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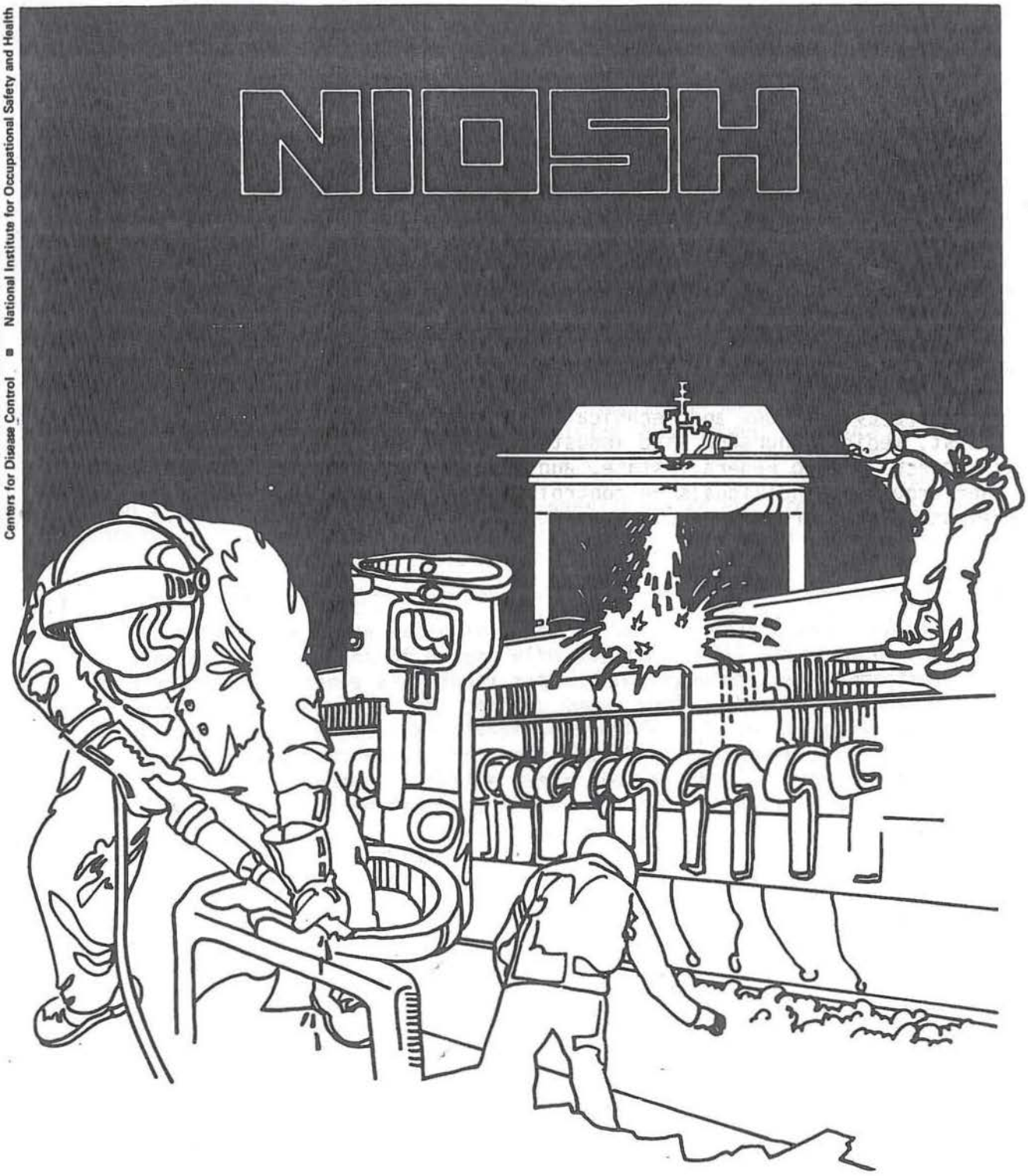

Health Hazard Evaluation Report

GHE 80-169-1300
MYLAN PHARMACEUTICALS
MORGANTOWN, WEST VIRGINIA

PREFACE

The Hazard Evaluations and Technical Assistance Branch of NIOSH conducts field investigations of possible health hazards in the workplace. These investigations are conducted under the authority of Section 20(a)(6) of the Occupational Safety and Health Act of 1970, 29 U.S.C. 669(a)(6) which authorizes the Secretary of Health and Human Services, following a written request from any employer or authorized representative of employees, to determine whether any substance normally found in the place of employment has potentially toxic effects in such concentrations as used or found.

The Hazard Evaluations and Technical Assistance Branch also provides, upon request, medical, nursing, and industrial hygiene technical and consultative assistance (TA) to Federal, state, and local agencies; labor; industry and other groups or individuals to control occupational health hazards and to prevent related trauma and disease.

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MYLAN PHARMACEUTICALS
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I. SUMMARY

In June 1980, the Division of Respiratory Disease Studies received a request to evaluate asthmatic symptoms in employees working with penicillin at Mylan Pharmaceuticals, Morgantown, W.Va. A combined industrial hygiene and medical-epidemiological evaluation of 36 penicillin workers and a comparison group of 27 employees was conducted. Personal breathing zone environmental samples determined that the comparison group had an average total dust exposure of 0.30 milligrams per cubic meter (mg/m^3). Among workers exposed to penicillin the following levels of exposure were found: production workers averaged 5.97 mg/m^3, nonproduction workers averaged 0.29 mg/m^3 among packers and 0.50 mg/m^3 in quality control. Medical evaluation consisted of a NIOSH respiratory questionnaire, skin questionnaire and pre- and post-shift spirometry.

The penicillin group was characterized by an excess prevalence of attacks of shortness of breath with wheezing (42%). The increased prevalence of three additional asthma-like symptoms was demonstrated in female penicillin workers; chronic cough (50%), wheezing (54%), and breathlessness (35%). No significant difference in the prevalence of the above symptoms was found among penicillin exposure subgroups. Analysis of pulmonary function tests did not show a significant difference among the examined groups. A significantly higher prevalence of dry cracked skin was found in the penicillin group than in the comparison group. Recommendations are contained in this report for reducing exposure among production workers and developing a medical surveillance program.

Key Words: (SIC 2833 Drug Grading, Grinding and Milling) Penicillin, dermatitis, respiratory.

II. INTRODUCTION

In June 1980, the Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health (NIOSH), received a request from the Oil, Chemical and Atomic Workers International Union for a Health Hazard Evaluation at Mylan Pharmaceuticals, Morgantown, West Virginia. The request specified four types of health effects which might be related to drugs produced at Mylan:

1. asthma-like respiratory symptoms
2. skin rashes
3. complaints of excessive urination
4. psychoneurologic problems such as dizziness, drowsiness, and depression.

This report presents the results of an epidemiological study designed to evaluate the prevalence of respiratory and skin symptoms in employees working with penicillin at Mylan Pharmaceuticals.

III. BACKGROUND

Mylan Pharmacueticals Inc. employs 225 people in the manufacture of specialty generic prescription drugs. Mylan manufactures bulk solids dosage forms of a stable list of 20 to 25 drugs formulated in a variety of dosages. Mylan's Morgantown facility began operations in a single building around 1970 and has since expanded to a facility consisting of an Administration Building (16 salaried personnel), and two manufacturing buildings: the Main Building (39 salaried and 116 hourly personnel) and the Penicillin Building (8 salaried and 44 hourly personnel). In compliance with Food and Drug Administration regulations, the operation of the Penicillin Building is completely separate from operations in the Main Building. Strict procedures are followed that prevent anyone who has been inside the Penicillin Building from entering the Main Building until proper decontamination measures have been taken.

Because no chemical synthesis or conversions are performed at Mylan, the manufacturing process is fairly straightforward. Very simply stated, the raw ingredients are blended together in specified amounts and the bulk powder is then dispensed in the prescribed forms and dosages. There are a number of steps in the overall process. Several steps are common to all products: Weighing and Blending of the ingredients and Packaging of the final product. Quality control measures are taken before, during and after each step and 100% of the final product is inspected. Thus, a significant portion of the employees work as Inspectors or Acceptable Quality Level Technicians (AQL Tech). The number of additional steps taken depends on the form in which the final product is dispensed. If the final form is simply a powder for oral suspension or oral solution, then Powder Filling is the only additional step. This simply involves filling bottles with a powder. If called for, the powder goes through an Encapsulation step in which it is dispensed into gelatin capsules before packaging. If the final product takes the form of a tablet, then a number of additional steps take place. In Granulation, the blended

ingredients are granulated to achieve desired flowability. The granulated powder is then taken to the tablet press where it is pressed into tablets of carefully controlled size, weight, hardness, etc. Some tablets then go through a Coating step. Some tablets then go through an Imprinting step in which a pharmaceutical grade ink is used to print on each tablet. These operations are common to both production plants and the equipment used is similar if not identical. Thus, an employee can transfer from one plant to the other without extensive re-training. Many employees are quite capable of operating several types of equipment. This flexibility is frequently exercised as necessitated by changing production requirements, by absenteeism, or other concerns.

A continuing effort has been made to improve dust control. Improved dust control serves several purposes: it improves working conditions; it reduces product loss; and it increases the purity of the final product. The Penicillin Building is the newest building. It was designed to control dust by handling powders in bulk form and eventually eliminating the use of drums and the scooping of materials by hand. This goal has yet to be achieved but efforts continue in this regard.

IV. METHODS/MATERIALS

The aim of this study was to answer the following questions:

1. Does exposure to penicillin dust at Mylan produce pulmonary abnormalities manifested by symptoms and decrements in pulmonary function?

2. Are there skin symptoms associated with exposure to penicillin dust?

The study population consisted of 44 workers from the Penicillin Building. The comparison group consisted of 49 workers from the Main Building (packers, maintenance, lab personnel) who usually are not exposed or exposed only to small amounts of pharmaceutical dusts.

A. Environmental Methods

Environmental sampling was conducted to characterize the exposure of each job category within the study population. The average exposure of each group was then studied to determine whether dust exposure correlated with the prevalence of symptoms. Initially both total dust and respirable dust samples were collected. However, as early sampling results became available there was a lack of correlation between total dust and respirable dust samples. In view of the limited number of people in the study population, it was decided to determine a single index of exposure (total dust concentrations) with as much certainty as possible and then if warranted to examine other indices of exposure (such as respirable dust concentrations) at a later date.

Area samples were collected as time permitted to provide potentially useful background information. Typically, area samples consisted of paired, side-by-side total and respirable dust samples in hope that a pattern might emerge as the ratios of respirable dust to total dust were compared. Total dust samples were collected using pre-weighed filters in 2-piece, closed-face cassettes. Initial samples were collected at 1.5 liters per minute (L/m). To optimize sample weights, later samples were collected at 2.0 L/m. Respirable dust samples were collected using Dorr Oliver 10-millimeter cyclone assemblies to separte out nonrespirable particles. All respirable samples were collected at a flow rate of 1.7 L/m.

B. Medical Methods

A. Questionnaire of Occupational Respiratory Disease

A NIOSH respiratory questionnaire based upon the British Medical Research Council Questionnaire (1) was administered by NIOSH personnel to each employee. Questionnaires included job history and smoking history. Major respiratory symptoms were defined as follows:

a. chronic cough: cough on most days for as much as three months a year for at least two consecutive years.

b. chronic phlegm: phlegm on most days for as much as three months a year for at least two consecutive years.

c. chronic productive cough: cough and phlegm for as much as three months each year, for at least two consecutive years.

d. wheezing: ever having wheezing or whistling noises in one's chest.

e. attacks of shortness of breath with wheezing: ever having had attacks of shortness of breath with wheezing.

f. asthma: ever having "asthma".

g. hay fever: ever having "hay fever" or other allergies which cause runny or stuffy nose apart from colds.

h. breathlessness: shortness of breath while walking with people of the same age at an ordinary pace on the level ground.

Smoking status was determined according to the following criteria:

Nonsmoker: never smoked cigarettes regularly.

Smoker: currently smokes cigarettes or smoked regularly in past but presently does not smoke.

1. Pulmonary Function Tests

Spirometric tests on all current workers in the Penicillin Building and the control population in the Main Building were administered according to standard NIOSH techniques. The test consisted of 5 blows into an Ohio 840 spirometer generating flow-volume curves which were electronically recorded. A minimum of three acceptable maneuvers were obtained on each subject. All workers were examined both before and at least 6 hours into the work shift. As it is a well known phenomenon that baseline pulmonary function (determined by the morning test) may be influenced by the persistent pulmonary changes from the previous day's exposure, testing was performed on the first day back to work, after two days off work. (2)

2. Skin Questionnaire:

A skin questionnaire, developed by a NIOSH dermatologist, included questions about the presence or absence of the following skin symptoms: a) red, itchy skin with or without scaling; b) dry, cracked skin; c) patches of thickened, heavy skin; e) unusual patches of skin with color changes; and f) frequent skin sores. These questions were followed by questions designed to determine more specific features of present symptoms (location, clearing on weekends and vacation, how long present, etc).

V. EVALUATION CRITERIA

A. Environmental

A review of the literature reveals that there are no federal standards applicable to airborne pharmaceutical exposures. However, this was not a hindrance since the study sought to compare exposure levels with the prevalence of symptoms and in this sense the study served as its own standard.

Two authors suggested exposure levels of 0.1 mg/m^3 for benzylpencillin and penicillin in general (8,15). This is an extremely low exposure level typically reserved for only the most toxic of substances with well documented health effects. A major concern in establishing a recommended exposure level is the feasibility of achieving that level with existing control technology. Neither author addressed this concern.

There is a federal standard that serves as a catch-all for all types of dust exposure. The OSHA standard for inert nuisance dust is 15 mg/m^3. NIOSH has no recommended standard for nuisance dust. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends that exposures to nuisance dusts be controlled to not more than 10 mg/m^3. Although penicillin cannot be considered biologically

inert, this 10 mg/m^3 level serves as a useful reference. It is useful in that it provides a definite upper limit of exposure and it is technologically achievable.

B. Medical (Evaluation Criteria)

For each set of five forced expiratory maneuvers, spirometry was deemed uninterpretable if the two test values of Forced Vital Capacity (FVC) were not within 5% of each other. In technically satisfactory sets of blows, the longest FVC and Forced Expiratory Volume in the first second (FEV_1) were used to indicate obstruction and/or restriction, and for calculating over-shift changes in pulmonary function (3) as follows:

1. Obstruction - FEV_1/FVC ratio < 0.70:

2. Restriction - FVC observed/FVC predicted < 0.80. The predicted values used are those of Knudson et. al. (14)

3. Clinically significant over-shift decrement in FEV_1:

$$\frac{\text{preshift } FEV_1 - \text{post shift } FEV_1}{\text{preshift } FEV_1} \times 100\% \geq 10\%$$

VI. RESULTS

A. Environmental

Pertinent sampling results are summarized in Table 10. Area samples and personal respirable dust samples are not included in the summary because these results did not appear to be particularly meaningful. Also deleted from this listing are the highest and lowest value obtained in each group. All sampling results, however, were sent to both the company and the union as soon as they became available. For this report, the raw data were distilled and only the pertinent results are included.

At the start, job categories seemed to fall into 3 levels of exposure. Exposures were expected to be high among production workers since they had direct contact with the powdered material. Subgroup C is comprised of these production workers whose exposures ranged from 2.48 to 12.47 mg/m^3 and averaged 5.97 mg/m^3. Exposures were expected to be low in nonproduction areas such as packaging because at this point in the manufacturing process the powdered material is enclosed in capsules, tablets, or bottles. Subgroup A is comprised of these nonproduction workers whose exposures ranged from 0.12 to 0.45 mg/m^3 and averaged 0.29 mg/m^3. Then there were job categories expected to have intermediate exposures because although they do not handle powdered material directly, they do spend a large portion of their time in the production areas. The sampling results did not support this

expectation. The exposure of this group of workers (subgroup B) ranged from 0.08 to 1.48 mg/m^3 and at an average of 0.50 mg/m^3 did not differ substantially from the exposure of subgroup A. However, for the purposes of medical comparisons subgroups A and B were kept separate because of the nature of the jobs in these two groups.

A comparison group was selected. This group was similar to the study population in many respects but had no occupational exposure to penicillin dust and very little exposure to other pharmaceutical dusts. This Nonpenicillin Group consisted of workers in the packaging department of the Main Building. This group's exposures ranged from 0.20 to 0.74 mg/m^3 and averaged 0.30 mg/m^3.

B. Medical

As reported in Table 1, 36 of 44 (82%) present workers from the Penicillin Building participated in the survey. Within the penicillin - exposed group the lowest participation rate was in subgroup A (76%) and the highest in subgroup C (100%). In the subgroup B, 78% participated. The comparison group consisted of 34 of 49 (69%) workers from a low dust area in the Main Building. Of these 34, seven workers were excluded from analysis since they had been transferred due to respiratory complaints either from the Penicillin Building (n = 3) or high exposure areas in the Main Building (n = 4).

As indicated in Table 2, the average age of the four examined groups was rather similar (range: 36 - 41 years). The groups differed in sex, smoking history and tenure at Mylan.

1. Respiratory Symptoms

The prevalence of respiratory symptoms is displayed for all workers (Table 3), female workers (Table 4), the nonsmokers (Table 5) and penicillin exposure subgroups (Table 6). The penicillin group was characterized by a higher prevalence of attacks of shortness of breath with wheezing (42% vs. 7%, $p = 0.004$) than the nonpenicillin group (Table 3).

As 72% of the penicillin group consisted of females, the prevalence of respiratory symptoms among females only in the penicillin and nonpenicillin groups was analyzed. Excess in the prevalence of chronic cough (50% vs 9%, $p = 0.004$), wheezing (54% vs 9%, $p = 0.002$), attacks of shortness of breath (50% vs 9%, $p = 0.004$) and breathlessness (35% vs 4%, $p = 0.02$) were found (Table 4).

When the nonsmokers in the penicillin group and nonpenicillin group were compared, the only significant difference found was in the prevalence of wheezing (44% vs. 0%, $p = 0.02$). The difference for attacks of shortness of breath was borderline significant. (33% vs. 0%, $p < 0.1$) (Table 5).

The prevalence of respiratory symptoms in the two most numerous subgroups: A (n = 19) and C (n = 10), was compared to the prevalence of symptoms in the nonpenicillin group (Table 6). There were no significant differences in the prevalence of respiratory symptoms between subgroup C and the nonpenicillin group. For two symptoms: wheezing (50% vs. 15%) and attacks of shortness of breath (40% vs 7%), the differences were borderline significant. On the contrary, the same two symptoms were significantly more often manifested in subgroup A than in the nonpenicillin group: wheezing (53% vs 15%, p = 0.01), attacks of shortness of breath (53% vs 7%, p = 0.002). There were no statistically significant differences between the prevalence of respiratory symptoms in the subgroups A and C.

2. Pulmonary Function Tests

Mean preshift spirometry results and average decrements in FEV_1 are shown in Table 7. Mean FVC was greater than 100% predicted, and FEV_1 greater than 98 percent predicted in all exposure categories. There were no statistically significant differences among the exposure subgroups. Mean FEV_1/FVC ratios were greater than 0.74 for all categories with no significant differences. The subgroup C showed the greatest shift decrement in FEV_1 (-1.8%), but differences among the nonpenicillin group and three exposure subgroups were not significant. Only one subject had a shift decrement in FEV_1 of more than 10 percent. This was a packer with a 17 percent fall, who had been asthmatic for four years with no obstruction noted on baseline spirometry. Five other subjects had FEV_1 decrements between 5 and 10 percent: one in subgroup C, one in B, one in A, and two in the nonpenicillin population.

Some symptomatic workers used bronchodilators during the shift. (4% of nonpenicillin group, 11% of penicillin group).

3. Skin Symptoms

The results of the skin symptoms survey revealed a higher prevalence of symptoms in workers in the penicillin group, than in the nonpenicillin group (57% vs 26%, $p < 0.05$), with no difference among penicillin subgroups (Table 8). The most common problem appeared to be dry, cracked skin. Fifty-one percent of all workers in the penicillin group had this kind of skin complaint, and only 19% of nonpenicillin group ($p < 0.02$). The difference among penicillin subgroups were small and insignificant. Red, itchy skin appeared to be the second most common problem. Twenty-nine percent of workers in the Penicillin Building reported this symptom (15% in comparison group). It was manifested more often in penicillin subgroup C (40%) than in subgroup A (28%) (Table 9). Exposed parts of the body (face and hands) were more often involved in the workers

with skin problems in the Penicillin Building than in the nonpenicillin group (Face: 35% vs 14%; hands 75% vs 57%). There were no differences between the penicillin and the nonpenicillin group in the temporal relationship of symptoms to work. Fifty percent of penicillin workers with skin symptoms and 43 percent of nonpenicillin workers with skin symptoms reported that their skin symptoms bothered them mostly at work. Also, 85% of all workers with skin symptoms in the penicillin group and 86% of nonpenicillin group noticed that their symptoms got better or cleared during weekends and days off.

VII. DISCUSSION

A. Environmental

A worker's exposure can vary widely from day to day so that his chronic exposure would be difficult to determine. As an estimate of chronic exposure a worker was evaluated only in his regular job on a day when production was typical.

It is noteworthy that subgroups B and C often work in the same room at the same time yet their exposures are very different (0.50 vs. 5.97 mg/m^3 respectively). Subgroups A and B work in different areas yet their exposures are similar (0.29 vs. 0.50 mg/m^3 respectively). This is consistent with the finding that as a rule area samples did not correlate well with personal samples. One possible explanation for such radically different exposure levels in two groups working in the same room is that workers in subgroup C at some point in their job manually transfer powder using a scoop; workers in subgroup B do not. Thus, achievement of the company's goal of eliminating hand scooping could go a long way toward reducing exposures.

The lack of correlation between respirable and total dust samples can be explained by studying the list of penicillin products produced at Mylan. The list consists of 4 types of penicillin produced in a variety of dosages for a total of 17 different formulations. In turn, each formulation may undergo a change in consistency at each step in the manufacturing process. If the number of formulations produced on any given day is multiplied by the number of steps in each formulation it soon becomes apparent that in effect a large number of different dusts are being sampled and thus it is unreasonable to expect the ratio of respirable dust to total dust to be consistent throughout the plant.

It is possible that in the weighing room a given exposure could represent an exposure to nuisance dust only since pure inert ingredients as well as pure active ingredients are handled here. Even in this case, however, such exposures should be kept below 10 mg/m^3. All other exposures in the production area would involve active ingredients as well as inert ingredients and therefore the 10 mg/m^3 criterion is not applicable.

B. Medical

There is evidence that exposure to penicillin in the work environment can cause asthma. Several authors have described cases of workers employed in the manufacture of semisynthetic penicillin antibiotics, who developed attacks of shortness of breath and wheezing (4,5,6). In two situations (4,6), inhalation challenge testing with penicillin compounds produced asthmatic reactions. In the third case (5) such tests were not made. Brusilovskii (7) examined 135 workers employed in the production of penicillin with questionnaires, clinical examination, skin testing and provocation inhalation testing. He found 9 persons (7%) who demonstrated sensitization of the respiratory airways to penicillin. One hundred and sixty nine employees of a synthetic penicillin plant participated in a NIOSH study, which found statistically significant correlations among dust concentrations, allergic symptoms, and penicillin specific antibodies. Respiratory symptoms (wheezing) were found in 2% of those examined. (8)

In this study, the penicillin group was characterized by an excess in the prevalence of attacks of shortness of breath. The female sub-group demonstrated increased prevalence of chronic cough, wheezing, attacks of shortness of breath, and breathlessness. The nonsmoker population in the penicillin group demonstrated an increased prevalence of wheezing. The small proportion of nonsmokers in the nonpenicillin group (n = 11) was a severe obstacle in our comparisons. It can explain the lack of significant differences for other symptoms.

There were clear trends in the distributions of asthma-like symptoms in the penicillin subgroups. In general, subgroup A was characterized by a higher prevalence of symptoms; wheezing, attacks of shortness of breath, than subgroup C. When we recall that subgroup A consists of individuals with low exposure to penicillin, and subgroup C of high exposure, this trend is interesting. It can be explained in at least four ways:

1) Individuals with pre-existing, non-occupational asthma may choose jobs in low dust areas.

2) Affected workers may be transferred or leave the pharmaceutical industry more frequently from the high exposure areas than from the low exposure areas.

3) Eight of 19 individuals in subgroup A worked in the past in the high exposure area. They were transferred to the low exposure area due to health problems, which can be related to their exposure. Six of them had wheezing at the time of the study. These findings confirmed the opinion that sensitized individuals can remain symptomatic even with exposure to very low concentrations of an allergenic agent. (9)

4) There is no dose-response relationship between the degree of exposure and the development of sensitization. It is recognized that in hypersensitivity disease the level of exposure plays an insignificant role compared to individual susceptibility. We found a prevalence of hay fever (common in atopic individuals) of 44% in the nonpenicillin group, and 31% in the penicillin group, with no difference between subgroup A and B. Among 11 persons with hay fever in the penicillin group, 10 (91%) reported that they suffer from wheezing, or attacks of shortness of breath. Among 12 individuals with hay fever in the nonpenicillin group only 2 (17%) complained of wheezing ($p = 0.001$). This suggested that atopic individuals may be at enhanced risk of developing occupational asthma to penicillin at Mylan.

Although asthma may be characterized by airway obstruction (FEV_1 / FVC % < 70%) and/or a 10% or greater fall in FEV_1 when it occurs, this study was unable to document objective spirometric evidence of asthma. Two possible explanations can be proposed for these findings;

1. Some symptomatic workers used bronchodilators during the shift.

2. Tests were done after 6 hours of exposure. Occupational asthma induced by penicillin can have delayed reactions. In this case, the decrement in FEV_1 can occur several hours after exposure. In addition, there can be recurrent, nocturnal reactions. These can reoccur in a gradually decreasing manner for several consecutive nights after a single exposure. (4,10,11)

In summary, the study was unable to establish definitive patterns of occupational asthma resulting from penicillin exposure at Mylan Pharmaceuticals. However, there appears to be excessive prevalence of asthma-like respiratory symptoms in penicillin-exposed workers.

Skin Symptoms and Signs

There is little evidence in the literature indicating that occupational exposure to penicillin can cause skin diseases (symptoms, signs). In two studies authors managed to establish the diagnosis of dermatitis (8) and contact eczema (12). Two other authors have confined themselves to reporting singular symptoms -- itching red skin (5) and signs -- papular rashes, generalized urticaria (13).

This study found a significantly higher prevalence of skin symptoms and signs among workers in the penicillin group than in the nonpenicillin. Two major problems were manifested; dry, cracked skin and red, itchy skin. The job relatedness of these signs was indicated by the fact that exposed parts of the body were more often involved

among penicillin workers than among nonpenicillin workers. The statistically significant difference between the nonpenicillin and the penicillin group was demonstrated only for dry, cracked skin. Although in the literature there is no evidence that such symptoms can be produced by the exposure to penicillin, we can not exclude such a possibility. These symptoms might also be related to prolonged exposure to the low relative humidity maintained in the Penicillin Building throughout the year. Humidity in the Main Building during the year, except the heating season, is higher than in the Penicillin Building. As no significant differences were demonstrated between the penicillin and the nonpenicillin group for red, itchy skin, the high prevalence of the sign can not be attributed to the exposure to penicillin. However, we must emphasize that the nonpenicillin group, having contact with a variety of drugs, can not be regarded as an appropriate control. The prevalence of skin symptoms in this population may be higher than in a population with no contact with pharmaceutical products.

VIII. CONCLUSIONS

A. The penicillin group was characterized by an excess in the prevalence of attacks of shortness of breath with wheezing (42%). An increased prevalence of three additional asthma-like symptoms was demonstrated in female penicillin workers: chronic cough (50%), wheezing (54%), breathlessness (35%).

B. A dose-response relationship was not found between asthma-like symptoms and exposure to penicillin dust. Subgroup A (low exposure) demonstrated a higher prevalence of respiratory symptoms than Subgroup C (high exposure).

C. The atopic status of a worker (presence of hay fever) can be a predisposing factor for development of asthma. The prevalence of asthma-like symptoms was higher among atopic workers in the penicillin group than among atopic workers in the nonpenicillin group.

D. Analysis of pulmonary function tests did not show significant differences among the exposure groups. Lack of impairment of pulmonary function of symptomatic workers can be explained in part by the fact that some of them used bronchodilators during the shift.

E. Because spirometry results did not reveal evidence of impairment of ventilatory function during the time of exposure, we could not conclude unequivocally that occupational asthma due to penicillin dust occurs in Mylan Pharmaceuticals.

F. Significantly higher prevalence of dry, cracked skin was found in the penicillin group than in the nonpenicillin group. This skin problem may be a result of penicillin exposure, or due to low relative humidity.

IX. RECOMMENDATIONS

A. Environmental

1. Elimination of Scooping

Various dust control measures are currently in effect yet some exposures continue to be high. The one task common to all job categories having high exposures is that of scooping powdered materials by hand. The elimination of such scooping appears to be the single, most beneficial dust control measure to be pursued at this time. It is recommended that efforts in this regard be continued and that these efforts be accelerated in areas where exposure levels sometime exceed 10 mg/m^3 (Encapsulation, Granulation, and Weighing in Table 10).

2. Use of Respirators

Until the manual scooping of powders can be eliminated it is recommended that respirators be worn whenever scooping is being done especially in areas where exposures have been shown to exceed 10 mg/m^3. Presently, respirators are available for workers to use at their own discretion. This practice is commendable and should be continued for operations other than scooping. However, it is recommended that respirators be required during scooping. This would require a minimum period of discomfort while optimizing respiratory protection.

B. Medical

The high prevalence of asthma-like symptoms in the penicillin group may be attributed to the sensitizing properties of this antibiotic. There are no established methods to determine whether a worker may become sensitized after exposure to penicillin dust. The following surveillance program is recommended to protect the workers' health from potential occupational dust exposure.

1. Every worker should have a preplacement evaluation which includes:

   a. respiratory symptoms questionnaire (including history of atopy and asthma)

   b. physical examination

   c. shift spirometry should be performed during the first day of work (FVC, FEV_1, percent change in FEV_1 during shift) acccording to standard NIOSH techniques.

Symptomatic workers (chronic cough, wheezing, attacks of shortness of breath), atopic (hay fever) and workers with obstructive spirometric findings and those with shift decrement in FEV_1 of 10% or more should be informed that they are at enhanced risk of developing respiratory reaction to penicillin.

2. Above specified tests should be repeated annually in each worker.

3. Shift spirometry should be performed on a day when the examined worker is doing the job of the highest dust exposure, and is not using any lung medication.

4. Individuals with decrement in FEV_1 of 10% or more during the shift, should be transferred to a nonpenicillin exposure work assignment.

5. We do not recommend skin tests with penicillin allergen or immunologic tests looking for antipenicillin antibodies. These tests are of no value in predicting sensitivity to the penicillin in occupational exposure.

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Copies of this report have been sent to:

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TABLE 1

PARTICIPATION RATES

LOCATION		# OF WORKERS	# OF PARTICIPANTS	PERCENTAGE
Main Bldg:	Nonpenicillin Group	49	34*	69
PENICILLIN BLDG.	Subgroup A (nonproduction)	25	19	76
	Subgroup B (quality control)	9	7	78
	Subgroup C (production)	10	10	100
	TOTAL	44	36	82
	TOTAL	86	70	81

* 7 workers excluded, total analyzed = 27

TABLE 2

AVERAGE AGE, SEX, TENURE AND SMOKING STATUS OF EXAMINED WORKERS

GROUP		AGE	Sex		Tenure		Smoking Status	
			FEMALE	MALE	≤8 yr	> 8 yr	S*	NS**
Nonpencillin		41.3	23	4	12	15	11	16
PENICILLIN	SUBGROUP A	38.8	13	6	15	4	8	11
	SUBGROUP B	35.1	7	0	5	2	3	4
	SUBGROUP C	36.4	6	4	6	4	7	3
	TOTAL	37.4	26	10	26	10	18	18
Bldg. TOTAL		39.4	49	14	38	25	29	33

* S - smokers and ex-smokers
**NS - nonsmokers (never smoked)

TABLE 3

RESPIRATORY SYMPTOMS: COMPARISON BETWEEN PENICILLIN AND NONPENICILLIN GROUPS

SYMPTOMS	NONPENICILLIN GROUP		PENICILLIN GROUP	
	NUMBER	PERCENT	NUMBER	PERCENT
chronic cough	4	15	13	36
chronic phleghm	4	15	9	25
chronic productive	2	7	8	22
wheezing	4	15	17	47
attacks of shortness of breath	2	7	15**	42
asthma	2	7	5	14
hay fever	12	44	11	31
breathlessness+	2	7	10*	29
Total # of Workers	27	100	36	100

Fisher's exact test of 2 x 2 Chi square (nonpenicillin vs. penicillin group)

* $0.05 < p < 0.1$
** $p < 0.01$

+one man excluded from penicillin group, who claimed that he was disabled from walking.

TABLE 4

RESPIRATORY SYMPTOMS IN FEMALES: COMPARISON BETWEEN PENICILLIN AND NONPENICILLIN GROUPS

SYMPTOMS	NONPENICILLIN GROUP		PENCILLIN GROUP	
	NUMBER	PERCENT	NUMBER	PERCENT
chronic cough	2	9	13***	50
chronic phleghm	4	17	9	35
chronic productive cough	2	9	8	31
wheezing	2	9	14***	54
attacks of shortness of breath	2	9	13***	50
asthma	2	9	4	15
hay fever	9	39	9	35
breathlessness	1	4	9**	35
Total # of Workers	23	100	26	100

Fisher's exact test for 2 x 2 Chi-square (nonpenicillin vs penicillin workers)

** $p < 0.05$
*** $p < 0.01$

TABLE 5

RESPIRATORY SYMPTOMS IN NONSMOKERS: COMPARISON BETWEEN PENICILLIN AND NONPENICILLIN GROUPS

SYMPTOMS	NONPENICILLIN GROUP		PENCILLIN GROUP	
	NUMBER	PERCENT	NUMBER	PERCENT
chronic cough	1	9	6	33
chronic phleghm	0	0	4	22
chronic productive cough	0	0	4	22
wheezing	0	0	8**	44
attacks of shortness of breath	0	0	6*	33
asthma	1	9	1	6
hay fever	4	36	5	28
breathlessness[+]	2	18	6	35
Total # of Workers	11	100	18	100

Fisher's exact test for 2 x 2 Chi square (nonpenicillin vs. penicillin group)

* $0.05 < p < 0.1$
** $p < 0.05$

[+]one man excluded from penicillin group, who claimed he was disabled from walking.

TABLE 6

RESPIRATORY SYMPTOMS: COMPARISON AMONG NONPENICILLIN GROUP AND TWO SUBGROUPS OF PENICILLIN GROUP

	NONPENICILLIN GROUP		PENICILLIN GROUP			
			SUBGROUP A		SUBGROUP C	
	NUMBER	PERCENT	NUMBER	PERCENT	NUMBER	PERCENT
chronic cough	4	15	7	37	4	40
chronic phleghm	4	15	4	21	3	30
chronic productive cough	2	7	4	21	3	30
wheezing	4	15	10**	53	5*	50
attacks of shortness of breath	2	7	10**	53	4*	40
asthma	2	7	4	21	0	0
hay fever	12	44	7	37	3	30
breathlessness+	2	7	7	39	1	10
TOTAL NUMBER OF WORKERS	27	100	19	100	10	100

Fisher's exact test for 2 x 2 Chi square (nonpenicillin group vs. subgroup A; nonpenicillin group vs. subgroup C).

* $0.05 < p < 0.1$
** $p < 0.05$

+one man exluded from subgroup A, who has claimed that he was disabled from walking.

TABLE 7

PULMONARY FUNCTION TESTS: COMPARISON AMONG NONPENICILLIN GROUP AND PENICILLIN SUBFROUPS

(Percent of predictive values ± standard deviation)

GROUP		% PRED. FVC	% PRED. FEV_1	FEV_1/FVC%	% SHIFT CHANGE IN FEV_1
Main Bldg:	Nonpenicillin Group n = 27	107.0 ± 13.6	98.0 ± 13.5	75.1 ± 8.3	-0.4 ± 3.3
PENICILLIN Bldg.	Subgroup A n = 19	104.5 ± 21.4	96.8 ± 25.6	75.5 ± 10.7	-0.1 ± 5.4
	Subgroup B n = 7	100.4 ± 11.9	98.0 ± 19.7	79.6 ± 0.01	-0.7 ± 3.8
	Subgroup C n = 10	104.1 ± 16.2	104.3 ± 11.7	82.7 ± 7.2	-1.8 ± 3.2
	Total Penicillin n = 36	103.6 ± 18.2	99.3 ± 20.6	78.8 ± 9.8	0.7 ± 4.5

TABLE 8

SKIN SYMPTOMS AND SIGNS: COMPARISON BETWEEN NONPENICILLIN AND PENICILLIN GROUP

Symptoms and Signs	Nonpenicillin Group		Penicillin Group	
	Number	Percent	Number	Percent
Red itchy skin	4	15	10	29
Dry cracked skin	5	19	18**	51
Red skin with blisters or pus pimples	1	4	2	6
Patches of thickened heavy skin	3	11	2	6
Unusual patches of skin with color change	1	4	2	6
Frequent skin sores	1	4	1	3
Any of above symptoms or signs	7	26	20*	57
TOTAL # OF WORKERS	27	100	35+	100

2 x 2 Chi-square test (nonpenicillin vs. penicillin group)

* $p < 0.05$
** $p < 0.02$

+one person did not complete the portion of the questionnaire referring to skin symptoms and signs.

TABLE 9

SKIN SYMPTOMS AND SIGNS: COMPARISON AMONG NONPENICILLIN GROUP AND PENICILLIN SUBGROUPS

SYMPTOMS AND SIGNS	NONPENICILLIN GROUP		PENICILLIN GROUP			
			SUBGROUP A		SUBGROUP C	
	NUMBER	PERCENT	NUMBER	PERCENT	NUMBER	PERCENT
Red itchy skin	4	15	5	28	4	40
Dry cracked skin	5	19	9	50	5	50
Red skin with blisters on pus pimples	1	4	2	11	0	0
Patches of thickened heavy skin	3	11	2	11	0	0
Unusual patches of skin with color change	1	4	1	6	1	10
Frequent skin sores	1	4	1	6	0	0
Any of above symptoms or signs	7	26	10	56	6	60
TOTAL # OF WORKERS	27	100	18	100	10	100

TABLE 10

SUMMARY OF SAMPLING RESULTS

All concentrations in mg/m^3, of total dust

NONPENICILLIN GROUP

Packaging	0.22
"	0.74
"	0.14
"	0.20
"	0.20

Mean Exposure = 0.30
Standard Deviation = 0.25

PENICILLIN GROUP

Subgroup A (low)		Subgroup B (medium)		Subgroup C (high)	
Packaging	0.43	Inspector	0.65	Weighing	11.29
"	0.30	"	0.72	"	5.84
"	0.20	"	0.35	"	2.69
"	0.31	"	0.20	Granulation	6.92
"	0.45	AQL Tech.	0.30	"	4.87
"	0.33	" "	1.48	"	12.47
"	0.16	" "	0.08	Encapsulation	2.48
"	0.12	Dept. Coord.	0.24	Encapsulation	11.68
				Dept. Coord.	2.60
				Tablet Press	2.30
				" "	4.73
				Powder Filling	3.80
Mean	= 0.29	Mean	= 0.50	Mean	= 5.97
Std. Dev.	= 0.12	Std. Dev.	= 0.45	Std. Dev.	= 3.80

Sampling Conducted on October 5 & 19, 1981 and January 18, February 1 & 8, 1982.

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