WALK THROUGH SURVEY REPORT

EXPOSURE TO NATURAL CONJUGATED ESTROGENS

at

AYERST LABORATORIES INCORPORATED
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION
ROUSES POINT, N.Y. 12979

Survey Dates

September 13-14, 1978
and October 26, 1978

Surveys Conducted By

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Date of Report

October 15, 1979

Industry-wide Studies Branch
Division of Surveillance, Hazard Evaluations and Field Studies
National Institute for Occupational Safety and Health
Center for Disease Control
Cincinnati, Ohio

PLACE VISITED:	Ayerst Laboratories Inc. Division of American Home Products Corporation Rouses Point, N.Y. 12979
DATE OF VISITS:	September 13-14, 1978 and October 26, 1978 (Biometry only)
PERSON(S) MAKING VISITS:	Dennis Zaebst Shiro Tanaka Marie Haring Richard Waxweiler Sandford Leffingwell, M.D.
OFFICIAL TITLES OF PERSON(S) CONTACTED AT PLANT:	Executive Vice-President & General Manager V.P. Engineering & Technical Services Project Engineer Manager, Regulatory Compliance, Ayerst Laboratories, N.Y. Asst. Director, Regulatory Affairs, Ayerst Laboratories, N.Y.
UNION:	President, Local 95, International Chemical Workers Union
PURPOSE:	To conduct a preliminary investigation of pharmaceutical manufacturing operations involving potential exposure to estrogenic substances as part of the current NIOSH-IWSB study of occupational exposure to estrogens.

INTRODUCTION

Background

The National Institute for Occupational Safety and Health (NIOSH), Division of Surveillance, Hazard Evaluations and Field Studies (DSHEFS), Industry-wide Studies Branch (IWSB), is currently conducting an investigation of health effects resulting from occupational exposure to estrogenic substances. This study, initiated in the fall of 1977, was prompted in part by epidemiological reports of chronic health effects found among users of oral contraceptives and by a joint CDC-NIOSH investigation of a manufacturer of oral contraceptive products, which found possible adverse health effects due to occupational exposure among its workers.

Occupational exposure to estrogens may occur in the manufacture of a variety of commercial preparations marketed by a large number of pharmaceutical manufacturers. Examples of such preparations are oral contraceptive tablets, tablets for estrogen replacement therapy, and a large variety of topical creams and injectable solutions or pellets.

This survey of Ayerst Laboratories in Rouses Point, N.Y. was conducted as one of a series of initial walk through surveys in a representative sample of firms manufacturing products containing synthetic and/or natural estrogens.

Authority

Studies of this nature are authorized under the Occupational Safety and Health Act of 1970, Public Law 91-596, December 29, 1970. Specifically, NIOSH has been designated responsibility for conducting field research studies in industry, to evaluate findings, and report on these findings. Section 20(a)7 states that NIOSH shall conduct and publish industrywide studies of the effects of chronic or low level exposure to industrial materials, processes, and stresses on the potential for illness, disease, or loss of functional capacity in the aging adults. Section 20(b) further states that NIOSH is authorized to make inspections and question employers and employees as provided in Section 8 of this Act in order to carry out the functions and responsibilities under this Section. Section 20(c) further states the authority to enter into contracts, agreements, or other arrangements with appropriate public agencies or private organizations for purposes of conducting studies relating to responsibilities under the Act.

DESCRIPTION OF FACILITY

Ayerst Laboratories, Inc. is located on a sixty acre site in Rouses Point, New York and consists of 20 or so manufacturing, warehouse, and office buildings comprising of a total of approximately 450,000 sq. ft., of which approximately 130,000 sq. ft. were added in a major expansion in 1974-75.

The company is a division of American Home Products Corporation, and was established and operating in the mid 1930's. During the early years (prior to the mid 1940's) the conjugated estrogen product line consisted of small quantities of Emmenin(R) (extract of natural conjugated estrogens from human female urine). The products containing natural conjugated estrogens (NCE) from pregnant mare's urine, e.g. Premarin(R), were introduced sometime between 1940 and 1945. The number and quantity of conjugated estrogen products has steadily increased over that time to the present.

The company presently manufactures a variety of pharmaceutical products at this site, among which are 26 different preparations containing natural conjugated estrogens (NCE). NCE is the sole active ingredient in Premarin(R) and is used in other preparations in combination with vitamins, methyl testosterone, and meprobamate, and is distributed in the form of tablets, capsules, liquids, creams, parenterals, and powders, both sterile and non-sterile. A list of most of the products containing NCE is included as Table 1 (Appendix). Of these, the tablets containing NCE (alone or in combination) are manufactured by far in the largest volume.

DESCRIPTION OF WORKFORCE AND PERSONNEL RECORD KEEPING SYSTEM

Workforce

The Rouses's Point facility currently employs 763 as of August 31, 1978, of which 335 are salaried and 452 are hourly. Of these, 447 are males and 316 are females. There are few blacks or other minorities employed, as there are only 0.9% blacks in Clinton County. Turnover is below 10% per year.

Job classifications and the number of employees are listed in Table 2 (Appendix). Approximately 70 employees are involved in the manufacture of products containing NCE, from granulation through packaging. Of these, approximately 30 are assigned to tasks where the company has on occasion detected measurable concentrations of NCE in the air. These 30 employees are on the average assigned to these tasks for approximately 10% of their work load. Although few in number, women do perform those tasks where the company has on occasion detected NCE in the air. Company policy does not exclude women from working in these areas. A large number of women traditionally work in the packaing area, where potential for exposure is considered low.

Records

Records of current personnel are contained in manila envelopes, organized in alphabetical order and kept in file cabinets in the personnel office. Information contained in the folders include:

a) Application for employment - includes name, address, social security number, educational and professional record, position title.

b) Notice of employment - includes name, sex, marital status, address, DOB, date employed (this form originated in 1967-68).

c) Personnel change report - indicates change of job status, including leaves of absence, termination and rate changes.

d) Employee service record - this card is not placed in the folder until the employee terminates. While the employee is current, it is retained in a cardex file. It contains employee name, social security number, DOB, employment date, length of service, sex, address and any change of address. This form primarily records the types of job in which the employee is involved and the rate of pay. For each job or rate change there is a notation indicating the action taken. But, there is no documentation on the specific products with which an employee may have worked.

Since 90% of the workload of the 30 employees working in the NCE areas is not in the NCE production areas, the probability that employees have been exposed to products other than the estrogens is high. However, the extent of such exposure was not investigated during the survey. It is likely that names of persons involved in the granulation step are recorded due to FDA regulations; but no other operation would be documented as well.

Personnel records on terminated employees are retained without alteration indefinitely. Records are kept in the personnel office for the year post-termination, then sent to the archives (basement) for storage. The archived records are arranged in alphabetical order in file cabinets. Records of persons hired in 1935 reviewed by the NIOSH investigator contained approximately the same information as the current files. Even though Social Security was not enacted until 1937, the social security number was typed in the records of people employed before 1937 and still working at the time. Death certificates are obtained for only those persons dying while employed at Ayerst. Records of pensioned and deceased employees are treated as terminated with no separation of records for either.

American Home Products administers the Pension and Retiree Fund as well as the death benefits program.

It appears that the personnel records of workers hired and terminated between 1935 and 1943 are not available, possibly due to the change in company ownership to American Home Products in 1943. However, all of the data on personnel hired after 1944 and those employed before 1944 and who continued with Ayerst after 1944 are readily accessible.

DESCRIPTION OF PREMARIN MANUFACTURING PROCESS

Although the company manufactures products containing natural conjugated estrogens in a variety of forms, the following discussion will be limited to a description of the manufacture of Premarin(R) tablets, since this process is representative of the tablet manufacturing process and is the single product manufactured in largest quantity.

The active ingredient is the NCE which constitutes approximately 10% of the basic raw material. This basic raw material is manufactured at the company's Canadian facilities. In this process, the estrogens are extracted from pregnant mare's urine (pmu), partially purified, concentrated, and dried on an inert carrier. The dried concentrate contains, in addition, to the estrogens, non-estrogenic organic compounds, inorganic salts, and the inert carrier. The estrogenic component is a mixture of at least 9 conjugated estrogens, of which approximately 90% are the sodium (estrogen) sulfates of estrone, equilin and 17-alpha dihydroequilin.

The manufacture of Premarin(R) tablets is essentially a step wise process involving batch mixing of ingredients followed by compression of the finished granulation into tablets. The tablets are then coated, imprinted, and stored prior to packaging. The manufacturing steps are outlined in the following paragraphs.

Batch Assembly

Both active components and excipients (components other than the actives) are weighed out on a batch basis in a central weighing area under local exhaust ventilation. Assembled ingredients for specific batches are then moved as necessary to the compounding area for mixing.

Compounding (blending)

The granulation (compounding) step typically involves preparation of a premix (dessication) by combining NCE with two excipients, followed by dry milling, reblending (wet mixing) the dessication with the remainder of the excipients. The wet mix is then wet milled, dried in a fluid bed dryer, dry milled, and finally, blended with a lubricant to facilitate compression. The granulation is then placed in stainless steel transports, sampled and assayed by quality control, and staged for the tableting operation. The process up to this point may take 8 hours or slightly more per batch.

Tableting

Transports containing the granulation are moved as needed to the second floor and are located directly over the tablet press. The bottom of the transports is connected directly to a pipe which extends through the floor to the press hopper. The granulation is then fed automatically at a controlled rate to the tablet press. Formed cores exit the press through evacuated "deduster" arms to open drums lined with plastic bags. The area above the tablet press also contains an area in which the transports are manually washed down with detergent and water. The waste water is flushed into a sanitary drain through a connecting hose.

The tablet process is continuously monitored by the press operator; he inspects the cores for physical attributes and collects samples for laboratory assay.

Tablet Coating and Imprinting

Pressed cores are then moved to a separate area in which they receive a multiple layer coating. The cores first receive an impervious coating, followed by many layers of other coatings. The coating is done by manually loading the tablets into one of several locally exhausted coating pans. The appropriate coating material is then added by an automated system and the batch is allowed to tumble in the pan for a length of time sufficient to assure even coating of the tablets. The tablets are then polished, imprinted with the appropriate markings, inspected, and staged for packaging operations.

After the impervious coatings are applied, the potential for generation of estrogen containing dust (e.g. in packaging and tablet inspection) is virtually eliminated, barring the possibility of breakage or crushing of tablets during subsequent operations.

Packaging

The majority of Premarin(R) products are bottled. In the main packaging area, (where all products are packaged) the coated tablets are manually loaded into the hopper of a bottle filling machine. The machine automatically counts and feeds the tablets to the bottles. The filled bottles are then conveyed down a line where they are plugged with cotton inserts, inspected, capped, and labeled. After packaging, the tablets are quarantined, sampled by quality control, and when released, are moved to the warehouse and shipped.

DESCRIPTION OF MEDICAL, INDUSTRIAL HYGIENE AND SAFETY PROGRAMS

Safety and Industrial Hygiene Programs

Safety and health programs at this site center around two safety committees, one of which includes the Vice President of Engineering and Technical Services, the Executive Vice President and General Manager, a project engineer (who also serves as safety director) and a number of plant supervisory personnel. The second committee includes a member of the union local (ICWU, No. 95), the project engineer, and several department and junior supervisors. These committees meet regularly to discuss problems and approaches in the safety and health area. The plant also has a "housekeeping" committee which regularly tours the facilities. The plant also receives periodic safety inspections from the American Home Products Corporation safety engineer.

Communications to employees on matters of safety and health are accomplished principally by means of a general safety orientation at the beginning of employment, and by written standard operating procedures (or flow sheets) which specify safety gear requirements for specific jobs. There is no written respiratory protection program outlining the use and care of protective

equipment by employees, nor does there appear to be a formalized system for training employees in the use and care of equipment. However, the company indicated at a later date that audio/visual employee and safety training programs including one for respiratory protection were being developed and that a few had been in use at the time of the survey.

In addition, although there are facilities available for changes of clothing, showers, etc, there are no specific formalized requirements prepared and communicated to employees on specific work practices (e.g. change of clothing, showers) or for entry or exit to areas where estrogenic products are used and where potential for exposure to estrogens exists. Although granulation rooms, compression cubicles, and similar areas are under negative pressure relative to access hallways (following good manufacturing procedures specified by FDA), the processing and tablet manufacturing areas are not totally isolated from adjacent areas (for example, by means of air-locks). It is thus conceivable that some migration of air and process generated dust to adjacent areas might occur, possibly resulting in some degree of inadvertent exposure to employees not working directly in the manufacturing area ("halo" effect).

According to plant officials, however, there are plans for facilities improvements relating to these considerations, including the planned installations of an air shower and a gowning room to be used by personnel entering or exiting the granulation and blending areas. Until May 1978 there were no requirements for the use of respiratory or other personal protective equipment by employees working in the tablet manufacturing area, although various types of respiratory protective equipment were said to be provided. In early May, 1978, however, the company began requiring the use of respirators (and gloves) for high potential exposure jobs such as granulation, blending, tablet inspection, and tablet core coating as well as for QC technicians and roving inspectors, and for other personnel required to enter the manufacturing areas. Operators are given a choice of wearing either a disposable, single use dust mask (such as the 3M Corp. No. 8710), a half-mask, air purifying respirator using replaceable filter cartridges, or an air supplied hood.

No personal or area sampling for airborne estrogens had been conducted prior to 1978 at this site. Industrial hygiene data is limited to a body of samples obtained during 1978 for the various tablet manufacturing steps. These samples were obtained using personal sampling pumps & glass fiber filters. Subsequent quantitation was done by gas chromatography after hydrolyzation of the estrogen to the free form, extraction from the filter, evaporation to dryness, and silylation. The results of sampling various jobs and areas have indicated highly variable concentrations of total conjugated estrogens in air, ranging from below the limit of detection (limit of detection $\sim$0.1-1.0 micrograms per filter) to approximately 550 micrograms per cubic meter, representing sampling periods from approximately 1/2 to 8 hours.

The significance of these results is not clear, since conjugated natural estrogens apparently have considerably less activity (when orally administered), than the synthetic estrogens (e.g. mestranol or ethynyl estradiol). These results very likely do indicate extent of exposure of workers to estrogens in the recent past. However, since the use of respirators has been required since the spring of 1978, actual exposure after this time may be somewhat below that indicated by the personal sampling results.

Medical Program

There are two local physicians who alternately attend the plant dispensary once a week, about two hours each time. In addition, the plant employs a full-time and a part-time nurse.

Pre-employment physical examinations include history, physical, ventilatory function test, audiometry, EKG, blood chemistry (some at employees option and expense) and pap smear for females. Periodic medical examination is voluntary and offered once every two years for those over age 40 and every three years for under 40 years old, except that biennial serology test and chest x-ray are mandatory.

Company officials and one of the physicians stated that they have not experienced a single case of adverse estrogen effects from occupational exposure.

No particular examination or inquiry is conducted on estrogen workers to detect signs or symptoms of over exposure. There is no formal worker education program as to the potential toxicity of estrogens in the workplace. However, one company official commented that should a worker develop any suspect adverse reaction to estrogens, he would be kept away from operations involving the suspected agent but not transferred to another department. No scheduled rotation system is currently in effect at this plant.

DESCRIPTION OF PAST EXPOSURES

Data on exposure of employees to conjugated estrogens is limited to area and personal sampling data collected in 1978. No data is available to document earlier exposures and their relationship to present exposures.

Potential exposures (exclusive of respiratory equipment) to estrogens in the past were very likely higher than that at present due to the steady improvements in ventilation controls and materials handling methods. However, the lack of data from earlier years makes it impossible to substantiate this conclusion. The institution of requirements for respiratory protection in the most hazardous jobs in May 1978, however, may have had some impact in reducing actual exposures during the various processing steps.

INSPECTION OF PLANT

Company officials emphasized that NCE have about 50 times less potency than synthetic estrogens. As observed, control of exposures of employees to NCE containing dust at this site was not as stringent as that of some other companies manufacturing products from synthetic estrogens. This was evident in the lack of specific written protocols for entry and exit (e.g. change of clothing, showers, etc.) to and from manufacturing areas in which the estrogens are used, lack of a well developed and defined respiratory conservation program, and lack of formal training programs for employees in the use and care of protective equipment. Also, the areas in which compression of cores is conducted were not totally isolated, possible allowing migration of contaminated air to adjacent (peripheral) areas of the building. The specific rooms used for the manufacturing of tablets (blending, granulation, compression rooms, etc,), however, were equipped with numerous local ventilation system

and were kept under negative pressure gradients to achieve air flow into (rather than out of) potentially contaminanted areas. In general, materials handling methods also appeared to be well designed, thus limiting generation of dust during transfers of raw materials, intermediate blends, granulation, or uncoated tablets.

It is not clear at this time whether the strict procedures employed by users of synthetic estrogens are warranted in the manufacture of products containing the conjugated, natural estrogens. Although natural estrogens are apparently not as pharmacologically active as the synthetic estrogens, it is also true that the natural estrogen products are formulated with higher concentrations of total estrogen by weight. Another difference is that the conjugated estrogens are water soluble, and may be more rapidly absorbed in the lungs or through the skin than the synthetic estrogens. Thus, although the estrogen may be less potent, the dust generated during processing may be nearly as hazardous as an equivalent amount of dust containing lower concentrations of synthetic estrogen. Further research would be required to clarify these considerations.

The industrial hygiene data obtained by the company during 1978 indicates that potential exposures of manufacturing area employees are highly variable, but may at times approach pharmacologically active dosages. For example, an eight hour personal exposure to an air concentration of 100 ug/m^3 of air would (assuming an employee doing light work inhales eight cubic meters of air, and absorbs 100 percent of the inhaled estrogenic substances) result in an inhaled dose of 0.8 milligrams of natural, conjugated estrogen.* However, it should be noted that these employees also work with a variety of other non-estrogenic drugs, and that their exposures to estrogens are therefore intermittent. Although no strict rotation schedule has been implemented, the company has estimated that these employees spend approximately 10% of their total work time in jobs in which a detectable exposure to estrogens might occur. Packaging area employees very likely are not exposed to detectable concentrations of estrogens, since all of the tablets are coated prior to packaging.

ENVIRONMENTAL SAMPLING

As part of NIOSH's current effort to develop valid sampling and analytical methods for estrogens and progestogens, a small number of air samples were obtained at this and several other sites, in an effort to supply actual field samples for development purposes to the Measurements Support Section, Division of Physical Sciences and Engineering (DPSE). In brief, the air samples were obtained at strategic locations in the areas where granulation and tableting were being done, using personal sampling pumps as area samplers in conjunction with glass fiber filters.

It had been intended that the results of the samples from all sites would be reported (when available) in a special technical report analyzing the comparative utility of the several different filter matrices used, and describing the development of the methods used for analysis of the samples. However,

*These figures are given for illustrative purposes only, and should not be construed as a basis for a suggested standard.

subsequent work with these samples in the laboratory has indicated that the filter matrix used was not suitable due to interfering compounds present in the filter material. Because the samples were intended only for method development purposes, the filters were not analyzed. Instead, efforts were directed at finding a filter type compatible with the analytical method.

CONCLUSIONS

The nature and extent of occupational exposure to natural conjugated estrogens and the ultimate health effects which might occur as a result of those exposures have not been thoroughly studied in the past. This site appears to be a logical place to conduct an in-depth industrial hygiene study to document the present extent of actual or potential exposure, as it is the largest and oldest site at which natural estrogen products are used. The results of such a study would be a useful adjunct to similar studies in plants using synthetic estrogens. Aspects of exposure which should be evaluated include absorption via inhalation, skin contact, and ingestion through the GI tract.

Health effects of occupational exposure to natural estrogen has not been studied extensively in the past. This plant appears to have a large volume of production and a fairly good size population of workers. An in-depth medical study of workers for health effects of estrogen is considered feasible and necessary at this site.

Although the number of employees at this facility is small, this plant should be more carefully considered as a possible site for an in-depth epidemiological study. The records maintained by the company are suitable for obtaining pertinent demographic data on the employees and would be helpful in follow-up. But, the records lack some essential data necessary for assessing exposure duration and frequency.

In addition, the company has been manufacturing conjugated estrogen products for approximately 30 years. In most occupationally acquired illnesses, particularly cancers, the latency period for the appearance of the disease is usually 20-30 years after exposure. In this population, we may be able to observe the effects of long-term exposure to exogenuous estrogens on a few workers.

TABLE I

LIST OF CONJUGATED ESTROGEN PRODUCTS

A. TABLETS

#752	MEDIATRIC(R)	(Conjugated Estrogens)
#865	PREMARIN(R), 2.5 MG.	" "
#866	PREMARIN(R), 1.25 MG.	" "
#867	PREMARIN(R), 0.625 MG.	" "
#868	PREMARIN(R), 0.3 MG.	" "
#878	PREMARIN(R)/METHYLTESTOSTERONE	" "
#879	PREMARIN(R)/METHYLTESTOSTERONE	" "
#880	PMB(R)-200	" "
#881	PMB(R)-400	" "
#883	FORMATRIX(R) (VITAMIN C, METHYLTESTOSTERONE, Conjugated Estrogens)	
#2280	MILPREM(R)	" "
#2281	MILPREM(R)	" "

B. CAPSULES

#252	MEDIATRIC(R)	" "

C. LIQUIDS/CREAMS

#872	PREMARIN(R) CREAM	" "
#910	MEDIATRIC(%) LIQUID	" "

D. PARENTERALS

#552	PREMARIN(R) I.V.	" "

E. POWDERS

LIST OF ESTROGEN PRODUCTS

A. PARENTERALS

#451	ESTRADURIN(R)	(Polyestradiol Phosphate)
#567	ESTROGENIC SUBSTANCE	(Estrone)
#568	ESTROGENIC SUBSTANCE	(Estrone)

TABLE 2

JOB CLASSIFICATIONS INVOLVED IN ESTROGEN MANUFACTURE

ASST. PROD. FOREPERSON	
ASST. FOREPERSON	
PHARMACEUTICAL SPECIALIST A	
PHARMACEUTICAL SPECIALIST B	
MANUFACTURING OPERATOR	
PROCESS OPERATOR	
PROCESS HELPER	
PRODUCTION HELPER	
CUSTODIAN	
TOTAL NUMBER OF PEOPLE	75