 presents a summary of the local exhaust ventilation survey. The only source of local ventilation at certain units was a nitrogen purge system, and this system was not designed as a local exhaust ventilation system. Face velocities measured at each of the hoods were compared against recommended criteria for capturing the appropriate contaminant. Readings obtained from a total of 17 hoods revealed that only three met or exceeded the ACGIH recommended capture velocities for the applicable hood design.[8,9]

Specific:

The general ventilation system serving the finishing and packaging areas, where the highest levels of airborne alkaloid have been measured, delivers tempered recirculated air to the work areas via supply and exhaust. Each system provides some (approximately 10%) fresh outside air makeup. Design air flow capacities based air room changes per hour (using makeup air) range from 0.9 to 3.2 (average of 1.8). The supply air is filtered through 0.23 micron filters to remove particulate. The limited number of supply and exhaust grilles indicates poor air distribution in the finishing and packaging areas. "Short circuiting" of distributed air was observed in the second floor batch morphine weighing room. No local exhaust ventilation is used to capture and control fugitive airborne alkaloid dust. Once dust is entrained into the work environment air, it remains until it settles or is slowly purged by the general ventilation system.

During cake "digout", excessive levels of airborne toluene were measured in the operator's breathing zone. Although no toluene was used in this process, it was determined that toluene vapor was entering this solids separator through duct work common to an adjacent unit. Venting for emergency pressure relief for separators, reactors, and other vessels is achieved via stainless steel pipe connected to common headers, which are then vented to the roof. Several process vessels were disconnected from this pressure relief system.

Hatchways and manways of reactors and separators are fitted with gaskets and fasteners to prevent vapor leakage. Incomplete seals were observed on some process units due to metal warping and gasket fatigue. This may result in fugitive vapor emissions.

In general, the existing ventilation systems indicate a need for maintenance and repair. For example, a supply fan located on the roof was found with a rusted-out bottom panel, allowing supply air to bypass the filter and heater coil. Supply and exhaust grilles throughout the building had buildups of dust and debris, thus reducing efficiency.

5. Personal Protective Equipment

General:

Employees are supplied with a clean cotton uniform each work day. Security requirements prohibit the use of workers' personal clothing in the plant and the

removal of work uniforms from the plant. Individual lockers are assigned for clean personal clothing and another for clean work uniforms. The contamination of workers' personal clothing is unlikely. The required use of additional personal protective equipment is outlined on each batch sheet for a given operation.

Respiratory protection is the predominant method to control exposure to airborne contaminants at this facility. Several types of respirators were being used. A written respiratory protection program is available but does not appear to reflect current plant practices. Discussions with plant management and workers indicate that fit testing procedures (quantitative or qualitative) have not been administered. Each worker is responsible for cleaning their respirator daily. A cleaning station is available in the locker room.

Specific:

When handling solid alkaloid material, the operator is required to wear disposable Tyvek® coveralls. An operator was observed emptying the dryer without a Tyvek® coverall, and as a result, white alkaloid material contaminated the worker's shirt and pants.

At the onset of this investigation, operators were using Edmont Neox® protective gloves made of neoprene for protection against toluene and butanol solvents. The Edmont selection guide indicates neoprene gloves are susceptible to degradation and permeation by toluene. When notified, the company replaced these gloves with nitrile-butadiene-rubber gloves. Workers are supplied with disposable latex wrist gloves for protection against contact with alkaloid powder. General duty gloves (Edmont Hynit (NBR)) are used for equipment operation and barrel handling. Although protective latex gloves were readily available, workers were observed, periodically, not using glove protection during alkaloid dust handling activities.

Excessive exposure levels to toluene (500 ppm) during a cake digout of 1-CF-2 prompted the investigators to recommend upgrading the respiratory protection for this operation, from a half-face to a full-face respirator equipped with organic vapor cartridges. This recommendation was implemented by the company.

Excessive exposures to methanol (2000 ppm) during the batch make up of 3-TA-4 prompted the investigators to recommend upgrading the respiratory protection required for this operation. The company changed the process and re-evaluated the exposures until acceptable levels were obtained.

Operators were observed using dual cartridge respirators with inappropriate cartridge filters (i.e., ammonia cartridges were being used during toluene and butanol exposures). Cartridges were also found to be inserted backwards, and inspection of several half-mask rubber respirators revealed deformed seals, faulty valves, and worn head straps.

During a tar cake handling operation on the first floor, several different inappropriate respirators were being used. A 3M 8500 paper dust mask and a 3M 7254 full face respirator fitted with ammonia/acid gas cartridges (TC-23c-440) were used by workers during operations involving measured overexposures to toluene. A review of the batch sheet for this operation found no recommendations for respiratory protection.

In March, 1988, interim recommendations were made to upgrade respiratory protection for all alkaloid dust operations from the non-toxic dust mask to a half-mask dual cartridge respirator equipped with high efficiency particulate absolute (HEPA) filters, and to include quantitative or qualitative fit testing. The

company implemented the use of half-mask respirators equipped with HEPA filters, but fit testing procedures have not taken place.

B. Medical

1. February 1988 Study

Participants

Thirty-nine current employees from the narcotics production area participated in the study. No suitable comparison group was available since all individuals were potentially exposed to narcotic dusts. The exact number of employees in the building was claimed to be a trade secret, so the specific participation rate cannot be presented.

The mean age of participants was 45 years (range 23-63). Thirty-seven of the participants (95%) were male. The mean duration of employment in the building was 11.2 years (range 0.3 to 36 yrs). Eleven employees were current smokers. Among current and former smokers, the average smoking history was 12.5 pack-years (range 0.1 to 78.8).

Questionnaire Results

Ten individuals reported having ever received a diagnosis of asthma from their physician. One individual had childhood asthma which was no longer active. A second individual reported the onset of asthma prior to working in the narcotics building. The remaining eight individuals all reported the onset of asthma after beginning work in the narcotics building. In addition, the medical records of two other individuals mentioned asthma subsequent to beginning work in the area.

Follow-up questioning of these individuals confirmed this information. Thus, of the 39 participants, 10 (26%) had received a diagnosis of new-onset adult asthma since beginning work in the narcotic production area. Four of these workers reported the development of asthma within 1 year of beginning work.

Twenty-four (62%) individuals reported a history of at least one episode of wheezing since employment in the narcotics building. Of these 24 individuals, 21 (85%) reported episodes of wheezing within the past month. Among the 21 individuals with wheezing during the past month, 17 (81%) reported that the wheezing occurred with shortness of breath, 14 (67%) with chest tightness, and 15 (71%) with coughing. Six (29%) of the individuals reported that the episodes lasted less than 1 hour.

Of the 21 individuals who reported wheezing during the past month, 20 (95%) reported less frequent episodes of wheezing during vacations or periods away from work. Ten (48%) said wheezing followed certain exposures at work, and 9 others said it occurred at least "sometimes" after these exposures.

Other reported symptoms at work included: itchy, runny nose (49%); stuffy nose (57%); and itching eyes (56%). Sixteen individuals (41%) reported a work-related rash within the preceding 2 months. The distribution of the rash for those reporting it was: hands (88%), face (56%), neck (62%), and forearms (75%).

Asthmatics vs. Non-Asthmatics

Those reporting new-onset asthma were not significantly different than those not reporting new-onset asthma with respect to age (42 vs 47), pack-years (15.2 vs

11.8), proportion of current smokers (40% vs 25%), or years in the building (10.8 vs 10.5). Asthmatics did report a higher percentage of episodes of wheezing [100% vs 46%; Relative Risk (RR)=2.15, 95% Confidence Interval (CI): 1.4, 3.2] and wheezing within the past month [90% vs 39%; RR=2.3, CI: 1.4, 3.8)

Pulmonary Function Tests

Thirty-eight individuals completed at least one set of pre- and post-shift pulmonary function tests. Five (13%) individuals demonstrated cross-shift decrements in their FEV1 of over 10%; three of them had a history of asthma.

Peak Flow Results

Thirty-six of the 39 participants completed at least 2 days of interpretable peak flow measurements. Nine individuals showed a single day decrease of over 20% in the peak flow. A tenth had a single-day drop of 19% but exhibited a stair-step type decrease over the week. One of the individuals with a single-day drop of over 20% had over 15% variations on the weekends as well. Two of the individuals with substantial peak flow decreases also demonstrated a cross-shift decrease in FEV1 of over 10%.

Urine Solvent Metabolites

No methanol was detected in any of the post-shift urine samples. Urinary formic acid levels showed considerable variation. The mean pre-shift value was 118 mg/g creatinine [Standard Deviation (S.D.)=415]; the mean post-shift value was 84 mg/g creatinine (S.D.=110). No individuals demonstrated a post-shift hippuric acid greater than 3.5 mgs/g creatinine.

Immunologic Tests

Serum from 35 participants in the February 1988 study was analyzed for the presence of IgG and IgE antibodies specific to gum opiate and the morphine-6-hemisuccinate-human serum albumin (M6HSA) conjugate. None of the sera tested demonstrated specific IgE antibodies (those associated with classical allergic reactions) to either compound. However, 20 of 35 individuals demonstrated low levels of IgG antibodies to the M6HSA (positive test was defined as a value which exceeded 2.5 times the mean value of the optical density of six laboratory controls not known to have had previous exposure to opiate compounds).

To confirm the specificity of the antibody, the serum from three individuals with the highest levels of IgG to M6HSA was re-analyzed using the enzyme-linked immunosorbent assay (ELISA) inhibition technique. In this test, the serum is pre-incubated with a similar compound, in this case morphine sulfate and morphine 6-hemisuccinate, and the amount of antibody is remeasured. Both compounds did inhibit the reaction, indicating the presence of a specific IgG antibody to the morphine nucleus.

Serum Opiates

Twenty-three individuals returned consent forms for participation in this phase of the study. Of this number, 17 has sufficient serum remaining for analysis. Three individuals had trace quantities of opiates detected by the radioimmunoassay method. (The possibility that these represented "false positive" reactions cannot be excluded unless gas chromatography is used, a procedure that was not necessary for our purposes). The levels found in three specimens were just above the limit of

detection. Thus, interference from opiate-like compounds in the serum was not a likely source of error in the determination of the IgE or IgG antibodies to the M6HSA conjugate.

2. Follow-Up Study (December 1988)

Participants

Thirty-one of the 39 previous participants agreed to participate in the December 1988 study. Of the eight individuals who did not participate, two current employees were ill, and one had difficulty scheduling a convenient time for the testing. Five of the original 39 participants, including one individual who indicated new-onset asthma, had terminated employment since the previous visit. Three additional current narcotic production employees, including one other employee who indicated new-onset physician-diagnosed asthma, were also enrolled in the study, even though they did not participate in the previous study. Thus, the December 1988 study participants included 34 current narcotic production workers.

Eight workers serving as a referent group consisted of management employees and maintenance workers. Most of the maintenance workers had worked in the narcotic production area but did not participate directly in manufacturing operations and thus were judged to have much less potential for exposure to the narcotic dusts.

Thirty-one of the 34 (91%) narcotic production participants were male, as were seven of the eight (88%) referent workers. There was no statistically significant difference between the mean age of the narcotic production and the reference group participants (47 vs 46 years, respectively). One of the referent group participants indicated a history of childhood asthma. Of the 34 current narcotic production participants, 10 (29%) indicated that they had received a physician diagnosis of asthma since beginning work in the building.

Hematologic Parameters and Immunoglobulins

The results of the standard hematologic parameters are seen in Table 7. There was no statistically significant difference in the hemoglobin, hematocrit, or white blood cell count between the narcotic production area and other participants. The narcotic production participants had a higher number of basophils (58 vs 41, pooled t: $p = 0.02$). When one individual with a markedly abnormal IgE value and another with a pre-existing medical condition that could affect interpretation were excluded from analysis, there was no difference in total IgE between the narcotic production employees and those in the reference group. When asthmatics within the narcotic production area were compared to their co-workers who did not report the diagnosis of asthma, asthmatics were found to differ only in having a lower concentration of total IgG (1068 vs 1537, pooled t: $p = 0.02$) (Table 8).

Immunologic Tests

Of the 40 blood specimens collected, 31 had sufficient serum for analysis. These 31 specimens consisted of 25 from the narcotic production workers and six from the Penick referent population. None of the sera from the 25 workers from the narcotic production or from the six referent group employees who had the blood test had evidence of IgE antibodies to the M6HSA compound. No serum from any participants contained evidence of specific IgG4 antibodies to the same M6HSA. (IgE, and possibly IgG4, antibodies are associated with classical allergic reactions.)

Only two of the 25 narcotic production workers in this survey had evidence of IgG antibodies to the M6HSA. One of the six Penick referent group workers had a value 2.5 times the mean value of the laboratory reference group, indicating the presence of an IgG antibody to the compound.

For the 21 workers who participated in both studies, a significant reduction in antibody levels was found between the two test periods. The mean absorbance ratio (an indicator of IgG concentration) decreased from 5.4 ± 0.95 in February 1988 to 1.19 ± 0.95 in December (Wilcoxon signed-rank test: $p<0.001$).

Lymphocyte Surface Markers

Individuals from the narcotic production area demonstrated statistically significant differences from the referent group in the following lymphocyte subpopulations: percentage of B-cells (15 vs 11, pooled t: $p=0.005$), B cell number (345 vs 246, pooled t: $p=0.01$), and percent helper cells (36 vs 52, pooled t: $p=0.02$) (Table 9). Within the narcotic production area asthmatics had an increased percent of helper cells (45.3 vs 32.6, pooled t: $p = 0.02$), a decreased number of suppressor cells (409 vs 694, pooled t: $p=0.007$), a decreased percent suppressor cells (19.5 vs 28.6, pooled t: $p = 0.07$), and a decreased percent natural killer cells as determined by the LEU72 marker (1.1 vs 3.1, pooled t: $p=0.01$) (Table 10). (These analyses excluded a non-asthmatic individual from the narcotic production area who had a pre-existing un-related medical condition. Inclusion of this person resulted in no significant changes in the results.)

Mitogenesis

Narcotic production participants demonstrated a statistically significant decrease in lymphocyte proliferation in response to all concentrations of pokeweed mitogen, but not to other mitogens (Table 11). There were no differences between asthmatics and non-asthmatics with respect to the mitogenesis assays (Table 12).

Skin Prick Tests: Aeroallergens

All participants demonstrated a positive response to the histamine control, and none showed a positive response to the PBS negative control. Therefore, no results were excluded on the basis of an atypical reaction to a control.

The number of positive reactors to common aeroallergens for each group is presented in Table 13. When atopy was defined as a positive reaction to two or more of these allergens, there was again no difference between the narcotic production participants and the referent group. Similarly, a comparison of asthmatics and non-asthmatics within the narcotic production area showed no differences in reactivity to common allergens and no difference in the percentage of individuals classified as atopic.

Opiate Skin Test Reactivity

The skin test results were dichotomized as reactive and non-reactive. The frequency distribution of all skin tests for the narcotic production area and referent groups are seen in Table 14. The percentages of reactors in each group can be seen in Table 15. With the exception of oxycodone and morphine, the narcotic production group had a significantly greater percentage of individuals with reactions to all substances tested. It is impossible to predict the effect of using increased concentrations of the skin test agents.

However, based on codeine's ability to release histamine directly from mast cells, an increased percentage of the non-reactors could be expected to react at higher concentrations of codeine, and possibly morphine as well.[10] However, since this study was designed to provide information about the possibility that opiate workers might have an increased sensitivity to the compounds (i.e., have a positive reaction as lower concentrations), the concentrations used were sufficient for our purposes.

Tables 16 and 17 compare the mean sensitivity score of the narcotic production workers with those of the combined and specific referent groups, respectively. With the exception of oxycodone, the narcotic production workers demonstrated a positive reaction at lower test concentrations of the opiate compounds than the referent groups. These differences were statistically significant for each referent group and for both groups combined. This analysis, however, does not permit us to determine whether the mean concentration among groups differs by a factor of 100, the minimal difference believed to indicate the possibility of an allergic reaction. The relatively high percentage of non-reactors precluded a more detailed analysis of these data.

VII.   DISCUSSION

A.   Environmental

The environmental samples collected for organic solvents indicate that the greatest potential for exposures occurs during episodic jobs that require the employees to come into close contact with the process. Those jobs identified as having a potential for high solvent exposures include: vessel openings, separator digouts, and dumping, mixing and unloading of products from various vessels. Generally, these operations take less than 30 minutes to complete, but they require the worker to open a closed process, thus increasing the potential for a release of organic vapors into the ambient environment. In addition, the sample results and ventilation survey illustrate that there is a lack of adequate local exhaust ventilation throughout the building to control the release of vapors during these operations. The existing general ventilation system provides minimal dilution of organic vapor in the general work place environment and does not prevent direct operator exposure to organic vapors. Finally, the primary control method during the episodic solvent exposures was respiratory protection. However, during many of the observed exposures, the respirator was found to be either inadequate or inappropriate for the specific contaminant.

The full-shift environmental samples collected for organic solvents further illustrate that the greatest potential for significant employee exposure is during the short-term episodic jobs. The full-shift samples did not reveal any significant overexposures to any of the solvents, individually or collectively, except for the detarring operators. A high short-term exposure to toluene (625 ppm) measured during a separator digout operation contributed to both the full-shift TWA overexposure to toluene and the composite solvent exposure level. The full-shift overexposures are dependent upon the number of times that the employee is required to come into contact with the operating system.

Airborne alkaloid dust was measurable at all operations evaluated in this study. The exposure levels varied greatly depending upon the moisture content of the material being handled. Significantly higher levels of alkaloids were measured during the handling of dry material, as illustrated by the short-term sample collected during the hand-scooping of dry codeine powder (23,564 ug/m^3). To further illustrate, the mean concentration of alkaloids during the short-term dry powder handling operations (mean time = 22 minutes) was 4,823 ug/m^3, whereas the mean concentration of alkaloids during the short-term damp powder operations (mean = 19 minutes) was 210 ug/m^3. More continuous exposures were found during the processing of dry alkaloid powder which may last for up to an entire work shift. The lack of engineering control measures (i.e.,

local exhaust ventilation) at the dry powder handling operations has resulted in uncontrolled "clouds" of particulate to be present during these operations. In addition, prior to March 1988, the workers were supplied with 3M 8500 Non-Toxic Particle Masks, which are not NIOSH-approved and may be inadequate respiratory protection for exposures to narcotic dusts. In March of 1988, the company implemented our interim recommendation to upgrade to a NIOSH-approved half-mask dual-cartridge respirator equipped with high-efficiency particulate air filters.

Skin contact with alkaloids takes place whenever workers handle material due to inadequate protective measures. Skin contact is also possible when workers are near but not directly involved with dust handling operations due to the generation of uncontrolled airborne alkaloid dusts that may settle onto exposed skin.

Reducing workplace exposures to etiologic agents of occupational asthma has been reported to be effective in lowering rates of sensitization among workers.[11,12] The control of narcotic dusts, which are responsible for asthmatic health effects through a hypersensitivity mechanism, must be adequate in reducing exposure to the lowest levels possible. To this end, a multiple level of protection is necessary to be incorporated in plant operations where exposure exists. Engineering controls are necessary to contain and remove exposures away from workers such as using process changes, local exhaust ventilation, and isolation techniques. When necessary, respiratory protection may be required for some workers as an added level of precaution to reduce the level of exposure even further. It may be necessary to remove individuals with persistent heath effects from exposure to the causative agent. The medical removal of workers is intended to protect employees' health and should not penalize the workers by loss of earnings, seniority, or other employment rights and benefits as a result of the removal. An expert medical opinion should be sought to determine when respiratory protection and medical removal measures are appropriate.

The final mode of protection to prevent adverse health effects is a medical surveillance program designed to track health effects and to identify workers at risk. The medical surveillance of workers' respiratory performance should be used to track any changes that may result because of exposure reduction. The combined use of air exposure monitoring with medical surveillance is needed for the management of asthmatic individuals.

B. Medical

The paucity of data concerning occupational exposure to opiates was one of the chief difficulties encountered in this evaluation. A previous report by Alenia, et al. revealed a high prevalence of asthma (13%) among 119 workers exposed to morphine dust.[13] Neither industrial hygiene data nor details of pulmonary function tests were described, however. In our study, 11 (26%) of 42 opiate workers studied during both of two test periods were found to have either self-reported and/or medical record evidence of new-onset asthma since beginning work in the narcotics building.

Since there can be a wide range of diagnostic criteria for asthma, both false positive and false negative diagnoses of occupational asthma can be expected. The opiates are pharmacologically complex substances. They are capable of directly releasing histamine from mast cells, and on this basis alone might be predicted to cause allergic-type symptoms in workers directly exposed to dusts. Evidence that opiates are capable of producing immunological changes can be found in one study of contact dermatitis due to opiates,[14] an immunological study of heroin addicts,[15] and animal studies of anti-morphine antibodies.[16-17]

In a recent case report from the United Kingdom, Agius described an opiate worker with decreased pulmonary function and bronchospasm temporally related to work with

dry morphine dust.[18] The finding that an adverse effect on pulmonary function could be attributed to exposure to morphine dust is supported in our study by the observed changes in cross-shift spirometric measurements, peak flow changes, and questionnaire information. Further studies are necessary, however, to establish a causative role of narcotic dusts in the development of any chronic airways dysfunction.

The industrial hygiene data did not indicate other materials in the narcotic production area that would be likely etiologic agents of occupational asthma. Some compounds with irritant properties, such as some of the organic solvents, might theoretically exacerbate symptoms in individuals with non-specifically hyperactive airways. Some researchers have reported the development of a generalized non-specific airway hyperresponsiveness following exposure to high levels of an irritating aerosol, vapor, fume or smoke.[19] This condition was termed the reactive airways dysfunction syndrome.

The low levels of M6HSA specific IgG found in our study argue against any symptoms being due to the presence of this antibody. The inability to detect either a specific IgE or IgG4 to morphine makes it difficult to ascribe any of the observed symptoms and medical conditions to a specific immunological mechanism. Many of the reported symptoms mimic those seen in individuals with classic allergies, and, in the absence of evidence of an immunologic mechanism, such symptoms have been termed 'pseudo-allergic' in the pharmacologic literature.[20]

Further studies of the specificity of this M6HSA IgG antibody are necessary before any definitive statements can be made concerning the physiologic role of this antibody in opiate-exposed workers. The existence of multiple endogenous opiates in the human body precludes the conclusion that all of the specific IgG found in this study is directly attributable to occupational exposure to narcotic dusts. The possibility exists that the observed levels of M6HSA specific IgG may represent a cross-reactivity to other endogenous opiates.

Very few longitudinal studies of immunologic markers of occupational chemical exposures have been performed. At least one demonstrated that over an 18-month period of exposure to isocyanates, about half of the workers initially found to have hexamethyl-diisocyanate (HDI) IgG antibodies showed decreased levels a year later, while the other half showed increases.[21] In a similar study of workers exposed to trimelittic anhydride (TMA), a significant decrease in levels of specific IgE to TMA was seen following improvements in the ventilation.[22] Presumably, this was due to decreasing airborne antigen levels. In our study, the vast majority of individuals demonstrated significant decreases in M6HSA-specific IgG between February and December 1988.

Coincidental with the decrease in antibody level was the improved respiratory protection program (half-face respirators with high-efficiency particulate cartridges) after the initial survey. There are no specific data to determine the respiratory protection factor afforded by the new respirators, nor do we have specific data on compliance with the respirator program by current employees. Informal worker interviews during the December 1988 survey did indicate that many of the irritant symptoms were reduced or eliminated. Whether this is due to decreased narcotic dust exposure or improved protection against some of the solvents used in the manufacturing process cannot be determined.

There are multiple, structurally similar compounds produced in the narcotic production area and the possibility that some of the specific M6HSA may be immunologically cross reactive with other substances cannot be excluded at this time. Our study cannot adequately address changes in production quantities or type of compounds during the time periods immediately preceding the second survey. These factors may also be responsible for some of the observed decreases in the specific IgG levels, since the half-life of IgG in the serum has been estimated at 9 days.[23]

Proper interpretation of the skin test results is limited by the small number of participants. To assess the effects of age, sex, race, smoking status, family history, atopy, or underlying medical conditions, a larger population of both exposed and unexposed persons would be required. There is virtually no information available on opiate skin prick test results from other studies; therefore, comparing our results with those from other studies is not possible.

In general, skin prick test results can be extremely useful in determining which specific substances may be responsible for causing allergic symptoms, including some asthmatic conditions. The opiates are unique in that they will generate an immediate release of histamine (one of the main substances responsible for the symptoms and signs seen in allergic reactions) from the mast cells in the skin. Many common allergens usually produce this effect through an immunologically mediated mechanism (specific IgE, chiefly, and possibly IgG4). In this study we were unable to identify a specific IgE or IgG4 to morphine. We cannot, however, rule out the possibility of specific IgE or IgG4 to one of the other compounds.

The results of the opiate skin prick testing do suggest a variability in test response to many of the compounds. The narcotic production workers had a greater prevalence of positive skin test reactions to the compounds than the Penick referent group.

Little is known about the mechanisms responsible for variability in physiologic reaction to the opiates. The extremely complex pharmacological nature of the opiates precludes definitive statements about opiate sensitivity at this time. Histamine release from mast cells is a complex process and involves both immunologic and non-immunologic stimuli. Whether occupational exposure to opiates may be responsible for an altered skin test reactivity is still unclear.

VIII.   CONCLUSIONS

1.   The employer's occupational health program fails to protect workers from exposure to chemical agents suspected of causing occupational asthma. This type of program should include the following: exposure monitoring, regulated areas, abatement program personal protective equipment, hazard communication, worker training, housekeeping, and medical surveillance.

2.   High exposures to organic solvents during short-term episodic jobs were measured throughout the narcotic production area. Full-shift exposures are dependent upon the number of episodic jobs that the employees are required to complete during the shift.

3.   Due to the uncontrolled handling of alkaloid materials in this work place, workers are directly exposed while involved in powder handling operations and indirectly exposed whenever they may be working near a powder handling operation. Several routine powder handling operations are performed by any available personnel. Therefore, any individual of the entire work force may be exposed to significant airborne levels of alkaloid during their course of employment in the narcotics department.

4.   Substantial exposures to alkaloid dusts were measured throughout the building. The highest exposures were measured when the alkaloids were handled in a dry powder form. There is no established occupational exposure limit for opiates. While one paper presents a recommended exposure control limit for morphine and codeine, these levels represent only theoretical bases for minimizing the pharmacologic effects of occupational exposure to these compounds.[7] Thus, the recommended limit may not be adequate to prevent allergic, idiosyncratic, or pseudo-allergic reactions to opiates.

5. There is a lack of local exhaust ventilation in the building to reduce personal exposure levels to organic vapors during the short-term episodic jobs and the handling of dry alkaloid dust.

6. There is a high prevalence of asthma in the workforce of the narcotic production area. Approximately 29% of the workforce studied revealed evidence of new onset asthma since beginning work in the building. By contrast, the prevalence of asthma in the general population is estimated at 2-5%.

7. As judged by skin testing and determination of serum IgE, there was not a high prevalence of atopy in the narcotic production workers. Thus, it does not appear likely that the asthma and allergic symptoms reported by the narcotic production workers are due to common aeroallergens.

8. This study and previous studies strongly implicate exposure to narcotic dusts as an etiologic agent for the development of an asthma-like condition, contact dermatitis, and allergic-type symptoms. The immunologic studies here suggest that the asthmatic symptoms reported by workers do not appear to be due to a specific IgE or IgG4 to the morphine nucleus (true allergic reaction). The possibility of a specific IgE or IgG4 to one of the other substances present in the building cannot be excluded at this time.

9. The results of the skin testing with opiates indicate a wide variability in individual response to the different compounds. The finding that the narcotic production workers, for the most part, produced a 4-mm wheal at a lower concentration than the referent population cannot be interpreted as definitive evidence for an immunologic hypersensitivity or allergy, since other mechanisms may be operative.

IX. RECOMMENDATIONS

A. Environmental

1. Solvents

   a. Provide adequate local exhaust ventilation (LEV) to those processes where short-term overexposures to solvents were identified. The ventilation should achieve a minimum face velocity of 100 fpm, measured across the vessel opening. The present use of the general ventilation system for LEV, should be re-evaluated. A separate LEV system should be installed for more effective control of organic vapors, and to reduce the potential for distributing vapors throughout the building via the general ventilation system.

   b. Install level sight tubes, sampling lines, and additional ports on each of the reactor vessels to reduce the number of times that the vessel hatchways need to be opened.

   c. Enclose reactor vats on the second floor finishing room and provide local exhaust ventilation to contain the vapors while mixing takes place.

   d. Devise a method to drain the solid slurry from reactors into open barrels via an enclosed system.

   e. Inspect all reactors, vessels, and separators to ensure that a tight seal is obtained at the hatchway. Repair all hatches and fasteners that do not provide an adequate seal. Replace all worn or damaged hatchway gaskets. Gasket material should be resilient to the solvent being used and pliable enough to provide an adequate seal.

2. Alkaloids

   a. Whenever possible, all handling of narcotic substances should take place while the material is damp. Water should be used instead of a solvent to dampen the material. However, when the material must be handled in a dry powder form (i.e., batch weighing), LEV should be provided.

   b. Construct a weighing station equipped with an enclosed hood at the batch weighing area to isolate this process. The hood should be equipped with LEV to reduce airborne narcotic levels.

   c. Provide an enclosure hood equipped with LEV on the barrel platform station to capture fugitive dust emissions during the powder blending operations.

   d. Provide LEV at the dryer loading and unloading operations to collect airborne dust that is generated during these processes.

   e. Provide LEV at the feed port and the body of the dryer to capture fugitive dust emissions.

   f. A substitute milling operation that automatically feeds the narcotic powder should be investigated. The auto-feed system will isolate the operator from the exposure. If an automatic system cannot be designed, LEV should be provided at this station.

   g. The transfer of narcotic dusts via hand scooping in the packaging room should take place in an enclosed hood with LEV.

   h. The finishing, packaging, weighing, milling and blending areas should be designated as regulated areas with access limited to authorized personnel.

   i. The use of LEV to control narcotic dust exposure operations on the second floor may require a dedicated dust collection system. A dedicated system would ensure that adequate exhaust capacity is being supplied to each hood. Also, with appropriate air cleaning devices the captured dust could be reclaimed and returned to the product line. Ideally, all exhausted, filtered air for the LEV system should be vented to the outside and not recirculated back into the work environment. If exhausted air is recirculated, then monitoring devices with alarms are needed to ensure that particulate and solvent vapor do not reenter the work environment.

   j. To reduce exposure to process related narcotic dust, the use of an integrated vacuum transfer system is recommended to eliminate the manual handling of powders.

   k. Exposure evaluations have determined that significant exposure reduction can be achieved by the Overhead Air Supply Island System (OASIS).[24,25,26] This method consists of a directed stream of clean, low velocity air through the workers' breathing zone while operating at fixed work station. OASIS is recommended for dryer loading and unloading, batch weighing, milling, powder blending, dryer loading and unloading, and packaging room weighing.

3. Personal Protective Equipment

   As an interim measure, while engineering controls are investigated and installed:

a.   Provide the employees with positive pressure supplied air respirators for performing the following narcotic dust operations:

1. Dryer loading and unloading,
2. Blender loading and unloading,
3. Package room handling and weighing, and
4. Weighing room handling and weighing.

b.   Provide full-face respirators equipped with dual organic and high efficiency particulate air (HEPA) filter cartridges in combination for all separator digout operations. The full-face respirator will also provide additional eye protection.

c.   Provide half-mask respirators with appropriate organic cartridges for vessel addition operations.

d.   All disposable/single use respirators should be discontinued from use and removed from the work area.

e.   The written respirator protection program should be updated to reflect current respirator use. Qualitative or quantitative fit testing for all workers who are required to wear respirators is recommended as soon as possible. This testing should be performed annually.

f.   Update all batch sheets with current hazard information and protective equipment requirements. If negative filtering respirators are required, then the specific cartridge type to be used should be included on the batch sheet.

g.   Supply protective gloves and Tyvek clothing to those employees handling alkaloid dusts.

4.   Industrial Hygiene Monitoring

a.   Perform semi-annual full-shift and short-term sampling for airborne alkaloid particulates. This monitoring should also take place when there is a change or addition to a process.

b.   Perform annual full-shift and short-term sampling for organic vapors. This monitoring should also be performed when there is change or addition to a process.

c.   Provide direct reading sampling equipment for organic vapor which is readily available to be used in the event of a solvent spill. Provide training for the use of this equipment.

d.   Previous exposure monitoring for respirable silica during handling of Hyflo super-cel failed to analyze for crystobalite. Perform respirable air sampling during the addition of Hyflo material to vessels. The sample should be analyzed for total crystobalite and quartz content.

e.   All monitoring results should be provided to employees as required by the OSHA 1910.120 regulation.

5.   A general housekeeping policy should be implemented and enforced to clean the organic residue present on the equipment and floors. To prevent the resuspension of dry powder during clean up, only HEPA filtered vacuums are recommended for use for powder clean up (dry sweeping should not be used for dry powder clean up).

6. A thorough evaluation of the general ventilation system should be conducted. The system should be cleaned, repaired, and balanced to obtain adequate air distribution throughout the building. To prevent the recirculation of airborne particulate in the finishing, packaging, milling, and blending areas, filtration units should be placed in each return duct serving this areas. Each filter bank should consist of two coarse pre-filters and an final HEPA filter.[27] The fresh, outside air make-up should be increased to maximize the dilution effect in these work areas.

7. Training

   a. The respiratory protection program should be used to provide adequate training on the proper use of respiratory protection to all employees. This training should take place annually and within one month of hiring.

   b. Training should take place to fulfill the requirements of OSHA Hazardous Communication Standard 1910.1200 for all employees.

   c. Training should be conducted to instruct employees on responding to hazardous spills, releases, and other related conditions.

8. Safety

   a. Inspect all vessels, reactors, and separators to ensure that proper pressure relief venting is in place.

   b. Inspect all separators to ensure that nitrogen blanketing is available and operating where organic solvent may present an explosive condition.

B. Medical

1. We recommend a continued medical surveillance program with particular emphasis on the respiratory tract and skin conditions. Pulmonary function testing should be performed according to the recommendations of the American Thoracic Society.[3]

2. All individuals whose job involves the use of a respirator should, as required by OSHA standard 29 CFR 1910.134, have a medical evaluation to determine their fitness to use a respirator. The recommended content of this evaluation is described in the NIOSH Respirator Decision Logic, which is included as an appendix to the NIOSH Guide to Industrial Respiratory Protection.[28]

3. Individuals with signs or symptoms of asthma should be thoroughly evaluated by a physician experienced in the diagnosis and management of occupational pulmonary disease. It is also important to identify those individuals with asthma or other medical conditions whose disease, although non-occupational in etiology, may be exacerbated by specific occupational exposures.

4. Individuals with evidence of skin reactions to opiate compounds should be evaluated by a dermatologist. Contact dermatitis from exposure to opiates has been described, and only expertly performed skin patch testing can adequately document a true allergic contact dermatitis due to opiates. Identifying specific causative agents in occupational dermatoses is central to implementing adequate protective measures for employees.

X.   REFERENCES

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XII.   DISTRIBUTION AND AVAILABILITY OF REPORT:

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1. Penick Corporation
2. International Chemical Workers Union (ICWU), Local 153
3. International Chemical Workers Union
4. New Jersey Department of Health
5. OSHA Region II

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

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

Personal Short-Term Organic Vapor Sampling Results

Location	No. of Samples	Avg. Mins Sampled	Concentration Range in PPM (Average)				
			Toluene	Butanol	DMA	Methanol	Ethanol
Separator Digout							
1-1	1	8	600	N/A	N/A	N/A	N/A
1-2	5	22	37-625 (368)	N/A	N/A	N/A	N/A
2-2	1	17	N/A	N/A	N/A	N/A	3200
3-4	3	32	N/A	271-1300 (724)	N/A	N/A	N/A
3-5	1	14	N/A	300	N/A	N/A	N/A
3-8	2	42	N/A	N/A	N/A	N/A	6000-9000 (7500)
Vessel Openings							
1-ta-11	3	7	N/A	145-187 (170)	N/A	N/A	N/A
2-ta-4	3	20	N/A	N/A	N/A	400-2000 (1300)	N/A
3-ta-4	1	23	26	N/A	N/A	N/A	N/A
3-st-8	4	8	N/A	368-1030 (800)	N/A	N/A	N/A
Vat Mixing	2	5	N/A	N/A	N/A	N/A	2000-4000 (3000)
Cake Handling	3	25	5-300 (104)	N/A	N/A	N/A	N/A
Sparkler Unloading							
3-ta-6	2	23	52-96 (74)	N/A	N/A	N/A	N/A
Dump Solids	3	20	4-185 (123)	N/A	N/A	N/A	N/A
Liquor Spill	2	30	250-400	N/A	N/A	N/A	N/A
OSHA Short Term Exposure Limits			150 (STEL)	50 (Ceiling)	10 (STEL)	250 (STEL)	3000 (ACGIH)

Note: N/A = Not Applicable

TABLE 2

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

Personal Full-Shift Organic Vapor Sampling Results

Location	No. of Samples	Avg. Mins Sampled	Average TWA Concentration in PPM				
			Toluene	Butanol	DMA	Methanol	Ethanol
Area 1							
Press	2	336	15	0.1	BDL	0.5	NS
Detarring	2	339	123	1.2	BDL	2.5	NS
Area 2							
Finishing	3	433	7	0.1	BDL	BDL	436
Methylation	6	353	19	0.1	BDL	11.0	NS
Area 3							
Concentrator	1	354	3	14.9	BDL	0.4	NS
Morpheme Isol	1	350	1.3	7.6	BDL	2.0	NS
MFFM Process	1	336	1.2	26.3	BDL	1.9	NS
SYN Platform	2	331	51.0	1.0	BDL	0.5	NS
Tol Platform	2	324	3.0	0.7	BDL	10.3	NS
OSHA Permissible Exposure Limits			100	N/A	5	200	1000
Lowest Detectable Limit			0.1	0.2	0.1	0.4	0.5

Note: BDL = Below Detection Limit
               NS = Not Sampled

TABLE 3

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

Personal Short-Term Alkaloid Dust Sampling Results

Location	Minutes Sampled	Concentration ug/m^3)	
		Morphine	Codeine
Hand Scooping			
Loading 2-st-5	7	BDL	23564
Loading 2-st-2a	10	10,523	(64)
Loading 3-ta-11	17	(112)	(98)
Loading 3-ta-11	9	(228)	BDL
Product Weighing	14	7,945	BDL
Powder Blending			
Loading blender	14	BDL	8,652
Unloading blender	41	BDL	2,074
Unload (Area Sample)	21	BDL	3,741
Dryer Unloading			
2-dr-14	18	BDL	3,723
2-dr-14	29	BDL	284
2-dr-14	33	BDL	234
2-dr-14 (acct)	27	BDL	(72)
Dryer Loading			
2-dr-14	17	BDL	(166)
2-dr-14	16	BDL	193
2-dr-14	15	BDL	BDL
Dryer 2-dr-5			
Load & Unload	23	930	(45)
Load & Unload	25	717	BDL
Load & Unload (acct)	23	(133)	BDL
Separator Unloading			
3-4	16	1,539	BDL
3-4	25	214	BDL
2-2	13	BDL	294
2-2	21	BDL	BDL
2-2	10	BDL	BDL
3-5	16	BDL	BDL
3-5	19	(100)	BDL
3-8	16	BDL	BDL
S-Filter Unloading			
3-ta-6	54	BDL	BDL

Note: acct = accountability officer
       BDL = below detection limit
        ( ) = Reported Value Between LOD and LOQ

TABLE 4

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

Personal Short-Term Alkaloid Dust Sampling Results

Location	Minutes Sampled	Concentration (ug/m3)	
		Morphine	Codeine
A) product finishing room			
1) codeine processing	431	BDL	32
2) " "	441	BDL	183
3) " " (acct)	381	BDL	43
4) " "	431	BDL	56
5) " "	422	BDL	94
6) " " (acct)	416	BDL	178
B) milling room			
1) am-pm milling	430	BDL	364
2) milling (area)	410	BDL	222
3) am mill / blend	284	BDL	594
4) pm milling	151	(24)	491
C) packaging			
1) product packaging	237	BDL	1,572
2) screening of hydrocodone	434	BDL	(7)

NOTE: acct = accountability worker
       BDL = below detection limit
       ( ) = between LOD and LOQ

TABLE 5

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

General Ventilation Survey Results

Area 1

A) Supply ventilation

Field I.D.#	Measured	Design	% of Design
1	200 cfm	1000 cfm	20
2	650 "	1000 "	65
4	700 "	1500 "	47
7	675 "	1500 "	45
9	800 "	1000 "	80

B) Exhaust ventilation

Field I.D.#	Measured	Design	% of Design
3	150 cfm	500 cfm	30
5	600 "	500 "	120
6	250 "	500 "	50
8	460 "	500 "	90
10	90 "	500 "	20
11	175 "	500 "	35

Area 2

A) Supply ventilation

Field I.D#	Measured	Design*	% of Design
17	closed	not operational	
18	350 cfm	1500 cfm	23
19	375 "	1500 "	25
21	360 "	1500 "	24
23	420 "	1500 "	28
24	180 "	500 "	36
26	225 "	1500 "	15
27	450 "	1500 "	30

* Data not on drawings, therefore, the design flow was estimated by assuming that the total fan capacity was divided equally across the diffusers (12000 cfm/8 diffusers = 1500 cfm each) and (1500 cfm/3 diffusers = 500 cfm each).

TABLE 5 (cont.)

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

General Ventilation Survey Results

B) Exhaust ventilation

Field I.D.#	Measured	Design**	% of Design
12	100 cfm	400 cfm	25
15	230 "	400 "	57
16	220 "	400 "	55
20	250 "	400 "	62
22	400 "	400 "	100
25	50 "	500 "	10

** Data not on drawings. CFM was estimated same as in area 2(A). (6000 cfm/15 exhaust diffusers = 400 cfm each) and (1500 cfm/3 exhaust diffusers = 500 cfm each)

Area 3

A) Supply ventilation

Field I.D.#	Measured	Design	% of Design
37	320 cfm	400 cfm	80
38	160 cfm	400 "	40
40	170 cfm	500 "	34
41	250 cfm	500 "	50
42	480 cfm	1000 "	48

B) Exhaust ventilation

Field I.D.#	Measured	Design	% of Design
34	950 cfm	700 cfm	135
35	185 "	750 "	25
36	285 "	750 "	38

TABLE 6

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

Local Exhaust Ventilation Survey Results

Area 1

Location Recommended	Type	Measured	Recommended	% of
1-cf-1	draw thru	0 fpm	100 fpm	0
1-cf-1	slot hood	44 cfm	829 cfm	5
1-cf-2	draw thru	0 fpm	100 fpm	0

Area 2

Location	Type	Measured	Recommended	% of
2-st-2b	slot hood for drumming	200 fpm	>100 fpm	200
2-st-3a	slot hood for drumming	220 fpm	>100 fpm	220
2-ta-4	draw thru	20 fpm	100 fpm	20
2-ta-5	draw thru	40 fpm	100 fpm	40
2-ta-20	barrel slot hood	29 cfm	829 cfm	3
2-cf-2	draw thru	20 fpm	100 fpm	20
2-cf-1	no draw thru ventilation		100 fpm	0

TABLE 6 (continued)

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

Local Exhaust Ventilation Survey Results

Area 3

Location Recommended	Type	Measured	Recommended	% of
3-rc-2	slot hood for drumming	430 fpm	> 100 fpm	430
3-cf-4	no draw thru ventilation		100 fpm	0
3-cf-4	slot hood	0-41 cfm	829 cfm	0-5
3-cf-5	draw thru	0-20 fpm	100 fpm	0-20
3-cf-5	slot hood	0 fpm	829 cfm	0
3-of-6	draw thru	0 fpm	100 fpm	0
3-cf-8	no draw thru ventilation		100 fpm	0

Table 7

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

Follow-Up Study: December 1988

Hematologic Parameters and Immunoglobulins Among All Participants

	Narcotics Area	Referent Group	p (t test)
Number	33	8	
Albumin	4.5 (.33)*	4.7 (.32)	.14
White Blood Cell	7.0 (2.4)	6.8 (1.5)	.75
Polys	3891 (1575)	4159 (1505)	.66
Lymphs	2431 (1049)	2015 (409)	.08
Eosinophils	191 (134)	129 (69)	.08
Basophils	58 (33)	41 (14)	.02
Monos	377 (161)	442 (127)	.30
Hematocrit	44.3 (4.1)	46.2 (2.0)	.24
Hemoglobin	14.0 (1.4)	14.9 (1.5)	.11
IgE	97 (87)	59 (52)	.25
IgA	308 (133)	257 (94)	.34
IgG	1401 (518)	1279 (328)	.56
IgM	162 (110)	106 (55)	.20

* Mean and (Standard Deviation)

Table 8

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

Follow-Up Study: December 1988

Hematologic Parameters and Immunoglobulins Among Narcotic Production Participants

	Asthmatics	Non-Asthmatics	p (t test)
Number	10	22	
Albumin	4.5 (.3)*	4.5 (.4)	.89
White Blood Cell	7.8 (2.9)	6.6 (2.1)	.20
Polys	4656 (1988)	3543 (1250)	.06
Lymphs	2543 (1308)	2379 (940)	.69
Eosinophils	130 (92)	221 (142)	.07
Basophils	52 (18)	61 (38)	.40
Monos	447 (173)	345 (149)	.10
Hematocrit	43.2 (3.7)	44.9 (4.3)	.30
Hemoglobin	13.5 (1.1)	14.3 (1.4)	.13
IgE	110 (69)	90 (95)	.56
IgA	271 (90)	324 (146)	.32
IgG	1068 (382)	1537 (510)	.02
IgM	145 (88)	169 (120)	.58

* Mean and (Standard Deviation)

Table 9

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

Follow-Up Study: December 1988

Lymphocyte Surface Markers Among All Participants

	Narcotics Area	Referent Group	p (t test)
Number	30	6	
% T-cells %	65 (11.5)*	75 (11.3)	.06
# T-cells #	1570 (772)	1619 (259)	.78
% B-cells %	14.9 (5.9)	10.9 (2.2)	.008
# B-cells #	341.9 (188)	235.7 (56.6)	.02
% helper cells	36.8 (13.6)	51.6 (10.6)	.02
# helper cells	909.5 (575)	1120.6 (280)	.39
% suppressors	25.97 (8.8)	20.7 (7.4)	.18
# suppressors	609 (346)	485 (168)	.40
Helper/Supp	1.76 (1.54)	2.96 (1.9)	.11
% Leu7+ cells	7.6 (7.5)	8.1 (10.0)	.88
# Leu7+ cells	185.5 (283)	180 (219.9)	.96
% Leu72 + cells	2.45 (2.7)	2.1 (2.6)	.79
# Leu72+ cells	51.4 (56)	47.3 (62)	.87

* Mean and (Standard Deviation)

Table 10

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

Follow-Up Study: December 1988

Lymphocyte Surface Markers Among Narcotic Area Participants

	Asthmatics	Non-Asthmatics	p (t test)
Number	9	21	
% T-cells	68.7 (11.3)*	63.5 (11.5)	.26
# T-cells	1623 (911)	1547 (728)	.81
% B-cells	12.9 (4.7)	15.9 (6.2)	.22
# B-cells	285 (171)	366 (194)	.29
% helpers	45.3 (14.2)	33.2 (11.9)	.02
# helpers	1119 (781)	820 (456)	.30
% suppressors	19.5 (7.2)	28.7 (8.2)	.007
# suppressors	409 (173)	694 (368)	.007
helper/suppressor	2.83 (2.2)	1.31 (.83)	.08
% Leu7+ cells	7.5 (10.8)	7.6 (6.1)	.97
# Leu7+ cells	237 (484)	164 (144)	.67
% Leu72 cells	1.1 (.73)	3.0 (3.0)	.01
# Leu72 cells	28 (32)	62 (61)	.13

* Mean and (Standard Deviation)

Table 11

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

Follow-Up Study: December 1988

Mitogen Assays Among All Participants

Mitogen/Concentration	Narcotic Area	Referent Group	p (t test)
Number	25	6	
Concanavalin A/Control	3834 (8843)*	2051 (1998)	.63
Concanavalin A/Low	18761 (15639)	29362 (6825)	.12
Concanavalin A/Medium	14756 (10924)	20607 (6956)	.22
Concanavalin A/High	8742 (5949)	6564 (3364)	.40
	31	7	
Phytohemagglutinin/Control	873.7 (1872)	292 (173)	.10
Phytohemagglutinin/Low	19702 (14003)	26341 (7080)	.23
Phytohemagglutinin/Medium	19302 (9991)	76211 (135806)	.31
Phytohemagglutinin/High	3822 (3179)	5286 (3079)	.28
	28	7	
Pokeweed/Control	1983 (1668)	1887 (1003)	.89
Pokeweed/Low	3150 (2479)	6696 (3908)	.005
Pokeweed/Medium	20110 (10437)	29603 (8673)	.03
Pokeweed/High	22912 (12148)	36365 (9280)	.01

* Mean and (Standard Deviation)

Table 12

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

Follow-Up Study: December 1988

Mitogen Assays Among Narcotic Area Participants

	Asthmatics	Non-Asthmatics	p (t test)
Number	9	16	
Mitogen/Concentration			
Concanavalin A/Control	6845 (14562)*	2140 (1873)	.36
Concanavalin A/Low	16199 (10198)	20202 (18158)	.55
Concanavalin A/Medium	15666 (9428)	14243 (11948)	.76
Concanavalin A/High	11216 (6093)	7505 (5660)	.15
	10	20	
Phytohemagglutinin/Control	384 (202)	1151 (2299)	.15
Phytohemagglutinin/Low	21162 (12869)	19081 (15146)	.71
Phytohemagglutinin/Medium	21667 (8835)	17719 (10569)	.32
Phytohemagglutinin/High	3744 (2850)	3853 (3479)	.93
	10	18	
Pokeweed/Control	2914 (2078)	1465 (1156)	.06
Pokeweed/Low	3844 (2074)	2766 (2654)	.28
Pokeweed/Medium	25864 (8654)	16913 (10152)	.03
Pokeweed/High	27142 (10769)	20562 (12515)	.17

* Mean and (Standard Deviation)

Table 13

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

Follow-Up Study: December 1988

Common Aeroallergens: Narcotic Area vs Penick Referent Group

Common Allergens	Narcotic Area	Penick Referent Group	Relative Risk (95% C.I.)
Bluegrass	9 (28%) *	2 (25%)	1.1 (.3, 4.1)
Elm	7 (21)	1 (13%)	1.7 (.2, 11.9)
Redoak	6 (18%)	1 (13%)	1.4 (.2, 10.4)
Orchard Grass	7 (21%)	1 (13%)	1.7 (.2, 11.9)
Cat	5 (15%)	0	p=0.56 **
Alternaria	5 (15%)	0	p=0.56
Hormodendrum	4 (12%)	0	p=0.57
Dustmite	4 (12%)	0	p=0.57
Ragweed	10 (30%)	3 (38%)	0.8 (0.3, 2.3)

Narcotic Area Participants: Asthmatics vs Non-Asthmatics

	Asthmatics	Non-Asthmatics	Relative Risk (95% C.I.)
Number	9	24	
Bluegrass	2 (22%)	7 (29%)	0.8 (.2, 3.0)
Elm	2 (22%)	5 (21%)	1.1 (.2, 4.6)
Red Oak	2 (22%)	4 (17%)	1.3 (.3, 6.0)
Orchard Grass	1 (11%)	6 (25%)	0.4 (.1, 3.2)
Cat	0	5 (21%)	p=0.29 **
Alternaria	2 (22%)	3 (13%)	1.8 (.4, 8.9)
Hormodendrum	2 (22%)	2 (8%)	2.7 (.4,16.2)
Dust Mite	1 (11%)	3 (13%)	0.9 (.1, 7.5)
Ragweed	2 (22%)	8 (33%)	0.7 (.2, 2.6)

 * Number (Percent) Reactive
** RR is undefined; Fisher's exact, two-tailed p value

Table 14

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

Follow-Up Study: December 1988

Frequency Distribution of Skin Test Responses

		Lowest Concentration at Which Reaction Occurred				
	No Reaction	10 mg/ml	1 mg/m	0.1 n	0.01 n	0.001 n
M6HSA						
Penick Exposed	21	7	4	1	0	0
Penick Referent	7		1	0	0	0
Cincinnati Referent	16		1			
Opium						
Penick Exposed	3	15	13	2		
Penick Referent	2	4	2			
Cincinnati Referent	10	6	1			
Opium A2						
N.J. Exposed	4	17	10	2		
N.J. Referent	2	3	3			
Cincinnati Referent	10	6	1			
Opium B2						
Penick Exposed	1	25	6	0	0	1
Penick Referent	2	4	2			
Cincinnati Referent	9	7	1			
Didrate						
Penick Exposed	0	8	19	5	0	1
Penick Referent	0	3	5	0	0	0
Cincinnati Referent	3	9	4			
Oxycodone						
Penick Exposed	28	3	2	0	0	0
Penick Referent	7		1			
Cincinnati Referent	3	9	4			

Table 14 (cont'd)

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

Follow-Up Study: December 1988

Frequency Distribution of Skin Test Responses

		Lowest Concentration at Which Reaction Occurred				
	No Reaction	10 mg/ml	1 mg/m	0.1 n	0.01 n	0.001 n
Hydrocodone						
Penick Exposed	0	11	18	4		
Penick Referent	2	3	3			
Cincinnati Referent	5	8	3			
Thebaine						
Narcotic Area	19	9	3	2		
Penick Referent	7		1			
Cincinnati Referent	16					
Codeine						
Narcotic Area	1	4	18	10		
Penick Referent	0	2	4	2		
Cincinnati Referent	3		4	6		
Morphine						
Narcotic Area	4	6	12	1		
Penick Referent	1	2	4	1		
Cincinnati Referent	3		7	2		

Table 15

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

Follow-Up Study: December 1988

Prevalence of Positive Skin Test Reactions

Substance	Narcotics Area	Penick Referent	Cincinnati Referent	p value**
M6HSA	12 (36%) *	1 (13%)	1 (6%)	0.04
Opium	30 (91%)	6 (75%)	7 (41%)	0.0007
Opium A2	29 (88%)	6 (75%)	7 (44%)	0.004
Opium B2	32 (97%)	6 (75%)	8 (47%)	0.0002
Didrate	33 (100%)	8 (100%)	13 (81%)	0.02
Oxycodone	5 (15%)	1 (13%)	1 (6%)	0.63
Hydrocodone	33 (100%)	6 (75%)	11 (69%)	0.004
Thebaine	32 (97%)	1 (13%)	0 (15%)	0.004
Codeine	32 (97%)	8 (100%)	10 (77%)	0.04
Morphine	29 (88%)	7 (88%)	9 (75%)	0.55

 * Number and (%) with Positive Reaction

** Determined using 2x3 table and X^2.

Table 16

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

Follow-Up Study: December 1988

Mean Sensitivity Scores*

Substance	Narcotics Area	Both Referent Groups Combined	p value **
M6HSA	26.0 (33)***	34.2 (25)	0.01
Opium	23.0 (33)	38.1 (24)	0.0003
Opium A2	24.2 (33)	35.6 (24)	0.006
Opium B2	24.3 (33)	36.4 (25)	0.002
Didrate	23.2 (33)	36.9 (24)	0.0008
Oxycodone	28.7 (33)	30.6 (25)	0.46
Hydrocodone	22.5 (33)	38.0 (24)	0.0002
Thebaine	24.3 (33)	35.4 (24)	0.001
Codeine	23.5 (33)	33.7 (21)	0.01
Morphine	22.9 (33)	33.8 (20)	0.01

   *   Scores are: 6 = no reaction: 5 through 1 = reactions at increasingly greater dilutions (see text).
  **   Kruskal-Wallis Analysis of Variance: all scores are corrected for ties.
*** Mean Score (Number Tested)

Table 17

Penick Corporation
Newark, New Jersey
HETA 87-311-2087

Follow-Up Study: December 1988

Mean Sensitivity Scores*

Substance	Narcotics Area	Penick Ref.	Cincinnati Ref.	p value **
M6HSA	26.0 (33) ***	32.4 (8)	35.0 (17)	0.04
Opium	23.0 (33)	30.9 (8)	41.6 (17)	0.0004
OPA2	24.2 (33)	27.1 (8)	39.8 (16)	0.004
OPB2	24.3 (33)	28.9 (8)	39.9 (17)	0.0017
Didrate	23.2 (33)	29.5 (8)	40.7 (16)	0.0008
Oxycodone	28.7 (33)	29.2 (8)	31.2 (17)	0.68
Hydrocodone	22.5 (33)	34.5 (8)	39.7 (16)	0.0007
Thebaine	24.3 (33)	33.2 (8)	36.5 (16)	0.0046
Codeine	23.5 (33)	26.2 (8)	38.3 (13)	0.0072
Morphine	22.9 (33)	27.2 (8)	38.1 (12)	0.0097

   * Scores are: 6 = no reaction: 5 through 1 = reactions at increasingly greater dilutions (see text).
  ** Kruskal-Wallis Analysis of Variance: all scores are corrected for ties.
*** Mean Score (Number Tested)