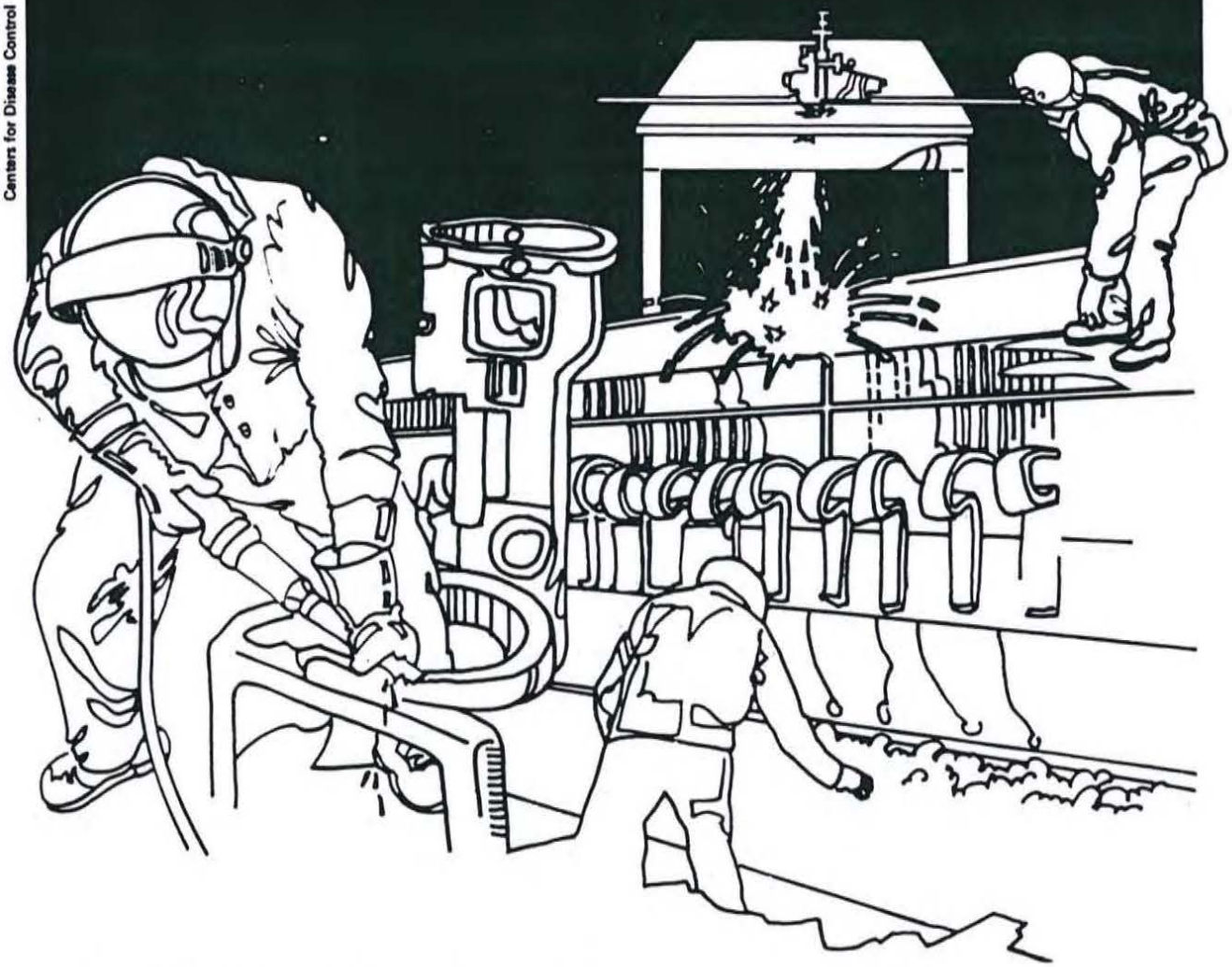
FILE COPY

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES ■ Public Health Service
Centers for Disease Control ■ National Institute for Occupational Safety and Health

NIOSH



Health Hazard Evaluation Report

HETA 81-322-1228
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.

Mention of company names or products does not constitute endorsement by the National Institute for Occupational Safety and Health.

HETA 81-322-1228
NOVEMBER 1982
MYLAN PHARMACEUTICALS
MORGANTOWN, WEST VIRGINIA

NIOSH INVESTIGATORS:
Arthur S. Watanabe, Pharm. D.
Richard Patnode, I.H.
Mitchell Singal, M.D.
Rick P. Ferguson, I.H.

I. SUMMARY

In May 1981, the National Institute for Occupational Safety and Health (NIOSH) received a request from the Oil, Chemical and Atomic Workers Union to evaluate occupational exposures to chlorthalidone (a prescription diuretic used to treat high blood pressure) at Mylan Pharmaceuticals Company, Morgantown, West Virginia. Chlorthalidone production had recently begun, and employees had reported symptoms such as lightheadedness and excess urination, consistent with the drug's pharmacologic effects.

On May 18-19 and 28-29, 1981, NIOSH investigators collected personal (breathing zone) air samples on 10 chlorthalidone workers for measurement of total and respirable dust exposure. Time-weighted average (TWA) total dust concentrations ranged from 0.6 to 14.4 mg/m^3; respirable dust concentrations ranged from 0.1 to 0.5 mg/m^3. An effort was made to determine personal airborne exposure to chlorthalidone, but problems in laboratory methodology precluded that analysis. Airborne chlorthalidone concentrations determined by area samples at sites of dust generation ranged from 1.1-2.3 mg/m^3.

NIOSH investigators administered a health questionnaire to 10 chlorthalidone-exposed workers and 10 unexposed production workers; made pre- and post-shift measurements of pulse and blood pressure; analyzed pre- and post-shift blood specimens for sodium, potassium, chloride, uric acid, and glucose levels; analyzed post-shift blood for aldosterone and chlorthalidone concentrations; and analyzed pre- and post-shift urine for sodium, potassium, and chloride levels. Chlorthalidone workers reported a variety of symptoms, many not specific for chlorthalidone, but no more so than other production workers. Chlorthalidone workers showed a diminution in the orthostatic (mainly diastolic) blood pressure response from the beginning to the end of the work shift and an associated widening of the pulse pressure; the unexposed workers had no pre- to post-shift difference in orthostatic response or pulse pressure. Chlorthalidone workers had a smaller pre- to post-shift decrease in serum glucose than did unexposed workers, and did not have the pre- to post-shift decrease in the urine sodium/potassium ratio that the unexposed workers had. With respect to all other pulse and blood pressure measurements and laboratory test results, the two groups were similar or differed in a direction opposite to the predicted effects of chlorthalidone. Seven of the 10 chlorthalidone workers had measurable levels of chlorthalidone in their blood samples, but the concentrations did not correlate with total or respirable dust exposure levels and were one to two orders of magnitude less than the blood chlorthalidone concentration in an unexposed worker who took a 50-mg chlorthalidone tablet on the day of the study.

The blood chlorthalidone data collected in this investigation indicate that workers at Mylan Pharmaceutical Company had absorbed chlorthalidone, presumably by inhalation of airborne particles, in the course of their work. While some medical data were consistent with the pharmacologic effect of chlorthalidone in the exposed workers, most of the medical data did not suggest such an effect. These results are consistent with the relatively low blood chlorthalidone levels in the exposed workers and with the inherent limitations of studying small groups in experimentally uncontrolled settings. Certain individuals, however, may be unusually susceptible to chlorthalidone, so environmental exposures should be kept as low as possible. Recommendations to accomplish this are included in Section VIII of this report. Ultimately, however, occupational exposure standards need to be developed for chlorthalidone and other pharmaceuticals; it is inappropriate to treat such biologically active materials as though they were "inert" nuisance dusts.

KEYWORDS: SIC 2834 (Pharmaceutical Preparations Manufacturing), chlorthalidone, pharmaceuticals, diuretics, antihypertensives.

II. INTRODUCTION

On May 12, 1981 the National Institute for Occupational Safety and Health (NIOSH) received a request from the Oil, Chemical and Atomic Workers Union to evaluate employee exposures to chlorthalidone at the Mylan Pharmaceuticals Company, Morgantown, West Virginia. Production of chlorthalidone, a prescription diuretic used to treat high blood pressure, had recently begun at the facility. Fourteen of 20 employees involved in the production of chlorthalidone tablets reportedly had symptoms, such as excess urination and lightheadedness, suggestive of the drug's diuretic and hypotensive effects.

NIOSH conducted environmental and medical surveys on May 18-19 and May 28-29, 1981. NIOSH sent an interim report to the company and union in July 1981 and notified participants in the medical study of their test results in October 1981.

III. BACKGROUND

Mylan Pharmaceuticals, Inc. manufactures generic prescription drugs. The Morgantown, West Virginia facility, which began operation in 1970, employed 225 people at the time of the NIOSH investigation: 160 production employees and 65 administrative, clerical, and laboratory personnel.

There are no operations involving chemical synthesis or conversions. Products are run in batches. Ingredients, which are synthesized elsewhere, are weighed and blended, and the bulk powder is then dispensed and packaged in the various forms (capsules, tablets) and dosages. If the final product is a tablet, as is the case with chlorthalidone, the process includes granulating, tablet pressing, coating, and printing. Employees commonly change from one product line to another.

At the time of NIOSH's first visit, approximately 20 employees had worked at some time in 1981 on the chlorthalidone line; ten employees were currently working there.

IV. METHODS

A. Environmental

NIOSH collected personal air samples for measurement of total and respirable dust exposures on 10 workers in the chlorthalidone department. Total dust samples were collected using battery-powered vacuum pumps operating at a flow rate of 2.0 liters per minute (lpm) with 2-piece closed-face 37-millimeter (mm) cassettes containing Millipore M5 filters, which are made of polyvinyl-chloride and have a 5.0-micron pore size. Respirable dust samples were collected using Dorr-Oliver 10-mm nylon cyclone separators operating at a flow rate of 1.7 lpm with 2-piece closed-face 37-mm cassettes containing Millipore M5 filters. Impingers containing distilled water were used to collect airborne dust for determination of chlorthalidone concentration. Chlorthalidone was assayed by high performance liquid chromatography using an ultraviolet

using an ultraviolet absorbance detector with the wave-length set at 254 nanometers. The method has a detection limit of 0.05 microgram per milliliter.

Chlorthalidone and methylene chloride, which is used in the production area, can both cause some of the reported symptoms. To evaluate any potential confounding effect of methylene chloride exposure on the medical findings, NIOSH collected 15 area air samples in the coating room to determine concentrations of methylene chloride vapor. Samples were collected using MSA Model G pumps operating at a flow rate of 1.0 lpm. Two full-shift samples were collected on large (200/400 mg) charcoal tubes; the others, 1-hour samples, were collected on small (50/100 mg) charcoal tubes. Samples were analyzed according to NIOSH P & CAM No. S329.[1]

B. Medical

NIOSH administered a questionnaire to 28 of the 29 employees identified as having worked at some time in chlorthalidone production, including all 10 current chlorthalidone workers, and to 12 employees who had not worked in chlorthalidone production. The latter "control" group was a convenience sample of employees selected to make the group comparable, with respect to age and sex, to the chlorthalidone workers. The questionnaire sought data on various symptoms and their relationship to work, on general health background, and on specific job information. To assess the possible effects of exposure to chlorthalidone, the 10 current chlorthalidone workers and 10 of the 12 workers not exposed to chlorthalidone had the following tests both before and after the workshift:

(a) measurement of pulse and blood pressure after resting quietly 5 minutes in the supine position, and (to determine the orthostatic blood pressure response, which can be diminished by chlorthalidone) repeat measurements after standing for 1-2 minutes. All blood pressure measurements were made on the right arm.

(b) analysis of venus blood for serum concentrations of sodium, potassium, chloride, uric acid, and glucose.

(c) analysis of urine for sodium, potassium, and chloride concentrations.

Finally, post-shift venus blood was analyzed for serum aldosterone level and whole blood concentration of chlorthalidone. Chlorthalidone was assayed as described above.

V. EVALUATION CRITERIA

A. Chlorthalidone

Chlorthalidone[2,3], a phthalimidine derivative is chemically distinct but pharmacologically similar to the benzothiadiazide (or "thiazide") diuretics. It increases the urinary excretion of sodium, chloride, and water. Chlorthalidone is used therapeu-

tically to decrease the body's fluid load, in congestive heart failure for example, and to treat hypertension (high blood pressure). Its antihypertensive effect seems to be related primarily to its effect on sodium excretion and the resulting fluid loss. The fluid loss may cause orthostatic hypotension, the impairment of the body's normal reflex of increasing blood pressure in response to changing from a sitting or lying position to standing. Although therapeutic doses of chlorthalidone may lower the serum potassium level and increase the serum level of uric acid and glucose, overt toxicity is relatively rare in the absence of underlying kidney or liver disease.

Increased urination would probably be the most noticeable symptom of biologically significant occupational exposure to chlorthalidone. Other symptoms might include lightheadedness upon standing up and, if excessive potassium loss occurs, muscle weakness. There are no published criteria or standards for occupational exposure to chlorthalidone. Because chlorthalidone is a pharmacologically active compound, environmental exposure criteria for nuisance dust are inappropriate.

B. Methylene chloride

Methylene chloride[4,5], a widely used industrial solvent, causes fatigue, weakness, sleepiness, lightheadedness, numbness and tingling of the hands and feet. The liquic irritates the eyes and skin, and its vapor is a respiratory tract irritant. Methylene chloride is metabolized to carbon monoxide, so its potential toxicity is additive to that of inhaled carbon monoxide. [Carbon monoxide, by combining with hemoglobin in the blood and preventing it from carrying oxygen, causes headache, weakness, dizziness, nausea, confusion, and loss of consciousness.[6]] NIOSH recommends that occupational exposure to methylene chloride (in the absence of carbon monoxide exposure) not exceed a 10-hour time-weighted average (TWA) of 75 parts per million (ppm), nor a 15-minute ceiling of 500 ppm.

VI. RESULTS AND DISCUSSION

A. Environmental

Total dust concentrations for exposed workers ranged from 0.6 to 14.4 milligrams per cubic meter (mg/m^3), with a median of 1.5 mg/m^3 (Table 1). Respirable dust levels ranged from 0.1 to 0.5 mg/m^3, with a mode of 0.2 mg/m^3. The highest personal exposure level was a TWA of two samples which represents the exposure of one individual who operated two machines, the fitzmill and the compactor. A spill occurred during operation of the fitzmill, resulting in unusually high exposure levels of 22.5 mg/m^3 total dust and 0.7 mg/m^3 respirable dust. While such a spill may or may not be a common occurence, the air sampling data show that when one does occur, high exposure levels can result. The percentage of airborne dust that was truly chlorthalidone (active ingredient rather than excipient) could not be determined by the attempted method. However, area samples were collected at five locations (Table 2), and airborne chlorthalidone concentrations ranged from

1.1 to 2.3 mg/m^3. These areas samples were not intended to reflect personal exposures, but rather to determine maximum workplace concentrations at sources of dust generation. Chlorthalidone is not an airborne contaminant routinely encountered in industry. Therefore, sampling methods for the determination of airborne concentrations are rather new and have not had a great deal of field testing or validation.

Methylene chloride concentrations ranged from 1 to 25 ppm (Table 3). These area samples reflect the highest concentrations found anywhere in the workplace and are much higher than any personal exposures. Even so, all were well below the NIOSH recommended standard of 75 ppm.

B. Medical

The questionnaire data show a high prevalence of symptoms among production workers. Some of the symptoms--including increased frequency of urination while working with chlorthalidone and chlorthiazide; drowiness/fatique/sleepiness with chlordiazepoxide, propoxyphene, and amitriptyline; and nasal irritation with tetracycline--are consistent with the pharmacologic or chemical properties of the drugs being produced. Of the 28 workers who had worked in chlorthalidone production, 22 (79%) reported one or more symptoms temporally related to it, with an overall median of 4.5 symptoms per worker (8 if asymptomatic workers are excluded). Eight (67%) of the 12 other production workers reported work-related symptoms, with an overall median of 4.5 symptoms per worker (6 if asymptomatic workers are excluded). Since there was a wide variety of symptoms among chlorthalidone workers, many not specific for chlorthalidone, and since work-related symptoms, in general, were not significantly more common among chlorthalidone workers than among other production workers ($p = 0.22$, Fisher's exact test, 1-tailed), we focused the remainder of the data analysis on the current chlorthalidone-exposed workers and the unexposed "control" group.

One "unexposed" worker had taken a 50-mg chlorthalidone tablet the day of the survey, so he was excluded from the data analysis. Two of the unexposed workers, a capsule filler and a maintenance person, were exposed to tetracycline, but since the drug would be unlikely to affect any of the crucial physical measurements or laboratory tests, they were not excluded from analysis. Other unexposed workers, who were mainly labeling and laboratory personnel, reported exposures to solvents, but the NIOSH investigators observed no apparent source of such exposures.

The chlorthalidone workers were comparable to the unexposed workers with respect to age and sex, as intended, and race. They seemed to have less departmental and total seniority, however, and appeared less likely to be current smokers, but these differences were not statistically significant (Table 4). Two persons had consumed alcohol (1-3 drinks) the day before the testing, but none reported having any alcohol the day of the survey. Three chlorthalidone workers used non-prescription medications containing pseudo-

ephedrine or phenylpropanolamine, either of which could elevate blood pressure, and one of them also used an oral contraceptive, which can also elevate blood pressure. One unexposed worker had used hydrochlorthiazide (a diuretic phamacologically similar to chlorthalidone) five days earlier. No participant included in the data analysis had a history of high blood pressure.

The chlorthalidone-exposed and unexposed groups had comparable pre-shift supine pulse rate and pre-shift orthostatic (supine to standing) increases in pulse rate (Table 5). Both groups had comparably wide ranges of differences in the pre- to post-shift supine and post-shift orthostatic pulse rate changes. While the exposed group seemed to have a greater median pre- to post-shift supine change and a lower median post-shift orthostatic change, the former difference is minimal and the latter is not in the direction that would be predicted on the basis of chlorthalidone's diuretic and hypotensive effects. The 2 groups had similar pre- to post-shift individual differences in orthostatic pulse change.

Except for two chlorthalidone workers (one of whom used an oral contraceptive and pseudoephedrine, and the other of whom used a medication containing phenylpropanolamine) with single systolic blood pressure measurements of 145 and 150 mm Hg, no one had a systolic blood pressure greater than 140 or a diastolic pressure greater than 90, the common threshold pressures for diagnosing hypertension.

The exposed and unexposed groups had comparable pre-exposure supine systolic and diastolic blood pressures, as well as comparable pre-exposure pulse pressures (the difference between systolic and diastolic blood pressure) (Table 5). They also had comparable pre-shift orthostatic changes in systolic, diastolic, and pulse pressures. Neither group had a pre- to post-shift change in systolic pressure, and only the unexposed group had a decrease in diastolic pressure. The unexposed group had essentially identical pre- and post-shift orthostatic changes, whereas the exposed group had post-shift systolic and diastolic orthostatic changes less than both the unexposed group and its own pre-shift changes, results consistent with the effect of chlorthalidone. With the exception of systolic pressure in the exposed group, these results were the same as those obtained by analyzing pre- to post-shift individual differences in orthostatic change. Orthostatic changes and pre- to post-shift differences in pulse pressures had wider ranges than the corresponding changes and differences for systolic and diastolic pressures and did not consistently support or refute a chlorthalidone effect.

None of the pre-shift blood tests showed any difference between the chlorthalidone-exposed and unexposed groups (Table 6). With one exception, the pre- to post-shift changes were either comparable or different in the direction opposite to that expected from chlorthalidone's pharmacologic effects. The one exception, serum glucose, showed less of a decrease among the exposed workers. (While serum glucose level depends on the time and amount of preceding food intake, both groups had comparable pre-shift levels and

presumably had comparable opportunities for lunch and snacks.) Contrary to what would be expected from the pharmacologic action of chlorthalidone[3], the chlorthalidone workers' (post-shift) serum aldosterone levels were no higher than those of the unexposed workers.

While chlorthalidone workers had higher median pre-shift urine sodium, potassium, and chloride concentrations than the unexposed workers, the two groups had similar, small median pre- to post-shift changes for each electrolyte (Table 6). While the chlorthalidone workers did not have the markedly increased urine sodium/potassium ratio associated with a therapeutic dose of chlorthalidone[7], the tendency for a slight increase was significantly different than the consistent decrease in the unexposed group. (Although urine electrolyte concentrations and the sodium/potassium ratio may depend on dietary factors, a comparable range of individual variation in diet would be likely to occur in each group, and the use of non-parametric statistics for comparing groups minimizes the effect of even markedly atypical individual test results.)

Seven of the 10 chlorthalidone workers had measureable concentrations of chlorthalidone in blood (Table 1); none of the unexposed workers did. There was no apparent correlation between chlorthalidone levels and total or respirable dust exposure. (Since personal airborne chlorthalidone exposures are not available, "dust" is used as a surrogate measure of relative exposure.) Indeed, the worker who had the highest blood chlorthalidone level had the lowest total and respirable dust exposure. Conversely, the workers with the second, third, and fourth highest total dust exposures had no measureable blood chlorthalidone.

The unexposed worker who was excluded from the data analysis because he had taken a 50-mg chlorthalidone tablet had a blood chlorthalidone concentration of 6.9 ug/ml. Since the blood chlorthalidone concentrations in the other workers were all less than 15%, and in all but one case less than 2%, of this value, the failure of this study to detect consistent evidence of a biologic effect of chlorthalidone in a relatively small group of workers in an experimentally uncontrolled setting is not suprising.

VII. CONCLUSIONS

The majority of the chlorthalidone workers had documented absorption of chlorthalidone. Some of the medical data suggested a pharmacologic effect, namely, (1) a decrease over the work shift of the normal orthostatic blood pressure change among the exposed workers, and (2) a slight increase over the work shift (compared to a substantial decrease in the unexposed group) in the urine sodium/potassium ratio. Most of the other data, however, did not suggest any effect. This apparent lack of effect is not suprising since workers' blood chlorthalidone levels were, with one exception, two orders of magnitude lower than that of the unexposed worker who took a 50-mg chlorthalidone tablet. This is not to say, however, that certain individuals may not have an effect, someone who is taking another antihypertensive

drug, for example, or someone who is hypersusceptible or reacts idiosyncratically to chlorthalidone. Environmental exposures, therefore, should be kept as low as possible. Occupational exposure standards need to be developed for chlorthalidone and other pharmaceuticals; it is inappropriate to treat such biologically active materials as mere nuisance dusts.

VIII. RECOMMENDATIONS

1. Respiratory Protection.

   Many tasks are such that there are brief periods of activity during which there is a high level of exposure to drug-containing dust. Then, typically, there are longer periods of much lower exposure. Disposable respirators are available for employees to use at their discretion. Respirators are never comfortable, but an employee can greatly reduce the amount of dust inhaled by simply wearing a respirator during these brief periods of relatively high exposure. This practice may explain why people who worked in areas of high exposure had low levels of chlorthalidone in their blood. This is a prudent practice which should be continued and encouraged.

2. Overhead Scooping.

   Powdered materials are routinely transferred by hand-scooping them from one container to another. This generates considerable dust. It would be desirable to eliminate such scooping altogether, but this is not feasible at present. There are instances where the height of the operator and the design of the machine are such that the operator must scoop powders into hoppers that are higher than the operator's head. When this occurs, any dust that is generated or any powder that spills passes directly through the breathing zone of the operator. This is very likely what caused the high exposure experienced by the fitzmill operator. Clearly, steps can be taken to eliminate all overhead scooping of powdered materials.

IX. REFERENCES

1. National Institute for Occupational Safety and Health. NIOSH manual of analytical methods. Vol 3, 2nd ed. Cincinnati, OH: National Institute for Occupational Safety and Health, 1977. (DHEW (NIOSH) publication no. 77-157-C).

2. Gilman AG, Goodman LS, Gilman , eds. Goodman and Gilman's The Pharmacological Basis of the Therapeutics, 6th ed. New York: Macmillan Publishing Company, 1980, pp. 803, 810, 899-903.

3. Craig CR, Stitzel RE, eds. Modern Pharmacology. Boston: Little, Brown and Company, 1982, pp. 338-341.

4. Proctor NH, Hughes JP. Chemical hazards of the workplace. Philadelphia: J.B. Lippincott Company, 1978, pp 342-343.

5. National Institute for Occupational Safety and Health. Criteria for a recommended standard: occupational exposure to methylene chloride. Cincinnati, Ohio: National Institute for Occupational Safety and Health, 1976. (DHEW publication no. (NIOSH) 76-138).

6. Proctor NH, Hughes JP. op. cit., pp. 151-153.

7. Ford RV. The newer diuretics. Med Clin North Am. 1961;45:961-72.

XI. AUTHORSHIP AND ACKNOWLEDGEMENTS

Report Prepared By:

Mitchell Singal, MD, MPH
Assistant Chief
Medical Section

Richard Patnode
Industrial Hygienist
Environmental Investigation Branch
Division of Respiratory Disease Studies

Medical investigator:

Arthur S. Watanabe, Pharm D.
Medical Section

Industrial hygiene investigator:

Rick P. Ferguson
Industrial Hygienist
Environmental Investigations Branch
Division of Respiratory Disease Studies

Originating Office:

Hazard Evaluations and Technical Assistance Branch
Division of Surveillance, Hazard Evaluations, and Field Studies

Report Typed By:

Terry R. O'Neal
Clerk-Typist
Medical Section

XII. DISTRIBUTION AND AVAILABILITY OF REPORT

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

1. Oil, Chemical and Atomic Workers Local 3-957
2. Mylan Pharmaceuticals, Inc.
3. NIOSH, Region III
4. OSHA, Region III

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

Dust Exposures and Blood Chlorthalidone Levels

Mylan Pharmaceuticals
Morgantown, West Virginia

May 1981
HETA 81-322

Job	Time-weighted Average Dust Exposure (mg/m^3)		Blood Chlorthalidone Level (ug/ml)
	Total	Respirable	
Weigher	3.0	0.2	0[A]
Press operator	1.0	0.2	0.07
Press operator	0.6	0.1	0.97
Inspector	1.4	(B)	0.07
Inspector	1.5	0.2	0.08
Inspector	1.6	0.3	0
Inspector	0.9	0.2	0.07
Inspector	0.8	0.2	0.07
Blender	9.5	0.2	0
Fitzmill and compactor operator	14.4[C]	0.5	0.07

A - Limit of detection: 0.05 ug/ml
B - Sample lost
C - Includes exposure during a spill

Table 2

Results of Area Air Sampling for Chlorthalidone in Tablet Press Room

Mylan Pharmaceuticals
Morgantown, West Virginia

May 19, 1982
HETA 81-322

Sample Location	Duration	Concentration of Chlorthalidone*
Near press hopper	12:30 - 1:00 pm	2.3
Near press hopper	1:05 - 1:36 pm	2.1
Near inspector	1:42 - 2:12 pm	1.4
On tablet press	5:07 - 5:31 pm	1.1
Near press hopper	8:50 - 9:22 pm	2.0

*Milligrams per cubic meter

Table 3

Methylene Chloride Air Sampling Results

Mylan Pharmaceuticals
Morgantown, West Virginia

May 1981
HETA 81-322

Location	Sampling Time	Time-weighted Average Concentration (parts per million)
May 18, 1981		
Right side of coating room at pan 5	8:21 am - 9:32 am	10
Right side of coating room at pan 4	8:29 am - 3:01 pm	10
Room behind right side of coating room	8:34 am - 11:38 am	8
At Pan 5	9:32 am - 10:34 am	25
At Pan 5	12:52 pm - 1:53 pm	18
Left side of coating room at pan 3	12:54 pm - 1:54 pm	1
May 29, 1981		
Left side of coating room at pan 1	7:55 am - 10:58 am	25
Left side of coating room at pan 2	7:55 am - 2:03 pm	9
Left side of coating room at pan 3	7:55 am - 10:58 am	17
NIOSH recommended standard		75

Table 4

Characteristics of Study Participants

Mylan Pharmaceuticals
Morgantown, West Virginia

May 1981
HETA 81-322

	Exposed to Chlorthalidone	Not Exposed to Chlorthalidone
Number of workers	10	9
Age at last birthday		
Range	21 - 49	22 - 46
Means ± S.D.*	34 ± 9.9	35 ± 9.2
Median	34[A]	40[A]
Years at plant		
Range	3 - 9	3 - 14
Median	6.5	9
Years in current department		
Range	<1 - 5[B]	1 - 9
Median	1[B]	4
Less than 2 years	5[B, C]	1[C]
Smoking status		
Current smokers	1[D]	5[D]
Former smokers	2	0

*Standard deviation
A - p =0.3, Wilcoxon rank sum test
B - Unknown departmental seniority in one case
C - p = 0.13, Fisher's exact test, 2-tailed
D - p = 0.06, Fisher's exact test, 2-tailed

Table 5

Pulse and Blood Pressure Measurements

Mylan Pharmaceuticals
Morgantown, West Virginia

May 1981
HETA 81-322

	Exposed to Chlorthalidone	Not Exposed to Chlorthalidone
Number of Workers	10	9
Pulse (beats/minute)		
Pre-shift supine	74 (64, 88)*	74 (64, 92)
Pre-shift orthostatic change	+11 (+2, +20)	+12 (+2, +20)
Pre- to post-shift supine difference	+2 (-8, +14)	-4 (-10, +10)
Post-shift orthostatic change	+5 (-4, +20)	+14 (0, +20)
Pre- to post-shift individual difference in orthostatic change	-4 (-24, +16)	-2 (-16, +12)
Blood pressure (millimeters of mercury)		
Pre-shift supine		
Systolic	110 (108, 140)	100 (90, 125)
Diastolic	65 (56, 90)	64 (50, 70)
Pulse Pressure	50 (26, 70)	44 (20, 75)
Pre-shift orthostatic change		
Systolic	+7 (-12, +16)	+10 (-2, +20)
Diastolic	+9 (0, +25)	+10 (-2, +20)
Pulse Pressure	-5 (-28, +12)	-5 (-10, +10)
Pre- to post-shift supine difference		
Systolic	0 (-10, +10)	0 (-35, +10)
Diastolic	+2 (-20, +20)	-6 (-20, +10)
Pulse Pressure	-5 (-20, +15)	+10 (-45, +20)
Post-shift orthostatic change		
Systolic	+3 (-16, +20)	+10 (0, +18)
Diastolic	0 (- 5, +15)	+10 (0, +20)
Pulse Pressure	+3 (-26, +20)	- 6 (-20, +16)
Pre- to post-shift individual difference in orthostatic change		
Systolic	+6 (-32, +10)	0 (-15, +10)
Diastolic	-9 (-20, + 6)	0 (-20, +10)
Pulse Pressure	+10 (-38, +30)	+4 (-20, +18)

*Median (range)

Table 6

Blood an Urine Test Results

Mylan Pharmaceuticals
Morgantown, West Virginia

May 1981
HETA 81-322

	Exposed to Chlorthalidone	Not Exposed to Chlorthalidone
Number of Workers	10	9
Serum electrolytes (mmoles/l)[1]		
Sodium: Pre-shift	139 (135, 142)[2]	138 (133, 141)
Pre- to post-shift change	-1 (-4, +6)	-1 (-6, +3)
Potassium: Pre-Shift	4.3 (3.9, 4.6)	4.4 (4.0, 5.0)
Pre- to post-shift change	-0.1 (-0.8, + 0.6)	-0.5 (-1.2, 0)
Chloride: Pre-shift	105 (104, 107)	106 (99, 109)
Pre- to post-shift change	0 (-6, +3)	0 (-6, +4)
Urine electrolytes (mmoles/l)		
Sodium: Pre-shift	127 (28, 256)	90 (23, 294)
Pre- to post-shift change	-3 (-132, +144)	-4 (-135, +126)
Potassium: Pre-shift	56 (11, 136)	28 (13, 99)
Pre- to post-shift change	+3 (-29, +54)	+5 (-36, +116)
Chloride: Pre-shift	206 (47, 235)	99 (24, 242)
Pre- to post-shift change	-4 (-129, +114)	-28 (-145, +119)
Urine sodium/potassium ratio		
Pre-shift	3.0 (0.3, 5.2)	2.6 (0.9, 8.9)
Pre- to post-shift change	+0.1 (-0.9, + 1.7)[3]	-0.8 (-2.3, -0.2)[3]
Serum uric acid (mg/dl)[4]		
Pre-shift	4.3 (3.1, 6.1)	4.2 (2.4, 5.9)
Pre- to post-shift change	-0.2 (-0.7, + 0.3)	0 (-0.8, +0.9)
Serum glucose (gm/dl)[5]		
Pre-shift	100 (81, 114)	101 (88, 119)
Pre- to post-shift change	-4(-27, +34)	-15 (-26, +5)
Serum aldosterone (post-shift) (ng/dl)[6]	13.4 (7.4, 26.1)[7]	21.3 (3.3, 60.2)[7]

1 - Millimoles per liter
2 - Median (range)
3 - p = 0.001, Wilcoxon rank sum test
4 - Milligrams per deciliter
5 - Grams per deciliter
6 - Nanograms per deciliter
7 - p > 0.39, Wilcoxon rank sum test