HAZARD EVALUATION AND TECHNICAL ASSISTANCE REPORT
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LEDERLE LABORATORIES
PEARL RIVER, NEW YORK
JULY 1990

Hazard Evaluation and Technical Assistance Branch
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Introduction

In September 1987, the National Institute for Occupational Safety and Health (NIOSH) received a health hazard evaluation request from the International Chemical Workers Union (ICWU) regarding working conditions at the Lederle Laboratories plant in Pearl River, New York. The request stated that two women who worked with Thiotepa, a cancer chemotherapeutic agent, had given birth to children with similar heart defects. In January 1988, the ICWU asked NIOSH to expand the scope of the original request to include potential long-term health effects, particularly cancer, resulting from exposure to Thiotepa.

On October 12-13, 1987, an initial site visit was conducted at this facility. A letter summarizing the activities and findings of this site visit was sent on November 3, 1987. This report summarizes our activities from the initial visit to the present, and includes recommendations, many of which were made previously. This report also serves to close-out the NIOSH health hazard evaluation.

Background

Bulk Thiotepa is prepared and shipped to the Pearl River facility for packaging. Sodium bicarbonate and sodium chloride are added to the bulk drug, which is then screened, milled, and sterilized. The product is refrigerated until needed, at which time it is transferred to the packaging area. The product is placed into a hopper, and 15 milligram (mg) quantities of active ingredient are mechanically dispensed into glass vials, which are then sealed with a rubber septum. This part of the process is performed in a Class 100 clean room. The dispensing machinery is housed within a laminar flow cabinet that has supply and exhaust high efficiency particulate air filters (HEPA) to maintain product sterility. Periodic dose checks are made by a quality control (QC) technician. Vials containing the 15-mg doses move via a conveyor into the adjacent capping room, through a small opening, approximately 6" x 6". A HEPA vacuum has been installed at this opening in an effort to capture air contaminants coming from the filling room, which is under positive pressure. An automated capping machine is used to seal the vials with a metal cap. A visual inspection is then made to ensure that all vials are sealed and intact. The unlabelled stock is then boxed and sent to the final inspection area.

A group of approximately 50 workers are involved in Thiotepa packaging. Seven employees work on the line during a given production run or "fill," and two employees are responsible for mixing and milling the Thiotepa prior to

packaging. The packaging operation runs intermittently, to fill current orders. In 1988, eight bulk lots (two fills per lot) were packaged, and in 1989, 14 bulk lots were packaged.

Toxicology and Evaluation Criteria

Thiotepa (triethylene thiophosphoramide) is a white, crystalline powder which is soluble in water.[1] The only known commercial use for this drug is as an antineoplastic (anti-cancer) agent, although it was investigated for use as an insect chemosterilant and an intermediate for flame retardants for cotton.[2] It is classified as a polyfunctional alkylating agent (of the ethyleneimine group) because it acts by alkylating deoxyribonucleic acid (DNA), the molecules that control cell function, growth and division. It is, therefore, considered a mutagenic agent. Thiotepa has also been shown to be teratogenic (a cause of birth defects) in animal studies.[3,4]

The International Agency for Research on Cancer (IARC) classifies Thiotepa as a group 2B agent, an agent which is probably carcinogenic to humans.[2] This is based on a review of the biological data, which IARC feels have provided sufficient evidence of carcinogenicity to animals (mice), yet inadequate evidence for carcinogenicity to humans. NIOSH classifies any agent as a "potential occupational carcinogen" if the substance causes an increased incidence of benign and/or malignant neoplasms, or a substantial decrease in the latency period between exposure and onset of neoplasms in humans or in one or more experimental mammalian species as the result of any oral, respiratory or dermal exposure, or any other exposures which results in the induction of tumors at a site other than the site of administration.[5] This definition also includes any substance which is metabolized into one or more potential occupational carcinogens by mammals. Thiotepa would, therefore, be classified by NIOSH as a potential occupational carcinogen.

Information is not available concerning adverse health effects from exposure to Thiotepa by inhalation. To our knowledge, Lederle is presently the only manufacturer of Thiotepa in the United States. Adverse reactions reported among patients receiving intravenous and intraperitoneal injections of Thiotepa have included bone marrow depression, nausea, vomiting, loss of appetite, dizziness, headache, anemia, and interference with spermatogenesis.[6] The material safety data sheet indicates that eye contact can result in severe eye irritation. Although Thiotepa is not considered a skin irritant, it can be absorbed through the skin in toxic amounts.[1]

Environmental evaluation criteria have not been established for Thiotepa by NIOSH, the Occupational Safety and Health Administration (OSHA), or the American Conference of Governmental Industrial Hygienists (ACGIH). Because Thiotepa is considered a potential occupational carcinogen, NIOSH recommends that exposures be reduced to the lowest feasible level. Lederle's parent company, American Cyanamid, has established an internal exposure limit for Thiotepa of 0.01 milligrams per cubic meter (mg/m^3) as a time-weighted average, a limit which the most current MSDS indicates is "established for women of child bearing potential."[1]

Environmental Evaluation

A walk-through survey was conducted in the areas where Thiotepa is handled, including the mixing and milling area, powder filling room (Class 100 clean room), capping room, and the QC and final inspection areas. There was no mixing or milling performed during our site visit, so this procedure could not be observed.

Set-up for the packaging operation began at 6:00 am and was performed by two employees. Sterilized parts were secured in place, and a trial run was conducted. Periodic adjustments of the miscellaneous parts were made to ensure that the equipment was operating properly and that the dose delivered was correct. Adjustments were frequently made during the course of the day as well, to correct problems that were encountered. Typical problems observed included incorrect dosages delivered to the vials, powder dispensed onto the belt without a vial underneath, vials proceeding down the line without a rubber septum, vials tipping over, vials forcibly expelled from the conveyor belt due to back-ups, and exiting vials being boxed without metal caps in place. Employees indicated that this had been a typical day in terms of the types of problems encountered. After the run was completed (approximately 2:30 pm), clean-up operations began. HEPA vacuums were used to remove the gross contamination on the equipment surfaces, following which the dispensing equipment was disassembled and wrapped in foil for additional cleaning and sterilization. A total of seven employees worked on the Thiotepa line that day, including two set-up workers, two supply operators, two sterile operators, and one quality control technician.

Personal protection for employees in the filling room consisted of full Tyvek suits, Racal Airstream® powered air-purifying respirators (PAPR) (with HEPA filters) and surgical masks underneath, and surgical latex gloves. A respiratory protection program has been established at Lederle. Employees working in the capping room wore uniform work pants and shirts, safety glasses, gloves, and half-mask air-purifying respirators with HEPA filters. The difference in protective equipment in these two areas appears to be due primarily to the desire to protect the product, maintaining product sterility and clean room conditions.

Medical Evaluation

The medical investigation consisted of interviews wih supervisors, Lederle medical clinic physicians, and current and past employees who work with the drug Thiotepa. The purpose of the interviews was to identify the adverse health effects of primary concern to the workers, to assess how typical the day we observed had been, and to obtain information on the two women who have children with heart defects. The primary concern expressed was the potential reproductive hazard of exposure to Thiotepa. In addition, there were scattered complaints of dry throat, headache, nausea, swollen glands, dizziness, and an unusual aftertaste present only when working on the Thiotepa line. There was also concern expressed about the potential for exposure to Thiotepa during the inspection process.

The medical records of the affected women and their babies were obtained for review. These records confirm that the children have heart defects. They have different types of heart defects, yet both are considered common birth defects. Review of the work histories of these two women show that both were removed from exposure to Thiotepa at 6 weeks of pregnancy. Prior to her removal from exposure, one women worked with Thiotepa on at least one day (day 35 of her pregnancy). The other woman's record states that she was in a probationary period and that during this period it is "unlikely" that she was assigned to work with Thiotepa.

Summary

Several concerns arose from observations made during our initial site visit in October 1987, including: (1) the potential for exposure to Thiotepa powder and vapor, (2) the adequacy of existing personal protective equipment, (3) the poor adherence to the appropriate use (or lack of use) of personal protective equipment during clean-up operations, (4) the performance of QC duties (dose checks, manual weighing) in an area where other unprotected workers were located, (5) the lack of a barrier (door or wall) separating the Thiotepa capping area and the adjacent hallway and (6) the potential for reproductive toxicity due to exposure to Thiotepa. Each of these issues will be discussed below.

(1) After reviewing Lederle's air sampling data and sampling and analytical method for Thiotepa, it became apparent that Thiotepa exists in both the particulate and vapor phases at room temperature. Air sampling data have shown the collection of Thiotepa primarily on the sorbent tube, when a sampling train consisting of a filter followed by a solid sorbent tube is used. Laboratory work performed at NIOSH also confirmed that Thiotepa exists as a vapor, as spikes of Thiotepa and methanol solutions directly onto a teflon filter followed in series with a Tenax tube, resulted in all of the Thiotepa being found on the Tenax tube. (The filters and tubes were analyzed after drawing air through the sampling train for approximately 8 hours at 1 liter per minute.)

(2) Since our initial visit, organic vapor cartridges have been added to the half-mask respirators used in the capping room and the PAPR respirators used in the filling room, in an effort to protect employees from Thiotepa vapor. We cannot comment on the effectiveness of the organic vapor cartridges for Thiotepa vapor, as they have not been tested in this manner. In addition, because Thiotepa is considered a potential occupational carcinogen, NIOSH recommends that only the most reliable and protective respirators be used by those workers exposed to the agent, such as a self-contained breathing apparatus or a supplied-air respirator with a full facepiece in combination with an auxiliary self-contained breathing apparatus.

(3) With regard to the appropriate use of personal protective equipment, we observed that some employees wore their half-mask respirators without the bottom strap fastened, resulting in an inadequate face seal. Employees did not always wear gloves and long-sleeved garments during cleaning, creating the potential for skin absorption of this drug.

(4) Since our initial visit, Lederle has provided a separate room for QC activities, thereby avoiding the potential exposure of unprotected workers when manual weighing operations are performed.

(5) Lederle has also walled off the area surrounding the capping room, which should minimize traffic and potential contamination of the hallway area.

(6) Two women were confirmed to have had children with heart defects. At least one of these women had brief exposure to Thiotepa 35 days after her last menstrual period. The period of formation of the organs occurs between day 35 and day 70 after the last menstrual period.[7] It is, however, impossible to determine whether this birth defect was due to exposure to Thiotepa without conducting a large scale study of births among workers exposed to Thiotepa. Heart defects are common types of defects, estimated to occur in about 4 out of 1000 births[8] and they can be caused by genetic factors, as well as exposure to a variety of toxins.

Recommendations

Based on our observations and findings, the following recommendations are offered.

1. Because Thiotepa is considered carcinogenic, mutagenic, and teratogenic, exposure to Thiotepa particulate and vapor should be reduced to the lowest feasible level. The use of engineering controls including a glove box or robotics are examples of control measures which can minimize worker exposures to this toxic drug. A glove box apparatus may be a practical means of controlling worker exposures, as the packaging process operates sporadically, and involves relatively small quantities of product.

2. While NIOSH recommends the reliance on process or engineering controls rather than personal protective equipment to control exposures, the use of respiratory protection should continue until further engineering controls are in place. NIOSH recommends the use of a self-contained breathing apparatus operated in positive pressure mode, or a supplied-air respirator with a full facepiece operated in pressure-demand mode in combination with an auxiliary self-contained breathing apparatus operated in pressure demand or other positive-pressure mode.

3. The use of personal protective equipment which provides skin, eye, and respiratory protection against Thiotepa particulate and vapor should be enforced. The present differences in the level of protection in the capping and filling areas does not seem appropriate from a health standpoint, as exposure to Thiotepa via inhalation, skin absorption and eye contact can occur in both areas. In addition, all work clothing should be removed prior to leaving the work area. Workers involved in protective equipment cleaning and maintenance should be adequately trained and should wear appropriate protective equipment to prevent eye, skin, and inhalation exposures.

4. Continue periodic exposure monitoring for Thiotepa and provide periodic employee training programs on potential health hazards associated with this drug, as well as on the use of personal protective equipment.

5. The MSDS for Thiotepa should be revised to include information on the potential for exposure to Thiotepa vapor (as well as particulate) at ambient conditions. This information should be included in the "Primary Route(s) of Exposure/Entry" section.

6. As an interim measure, until engineering controls are implemented, all women who are pregnant or women and men who are trying to have children in the immediately future should be offered removal from exposure to Thiotepa. During this interim period, Lederle should continue their policy of maintaining the worker's seniority and benefits rights.

This letter constitutes the final report of the Lederle Laboratories health hazard evaluation. In accordance with NIOSH regulations, a copy of this letter must be posted in the area(s) of the affected employees for a period of at least 30 days.

References

1. Lederle Laboratories. Material Safety Data Sheet for Thiotepa. Sheet No. 5003-04. September 15, 1989.

2. International Agency for Research on Cancer. IARC Monographs Supplement 4 -- Tris(1-aziridinyl)Phosphine Sulphide (Thiotepa) (Group 2B). 252- 254.

3. Murphy ML, Moro AD, Lacon C. The comparative effects of five polyfunctional alkalating agents on the rat fetus with additional notes on the chick embryo. Ann NY Acad Sci. 68: 762-781, 1958.

4. Tanimura T, Nishimura H. Teratogenic effect of thio-TEPA, a polyamineoplastic compound, upon the offspring of pregnant mice. Acta Anat Nipp. 37:66-67.

5. National Institute for Occupational Safety and Health. NIOSH Pocket Guide to Chemical Hazards. Cincinnati, Ohio. DHHS (NIOSH) Publication No. 85-114, February, 1987.

6. Lederle Laboratories. Drug insert for Thiotepa parenteral (sterile 15 mg/vial). 18452, revised March, 1987.

7. Schardein, JL. (1985) Chemically Induced Birth Defects. Marcel Dekker, New York. p. 6.

8. Ibid. p. 9.