HETA 89-278-2035
APRIL 1990
TWIN CITY FRUIT
F.L. THORPE CO.
DEADWOOD, SOUTH DAKOTA

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I. SUMMARY

On June 12, 1989 the National Institute for Occupational Safety and Health (NIOSH) received a request from the South Dakota Health Department to evaluate exposure to, and health effects from, methylene bisphenyl diisocyanate (MDI) among employees of a jewelry facility in Deadwood, South Dakota. The exposure occurred during insulation of the building with a MDI-polyol mixture on June 6-10, 1989.

On June 14 & 15, 1989 NIOSH investigators conducted an environmental and medical survey at the jewelry facility (F.L. Thorpe Co.). Sixteen area samples were collected for MDI. All employees who worked at the facility during the June 7-10, 1989 insulation spraying completed a self-administered symptom questionnaire. Employees who reported asthma-like symptoms were invited to participate in a medical evaluation consisting of: 1) individual medical and occupational histories, 2) physical examinations limited to the respiratory system, and 3) blood tests of the immune system for potential MDI allergy (MDI-specific serum IgE and IgG). NIOSH investigators returned on 8/11/89 to obtain additional information from these selected employees consisting of: 1) pulmonary function tests (PFTs), and 2) repeat medical and occupational histories, limited physical examinations, blood tests.

Five days after the insulation spraying ceased, 7 of the 16 (45%) area samples had detectable quantities of MDI, all of which were below NIOSH's recommended exposure limit (REL) of 50 ug/M^3 and the Occupational Safety and Health Administration's (OSHA) permissible exposure limit (PEL) of 200 ug/M^3. It was not possible to estimate the concentration of MDI in the jewelry facility during the spraying application.

Seventy-five of the 78 employees (96%) working during the week the spraying was conducted completed the self-administered symptom questionnaire. Thirteen employees (17%) were identified as having probable MDI-induced respiratory disease. Ten of these 13 had respiratory symptoms persisting at least 6 days after the acute exposure, and 4 employees (5%) continued to have respiratory symptoms 2 months later. Three employees (3%) had abnormal PFTs; 2 of the 3 having wheezing on physical examination. All blood tests for allergy to MDI were negative. Inadequate isolation procedures during application of the MDI insulating material resulted in a high prevalence of self-reported symptoms consistent with isocyanate exposure. Four employees had respiratory symptoms persisting for at least 2 months after the acute exposure, 3 of whom had abnormal PFT patterns, and 2 of whom had wheezing on physical examination. MDI exposure or cigarette smoking were the most likely causes of the abnormal PFTs.

On the basis of this survey, the investigators concluded that MDI exposure probably occurred during the application of the MDI insulation material. Most of the acute health effects associated with this exposure resolved, however a small number of employees reported persistent respiratory symptoms.

KEYWORDS: SIC code 3911, methylene bisphenyl diisocyanate, MDI, isocyanates, foam insulation, asthma, hypersensitivity pneumonitis, MDI-induced respiratory disease.

II. INTRODUCTION

On June 12, 1989 the National Institute for Occupational Safety and Health (NIOSH) received a request from the South Dakota Health Department to evaluate exposure to, and health effects from, methylene bisphenyl diisocyanate (MDI) among employees of a jewelry facility (F.L. Thorpe Company) in Deadwood, South Dakota.

On June 14 & 15, 1989 NIOSH investigators conducted an environmental and medical survey at Thorpe's jewelry. A follow-up medical visit was conducted on 8/11/89 to obtain additional information. The company was notified of the environmental results on 8/11/89, individual PFT results were mailed to participating employees on 10/5/89, and individual blood test results were mailed to participating employees on 12/20/89.

III. BACKGROUND

A. Process and Workforce Description

F.L. Thorpe Company manufactures gold jewelry for wholesale distribution. Within this facility gold is casted, soldered, buffed, finished, packaged, and shipped. The facility is operated by 85 women and 2 men.

B. Facility and Insulation Description

Since February, 1988, Thorpe's has operated in 2 rooms of a warehouse basement owned by Twin City Fruit (Figure 1). Twin City Fruit plans to convert the whole facility into a refrigerated warehouse for fruit storage. Refrigerated warehouses require insulation, which was applied by spraying MDI and polyol in a 1:1 mixture onto the warehouse ceiling, walls, and basement rooms adjacent to the jewelry facility. The insulation application was carried out by a construction firm contracted by Twin City Fruit. The application dates for the various warehouse sites were approximately:

4/30/89 to 5/10/89 - First floor.

5/22-23/89 - Two small basement rooms (Figure 1, Rooms 1 & 2).

6/7-10/89 - Two large basement rooms (Figure 1, Rooms 3 & 4).

Approximately 15,000 pounds (30 drums at 500 pounds per drum) of isocyanate were used to insulate the warehouse. The consulting firm provided supplied air respirators and protective suits to employees applying the insulation. No attempt was made to isolate the first story application because the building's ceiling and walls were in the construction phase, and the area was open to the outside air. During the spraying of basement rooms 1-4, the consulting firm attempted to isolate the application area with plastic sheets adhered to the basement ceiling, walls, and floor. The bathrooms are located in the basement room 4 (Figure 1), and during the spraying of this area (6/7-9/89) a "tunnel of plastic" was constructed to allow access to the bathroom. By employee accounts, this "plastic tunnel" failed to reach the basement floor, and the bathroom walls and ceiling had no plastic covering. During the spraying of the basement room 4 (6/7-9/89), employees reported a haze and strange odor in the bathroom and the jewelry facility. During this time many employees began experiencing symptoms, resulting in the jewelry facility closing at noon 6/9/89 and re-opening on 6/15/89.

On 6/12/89, a consultant performed Drager Tube Air Sampling for toluene diisocyanate (TDI) at three sites within the facility. All three results were below the limit of detection (20 ppb) for the sample analysis.

IV. METHODS

A. Environmental

1. Sample Collection

Sixteen area air samples were collected for MDI on June 14-15, 1989 at the locations identified in Figure 2. Samples were collected using battery-powered pumps attached via tygon tubing to impingers with 15 milliters of toluene containing 1-(2-methoxyphenyl)piperazine. Samples were collected at a flow rate of 1.0 liter per minute (Lpm), with toluene replacing evaporated solution. Upon completion of sampling, the impinger solutions were transfered to 20 ml glass vials and shipped refrigerated to the laboratory for analysis. Bulk samples of the unreacted isocyanate material used in the insulation process were not available for laboratory analysis.

The sample analysis was conducted using NIOSH Method 5505.[1] The impinger solutions were evaporated to dryness in a nitrogen atmosphere, leaving a sample residue which consists of the urea derivatives that are formed when 1-(2-methoxyphenyl)piperazine reacts with MDI. These residues were redissolved in 2 ml of 0.5% acetic anhydride in acetonitrile, and 50-microliter (ul) aliquots were injected into the high performance liquid chromatograph (HPLC). The ureas were identified and quantified by using the ratio of the outputs from an electrochemical and an ultraviolet detector. The limits of detection (LOD) and quantitation (LOQ) for MDI using this method are 0.02 and 0.06 micrograms per sample (ug/sample), respectively.

B. Medical

On June 15, l989, 75 of the 78 employees working during the June MDI spraying completed a screening questionnaire that elicited demographic and symptom information. Employees who answered "yes" to 2 of the following 3 questions were asked to participate in a medical evaluation.

1) Since June 7, 1989, have you experienced any wheezing?

2) Since June 7, 1989, have you experienced any shortness of breath?

3) Since June 7, 1989, have you experienced any chest tightness?

The medical evaluation consisted of:

a) a medical and occupational history, and

b) a physical examination of the lungs.

A probable case of MDI-induced respiratory disease was defined as 2 of the following 3 symptoms -wheezing, shortness of breath, and chest tightness- associated with work (symptoms began after 6/7/89, and abated away from the worksite).

Employees who met the above case definition and were continuing to have asthma symptoms during the NIOSH site visit, had:

1) pulmonary function tests (PFTs) performed on 8/11/89, and

2) serum tested for potential MDI allergy on 7/15/89 and 8/11/89.

The PFTs were performed using an Ohio Medical Model 822 dry rolling sealed spirometer attached to a Spirotech 220B dedicated computer. Measurements included forced vital capacity (FVC) and one-second forced expiratory volume (FEV_1). Tests were conducted according to the spirometry procedures outlined by the American Thorasic Society, which is briefly summarized below.[2] Participants were instructed in the FVC manuever, with a demonstration provided. Three acceptable FVC maneuvers were performed by the participant, with the largest FVC and FEV_1 recorded, even if the 2 values were not derived from the same curve. Tests were considered "reproducible" if the largest FVC and the second largest FVC did not vary by more than 5%, and if the largest FEV_1 and the second largest FEV_1 did not vary by more than 5%. A restrictive pattern was defined as an FVC <80% of predicted, and an FEV-1/FVC ratio >70%.[3] An obstructive pattern was defined as an FEV_1 <80% of predicted and a FEV-1/FVC ratio <70%.[3]

Employees' serum was tested for potential MDI allergy by measuring for specific antibody (IgE and IgG) to MDI-HSA (human serum albumin). Enzyme-linked immunosorbent assays (ELISA) were run on sera at 1:10 dilutions and interpreted as positive if absorbances exceeded mean control sera values by 2 standard deviations.

Controls were employees who did not report any of the three asthma-like symptoms listed above.

Probable cases were compared to controls for a) demographic information, b) previously diagnosed conditions of asthma, eczema, or allergies, and c) prevalences of other conditions listed on the screening questionnaire. Odds ratios (OR) were used to estimate the relative risk. Odds ratios and confidence intervals were calculated using Epiinfo.[4] P-values were calculated using a 2-tailed Fisher's exact test or the Student's t-test.

V. EVALUATION CRITERIA

A. Environmental Evaluation

As a guide to the evaluation of the hazards posed by workplace exposures, NIOSH field staff employ environmental evaluation criteria for assessment of a number of chemical and physical agents. These criteria are intended to suggest levels of exposure to which most workers may be exposed up to 10 hours per day, 40 hours per week for a working lifetime without experiencing adverse health effects. It is, however, important to note that not all workers will be protected from adverse health effects if their exposures are maintained below these levels. A small percentage may experience adverse health effects because of individual susceptibility, a preexisting medical condition, and/or a hypersensitivity (allergy).

In addition, some hazardous substances may act in combination with other workplace exposures, the general environment, or with medications or personal habits of the worker to produce health effects even if the occupational exposures are controlled at the level set by the evaluation criterion. These combined effects are often not considered in the evaluation criteria. Also, some substances are absorbed by direct contact with the skin and mucous membranes, and thus potentially increase the overall exposure. Finally, evaluation criteria may change over the years as new information on the toxic effects of an agent becomes available.

The primary sources of environmental evaluation criteria for the workplace are: 1) NIOSH Criteria Documents and Recommended Exposure Limits (REL), 2) the American Conference of Governmental Industrial Hygienists' (ACGIH)

Threshold Limit Values (TLV's), and 3) the U.S. Department of Labor/Occupational Safety and Health Administration (OSHA) occupational health standards [Permissible Exposure Limits (PEL)]. Often, the NIOSH's REL and ACGIH's TLV are lower than the corresponding OSHA's PEL. Both NIOSH's REL and ACGIH's TLV usually are based on more recent information than are the OSHA standards. The OSHA standards also may be required to take into account the feasibility of controlling exposures in various industries where the agents are used; the NIOSH-recommended standards, by contrast, are based primarily on concerns relating to the prevention of occupational disease. In evaluating the exposure levels and the recommendations for reducing these levels found in this report, it should be noted that industry is required by the Occupational Safety and Health Act of 1970 (29 USC 651, et seq.) to meet those levels specified by an OSHA standard.

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

B. 4,4-Methylenediphenyl isocyanate (MDI)

MDI is an aromatic diisocyanate. Although the majority of studies on aromatic diisocyanates have been done on toluene diisocyanate (TDI), studies done on both chemicals find similar health effects.[5] Exposure to MDI and TDI can occur via ingestion, skin contact, and inhalation. Inhalation of aerosolized isocyanates is responsible for the majority of reported health effects.

The lung is the primary organ affected by inhaled isocyanates. Adverse reactions include:

- upper airway irritation, characterized by cough, and rhinitis;[6-8]

- acute asthma, manifested as wheezing, breathlessness, and chest tightness occurring immediately after exposure;[9-14]

- delayed asthma, manifested as wheezing, breathlessness, and chest tightness occurring several hours after exposure;[9-14]

- dual asthma, manifesting as wheezing, breathlessness, and chest tightness occurring in both an immediate and delayed pattern;[9,10,14]

- hypersensitivity pneumonitis, characterized as chronic fever, malaise, dry cough, and progressive dyspnea;[15-17] and

- asymptomatic permanent loss of lung volumes.[18-21]

Certain individuals may develop diisocyanate sensitization, which is usually manifested as a debilitating asthma-like illness caused by very low, even unmeasurable diisocyanate concentrations.[5] Other adverse health effects in humans due to isocyanates exposure are skin and eye irritation[22,23], skin hypersensitivity[5,23,24], and psychologic symptoms.[5] In animals, isocyanates may cause renal toxicity and cancer.[5,32]
The current federal OSHA PEL and ACGIH TLV for MDI is a ceiling limit of 200 micrograms per cubic meter of air (ug/m^3) [20 parts of MDI per billion parts of air (ppb)].[25,26] The current NIOSH REL for occupational exposure to

MDI is 50 ug/m^3 (5 ppb) for up to a 10-hour workshift, 40-hour workweek, and a ceiling of 200 ug/m^3 (20 ppb) for any 10-minute sampling period.[5]

The NIOSH recommended standard applies to diisocyanate monomers only, and not to higher polymers of these compounds. Little is known about the toxicological effects of polymeric isocyanates. No long-term studies of the effects on humans of polymeric isocyanates have been conducted.[27] However, it is speculated that the inhalation of any species having multiple unreacted isocyanate groups may impair respiratory function or give rise to sensitization.[28-30]

VI. RESULTS

A. Environmental

Seven of the 16 (45%) area samples had detectable quantities of MDI; all were at least 2 orders of magnitude below NIOSH's REL and OSHA's PEL (Table 1). It was not possible to estimate the concentration of MDI in the jewelry facility during the spraying application which occurred 5 days prior to the NIOSH survey.

B. Medical

Demographic information and symptom prevalences of the survey participants are presented in Tables 2 and 3. Headaches, irritation of the nose & throat, and irritation of the eyes were the most frequently reported symptoms: 69%, 63%, and 59%, respectively.

Thirteen of the 75 (17%) survey participants satisfied the case definition for probable MDI-induced respiratory disease. Ten employees (13%) continued to have symptoms at the time of NIOSH's first site visit; all 10 participated in NIOSH's medical evaluation. Two employees (3%) had wheezing on lung examination. All blood samples were negative for antibody to MDI. Four employees (5%) continued to have respiratory symptoms at the time of NIOSH's second site-visit on 8/11/89, two months after the acute exposure. Three of these 4 employees (4%) had abnormal PFTs, including the 2 individuals who had wheezing on physical examination performed on 8/11/89 (Table 4). Two of the 3 abnormal PFTs were restrictive patterns (Table 4).

Comparing the probable cases of MDI-induced respiratory disease to the 45 controls revealed no significant difference between the two groups with regards to age, length of employment, and previous physician diagnosis of eczema or allergies. Probable cases appeared more likely than controls to have had asthma, although the difference was not statistically significant [Odds Ratio (OR)= 6.51, 95% confidence interval (95% CI)= 0.65, 37.01, p=0.069]. In addition, employees fulfilling our probable MDI-respiratory case definition were more likely to report 9 of the 16 symptoms not included in the respiratory case definition (Table 5).

VII. DISCUSSION

This survey identified 13 cases of probable MDI-induced respiratory disease. No workers died or were hospitalized, but 6 required evaluations or asthmatic treatments in the local emergency room or by their private physicians.

Environmental sampling for MDI was done 5 days after the spraying application. Isocyanates are very reactive chemicals and finding detectable amounts 4 and 5 days after the spraying suggests that much higher concentrations were probably present during the application.

Our respiratory case definition relies on subjective, self-reported symptoms. PFTs and allergy tests were performed to

obtain objective information. This facility did not utilize MDI in its routine operations, so pre- and post-shift PFTs to determine acute effects of exposure could not be conducted. PFTs performed at a particular time are helpful if abnormal, but due to asthma's episodic nature, a normal test result cannot be used to rule out the disease. Three employees had asthma-like symptoms and abnormal PFTs (2 had restrictive patterns). All 3 employees had long cigarette smoking histories and were current smokers. Cigarette smoking, like MDI, typically results in an obstructive, not restrictive, PFT pattern. This "unusual" restrictive PFT pattern could be due to: 1) severe asthma (however, this was unlikely due to the clinical presentation of these individuals); 2) a medical diagnosis known as hypersensitivity pneumonitis, which MDI has been reported to cause; [15-17] or 3) a technical error in performing the PFTs. In one of the cases the FVC maneuver continued for a full 6 seconds, but the test was terminated before the participant's PFT curve had "plateaued" (there was a 0.15 liter change in volume during the last 2 seconds). Thus, the measured FVC was lower than the "true" FVC so the person could actually have had an obstructive PFT pattern, which is more consistent for both smoking and MDI exposure. In either case, all three individuals had abnormal PFTs (whether restrictive or obstructive) and further medical evaluation by their private physicians was suggested.

An elevated IgE or IgG titer of MDI-HSA suggests that the individual is sensitized to MDI, and often correlates with pulmonary or dermal symptoms. The normal IgE and IgG MDI-ELISA titers observed in this study suggest either a) the disease was not "allergically" (antibody) mediated, b) the blood tests were false negatives, or c) these employees did not have isocyanate-induced respiratory disease. Although this test has false negatives, and the absence of detectable levels of specific IgE or IgG does not rule out "sensitization," 10 "false negative" results would be very unusual.[20,22] Disease misclassification is a potential bias, particularly since the majority of employees (9/13) recovered completely within 2 months. These 9 employee's respiratory symptoms may have been due solely to acute respiratory tract irritation. For the 3 employees with persistent symptoms and abnormal PFTs, these cases could represent a non-immunologically mediated disease process. The literature supports a non-immunologic mechanism causing isocyanate-induced respiratory disease from chronic isocyanate exposure.[31]
The symptoms known to be associated with MDI exposure are non-specific, and the prevalence of these symptoms in this population before the MDI exposure is unknown. However, both the type of symptoms reported from this facility and their magnitude are similar to those in another published account of high-dose isocyanate exposures.[8]

VIII. CONCLUSION

Inadequate isolation procedures during the application of an MDI insulating material resulted in a high prevalence of self-reported symptoms consistent with isocyanate exposure. Thirteen employees reported symptoms consistent with probable MDI-induced respiratory disease. Ten of these 13 had respiratory symptoms 6 days after the exposure ceased, and 4 employees continued to have respiratory symptoms 2 months after the acute exposure. Three of these 4 employees with persistent respiratory symptoms had abnormal PFTs most likely due either to cigarette smoking or MDI exposure.

IX. REFERENCES

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XI. DISTRIBUTION AND AVAILABILITY

Copies of this report are temporarily available upon request from NIOSH, Hazard Evaluations and Technical Assistance Branch, 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. Ms. Pamela Bonrud, South Dakota State Health Department
2. Mr. Paul Miller, Twin City Fruit
3. Mr. Lloyd West, F.L. Thorpes
4. U.S. Department of Labor/OSHA - Region VIII.
5. U.S. Department of Labor/OSHA - Bismark Area Office

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

Table 1

General Area Concentrations of MDI*
Twin City Fruit, Deadwood, South Dakota
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Sample #	Location	Sampling Time	ug/M^3 MDI
6/14/89			
1	Assembly	2:17 - 5:50	x
2	Assembly	2:17 - 5:50	x
3	Refrigeration	2:22 - 5:55	x
4	Refrigeration	2:22 - 5:55	x
5	Upstairs	2:27 - 5:58	x
6	Upstairs	2:27 - 5:58	0.2
6/15/89			
10	Assembly	6:45 - 1:05	x
11	Assembly	6:47 - 1:18	0.2
12	Assembly	6:49 - 1:12	x
13	Assembly	6:52 - 1:05	0.1
14	Assembly	6:53 - 1:00	0.1
15	Assembly	6:56 - 1:00	0.1
16	Bathroom	7:04 - 1:30	0.1
17	Refrigeration	7:06 - 1:30	x
18	Assembly	7:11 - 1:12	0.1
19	Office Area	7:13 - 1:35	x

Evaluation criteria NIOSH REL	50
NIOSH Ceiling (10-minute)	200
OSHA PEL	200
ACGIH TLV	200

Laboratory Limit of detection 0.2 ug/sample
*MDI–4,4-methylene diphenyl isocyanate
x–not detected in sample

TABLE 2

Demographics of Survey Participants
Twin City Fruit, Deadwood, South Dakota
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	Mean	Range
Age (years)	38	(17-62)
Length of Employment (years)	5	(1-28)
Sex	74 Females, 1 Male	
Race	74 White, 1 Asian	

Table 3
Symptom Prevalence Among Survey Participants
Twin City Fruit, Deadwood, South Dakota
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SYMPTOMS	#	%
Lower Respiratory Tract		
Chest tightness	21	28
Shortness of breath	16	21
Wheezing	9	12
Mucous Membrane Irritation		
Irritation of the nose and throat	47	63
Irritation of the eyes	44	59
Coughing	27	36
Gastro-intestinal		
Nausea	27	36
Abdominal Pain	16	21
Vomiting	4	5
Constitutional		
Headaches	52	69
Malaise/Tired all the time	23	31
Fever/Chills	3	4
Mood		
Very irritable	10	13
Difficulty sleeping	5	7
Depressed	3	4
Cognitive		
Difficulty concentrating	8	11
Difficulty remembering things	3	4
Skin		
Skin irritation	5	7
Balance Problems	9	12

TABLE 4

PFT and Physical Examination Results of the Four
Employees Who Remained Symptomatic on 8/11/89

Twin City Fruit, Deadwood, South Dakota
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Employee	Respiratory Symptoms (Wheeze	CT	SOB)	Physical Exam	FEV-1	%Pred	FVC	%Pred	FEV-1/FVC Ratio
1	Y	Y	Y	Wheeze	1.86	68%	2.51	73%	74%
2	Y	Y	Y	Neg	2.07	79%	2.84	89%	73%
3	Y	Y	N	Wheeze	2.02	73%	2.61	78%	77%
4	Y	Y	Y	Neg	2.37	81%	2.96	84%	80%

Table 5

Symptom Prevalences Between Probable MDI-Induced
Respiratory Disease Cases and Asymptomatic Controls
Twin City Fruit, Deadwood, South Dakota
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Symptom	Cases # (%)	Controls # (%)	OR*	95% CI**	P Valve***
Cough	8 (62%)	9 (20%)	6.40	1.42-30.50	.012
Fever	3 (23%)	0 (0%)	5.50	3.14- 9.63	.009
Nausea	9 (69%)	9 (20%)	9.00	1.90-46.22	.002
Abdominal Pain	6 (40%)	7 (16%)	4.65	1.00-22.56	.053
Nose & Throat Irritation	12 (92%)	22 (49%)	12.55	1.45-280.07	.006
Headache	12 (92%)	25 (56%)	9.60	1.11-214.43	.021
Concentration	3 (23%)	1 (2%)	13.20	1.03-369.17	.046
Imitable	4 (31%)	2 (4%)	9.56	1.21- 91.46	.019
Balance	5 (39%)	4 (9%)	6.41	1.14- 38.33	.021

* OR = Odds Ratio
** 95% CI = 95% Confidence Interval
*** P valve = 2-tailed Fisher's Exact Test

FIGURE 1
Rough Sketch of Basement Floor Plan

Twin City Fruit, Deadwood, South Dakota
HETA 89-278

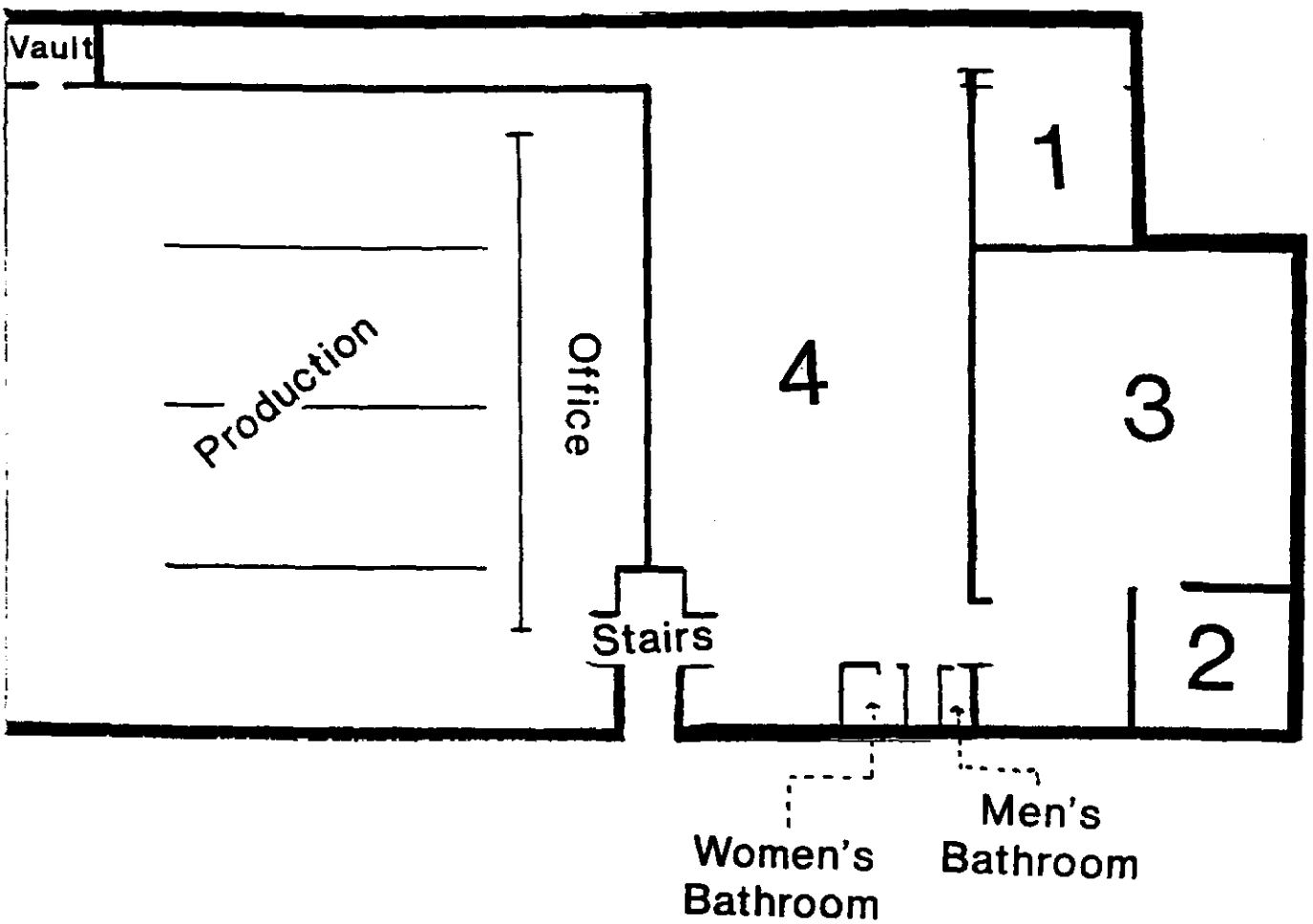

FIGURE 2
Locations of MDI Samples
Twin City Fruit, Deadwood, South Dakota
HETA 89-278