File Copy

HEALTH HAZARD EVALUATION REPORT 71-9-50

HAZARD EVALUATION SERVICES BRANCH

DIVISION OF TECHNICAL SERVICES

Establishment : Chemetron Chemical
Organics Division
Newport, Tennessee

Report Prepared By : David J. Burton
SA Sanitary Engineer
Division of Technical Services
Salt Lake City, Utah

Edward Shmunes, M.D.
Occupational Health Officer
Medical Services Branch
Cincinnati, Ohio

Field Evaluation : David J. Burton
Edward Shmunes, M.D.

James S. Taylor, M.D.
Medical Officer

Vernon B. Perone
Industrial Hygienist

Laboratory Analyses: Russell H. Hendricks, Ph.D.
Chief, Analytical Services, DLCD
Salt Lake City, Utah

Originating Office : Jerome P. Flesch, Chief
Hazard Evaluation Services Branch
Cincinnati, Ohio

June 1973

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

CINCINNATI, OHIO 45202

TABLE OF CONTENTS

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH
CINCINNATI, OHIO 45202

HEALTH HAZARD EVALUATION REPORT 71-9
CHEMETRON CHEMICAL
ORGANICS DIVISION
NEWPORT, TENNESSEE

JUNE 1973

I. SUMMARY DETERMINATION

A. Introduction

Section 20(a)(6) of the Occupational Safety and Health Act of 1970, 29 U.S.C. 669(a)(6), authorizes the Secretary of Health, Education, and Welfare, following a written request by 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 National Institute for Occupational Safety and Health (NIOSH) received such a request from an authorized representative of employees regarding exposure to the underlisted substances in the production of diethylstilbestrol at the Chemetron Chemical Organics Division in Newport, Tennessee.

B. Federal Standards

The substances used or found in the workplace with potentially toxic properties are listed below with their respective exposure standards as promulgated by the U.S. Department of Labor (Federal Register, Volume 37, §1910.93, October 18, 1972).

Material	8-hour time weighted average	Acceptable ceiling concentration	Acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift	
			Concentration	Maximum duration
Benzene (Z37.4-1969)	10 p.p.m.*	25 p.p.m.*	50 p.p.m.*	10 minutes
Diethylstilbestrol**				

*ppm - parts of vapor or gas per million parts of air

**No Standard Established

C. Environmental Evaluation Results

Results of environmental sampling for benzene at DES operations on June 26-28, 1972 indicate exposure levels in excess of Federal Standards. Levels ranged from 3 to 260 ppm, with a 48-hour average of 34 ppm. The ceiling concentration of 25 ppm was exceeded 43 percent of the time.

D. Medical Evaluation Results

Since 1969 Diethylstilbestrol (DES) accounted for 23 instances of breast tenderness and enlargement in male chemical workers in DES production. A urine study for DES excretion was done which showed that all full time workers who wore air suits when necessary all developed increasing levels of DES upon increasing days of exposure. At a certain range of excretion (40 ug/24hours) two workers became symptomatic. DES was also detected in one helper, and two individuals not directly connected with the area of known exposure.

Although no standard for DES exists, the following evidence points to the actuality of hazardous levels of exposure: (1) there has been a persistant history of DES reactions, year after year, (2) high urine levels and adverse reactions were found in workers participating in the medical studies of this evaluation, and (3) there was found widespread DES contamination of buildings and equipment, even extending as far away as the lunch room.

It should be noted that our study leads us to believe that much of the absorption of DES by employees was through the G.I. tract and the skin. This was brought about by the gross contamination of clothing, equipment, and skin by careless handling of DES and the lack of adequate decontamination procedures. For this reason no correlation between airborne exposure dose and physiological response has been attempted in this study.

E. Toxicity Determination

Based upon the results of medical and environmental studies conducted from March 1972 through January of 1973 by officers of the National Institute for Occupational Safety and Health it has been determined that there was a significant hazard to the health and well being of the workers from exposure to benzene and DES in the production of diethylstilbestrol at the T-6 facility of the Chemetron Chemical Corporation in Newport, Tennessee.

It should be noted however that as a result of the recent Food and Drug Administration order which prohibits the use of diethylstilbestrol for use in feeds, the Chemetron Chemical Corporation of Newport, Tennessee stopped the production of diethystilbestrol as of November 28, 1972.

Much of the equipment involved in the production of diethylstilbestrol had been dismantled as of February 8, 1973.

Should the production of diethylstilbestrol be resumed it is recommended that control procedures be instituted to protect the health and safety of workers.

F. Distribution

Copies of this Summary Determination of the evaluation are available upon request from the Hazard Evaluation Services Branch, NIOSH, U. S. Post Office Building, Room 508, 5th and Walnut Streets, Cincinnati, Ohio 45202. Copies have been sent to:

a) Chemetron Chemical Organics Division
b) Authorized Representative of Employees
c) U. S. Department of Labor - Region IV

For purposes of informing the approximately 130 "affected employees," the employer will promptly "post" the Summary Determination in a prominent place(s) near where affected employees work, for a period of 30 calendar days.

II. INTRODUCTION

Section 20(a)(6) of the Occupational Safety and Health Act of 1970, 29 U.S.C. 669(a)(6), authorizes the Secretary of Health, Education, and Welfare, following a written request by 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 National Institute for Occupational Safety and Health (NIOSH) received such a request from an authorized representative of employees regarding exposures to diethylstilbestrol (DES) and benzene at the T-6 operation, Chemetron Chemical Corporation, Newport, Tennessee.

The T-6 facility is involved solely with the production of diethylstilbestrol for use in animal feeds.

III. BACKGROUND HAZARD INFORMATION

A. Standards

Two chemical substances to which workers are exposed during the production of diethylstilbestrol are diethylstilbestrol and benzene.

The occupational health standards as promulgated by the U.S. Department of Labor (Federal Register, Part II, §1910.93, Table G-1) applicable to substances of this evaluation are as follows:

Material	8-hour time weighted average	Acceptable ceiling concentration	Acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift.	
			Concentration	Maximum duration
Benzene (Z37.4-1969)	10 p.p.m.*	25 p.p.m.*	50 p.p.m.*	10 minutes.
Diethylstilbestrol **				

*ppm - parts of vapor or gas per million parts of air.

**No Standard Established.

B. Toxic Effects

Benzene

Severity of Hazards: Moderate for acute exposure; high for chronic. Absorption occurs chiefly by inhalation. High concentrations irritate the respiratory tract and produce narcosis. Repeated exposure to benzene may cause bone marrow damage, resulting in a decrease in the circulating white blood cells. The red cells may occasionally show an increase in size in early poisoning. Many serious illnesses and fatalities have occurred in association with chronic exposures to benzene. It has been stated that symptoms may occasionally occur after exposure has ceased. Individual susceptibility varies widely with the remote possibility that an occasional individual may be affected by the prolonged exposure to 25 ppm. A primary irritant type of dermatitis may result from repeated skin contact. Percutaneous absorption is considered insignificant.

Short Exposure Tolerance: For many on single exposure, 3000 ppm is endurable for 30 to 60 minutes; 7500 ppm is dangerous in 30 to 60 minutes.

Atmospheric concentration immediately hazardous to life: 20,000 ppm is reported fatal in 50 to 10 minutes.[1]

Diethylstilbestrol

Diethylstilbestrol, also known as stilbestrol, is a synthetic female hormone which is the source of various non-steroid estrogens. (Its formula is C18H2002.) It can be ingested, inhaled or absorbed through the skin. Diethylstilbestrol is not listed in the Toxic Substance List, 1972 Edition, printed by the Department of HEW. Typical physiological reactions in males include gynecomastia and impotency. Little is reported in the literature concerning dose-response relationships in males. Watrous and Olsen have estimated that clinical evidence of exposure will be manifest after urine excretionary levels exceed 0.10 micrograms per milliliter. They also estimate that from 300 to 1000 micrograms of DES must be absorbed per day to reach the clinical manifestation stage.[2,3]

IV. HEALTH HAZARD EVALUATION

The evaluation consisted of three mutually exclusive parts: (a) An initial observational survey, (b) An environmental study of employee work practices, airborne concentrations of DES and Benzene, and DES contamination of property and equipment, and (c) A medical study of those working in the DES production area.

A. Initial Observational Survey

On the morning of March 15, 1972, Edward Shmunes, M.D., James Taylor, M. and David J. Burton, Industrial Hygienist, all of the National Institute for Occupational Safety and Health, met with Mr. W.H. Sutton, Branch Manager Mr. W.C. Gilbert, Personnel Manager, George Wiley, Safety Manager, and Ormand Lorenz, Development Manager, all employed by Chemetron Chemical Corporation.

(1) Background Information

The Newport Facility of Chemetron Chemical Corporation has been in operation since 1957. The plant operates 24 hours a day, 7 days a week and uses 4 shifts which overlap. There are approximately 130 hourly employees. Hourly employees are represented by the Oil Chemical and Atomic Energy Workers Local 3724. The president of the local union is William F. Murr, who joined us later that afternoon on a walk-through survey of the plant.

Employees are provided a central locker room with showers and a lunch room located in the Administration Building. There are three or four physicians on call out of a clinic in Newport. Employees are given a pre-employment physical. There are no periodic examinations, periodic tests or health programs. Employees absent for more than 3 days require a release from a physician for readmission to the job. Personal protective devices required by all employees are hard hats, safety glasses, and safety shoes. There is no system of regular monitoring of environmental conditions. There is a first aid room on the premises but no full time staff to staff it. Each shift has one person working who has completed a first aid course.

(2) DES Production Process

The production of DES is referred to as the T-6 operation and is located in Building #8. Diethylstilbestrol is made starting with the compound p-anisoin. Anisoin undergoes several chemical changes in another building. By the time it reaches Building #8C, it is in a form of ethyl-desoxyanizoin, which is purported not to cause hormonal-type reactions. This compound goes through another stage of synthesis and eventually the final product diethylstilbestrol is pumped in a water slurry into a room called the finish room. (See Figure 1) The water is drained off. The workers then manually shovel the wet cake and transfer it to a tank where the slurry is again washed. DES is then dissolved into hot benzene and is pumped back into Building #8C. The operation from this point on in Building #8C is a closed system. This mixture is filtered, de-watered,

IV. HEALTH HAZARD EVALUATION

The evaluation consisted of three mutually exclusive parts: (a) An initial observational survey, (b) An environmental study of employee work practices, airborne concentrations of DES and Benzene, and DES contamination of property and equipment, and (c) A medical study of those working in the DES production area.

A. Initial Observational Survey

On the morning of March 15, 1972, Edward Shmunes, M.D., James Taylor, M. and David J. Burton, Industrial Hygienist, all of the National Institute for Occupational Safety and Health, met with Mr. W.H. Sutton, Branch Manager Mr. W.C. Gilbert, Personnel Manager, George Wiley, Safety Manager, and Ormand Lorenz, Development Manager, all employed by Chemetron Chemical Corporation.

(1) Background Information

The Newport Facility of Chemetron Chemical Corporation has been in operation since 1957. The plant operates 24 hours a day, 7 days a week and uses 4 shifts which overlap. There are approximately 130 hourly employees. Hourly employees are represented by the Oil Chemical and Atomic Energy Workers Local 3724. The president of the local union is William F. Murr, who joined us later that afternoon on a walk-through survey of the plant.

Employees are provided a central locker room with showers and a lunch room located in the Administration Building. There are three or four physicians on call out of a clinic in Newport. Employees are given a pre-employment physical. There are no periodic examinations, periodic tests or health programs. Employees absent for more than 3 days require a release from a physician for readmission to the job. Personal protective devices required by all employees are hard hats, safety glasses, and safety shoes. There is no system of regular monitoring of environmental conditions. There is a first aid room on the premises but no full time staff to staff it. Each shift has one person working who has completed a first aid course.

(2) DES Production Process

The production of DES is referred to as the T-6 operation and is located in Building #8. Diethylstilbestrol is made starting with the compound p-anisoin. Anisoin undergoes several chemical changes in another building. By the time it reaches Building #8C, it is in a form of ethyldesoxyanizoin, which is purported not to cause hormonal-type reactions. This compound goes through another stage of synthesis and eventually the final product diethylstilbestrol is pumped in a water slurry into a room called the finish room. (See Figure 1) The water is drained off. The workers then manually shovel the wet cake and transfer it to a tank where the slurry is again washed. DES is then dissolved into hot benzene and is pumped back into Building #8C. The operation from this point on in Building #8C is a closed system. This mixture is filtered, de-watered,

and cooled. The benzene slurry of DSB is pumped back into the finish room into another filter pot from which the benzene is drained off, leaving a wet cake of DES. It is then manually shoveled into drying ovens. The consistency at this point is a rough lumpy powder. It is then milled to approximately 10 microns in size. Drums of DES are filled in the finish room and weighed.

Drums of finished DES are then put into a storage area and periodically shipped out in this raw form. The plant also provides a service of mixing diethylstilbestrol with animal feed in another area of the plant. This is a sporadic operation and at no time during our visits did we see this operation performed. There are at any given time two people working in Building #8, including the finish room. On a normal working day, 8 people per 24 hours are exposed in the DES process. One man per shift works in the finish room. This particular job is rotated among the workers every six weeks. This man is known as the "finish man", the "inside man", or the "full-time man."

(3) Medical Observations

The following table supplied by the company shows the number of employee reactions to DES during the past three years. Spot checks with employees indicated that perhaps these figures did not accurately reflect the actual number of reactions experienced.

Year	Number of DES Reactions
1969	10
1970	11
1971	2

The term "reaction" implies tenderness and enlargement of the male breast with or without accompanied periods of sexual impotence. All of those reported in the above table were referred to a physician.

B. Environmental Evaluation

(1) Sampling

During the period June 27-29, a follow-up environmental survey was made of the T-6 operations at the Newport Facility. The purpose of this survey was to obtain measurements of employee exposure to DES and Benzene.

Employee exposures to diethylstilbestrol and benzene were obtained using personal air sampling equipment, which sampled air in close proximity to the employee's actual breathing zone. MSA Model G battery powered vacuum pumps were used to draw air through open faced millipore air monitors to collect the diethylstilbestrol. Activated charcoal tubes were used to collect benzene samples.

Area samples in the Building #8 area, adjacent to the finish room, were taken using Research Appliance Company Sequential Samplers.

(2) Work Practices

During each shift 2 men worked in and around the diethylstilbestrol area. The outside man was called the "helper". The finish or inside man spent approximately 2 to 3 hours per day inside the finish room. While he was in the finish room the helper stood in Building #8 and watched him through windows connecting the finish room with Building #8. Before entering the finish room the finish man was helped into an air supplied plastic suit. He then entered a shower where he showered, disconnected his air hose, and entered the finish room where upon he reattached his suit to an inside air supply.

It was noted during one sampling period that the finish man was experiencing trouble with his air supply hose and during the course of the work disengaged the hose from the suit at least 5 times, blew it clean, and reattached the hose to the suit. At one point the outside man was requested to bleed the lines to flush out "water, rust, and oil which were clogging the inlet valve". It was noted that after the helper assisted the finish man, his gloves were contaminated with DES which he then proceeded to place in his rear pocket.

While the finish man was working in the finish room the helper was required several times to enter the finish room to deliver tools or to carry away filled containers. The helper at this time was wearing no respirator or any protective clothing.

As a drum was filled in the finish room it was brought to the double doors leading to the outside, whereupon the outside man washed the drum with water. The water-laden diethylstilbestrol was left on the ground.

Equipment was observed to be brought in from other work areas to be used in the diethylstilbestrol operation and returned without decontamination.

Following his activity in the finish room the finish man again re-entered the shower, disengaged the inside air hose and re-attached the outside air hose to his suit, showered, and then went into a small locker room adjacent to the shower room, where the helper assisted him in removing the suit. Upon leaving the finish room the finish man was noted to be covered with dust before taking his shower. The outside man used a brush to brush the dust from the finish man while he was in the shower.

(3) Ventilation and Housekeeping

Ventilation in the finish room consisted of two rudimentary systems. One was connected to a baghouse which collected some of the residue from milling and drying operation. The other system consisted of a roof-mounted fan which when activated simply blew the diethylstilbestrol out onto the roof of the finish room. Company officials stated that this fan was not to be on during operations in the finish room but during the days that we were there, it was activated and diethylstilbestrol was to be found in the roof. (See results of sampling.) There was evidence of diethylstilbestrol leaking through the windows into the adjacent room.

In spite of apparent employee fear of exposure to DES, there was surprisingly little attention or thought given to adequate housekeeping or the careful handling of DES. Spills were left untouched, usually until a maintenance man could be called. Decontamination, as a procedural practice was absent. On June 29th a pump to the clarity filter in 8C was leaking, spilling DES plus benzene on equipment and on the floor. Ventilation and decontamination for these episodes was completely inadequate, consisting of 1 wall fan on the east side of the building.

(4) Results, DES

Results of sampling are shown in Table 1. Environmental sampling was limited to 9 samples. These consisted of 3 wipe samples, 4 personal samples, and 2 area samples taken in Building #8C adjacent to the finish room. One area sample showed evidence of DES contamination in Building #8C.

Of the 4 personal samples, 2 were taken while the man was in the suit. Both of these samples showed DES exposure even while inside the suit. One personal samplerwas placed on the helper in Building #8C

and he received a high exposure. This was due presumably to his entering the finish room without adequate protection.

All three wipe samples showed contamination of DES at the location wiped. One was taken from the roof over the finish room and another was taken from the floor of Building #8C under the H_2O separator. The last wipe sample, which did show positive results for DES, was taken on the drink dispenser in the lunch room.

No area samples were taken inside the finish room due to the desire to keep equipment from being contaminated with DES. It is possible, however, to roughly approximate the level of diethylstilbestrol in the finish room. It is estimated that an air supply suit offers a factor of protection of about 1000. Thus from the data obtained from the sample inside the suit we could roughly estimate that the airborne concentration within the finish room to be from 0.4 mg/M^3 to 1.8 mg/M^3.

The analysis of DES was performed by the Warf Institute, Madison, Wisconsin, by the same methods (as outlined on page 10) which were used to determine urine-DES levels.

(5) Results, Benzene

Benzene levels in Building #8C of the T-6 operation are summarized in Tables 2-4 and Figure 2. Table 3 indicates that benzene levels were found to exist within the suit. Figure 2 shows time vs. benzene concentration in Building #8C. Note that much of the time the benzene level was at or above the TLV. In 4 cases it exceeded the ceiling value and in 2 cases the levels exceeded the maximum concentrations allowable. The single incident of 260 ppm occurred during a benzene spill in Building #8C. Apparently the mother-liquor pump was leaking at the time. DES and Benzene were observed to be accumulating on the floor around the leak. Table 4 shows benzene levels in the dressing and shower rooms during activity in the finish room. Concentrations in the shower room exceeded the capability of the method and were greater than 500 ppm.

C. Medical Evaluation, DES

(1) Background

Diethylstilbestrol is a non-steroid estrogen with a potent capacity to induce feminizing symptoms in males. Because it is a non-steroid estrogen, one can not use a 24 hour urinary total estrogen determination as an index of absorption and excretion. In the oral contraceptive industry, which uses steroidal forms of estrogen compounds, urine monitoring for 24 hour total estrogens is done periodically, as the feminizing risks to male workers are similar. Such monitoring systems are used satisfactorily these industries. When an individual begins to approach ranges of urinary estrogens that are known to correlate with symptoms, the individual is withdrawn from the exposure area.

It was thus desirable to try to adapt a similar urine assay for the non-steroid estrogen, diethylstilbestrol. Previous studies with diethylstilbestrol have used bioassay systems utilizing mice uteri.[3] This system is not specific for diethylstilbestrol but measures endogenous estrogen and androgen as well.[3]

Fluorometric methods for DES have been used in human urine studies although conclusions could not be drawn from the reported study.[4]

The non-steroid estrogens are slowly degraded in the body, and little is known of the mechanisms of the excretion products. A glucuronic acid derivative of DES has been isolated from the urine after large doses of the estrogen are given by mouth.[5]

Fortunately, recent interest in DES in cattle tissues by the Food and Drug Administration has led to a new specific chemical assay for DES. In this determination DES and the DES glucuronide are extracted from liver, kidney, or muscle with methanol and the samples are subjected to B-glucuronidase enzymatic hydrolysis to yield free DES. Free DES is extracted from fat with chloroform. The samples are purified by alkaline liquid extration. The DES is reacted in base with dichloroacetyl chloride to form the ester which is measured by gas chromatography using electron capture detection.

The method was developed by Eli Lilly and adapted by the Food and Drug Administration for its analysis on beef liver. Both sources felt that it could be easily adapted to human urine. Though the FDA originally agreed to perform the analyses on human urine, increased laboratory demands made this no longer possible. Both the FDA and Lilly recommended the WARF Institute, a private laboratory in Madison, Wisconsin, that specializes in DES Determinations.

(2) Medical Investigation

All members of the current eight member work force in the DES area of Building #8 were interviewed during the initial visits. Members of the DES work force at the time of urine collections were also interviewed.

In addition one previous employee who had had residual breast problems after having left the DES area was interviewed and examined.

Urine studies were not begun at the time of the initial visit because the employees had been working for different intervals. Arrangements were made to begin another group simultaneously in the future but a labor strike interrupted these plans for several months. Work was resumed in mid-September, 1972, and we were notified in time to begin the first 24 hour urine collection on the seventeenth day of exposure (Oct. 2, 1972).

At the day of the first sampling, spot samples were collected prior to the initiation of 24 hour urine collections to compare the efficacy of a spot sample to a 24 hour sample. The majority of the workers were resampled with 24 hour urines on the 59th day of exposure, and the 93rd day of exposure which was several days after DES production was shut down. The closure of the DES production was in response to the FDA's action to ban DES in animal feeds.

Additional 24 hour urine samples were collected at various time periods on a few individuals after termination of work in the DES area to study how long detectable quantities were excreted.

In addition, eight control urines from selected key personnel and a sample of tap water were submitted for analysis.

As a measure of completeness of 24 hour urine specimens, total urine creatinine determinations were performed on the samples and a record of total volume was made, before 100 ml. aliquot samples were submitted for analysis.

(3) Results

Of the 8 individuals in the work force at the time of the initial evaluation, all had had DES reactions at some time during previous six week rotations through the DES area. Five of this group had single episodes, one had two episodes and two individuals four reactions. The workers ranged in age from 19 to 33 with an average age of 29. In all but one instance, the DES reaction occurred when the individual was a suited worker as opposed to a helper. The reaction developed during the 4th or 5th week in all but one individual who remembered the reaction occurring during the last week. (Table 5)

The breasts were involved in all cases. In three instances, sexual changes accompanied the breast changes and consisted of decreased libido, painful ejaculation and post coital burning in three separate individuals.

A ninth individual with persistent breast lumps and periodic tenderness had been exposed during his second week on one occasion when a line broke. He has been assigned to the other side of Building #8 to work with DES precursor compounds, although periodic breast tenderness persisted at approximately monthly intervals.

Of the 9 individuals employed in the DES area during the urine collections, five were full time workers at some time and, four were helpers. Their ages ranged from 22 to 42 with an average age of 29. Seven of the nine had had previous DES reactions on other tours of duty. This data is summarized in Table 6.

At the day of the first sampling, spot samples were collected prior to the initiation of 24 hour urine collections to compare the efficacy of a spot sample to a 24 hour sample. The majority of the workers were resampled with 24 hour urines on the 59th day of exposure, and the 93rd day of exposure which was several days after DES production was shut down. The closure of the DES production was in response to the FDA's action to ban DES in animal feeds.

Additional 24 hour urine samples were collected at various time periods on a few individuals after termination of work in the DES area to study how long detectable quantities were excreted.

In addition, eight control urines from selected key personnel and a sample of tap water were submitted for analysis.

As a measure of completeness of 24 hour urine specimens, total urine creatinine determinations were performed on the samples and a record of total volume was made, before 100 ml. aliquot samples were submitted for analysis.

(3) Results

Of the 8 individuals in the work force at the time of the initial evaluation, all had had DES reactions at some time during previous six week rotations through the DES area. Five of this group had single episodes, one had two episodes and two individuals four reactions. The workers ranged in age from 19 to 33 with an average age of 29. In all but one instance, the DES reaction occurred when the individual was a suited worker as opposed to a helper. The reaction developed during the 4th or 5th week in all but one individual who remembered the reaction occurring during the last week. (Table 5)

The breasts were involved in all cases. In three instances, sexual changes accompanied the breast changes and consisted of decreased libido, painful ejaculation and post coital burning in three separate individuals.

A ninth individual with persistent breast lumps and periodic tenderness had been exposed during his second week on one occasion when a line broke. He has been assigned to the other side of Building #8 to work with DES precursor compounds, although periodic breast tenderness persisted at approximately monthly intervals.

Of the 9 individuals employed in the DES area during the urine collections, five were full time workers at some time and, four were helpers. Their ages ranged from 22 to 42 with an average age of 29. Seven of the nine had had previous DES reactions on other tours of duty. This data is summarized in Table 6.

(a) Spot Samples

The spot sample results of DES levels do not coincide well with the results of 24 hour excretions of DES, expressed in equivalent terms (ug/ml) as shown in Table III. One would most easily interpret these differences as probably reflecting the difference in specific gravity in one specimen at one time as opposed to a 24 hour determination which would be a collection of urines of varying solute dilution during the day. Without comparable specific gravity determinations on spot urines versus 24 hour collections, one could not assume this as fact. After the initial comparative sample collections, however, only 24 hour urine collections were made.

(b) Full-Time Employees (Data Summarized in Table 7)

Despite air suits and work procedures, all full time employees ("inside" men) in the DES area had detectable levels of DES in 24 hour urine collections by the 15th and 17th day. Levels ranged from 9.7 ug/ml to 37.8 ug/ml. The worker exhibiting the highest level had begun to be symptomatic at that level.

Two workers who became so symptomatic that they decided they would have to leave the area, had the highest recorded values in the study. These were the only specimens in the 40 ug/ml range, 46.2 ug/ml and 47.3 ug/ml. Two full time workers had levels in the 30 ug/ml range between collections 20 days apart, representing 47 days of exposure (Days of Exposure = 5 out of 7 day work week). Both remained asymptomatic.

Excretion data after discontinuance of exposure due to shut down varied. Of two individuals with detectable levels in the 30 ug range on earlier samples, two had low levels still detectable six days after exposure. Each showed decreases of 89% and 91% respectively, between their previous sample and the six day post-shut down samples. One individual with a detectable level in the 20 ug range, no longer had detectable levels at six days post-shut down.

Of the two individuals with barely detectable levels of DES at six days post-shut down, increased levels of DES were detectable at 16 days post-shut down. In the case with the more significant rise from 3.7 ug/24 hours to 15.5 ug/24 hours, exposure to the DES area in terms of clean-up duty had occurred. Twenty-one days later and without further exposure this individual did not have detectable levels.

(c) Helpers

Only one of the four helpers in the study had detectable levels by the 17th day which increased to a level of 27.0 ug/ml/24 hours by the 47th day of exposure. This worker's activity did not differ knowingly from the other helpers who at no time showed detectable levels. His level at day 47 was lower than any of the full time employees. He no longer had detectable levels by the 6th day post-shut down (Table 7).

(d) Controls (Table 8)

It is of interest that two of the individuals selected as controls (in the sense that they were not either full-time or part-time employees in DES production) showed detectable levels.

In one case, the supervisor of that half of the plant operation including DES production showed detectable levels on the spot sample only. The supervisor of the opposite half of the plant had no detectable levels.

The other control that was positive was a worker on the opposite side of Building #8. This area produces DES precursors. Though he had been asymptomatic, another individual (Control #9) had had episodic breast tenderness ever since an acute exposure several years ago.

(e) Creatinine Levels

In six out of twenty-seven 24 hour creatinine determinations at more than one point in time, involving six separate workers in the DES area, creatinine excretion levels differed more than the usually accepted coefficient of variability in an individual. This is suggestive of an incomplete specimen, thus giving rise to the possibility of a low determination of DES.

(4) Medical Summary

Since 1969 Diethylstilbestrol (DES) accounted for 23 instances of breast tenderness and enlargement in male chemical workers in DES production. A urine study for DES excretion was done which showed that all full time workers who wore air suits when necessary all developed increasing levels of DES upon increasing days of exposure. At or above an approximate level of excretion (40 ug/24 hours) two workers became symptomatic. DES was also detected in one helper, and two individuals not directly connected with the area of known exposure.

D. Conclusions

The results of the studies of the officers of the National Institute for Occupational Safety and Health to "determine whether any substance normally found in the place of employment has potentially toxic effects in such concentrations as used or found," have indicated that there was a significant hazard to the health and well being of the workers exposed to benzene and DES at the T-6 Facility, Diethylstilbestrol Operations, Chemetron Chemical Corporation.

(1) Benzene

Results of the environmental sampling as shown in Tables 5-7 and Figure 2 indicate exposure levels were in excess of federal standards at the DES operations at the time of sampling.

No medical studies were conducted. The potential toxicity of benzene exposure was assessed utilizing the existing federal standards as the best-estimate of allowable exposure to protect against adverse affects.

(2) DES

Although no standards exists, the following evidence points to the actuality of hazardous levels of exposure: (1) there has been a persistant history of DES reactions, year after year, (2) high urine levels and adverse reactions were found in the workers participating in the medical studies of this evaluation, and (3) there was found wide-spread DES contamination of buildings and equipment, even extending as far away as the lunch room.

It should be noted that our study leads us to believe that much of the absorption of DES by employees was through the G.I. tract and the skin. This was brought about by the gross contamination of clothing, equipment, and skin by careless handling of DES and the lack of adequate decontamination procedures. For this reason no correlation between airborne exposure dose and physiological response has been attempted in this study.

Regardless of the route of entry, the urine assay for DES used in this study produces consistent data which could be used to predict exposures that are approaching symptomatic levels. In the two individuals that developed DES reactions, levels had reached 40 ug/ml. It would seem prudent in a monitoring program to remove individuals that approach levels greater than the 30 ug/ml. This would depend on frequency of monitoring and other work practice changes. The 24 hour creatinine levels provide reasonable guides to completeness of specimen.

V. RECOMMENDATIONS

If DES production should ever be resumed, the following well-recognized practices should be instituted to protect employees and to avoid contamination of property and equipment:

1. Keep the process in a closed system as much as possible.

2. Provide environmental and medical monitoring. This would include periodic air sampling and urine analysis. Rotation of employees as a control measure should be the control-of-last-resort. However, at a urine level of 10 ug/ml, a second urine assay should be performed. At urine-DES-levels of 30 ug/ml or higher, an employee should be removed from exposure.

3. Develop and maintain an effective personnel protective equipment program.

4. Develop, maintain, and enforce an effective housekeeping and employee work procedure program.

5. Provide necessary ventilation and collection equipment.

6. Institute an employee training program.

7. Develop appropriate maintenance procedures.

VI. REFERENCES

1. "Benzene", Hygienic Guide Series, American Industrial Hygiene Association, 1961.

2. Dangerous Properties of Industrial Materials, N. Irving Sax, p. 719, Reinhold Publishing Company, New York City, New York, 1963.

3. "Diethylstilbestrol Absorption in Industry: A Test For Early Detection As An Aid In Prevention," R.M. Watrous and R.T. Olson, AIHA Journal, December, 1959, Vol. 20, No. 6., pp. 469-472.

4. Gibson, R.L. and Longley, M.Y. Occupational Health Study of Midwestern Formula Feed. Mills Division of Occupational Health Research Report 1, Sept. 24, 1962.

5. The Pharmacological Basis of Therapeutics. Goodman, L.S., and Gilman, A. (editors), Fourth edition. The MacMillan Co., 1970.

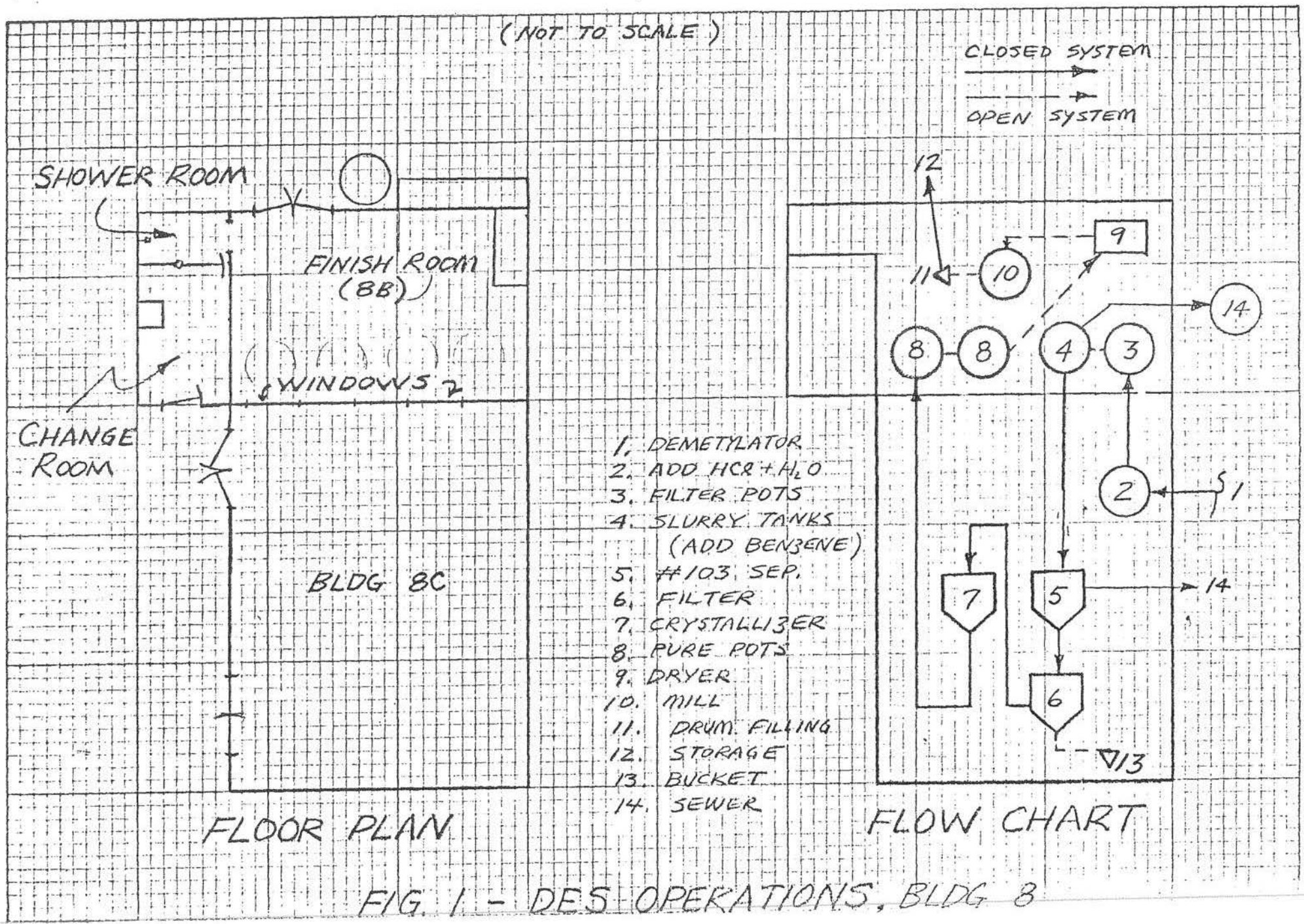


FIG. 1 - DES OPERATIONS, BLDG 8

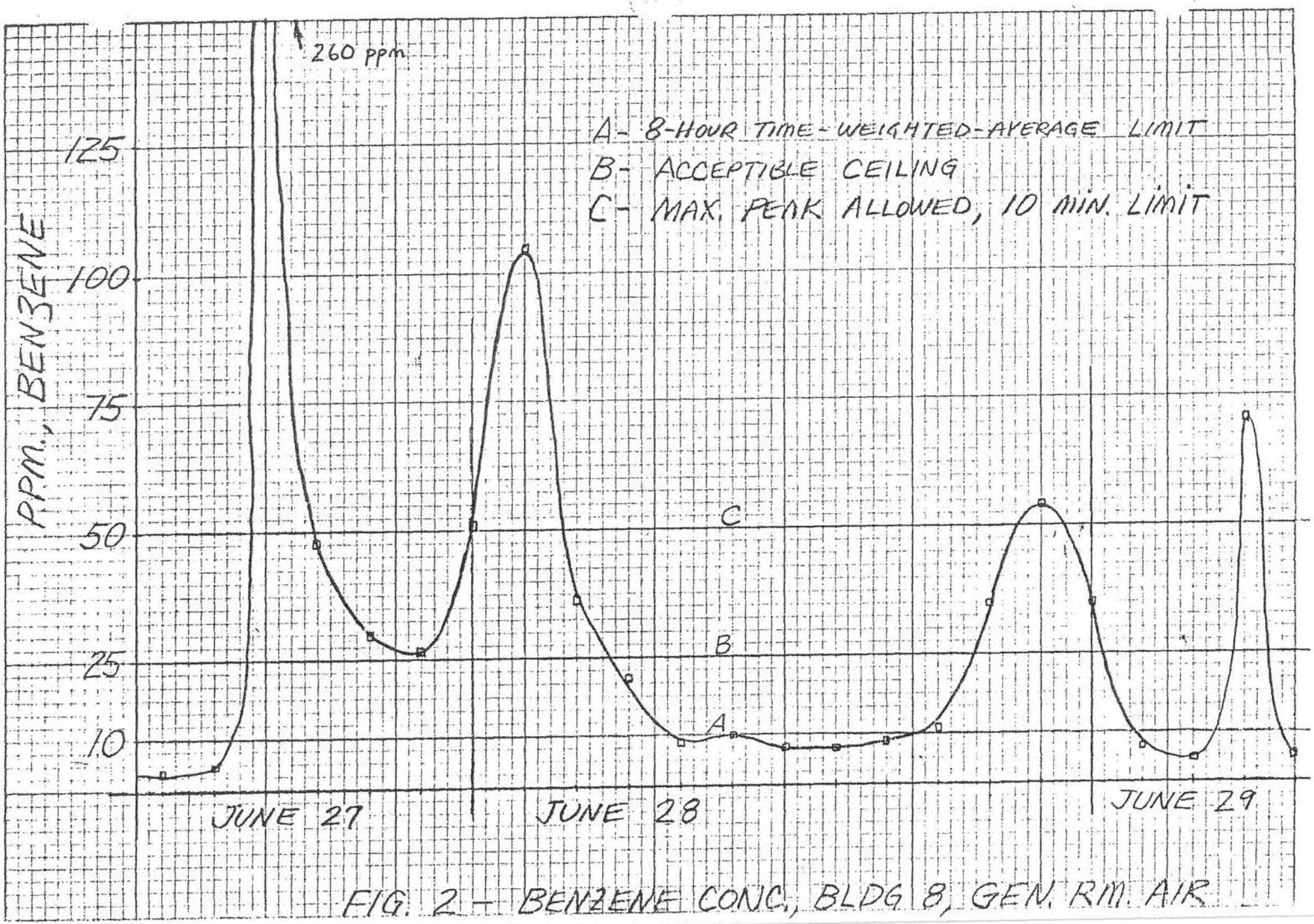


FIG. 2 — BENZENE CONC., BLDG 8, GEN. RM. AIR

TABLE I. DIETHYLSTILBESTROL CONCENTRATIONS AT T-6, AND ELSEWHERE.

Sample No.	DES Concentration $\mu g/M^3$	Type of Sample	Date	Location-Activity
158	0.4	Pers.	6/27	Inside Man, While Inside Finish Room
162	12.8	Pers.	6/27	Helper, 8-C
198	1.8	Pers.	6/28	Inside Man, While Inside Finish Room
199	0.5	Pers.	6/28	Inside Man, Various Activities
149	0.2	Area	6/28	8-C
182	1.8	Area	6/30	8-C
180	364*	Wipe	6/30	Roof, Over Finish Room
183	111*	Wipe	6/30	Floor of 103 Under H_2O Separator
200	0.6*	Wipe	6/30	Lunch Room, Drink Dispenser
	*In µg DES			

TABLE 2. BENZENE CONCENTRATIONS AT DES OPERATIONS (T-6), GENERAL ROOM AIR, 8-C AND SURROUNDING AREA).

Sample No.	Benzene Concentration ppm	Date	Comments
8	3	6/27	
52	4	6/27	
10	260	6/27	Benzene Spill (Worker's Report)
51	48	6/27	
1	29	6/27	
7	26	6/27	
19	51	6/27	
4	105	6/28	
36	36	6/28	
12	21	6/28	
6	9	6/28	
49	10	6/28	
20	7	6/28	
31	7	6/28	
50	8	6/28	
35	11	6/28	
16	35	6/28	
34	54	6/28	
3	35	6/28	
43	7	6/29	
38	4	6/29	
5	71	6/29	
45	5	6/29	

48 Hour Average (6/27-29) = 34 ppm

% of Time over 25 ppm = 43%

NOTE: Table 2 is shown graphically on Figure 2.

TABLE 3. BENZENE EXPOSURE LEVELS AT DES OPERATIONS (T-6)
PERSONAL BREATHING-ZONE SAMPLES

Sample No.	Benzene Concentration ppm	Date	Employee-Location-Activity
2	6	6/27	Inside Man, Working in 8-C
13	<1	6/29	Outside, Helper
15	9	6/27	Inside Man, Inside Finish Room
22	9	6/28	Inside Man, Inside Finish Room
40	5	6/29	Inside Man, Inside Finish Room
54	2	6/27	Outside, Helper

TABLE 4. BENZENE EXPOSURE LEVELS AT THE DES OPERATION (T-6)
DRAGER INDICATOR TUBES

Sample No.	Benzene Concentration	Location	Date	Activity
1	30 ppm	Finish Room Wall In 8-C	6/29	During Activity Inside Finish Room. Finish Man Was Inside Finish Room During Testing For 45 Total Minutes From 8:45 a.m. to 11:30 a.m.
2	75 ppm	Dressing Room	6/29	
3	>500 ppm	Shower Room	6/29	

TABLE I

REACTION EXPERIENCE OF WORKERS IN DES AREA AT TIME OF INITIAL VISIT

WORKER	GYNECOMASTIA	SEXUAL CHANGES	NUMBER OF EPISODES	JOB		
				SUITED	HELPER	OTHER REMARKS
1	Yes	Decreased libido	4			Maintenance man exposed without suit
2	Yes	Painful ejaculation	2	4th week*	Minor Rx**	
3	Yes	None	1	6th week	Minor Rx	
4	Yes	None	1	Minor Rx. 4-5 weeks		
5	Yes	Post coital burning	1	Minor Rx. 4-5 weeks		
6	Yes	None	1	5th week		
7	Yes	None	1	5th week		
8	Yes	None	4	4-5 week		First episode in pre-mix area

*Weeks - week of onset of reaction
**Rx - reaction

TABLE 6

REACTION EXPERIENCE OF DES WORKERS
AT TIME OF URINE STUDY

WORKER	CATEGORY	LAST REACTION	BREAST	IMPOTENCE
1	Helper	1½ years ago	X	X
2	Full-Time	Currently	X	
3	Full-Time	5 months ago	X	
4	Helper	2 years ago	X	
5	Full-Time	1 year ago	X	
6	Helper	6 months ago	X	
7	Full-Time	3 months ago	X	
8	Full-Time	Never		
9	Helper	Never		

TABLE 7

DES AND CREATINI[illegible]UES FOR WORKERS

	WORKER #1	WORKER #2	WORKER #3	WORKER #4	WORKER #5	WORKER #6	WORKER #7	WORKER #8	WORKER #9
CATEGORY	Full Time	Full Time	Full Time	Full Time	Full Time	Helper	Helper	Helper	Helper
DAY	17th	17th	17th	17th	15th	17th	17th	17th	17th
DES Spot Urine ug/ml	26.0	39.2	38.4	4.8		8.5	3.0	3.0	3.0
DES 24 Hr. Urine ug/ml	37.8	12.5	36.3	37.4	9.7	25.7	3.0	3.0	3.0
24 Hr creat.* mg/24hr.	1785	1184	1858	1360	1563	1980	1661	**620	1596
COMMENT	sore breasts starting								
DAY	39th	47th	47th	47th	48th	47th	47th	47th	
DES 24 Hr. Urine ug/ml	46.2	32.2	37.7	47.3	3.0	27.0	3.0	3.0	
24 Hr creat. mg/24hr.	2305	1945	2048	1496	1168	1744	1729	1656	
COMMENT	collection begun after removal due to reaction			collection begun 4 days after removal for reaction	collection 6 days after shutdown				
DAY	53rd	62nd	62nd		58th	62nd	62nd		
DES 24 Hr. Urine ug/ml	3.0	3.7	3.7		3.0	3.0	3.0		
24 Hr creat. mg/24hr.	1312	1404	**1232		**540	**1012	1250		
COMMENT	14 days after removal	6 days after shutdown	6 days after shutdown		16 days after shutdown	6 days after shutdown	6 days after shutdown		
DAY	107th	72nd	93rd				72nd		
DES 24 Hr Urine ug/ml	3.0	15.5	6.1				3.0		
24 Hr creat. mg/24hr.	1493	**825	1614				**756		
COMMENT	68 days after removal	16 days after shutdown but re-exposed at cleanup	16 days after shutdown				6 days after shutdown		
DAY		93rd							
DES 24 Hr Urine ug/ml		3.0							
24 Hr creat. mg/24hr.		1216							
COMMENT		37 days after shutdown							

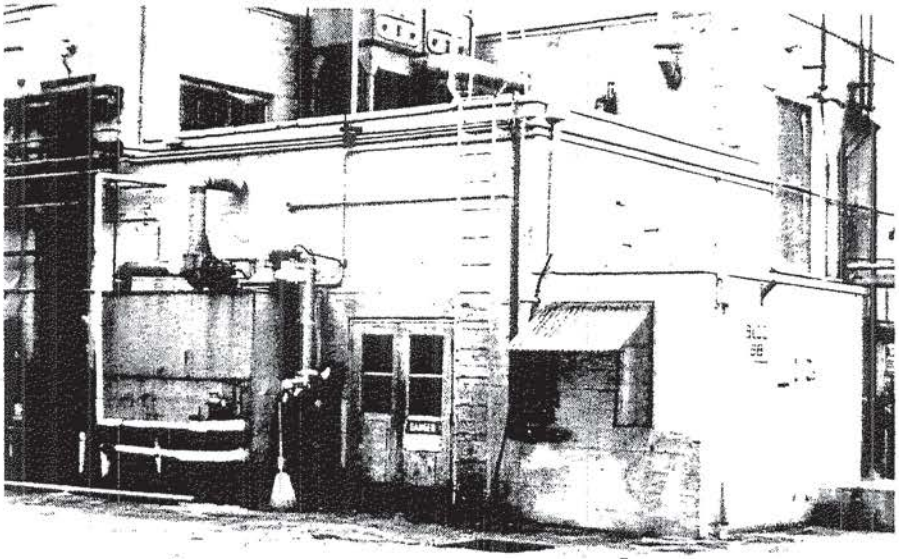
*Creat. = Creatinine
**Suggestive of incomplete specimen

TABLE 8

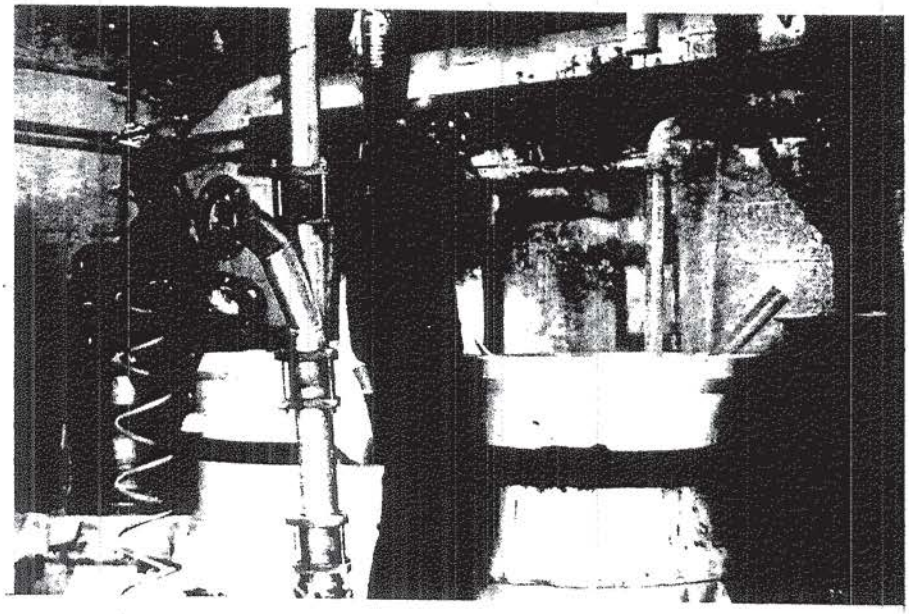
RESULTS OF DES DETERMINATIONS ON CONTROLS

CONTROL	SPOT URINE ug/ml	24 HOUR URINE ug/ml	CREATININE mg/24 HOUR	CATEGORY
1	<3.0	<3.0	1231	Administrative - infrequently in area
2	<3.0	<3.0	*731	Administrative - not in work area
3	3.3	<3.0	1256	Supervisor - includes work are
4	<3.0	<3.0	1856	Supervisor - different work ar
5	<3.0	-		Investigator
6	<3.0	-		Investigator
7	<3.0	-		Investigator
8	<3.0			Tap Water
9		<3.0	1588	Persistent problem since leav DES area, but works on opposi side of building
10		6.9	1528	Same assignment as Control #9

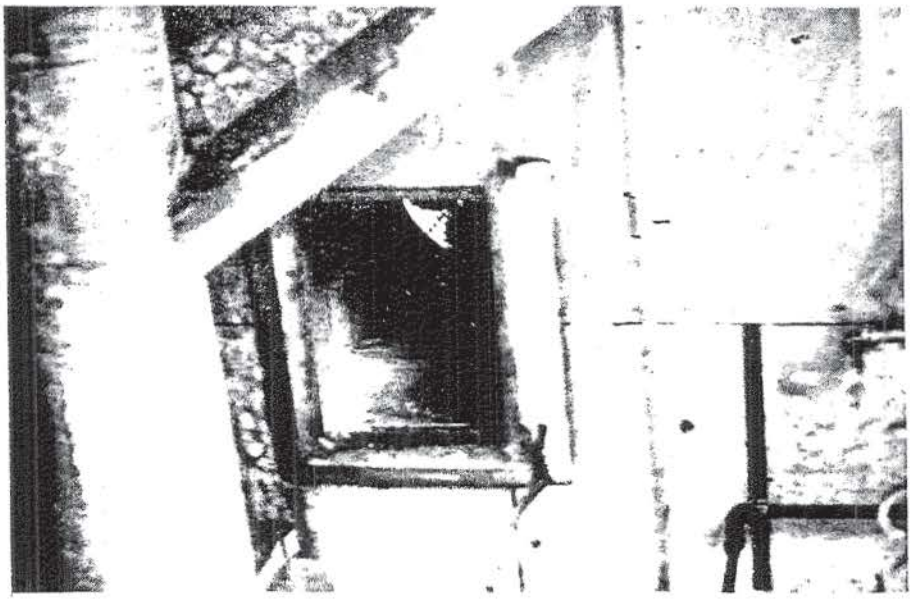
*Suggestive of incomplete specimen



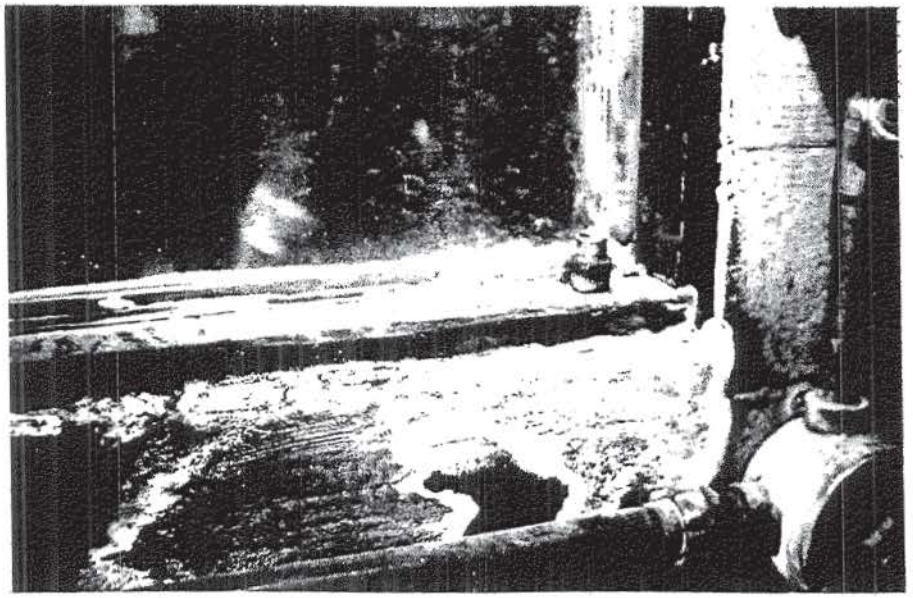
Photograph No. 1: Building #8, DES Production Facilities. Double doors enter Finish Room.



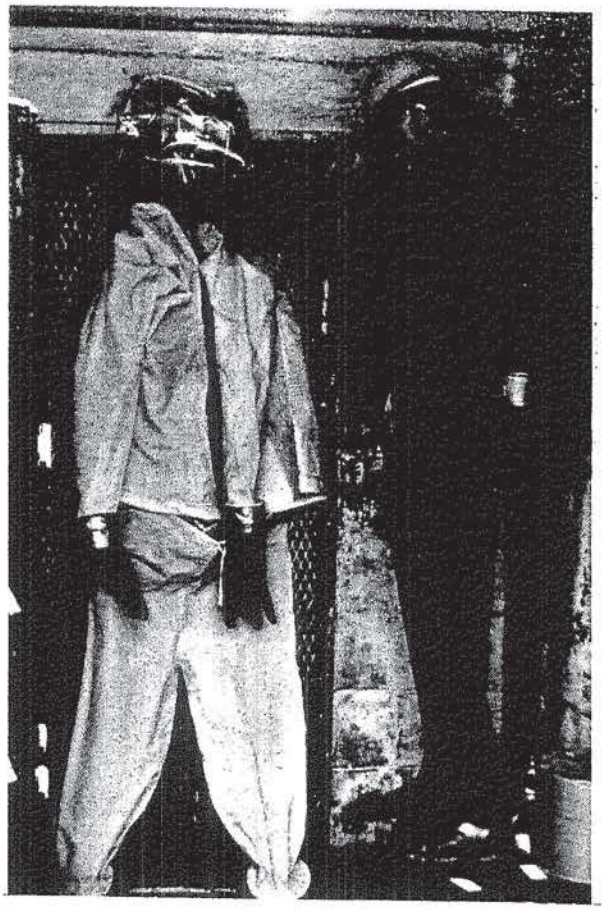
Photograph No. 2: Inside Finish Room. Much of the equipment has been dismantled.



Photograph No. 3: Roof fan in Finish Room.



Photograph No. 4: Window between Finish Room and Building #8C, note leaching of DES through window frame.



Photograph No. 5: Plastic suit worn by "Finish Man" while working in Finish Room.