U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES ■ Public Health Service
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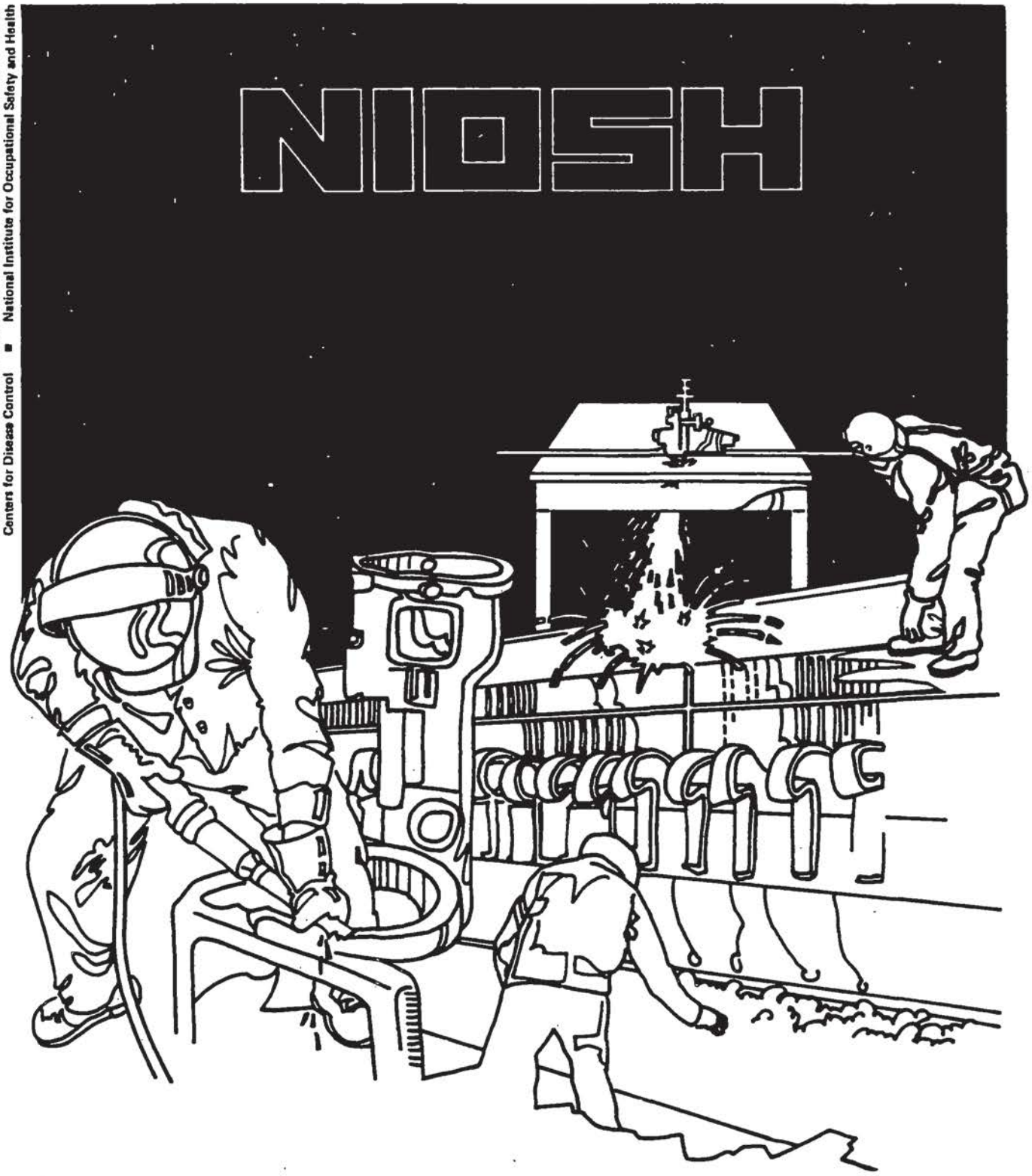
NIOSH



Health Hazard Evaluation Report

HETA 82-256-1342
EMANUEL HOSPITAL
PORTLAND, OREGON

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.

HETA 82-256-1342
JULY 1983
EMANUEL HOSPITAL
PORTLAND, OREGON

NIOSH INVESTIGATORS:
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I SUMMARY

In June 1982, the National Institute for Occupational Safety and Health (NIOSH) received a request from the employees at Emanuel Hospital, Portland, Oregon, to determine if the medication, prostaglandins, which were handled and mixed by pharmacy personnel in a horizontal laminar flow hood in the intravenous (IV) department, had been the cause of menstrual abnormalities and breast tenderness experienced by IV personnel.

On July 15, 1982, NIOSH investigators visited the IV department, reviewed procedures, examined the horizontal laminar flow hood, and examined the room to where the prostaglandin handling had been recently moved.

Prostaglandins had been mixed for 1 to 1-1/2 hours, once or twice a week, in a horizontal laminar flow hood located in the IV department. In February 1982 this process was moved to another room in the hospital and other changes in the IV room were instituted (which included opening the door to the hallway and turning off the hood when antineoplastic agents were mixed). In June and July, 1982, all IV personnel were asymptomatic.

A separate problem uncovered by this evaluation showed the widespread use in hospital pharmacies of horizontal laminar flow hoods for purposes for which they were not designed. This improper usage results in subjecting the hospital pharmacy staff to occupational exposure to the many drugs and chemicals used in these hoods.

Based on the data obtained from this evaluation, NIOSH determined that it is possible, but not probable that exposure to prostaglandins led to the symptoms experienced by the IV staff. Recommendations to reduce and/or prevent exposure to prostaglandins and other drugs are included in this report.

KEYWORDS SIC 8062 (General Medical and Surgical Hospitals) prostaglandins, laminar (horizontal and vertical) flow hoods, menstrual abnormalities.

II INTRODUCTION

In June 1982 NIOSH received a request from the employees at Emanuel Hospital, Portland, Oregon, to determine if the prostaglandins which had been handled and mixed by pharmacy personnel in a horizontal laminar flow hood in the IV department were the cause of menstrual abnormalities experienced by IV personnel. An environmental/medical survey was conducted on July 15, 1982 and a follow-up visit was made on April 6, 1983.

III BACKGROUND

Emanuel Hospital is a 550 bed general hospital built in 1915 and which has subsequentially undergone several major additions and remodeling projects.

The IV department is located in the basement and is approximately 600 square feet in area. Off of the main IV room are a small office, a small coffee shop, the pharmacy (the door to the pharmacy is always kept closed) and a 12 x 22 ft room where a horizontal laminar flow hood is located. There is an open archway between this room and the main IV room. In addition to the pharmacists, there are approximately 20 IV personnel who work in this room during a portion of their shift.

The medications and other solutions to be given to patients by IV are handled and mixed in the horizontal laminar flow hood. The purpose of the laminar flow hood is to protect the product from contamination.

Many intravenous medications are used in the hospital. Table 1 is a list of the medications handled in the IV room over a period of five months in late 1981.

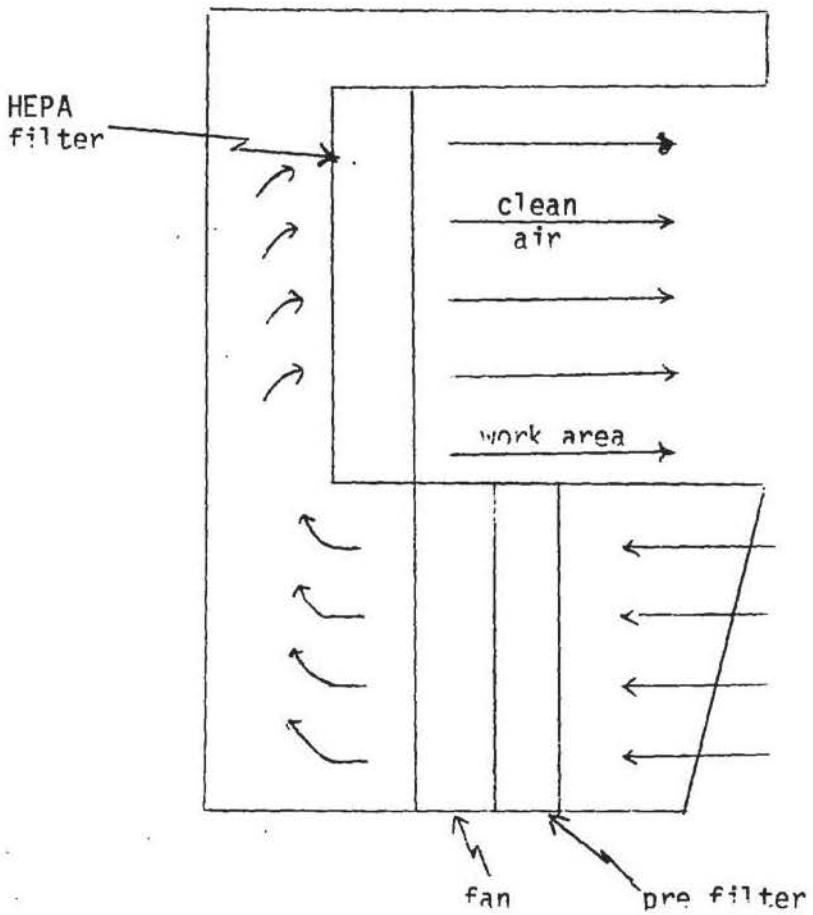
The mixing of prostaglandins started in the spring of 1981. Beginning in August 1981 the hallway door to the IV room was kept closed. (Prior to this it was left open.) In January 1982 the door was again allowed to remain open. In early 1982, after the women working in the IV room began experiencing menstrual irregularities, the prostaglandin mixing operation and another horizontal laminar flow hood were relocated to a room on the third floor. The only employee who does any work with prostaglandins in this room is a male pharmacist.

Emanuel Hospital uses prostaglandins (1) in the form of a vaginal suppository to induce contractions in abortion cases and (2) in a gel form that is applied topically to the uterus when the second stage of labor is delayed. The pharmacy makes their own gel form by removing the prostaglandins from a number of suppositories, grinding them in a mortar and mixing them into a gel. This operation is performed in a horizontal laminar flow hood, takes about one to two hours to complete, is performed once or twice a week and may be done on either the day or evening shift.

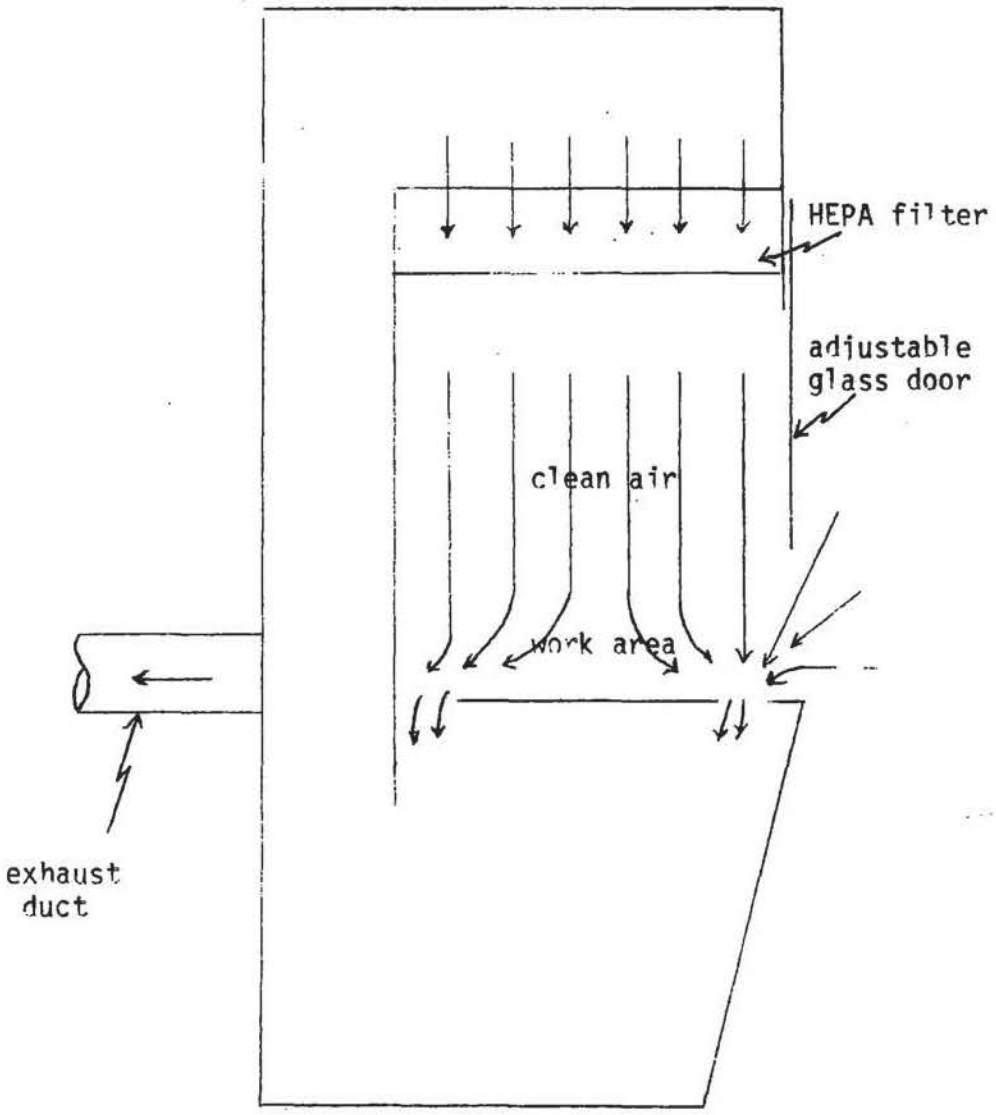
Laminar flow hoods were first used in the early 1960's in the electronic industry to provide a dust-free environment the assembly of electronic parts that were sensitive to dust particles. A laminar flow hood is a freestanding hood that draws the air from the room, through a high efficiency particle filter. The air then passes through a plenum, through small holes in a face plate to obtain an even flow of air, and then passes through the hood where the product to be kept particle-free is handled.

There are several types of laminar flow hoods including horizontal laminar flow hoods, vertical laminar flow hoods and negative pressure vertical laminar flow. The differences between the horizontal and negative pressure vertical laminar flow hoods are explained in the next two paragraphs.

Horizontal laminar flow hood: In a horizontal laminar flow hood the filtered air enters the hood from the back of the hood, passes over the product, exits the front of the hood where the operator stands and reenters the general room atmosphere. In this arrangement, any gas, vapor mist, aerosols, or particulates, released by the product can enter the operator's breathing zone.



Negative pressure vertical laminar flow hood: In a vertical laminar flow hood the filtered air enters the top of the hood. As it passes over the work area the air splits with half going through the vent along the back of the hood and the other half going through the vent along the hood opening. These hoods will have glass doors that slide vertically to reduce the opening into the hood. The exhausted air volume of the hood is greater than the filtered air volume entering the top of hood. This creates a negative pressure in the hood so that the makeup air enters the hood past the operator and into the vent along the hood opening. The exhaust air can then be exhausted to the outside. This configuration prevents gases, vapors, aerosols, mists, and particulates from the product from entering the breathing zone of the operator.



IV EVALUATION DESIGN

In January 1982, the hospital's nurse epidemiologist completed an epidemiological study of the affected workers and a control group of non-exposed workers in the hospital. During July and August the NIOSH physician contacted all affected workers regarding their current health status.

Since the use of horizontal laminar flow hoods does not provide optimum worker protection, NIOSH surveyed 102 licensed hospital pharmacies in the State of Washington to determine the prevalence of use of horizontal and vertical laminar flow hoods and the type of substances which workers prepare in the hoods.

Environmental samples for prostaglandins were not collected because of the short mixing time and difficulties with environment sample analysis. In addition, naturally occurring prostaglandins are present in the room since prostaglandins can be found in body sweat and other body fluids.

V EVALUATION CRITERIA

Currently there is no environmental standard or recommended standard for exposure to airborne prostaglandins.

Prostaglandins (data presented in this section were obtained from a pharmaceutical manufacturer of prostaglandin).(1-10)

Generic Name - Dinoprostone
Molecular Formula $C_{20}H_{32}O_5$ M.W. 352
Physical State: White crystalline powder
Melting Point: 64-71°C
Solubility: Soluble in ethanol and in 25% ethanol in water
Soluble in water to 130 mg/100 ml
Stability: Bulk drug stable for at least 72 hours at room temperature

Toxic Properties

Acute toxicity: LD_{50}, oral route, rats: 750-1000 mg/kg
LD_{50}, subcutaneous route, rats: 19 24mg/kg
LD_{50}, intravenous route, rats: 23 mg/kg

Repeated dose toxicity: Ten day study, intravenous route, rats: 0.3 mg/kg/day resulted in no histomorphic changes indicative of toxicity.
Ten day study, intravenous route, dogs: 0.3 mg/kg/day was nontoxic in this study.

Reproduction studies: Single dose, intravenous route, mice: 30 mg/kg administered on the 13th day of gestation was not considered toxic to pregnant or nonpregnant mice but caused fetal death.

	Subcutaneous route, mice: 750 ug/kg administered on day 12 of gestation resulted in teratogenic effects.
Mutagenicity studies:	Salmonella/microsome test, tester strains TA98, TA100, TA1537, and TA1538: No evidence of bacterial mutagenicity at any dose with or without in vitro metabolic activation. DNA damage/alkaline elution assay: No DNA damage was detected at any of the dose levels tested, nor when metabolic activation was conducted.

Biological and Pharmacologic Properties

Abortifacient:	Stimulates the myometrium of the gravid uterus to contract in a manner that is similar to the contractions seen in the term uterus during labor.
Smooth muscle stimulant:	Stimulates the smooth muscle of the gastrointestinal tract.
Vasodepression:	Large doses can lower blood pressure, probably as a consequence of the effects on the smooth muscles of the vascular system.
Bronchodilator:	Relaxes bronchial and tracheal smooth muscles and reduces airway resistance in asthmatic, but not normal subjects.

Occupational Exposure Risks (General)

Due to the potent biologic activity of this material, occupational exposure should be avoided. It is potentially harmful if swallowed, inhaled or absorbed through the skin. Good industrial hygiene practices must be incorporated when handling this compound because of its biologic potency and because the pure compound remains stable for a least 72 hours at room temperature. Symptoms attributed to occupational exposure to prostaglandins include flushing of the face and the extremities and irritation of the eye and respiratory passage mucous membranes. Other symptoms reported by employees working with prostaglandins include retrobulbar pain, photophobia and decrease in visual acuity, tightness or fullness in the throat, pharyngeal pain, and sinus fullness. Because of the oxytocic and teratogenic properties of dinoprostone, females of childbearing potential should not have contact with the pure compound. Equipment should be thoroughly cleaned after use.

VI RESULTS

A. Medical.

The IV department was staffed by 20 nurses and 5 clerks. All staff were female except for two male nurses, and 19 of the females were of menstrual age and not pregnant. The first person to complain was a 31-year old who experienced "increased cramping" during her October 1981 menstrual period and breast tenderness in October (from two weeks into her cycle until the end of menses). She sought medical attention, but no specific diagnosis or treatment was given. Additional menstruating workers complained of similar symptoms in November and December; therefore, the Emanuel Hospital epidemiology staff conducted an investigation in January 1982.

For the epidemologic investigation a case was defined by the Emanuel Hospital staff as a menstruating female who experienced more than her usual abdominal cramping or bleeding during menstruation and/or unusual breast tenderness. Data about other symptoms (e.g., GI symptoms or headache) were not systematically sought. Data were collected for the 19 menstrual-age IV department staff, and 21 systematically selected menstrual-age nurses who worked elsewhere in Emanuel Hospital. Nine of 19 IV staff and one of 21 control nurses were found to meet the case definition. Of the nine IV staff cases, four had onset in October, one in November, and four in December. Six had sought medical attention, none received a specific diagnosis, but one was given a prescription for Motrin®R. These nine ranged in age from 22 to 38 years, represented all 3 work shifts, and had worked in the IV department from six months to ten years. The symptomatic control worked night shift on a ward and experienced "increased cramping and bleeding" in November 1981 and January 1982. Neither cases nor non-cases from the IV department differed from control nurses in their use of birth control methods or medications.

In August 1981, in order to improve the security of the work area, hospital authorities had closed a previously open door which connects the IV department work area to a major hallway. Several IV staff had complained that their work area was then stuffy and uncomfortable. One general hypothesis was that a substance in the work environment was causing the symptoms. The concentration of this substance increased when the door was closed; therefore, the symptoms began. A specific hypothesis concerned prostaglandins which were being mixed (from solid suppository into a gel-suspension) in the IV department. In addition, there was concern about possible adverse health effects caused by exposure of workers to anti-neoplastic agents which they were mixing. (The latter concern was prompted by a note in JAMA on 1-1-82, Vol. 247, pp. 11-12 entitled "Hospital personnel who handle anti-cancer drugs may face risks.")

In March, the epidemiology staff re-questioned seven of the nine cases from the IV department. (They were unable to contact the other two at that time.) Five had been asymptomatic since January, a sixth was symptomatic in February, and the seventh was symptomatic in March (but had not been in February).

In July, eight of nine of the original cases from the IV department were again contacted by NIOSH. (One nurse no longer worked at the hospital, and and we were unable to reach her.) All were asymptomatic during June and July 1982. Four previously asymptomatic staff were questioned. They were still asymptomatic. The supervisor of the IV staff was not aware of any current staff who were experiencing symptoms.

In the absence of currently symptomatic workers, further epidemiologic investigation by NIOSH was not indicated.

B. Work Practices. In the IV preparation room is a large table. This table is frequently used for coffee breaks and lunch. There is also a coffee pot and a small lunch area attached to the IV room. Consumption of any food or beverages in an area where drugs are handled should be prohibited as the potential for ingestion of these products exists. The tables become contaminated, hands are not washed before handling food and even if they are, after touching items in the room, the hands are again contaminated.

C. Laminar Flow Hood Usage. Laminar flow hoods are used in pharmacies when handling drugs to protect the drug from contamination. The use of a horizontal laminar flow hood does this, but at the same time systematically exposes persons handling the drugs to gases, vapors, and particulate matter from the work area. Negative pressure vertical laminar flow hoods protect both the product and the operator. Results of recent studies suggest that workers who handle antineoplastic drugs in horizontal laminar flow hoods may experience adverse health effects[11,12].

A written questionnaire was sent to all licensed hospital pharmacies in Washington. Eighty-four (82%) of 102 licensed hospital pharmacies returned the questionnaire. Of the 84 responders, 29 served hospitals with 50 or fewer beds, while 55 served larger hospitals. Twenty-four percent (7/29) of pharmacies in small hospitals (less than 50 beds) had horizontal laminar flow hoods compared to 87% (48/55) of pharmacies in larger hospitals (more than 50 beds). Vertical laminar flow hoods were available in 7% (2/29) of small hospitals and 29% (16/55) of larger hospitals. Forty-eight percent (12/25) of the pharmacies in hospitals with more than 150 beds had vertical laminar flow hoods. Several pharmacies had both types of laminar flow hoods in their facility. 32% (27/84) had no laminar flow hood.

The following table shows the type of laminar flow hood in use in various size hospitals. It also shows the number of pharmacies handling antineoplastic agents and the type of hood used.

USE OF LAMINAR FLOW HOODS (LFH)
IN HOSPITAL PHARMACIES

	Total Number of Hospital Beds Served					
	<50	51-100	101-150	151-200	201-250	>250
1. Number responding to questionaire	29	11	19	7	8	10
2. Number (and %) with						
a. Horizontal LFH	7(24%)	9(82%)	17(89%)	6(86%)	7(88%)	9(90%)
b. Verticle LFH	2(7%)	2(18%)	2(11%)	4(57%)	1(12%)	7(70%)
c. No LFH	21(67%)	2(18%)	2(11%)	0(0%)	1(12%)	1(10%)
3. Number (and %) which prepare antineoplastic agents	10(34%)	9(82%)	15(79%)	7(100%)	7(88%)	8(80%)
4. Of the Pharmacies which prepare antineoplastic agents the number which prepare these agents in						
a. Horizontal LFH	4(40%)	7(78%)	13(87%)	3(43%)	5(71%)	1(12%)
b. Verticle LFH	1(10%)	1(11%)	1(7%)	4(57%)	1(14%)	6(75%)
c. Areas without LFH	5(50%)	2(22%)	1(7%)	0(0%)	1(14%)	1(12%)

NOTE: Seven pharmacies had acquired verticle laminar flow hoods since 1980. In six others the horizontal laminar flow hood was turned off whenever antineoplastic agents were prepared in the hood.

Based on this survey, we conclude that the use of horizontal laminar flow hoods in hospital pharmacies is widespread and workers are unknowingly being exposed to a wide variety of drugs. This practice violates good industrial hygiene principles and practices.

VII CONCLUSIONS

Based on the data obtained from the evaluation, NIOSH determined that it is theoretically possible that exposure to prostaglandins led to the symptoms; however, it is not a likely relationship. In order to associate only one drug (i.e., a prostaglandin) with the symptoms, it would be necessary to rule out the effect of all other drugs, as well as other non-drug exposures. It was not possible to do this. The prostaglandin mixing was done only every 7 to 10 days and done by a male pharmacist who came to the IV department in order to use the laminar flow hood. The mixing took about 1 to 1-1/2 hours and sometimes occurred on day shift, other times on evening shift. The pharmacists involved have not experienced side effects (e.g., nausea, vomiting, diarrhea, or headaches) which could be caused by the drug. If menstruating females were exposed to a sufficient quantity of prostaglandin to stimulate uterine cramping, then additional symptoms might also be prominent (in men and non-menstruating women). The IV nurses spend much of their time

on the wards, as compared to the IV ward clerks who have more intense exposure to the physical environment of the IV department. The case rate among clerks was 25% (1/4) vs 53% (8/15) among nurses. One of the symptomatic workers only worked every other weekend.

A separate problem uncovered by this evaluation showed the widespread use in hospital pharmacies of horizontal laminar flow hoods for purposes for which they were not designed. This improper usage results in an occupational exposure of hospital pharmacy staff to the many drugs and chemicals prepared in these hoods.

VIII RECOMMENDATIONS

1. All use of horizontal laminar flow hoods in the IV department and pharmacy should be discontinued. Negative pressure vertical laminar flow hoods should be substituted for the horizontal laminar flow hoods.

2. The exhaust from the negative pressure vertical laminar flow hoods should be exhausted to the outside of the building.

3. Prohibit all consumption of foods and beverage in the IV room.

4. Wash hands before consuming any food.

5. Thoroughly clean up any spill of drugs or other chemicals.

6. Maintain a log of any adverse health effect and date of occurrence by affected IV personnel so that chemical and or holding procedures can be identified and control procedures initiated.

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XI 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 the NIOSH Publications Office at the Cincinnati address. Copies of this report have been sent to:

1. Emanuel Hospital, Portland, Oregon.

2. Oregon State Accident Prevention Division, Salem, Oregon.

3. U. S. Department of Labor, Occupational Safety and Health Agency (OSHA), Region X, Seattle, Washington.

4. Oregon State Health Division, Portland, Oregon.

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

List of Medications Handled in the Horizontal Laminar Flow Hood
Located in the Intravenous Department

Emanuel Hospital
Portland, Oregon
HETA 82-256

KCL	Cefadyl	Tobramycin	Ampcillin	Cimetadine
Cistplatinum	Adriamycin	Cytoxan	Aminophylline	Nafcillin
Lasix	Lanoxin	Mefoxin	Solu-Medrol	Solu-Cortef
Flagyl	Vincristine	Keflin	Ancef	Digoxin
Claforan	Decadron	Ticarcillin	Vancomycin	Cefoxitin
Compazine	Cleocin	Gentamycin	Reglan	Mandol
Manitol	Velban	Procaine	Penicillin	Ag Penicillin
NAHco3	Aldomet	Dilantin	Erythromycin	Chlromycetin
Hydrocortisone	Methicillin	5 Fu	Tagamet	Thiamine
MUI	Oxacillin	BNCU	Bleomycin	Buritol
Chlrophenycol	Moxalactam	Velosef	Endicrin	Dexamethal
K. Phosphate	Methoreate	Actinomycin	Heparin	Danomycin
Cyloran	Tremethopine	Methyl Prednisolone	Bicarb	Diamox
Refandate	Amicar	Pictocin	Insulin	Cephasporin
Phenergan	Robinol	Amphotericin	Cystosine-Arabinoside	Clindamycin
Dextron	Premarin	Vibramycin	Medral	Cytosine
Intraped	Imferon	Cefamandol	Mitomycin	Mecongle
Metodopromide	Cagluconate	Dexamethasone	Methramycin	Histamine Disphospate
Vinblastine	Gluriate	Benadryl	Lidocaine	Tetracycline
Meloriten	Kafzol	Velbum	Myoxin	Stilphosterol
Folate				

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