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Occupational Safety and Health Administration

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OSHA Instruction PUB 8-1.1 JAN 29, 1986 Office of Occupational Medicine

Subject: Guidelines for Cytotoxic (Antineoplastic) Drugs

A. Purpose. This instruction provides a description of the hazard during the use of antineoplastic drugs in the health care delivery system and recommends controls and work practice technique to reduce the risks of that hazard.

B. Scope. This instruction applies OSHA-wide.

C. Reference.

1. OSHA Instruction CPL 2.45A, April 18, 1983.

2. OSHA Instruction CPL 2.59A, August 16, 1985.

D. Action. As another step in OSHA's Outreach program, Regional Administrators and Area Directors shall ensure that copies of Appendix A are mailed to all major health care facilities in SIC codes 8062 and 8069 in their respective areas. Appendix B is a letter that could be used as a vehicle to convey this document to those facilities. In conjunction with Area Offices being Full Service Resource Centers, copies of Appendix A shall be made available from the Area Office to members of health care facilities upon request.

E. Federal Program Change. This instruction describes a change in the Federal program for which a State response is not required. Each Regional Administrator, however, shall:

1. Ensure that this change is promptly forwarded to State designees.

2. Explain the technical content of this change as well as the Region's plans for implementing it to the State designee.

3. Encourage States to adopt similar program initiatives where such initiatives are not already in place by taking the action described in D and mailing Appendix A to the identified major health care facilities.

F. Background. In January and February of 1984, OSHA mailed to hospitals and clinics a document that described the hazards of hepatitis B infection to workers in the health care delivery system and recommended work practice techniques to reduce those risks of that hazard. As evidenced from the large number of letters thanking the Agency for producing such a document and the requests for additional copies of the document, this information was widely accepted and greatly appreciated in the

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professional community. As a result, this instruction is another aid to help both employers and employees recognize the hazard of handling antineoplastic drugs and prevent any adverse health effects from exposure to these drugs.

G. Mailing. The National Office will furnish either lists or labels of establishments' names and addresses for this mailing for most of the facilities existing in SIC codes 8062 and 8069. These mailing lists and additional copies of Appendix A will be sent to the Regional Offices in approximately 3 weeks. However, some of these facilities are not included in our mailing lists and Regional Administrators/Area Directors should try and identify these facilities to the extent

possible and add them to the lists. Regional Administrators shall immediately make these lists and/or labels for facilities -- State Plan States and additional copies of Appendix A available to State designees.

Patrick R. Tyson Acting Assistant Secretary

DISTRIBUTION: National, Regional and Area Offices All Compliance Officers State Designees 7(c)(1) Project Managers NIOSH Regional Program Directors

Appendix A

Work Practice Guidelines for Personnel

Dealing with Cytotoxic (Antineoplastic) Drugs

Office of Occupational Medicine Directorate of Technical Support Occupational Safety and Health Administration U.S. Department of Labor

January 29, 1986

PREFACE

It is not uncommon for health care professionals to regard themselves as immune from any harm arising from their work. Thus, during the course of treating their patients, they may inadvertently expose themselves and their staff to hazardous substances while taking every precaution to ensure that the administered drugs are protected from contamination. The guidelines that follow have been developed in response to requests for assistance from a number of disparate sources, including health care personnel concerned with the potential harm that may result from exposure to cytotoxic drugs (CDs).

The guidelines (not to be confused with mandatory standards) are designed to assist all health care personnel, including physicians, nurses, pharmacists, aides and the numerous and diverse health care support staff who may be exposed to cytotoxic drugs through inhalation, skin absorption or trauma. We are aware that the drugs are prepared and administered in a wide variety of places, ranging from doctors' private consulting rooms to large pharmaceutical preparation rooms. We cannot cover every situation, but offer what we believe is the most reasonable course of action, whether dealing with the drugs as a routine health care procedure or during an emergency situation such as a large spill. Because of the widespread use of these drugs and the general lack of written policies or standard operating procedures in most facilities, we hope this instruction will fulfill the need to provide a description of the potential hazards of CDs, as well as the proper safety procedures, personal protective equipment and engineering controls for CDs that will reduce contamination of workers.

The reader must be reminded that persons involved in health care, whether professionals or nonprofessionals, are workers, and that the hospital, clinic, pharmacy or even consulting room is a workplace. Some of the methods recommended may seem to be more suited to a nonclinical workplace. In particular, the suggested use of goggles where appropriate and a respirator where a biological safety cabinet is not available. Such recommendations must be considered in the light in which they are proffered; health professionals must walk the narrow line between alarming their patients unnecessarily and protecting their own health. We are aware of incidents where nurses, ridding syringes of air, inadvertently sprayed their eyes with a drug aerosol. If health professional are ROUTINELY careful during such procedures, goggles will not be essential. Similarly, if a biological safety cabinet is not in place, we know of no other way of avoiding inhalation of a carcinogen other than by an appropriate respirator.

Two elements are essential to ensure proper workplace practices:

0 Education and training of all staff involved in handling any aspect of CDs.

0 A biological safety cabinet (BSC). The costs of implementing the former and installing the latter are relatively minor. The potential benefits are major.

Finally, we are grateful to our reviewers including those who reviewed the document informally and whom we have not acknowledged by name. We have incorporated as many of their recommendations and/or corrections as possible and we are aware of the need to revise and update this document from time-to-time.

Ralph E. Yodaiken, M.D., M.P.H. Director Medical Officer Office of Occupational Medicine Office of Occupational Medicine Occupational Safety and Health Occupational Safety and Health Administration Administration

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LIST OF ABBREVIATIONS

ANSI American National Standards Institute

BSC Biological Safety Cabinet

CD Cytotoxic Drug

EPA Environmental Protection Agency

HEPA High Efficiency Particulate Air

NIOSH National Institute for Occupational Safety and Health

PAPR Powered Air-Purifying Respirator

PVC Polyvinylchloride

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I. INTRODUCTION.

A. Current practices in the preparation, storage, administration, and disposal of the widely used group of antineoplastic (anti-new growth; anti-cancer) drugs, also called cytotoxic drugs (CDs) because they are toxic to cells, may expose pharmacists, nurses, physicians, and other health care workers to high environmental levels of these drugs.

1. Although little research has been done on the long-term risks at the levels of exposure encountered by unprotected health care workers, these drugs have been associated with human cancers at high (therapeutic) levels of exposure (See references 4, 11, 17, 18, 39, 41, 44, 45 and 61.), and are carcinogens and teratogens in many animal species. (See reference 18,61.)

2. Under current work practices, CDs have demonstrated the ability to cause elevations in sister chromatid exchanges and chromosome breakage in circulating lymphocytes and mutagenic activity in urine.

3. In addition, many of these drugs have been shown to cause a variety of acute effects in humans, such as localized skin necrosis (death of tissue) after surface contact with abraded skin (See reference 42.), or damage to normal skin. (See reference 47.)

B. Several sets of work practice guidelines have been issued by various professional bodies in the U.S. and by foreign institutions. (See references 7, 10, 12, 14, 28, 29, 31, 32, 35, 48, 52, 53, 56 and 63.) The volume of requests to OSHA indicates a broader interest among administrators and health care professionals who are not aware of, or who have not had access to these guidelines. Moreover, recent surveys reveal that there is little standardization of work practices and that proper practices and adequate protective equipment are not being currently utilized. Therefore, OSHA considers implementation of its work practice guidelines important for protecting workers against these serious occupational hazards. The following information (II, III and IV) will:

1. Provide a brief summary of the short-term and long-term hazards now known to be associated with the drugs.

2. List work practice guidelines that will limit exposure of workers to CDs, and the equipment necessary to carry out these practices properly.

3. List the CDs currently in use.

C. These guidelines are addressed to persons who have a broad spectrum of qualifications and experience, and some readers may find them repetitious and too detailed. However, even the most qualified professionals do not always observe elementary and essential workplace safety practices; therefore, we have taken the precaution of covering as much detail as considered essential to good work practice. Any repetition is an attempt to make each section complete.

II. CYTOTOXIC DRUGS AND SITES OF POTENTIAL RISKS.

A. Cancer Chemotherapy.

1. The attempt to stop or reverse the growth of malignant growing cells with drugs, began in the late 1940's, when nitrogen mustard and its derivatives were first used therapeutically. Currently, approximately 30 cancer CDs are available commercially in the U.S.; these are administered to an estimated 200,000-400,000 patients annually. Consequently, several thousand health care employees may be exposed yearly to a variety of risks.

2. From the time of their initial use, these drugs were known to be potentially harmful to workers dealing with them. The nitrogen mustard drugs are extremely irritating to mucous membranes, eyes, and skin. (See reference 24.) Other agents developed later on, such as fluorouracil, also have well-known topical effects. (See reference 47.) Spills of agents such as doxorubicin onto abraded skin can lead to severe soft-tissue injury, such as necrosis and sloughing of exposed areas (See reference 42.) as well as possible effects on the fetus. (See reference 50.) Symptoms such as lightheadedness, dizziness, nausea, headache, and possible

allergic reaction also have been described in nurses after the preparation of antineoplastic drugs, and their subsequent administration, in unventilated areas. (See references 6 and 40.)

3. The potential for harmful effects developing over a longer term is also well-known. Most CDs either bind directly to genetic material, in the cell nucleus, or affect cellular protein synthesis, and may therefore damage growth and reproduction of normal cells as well.

B. Various Studies.

1. One study, on chlorambucil, shows that chromosome damage to cells among people to whom the drug is administered is related to both dose and duration of the therapy and is cumulative. (See reference 36.) Evidence that these drugs induce malignant tumors in animals,

and neoplasms and leukemias in the human beings to whom they are administered, was available as early as the 1940's and 50's, and continued to mount in the succeeding decades. (See references 41, 44, 45 and 61.)

2. In vivo, in vitro, and human studies have implicated antineoplastic drugs in chromosomal damage and teratogenesis (malformation) as well as carcinogenesis (cancer induction). (See references 13, 36, 43, 45 and 50.) Testicular and ovarian dysfunction including permanent sterility have been demonstrated in male and female patients respectively who have received CDs either singly or in combination. Congenital malformations have been attributed to fluorouracil. (See reference 50.) A study from Finland also indicates an association between CDs and fetal malformations in pregnant nurses who work with CDs. (See reference 13.) While this needs to be confirmed, fetal loss associated with cytotoxic drugs has been reported among nurses in Finnish hospitals. (See reference 43a.)

3. Finally, organ damage also has been associated with CDs, not only in animals (See references 27 and 51.) and human patients receiving long-term therapy (See reference 27.), but also among employees. Liver damage has been reported in nurses working in an oncology

ward; the damage appeared to be related to the intensity and duration of work exposure. (See reference 49.)

4. Various studies have shown that current practices expose workers to significant amounts of these drugs, and that these drugs may increase the risk of long-term harm. Detectable amounts of various drugs have been found in the urine of health care workers handling them. (See reference 15.) Attempts also have been made to show that mutagenic activity in the urine and chromosome damage are increased in workers handling CDs without proper protection and safe workplace practices.

a. Pharmacists who reconstituted anti-cancer drugs showed increasingly mutagenic urine over the period of exposure; when they stopped handling the drugs, mutagenic activity fell within 2 days to the level of unexposed controls. (See reference 25.) Also, the installation of a vertical flow containment hood, or biological safety cabinet (BSC), has been shown to reduce the levels of mutagenic substances in the urine of pharmacy workers preparing CDs. (See reference 1.)

b. A variety of chemical or physical agents have been associated with mutagenesis. Hair dyes and cigarette smoke are two that may concern health care personnel. Smokers exposed to CDs exhibit greater urine mutagenicity than smokers who did not

handle CDs (See reference 3.). Smokers who do not take simple protective measures such as gloving and handwashing may take in additional amounts of the drug orally through contaminated cigarettes. Other studies have shown a definite and significant reduction of urine mutagenicity in both smokers and nonsmokers who work with the agents when their work practices have improved. (See reference 21.)

c. Though the levels of absorption that may have taken place during work is hard to assess, it is essential to minimize exposure to these potent carcinogens and teratogens.

III. CURRENT PRACTICES IN PREPARATION, USAGE AND DISPOSAL:

POINTS OF EXPOSURE FOR PERSONNEL.

NOTE: The risks to workers handling CDs are a combined result of the drugs' inherent toxicity and the extent to which workers are directly exposed to CDs on the job. The main routes of exposure are through the inhalation of drug dusts or droplets, absorption through the skin, and ingestion through contact with contaminated food or cigarettes. Opportunity for exposure may occur at many points in the handling of these drugs.

A. Survey of Current Work Practices

A 1982 survey of 21 U.S. cancer centers revealed little standardization of work practices, equipment or training for personnel administering injectable CDs. (See reference 23.) In only 10 centers were the necessary BSCs used for preparation. A 1983 survey of 10 hospital oncology clinics (See reference 33.) showed that nine did not use BSCs for preparation, and that use of gloves was routine in only three clinics. Eating and drinking occurred in seven of the preparation rooms, greatly increasing the probability of oral intake of the drugs. Wastes were disposed of in covered receptacles in only seven of the preparation rooms. Air monitoring showed significant air levels of the two drugs in most common use in these clinics. Judging by these studies, the need for the adoption of guidelines, the provision of proper protection and equipment, and for appropriate training, is crucial.

B. Pharmacy or Other Preparation Areas.

1. In large oncology centers, CDs are usually prepared in the pharmacy by pharmacy personnel, but in many hospitals and smaller centers they may be prepared by physicians or nurses in patient-care or staff areas that are often inadequately ventilated. (See reference 6.) Many CDs must be dissolved, transferred from one container to another, or

manipulated before they can be administered to patients. Even if care is taken, opportunity for absorption through inhalation or direct skin contact may occur. (See references 14 and 33.)

Examples of manipulations that can cause splattering, spraying and aerosol generation include:

a. The withdrawal of needles from drug vials;

b. Drug transfers using syringes and needles or filter straws;

c. The breaking open of ampules; and,

d. The expulsion of air from a drug-filled syringe.

2. Aerosols can be generated by these activities, exposing not only the employee immediately involved, but also staff and patients in the surrounding areas. (See reference 63.) A properly enclosed and ventilated work area, respiratory and skin protection, and training in the proper handling of these drugs is essential. (See references 2, 6, 33, 53 and 63.) Smoking, drinking, applying cosmetics, and eating where these drugs are prepared, stored, or used should never take place, as these practices greatly increase the chance of exposure. (See reference 63.)

3. Even in the pharmacy, where protective clothing and gloves are worn and careful aseptic techniques used as a matter of course, opportunities for exposure can occur. A horizontal-air-flow, clean work bench is often used to provide an aseptic environment for the preparation of injectable drugs. Because this unit provides a flow of filtered air originating at the back of the workspace and exiting toward the employee using the unit, it provides protection for the drugs but increases the likelihood of exposure to the preparer of the drugs and the other personnel who may be in the room. The preparer and others are exposed to the aerosols generated during preparation procedures.

a. Class II vertical flow containment hoods, also called Biological Safety Cabinets (BSCs), provide appropriate protection. (See references 2 and 8.)

b. Type A BSCs are the minimal requirement. Type A hoods that are vented (some of these are now classified as Type B3) are preferred. (See reference 31.)

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C. Administration of Drugs to Patients.

1. The administering of drugs to patients is generally carried out by nurses or physicians injecting the drug into the IV line, clearing air from the syringe or infusion line, and leakage at the tubing, syringe, or stopcock connection present opportunities for both skin contact and aerosol generation leading to respiratory exposure. Clipping used needles and crushing used syringes, standard practice in some work situations, may produce a considerable aerosol. (See reference 33.)

2. Excreta from patients who have received certain antineoplastic drugs may contain high concentrations of the drug or hazardous metabolites. For example, patients receiving cyclophosphamide excrete large amounts of the drug and mutagenic metabolites (See references 19 and 46.) Patients treated with cis-platin excrete potentially hazardous amounts of the drug. (See reference 55) Handling the urine or urine-soaked sheets may lead to significant exposure. Nursing and housekeeping personnel may be exposed to CDs if they are not made aware of the potential hazard and not trained to take precautions.

D. Disposal of Drugs and Contaminated Materials.

1. Materials that have been used in the preparation and administration of CDs, such as gloves, gowns, syringes or vials, present a possible source of exposure or injury to support and housekeeping staff, as well as other health care workers not involved with their preparation and administration. The use of properly labeled, sealed and covered containers, handled only by trained and protected personnel, should be routine. Spills also represent a hazard, and all employees should be familiar with appropriate spill procedures for their own protection.

IV. GUIDELINES FOR THE HANDLING OF CDs.

A. Drug Preparation.

1. Personal Protective Equipment.

a. New research indicates that surgical latex gloves are less permeable to many CDs than the polyvinylchloride (PVC) gloves recommended in older guidelines. (See references 5, 22 and 31.) Surgical latex gloves therefore should be used for the preparation of CDs unless the manufacturer specifically

stipulates that some other glove provides better protection (Powdered gloves should never be used.) A double layer of gloves is substantially less permeable and should be used if doublegloving does not interfere with technique. Because all gloves are to some extent permeable and their permeability increases with time (See reference 5.), they should be changed regularly (hourly is preferable) or immediately if they are torn or punctured.

b. A protective disposable gown made of lint-free low permeability fabric with a closed front, long sleeves, and elastic or knit-closed cuffs must be worn, with the cuffs tucked under the gloves. Gowns and gloves in use should not be worn outside the preparation area.

c. A BSC is essential for the preparation of CDs, but where one is not currently available, a respirator with a high efficiency filter, preferably a Powered Air-Purifying Respirator (PAPR) used by personnel who have been trained to use respirators and provides the best protection until the BSC is installed. We realize that this would be a departure from usual hospital/clinic/pharmacy procedures, but in this case we are dealing with a variety of known carcinogens and therefore appropriate preventive measures are necessary.

d. Surgical masks do not protect against the breathing of aerosols. A plastic face shield or splash goggles complying with ANSI 28.7.1-1968 criteria also should be worn if a BSC is not in use and an eye wash fountain made available. (See Preface.)

2. Preparation Area. It is suggested that all CDs be prepared in one centralized area. If this is not practical, the number of areas used for preparation should be minimized. If possible, an isolated BSC, where only CDs are prepared, should be designated. Warning signs designating the area as a cytotoxic drug preparation area that should not be entered by unauthorized staff should be clearly posted. Spill procedures should also be posted. Eating, drinking, smoking, chewing gum, applying cosmetics, and storing food in or near the preparation area should be forbidden.

a. A Class II BSC that meets current National Sanitation Foundation Standard 49 (See reference 30.) must be used. (See references 2, 29, 31, 32 and 38.) The blower on the vertical airflow hood should be on at all times, 24 hours a day, 7 days a week. Venting to the outside is preferable where feasible, and

is required with a Type B BSC. If the hood has an outside exhaust system, filtered exhaust to the outside should be at an appropriate level and away from air intake units. BSCs should be certified by a qualified technician every 6 months or any time the cabinet is moved.

b. Technicians servicing these cabinets or changing High Efficiency Particulate Air (HEPA) filters should be warned of the nature of CDs and should use the same personal protective equipment as an employee dealing with a large spill. (See A.1.) Special containment procedures that should be used to avoid contamination, both of the service personnel and the room, are detailed in reference 2.

c. All used gowns and gloves and disposable materials used in preparation should be disposed of according to the hospital's toxic waste procedures and as described under "Waste Disposal." (See D., page A-14.)

3. Preparation Equipment. Work with cytotoxics must be carried out in a BSC on a disposable, plastic-backed paper liner, which should be changed after preparation is completed for the day, or after a shift, whichever comes first. Syringes and IV sets with Luer-lock fittings should always be used, and syringes should always be large enough so that they need never be more than three-fourths full. A nonsplash disposal collection vessel such as a plastic or metal tray lined with sterile gauze pads should be at hand to collect excess solution. All necessary items should be placed within the BSC before work is begun, and all extraneous items should be kept out of the work area in order to avoid contamination.

a. The work areas should be provided with a closable, puncture-resistant, shatter-proof container for disposal of contaminated sharp/breakable materials. Labeled sealable plastic or wire tie bags, as described under "Waste Disposal," should be at hand so that all boxes and other contaminated materials, including gloves, gowns and paper liners, can be immediately placed in them and disposed of according to the hospital's toxic waste procedures.

b. The cabinet should be cleaned daily with 70-percent alcohol, and decontaminated weekly, whenever spills occur, or when the cabinet requires service or certification. Ordinary decontamination procedures, which include fumigation with a

germicidal agent, are inappropriate in a BSC used for CDs because such procedures do not deactivate the drugs and in addition may cause chemical reactions (See reference 38.) Decontamination should consist of surface cleaning with high pH agents followed by thorough rinsing. Removable worktrays, if present, should be removed, and the back of the worktray and the sump below should be included in the cleaning.

4. Work Practices in Preparation. Proper aseptic techniques are essential for worker protection, but because it is generally accepted that these techniques are essential for patient safety, it is assumed they will already be standard practice in drug preparation. Therefore, general principles of aseptic technique will not be detailed here. It should be noted, however, that BSC benches differ from horizontal flow units in several ways, thus requiring special precautions; manipulations should not be performed close to the work surface, and unsterilized items, including liners and hands, must be kept downstream from the working area. Operators should be trained in these techniques (See reference 38.)

a. Syringes and IV Bottles. These should be labeled with patient's name and room number, drug name and quantity per total volume, route of administration, date and time prepared, dose, expiration date, and storage requirements if the drug is not to be transported immediately. All syringes, IV bags and bottles containing CDs should be labeled with a distinctive warning label such as "Chemotherapy -- handle with gloves -- dispose of properly."

b. Needles. The use of large-bore needles, #18 or #20, will ensure that high-pressure syringing of the solutions is avoided. However, some experienced personnel believe that large-bore needles are more likely to drip. The needle should be chosen with these advantages or disadvantages in mind.

(1) Drug administration sets should be attached and primed within the hood, before the drug is added to the fluid, to obviate the need to prime the set in a less well-controlled environment, and to ensure that any fluid that escapes during priming contains no drug.

(2) All syringes and needles used in the course of preparation should be placed in the puncture-proof container for disposal without being crushed, clipped or capped.

(Some professionals believe that capping the needle before disposal reduces the generation of aerosols; others warn that it increases the chances of needle-sticks.)

c. Handling Vials. Medication vials should not be vented unless a BSC is used as the work area or unless a hydrophobic filter-needles unit is available to eliminate pressure. (See reference 16.) Syringe and needle fittings should be of the Luer-lock variety.

(1) Diluent should be added slowly to the vial by alternately injecting small amounts, allowing displaced air to escape into the syringe. (All the diluent should not be injected at once: a large volume of displaced air will cause the syringe's plunger to back up and possibly spray the drug or cause leakage around the needles.) When all diluent has been added, a small amount of additional air may be withdrawn to create a negative pressure in the vial, but this should not be expelled into room air because it may contain drug residue. It should either be injected into a vacuum vial or remain in the syringe to be discarded.

(2) A sterile gauze should be wrapped around the needles and vial top when withdrawing solution (employees should take care to avoid needle-sticks during this procedure). The drug should be withdrawn from the vial while negative pressure is maintained. (The technique has been described in reference 62.) If this use of negative pressure is considered impossible, a syringe should be filled with air equal to the volume of drug required, and the solution withdrawn by alternately injecting small amounts of air into the vial and withdrawing equal amounts of liquid until the required volume is withdrawn. The drug should be cleared from the needle and hub (neck) of the syringe before separating to avoid spraying on separation.

d. Handling Ampules. Any material remaining in the top of an ampule should be tapped down before it is opened. A sterile gauze pad should be wrapped around the ampule neck before breaking the top to protect against cuts and to catch aerosolized material.

(1) The ampule top should not be removed close to the employee's face. If diluent is to be added, it should be injected slowly down the inside wall of the ampule. The ampule should be tilted gently to ensure that all the powder is wet before agitating it to dissolve the contents.

(2) The needle should be held vertically with the needle upwards; the syringe should be tapped to remove air bubbles and the air bubbles expelled into sterile gauze, not into the air.

B. Drug Administration.

1. Personal Protective Equipment. Consideration should be given by personnel administering CDs to wearing the following items: a. A gown as described under "Drug Preparation". b. Disposable surgical latex gloves; and, double if appropriate.

c. A surgical mask also may be used, but it should be noted that this provides only minimal protection against CD aerosols and is no substitute for the proper procedures, which have been described.

To avoid alarm or misunderstanding, patients should be informed that any protective equipment in use is necessary for workers to be protected against the directly irritating effects of the drugs to eyes and skin (long-term as well as short-term effects of the drug already should have been discussed with patients in terms of potential risks for themselves).

2. CD Administration Equipment. Protective equipment and other necessary items may be packaged together and labeled as a CD administration kit, which should include:

a. Personal protective equipment as described in IV.A.1;

b. Gauze (4 x 4) for cleanup;

c. Alcohol wipes;

d. Disposable plastic-backed absorbent liner;

e. Empty vials to be used as receptacles for excess drug solution;

f. Puncture-proof container for needles and syringes;

g. A 4-mil sealable plastic or wire tie bag (with warning label) large enough to contain waste materials, and accessory warning labels;

i. If additional preparation that cannot be done in a BSC is required before administration, a respirator (See IV.A.1.) used perhaps in a specially assigned side room, splash-proof goggles and a 32-oz. bottle of sterile isotonic eye and face wash should be readily available for emergencies.

3. Work Practices. Personnel shall follow safe work practices which include:

a. Hands should be washed before putting on gloves. Gowns or gloves that become contaminated should be changed immediately.

b. Infusion sets and pumps, which should have Luer-lock fittings, should be watched for signs of leakage during use. A plastic-backed absorbent pad should be placed under the tubing during administration to catch any leakage. The line should be bled into a gauze inside a sealable plastic bag.

c. Priming should be carried out under a BSC but if for some reason it must be carried out at the bedside, when priming IV sets or expelling air from syringes, a gauze in a plastic bag should be used as a receptacle. Syringes, IV bottles and bags, and pumps should be wiped clean of any drug contamination with an alcohol wipe. Needles and syringes should not be crushed or clipped, but should be placed in a puncture-resistant container to go into the CD disposal bag, along with all other contaminated materials. The bag should be disposed of in accordance with the hospital's toxic waste disposal procedures.

d. Protective goggles should be wiped several times with an alcohol wipe and properly rinsed. Hands should be washed after removal of gloves. All gauze and alcohol wipes must be put in an appropriate container for disposal.

NOTE: Currently, a large number of investigational CDs are under clinical study in health care facilities. Personnel not directly involved in the investigation should not administer these drugs unless they have received adequate instructions regarding safe handling procedures.

C. Caring for Patients Receiving CDs.

1. Personal Protective Equipment. Personnel dealing with blood, vomitus, or excreta from patients who have received CDs in the last 48 hours should wear surgical latex gloves and disposable gowns, to be discarded after each use as detailed under Waste Disposal. (No protective equipment is necessary for ordinary patient contact for employees not dealing with drug administration or bodily secretions.) Hands should be washed after removal of gloves or after contact with the above substances.

2. Linen. Linen contaminated with CDs, blood, vomitus, or excreta from a patient who has received CDs up to 48 hours before should be placed in a specially marked laundry bag and the laundry bag placed in a labeled impervious bag. This laundry bag and its contents should be prewashed, and then the linens should be added to other laundry for an additional wash. Laundry personnel should wear surgical latex gloves and gowns while handling this material. (No additional gain is made by autoclaving items contaminated with CDs, unless they are also contaminated with infectious waste.)

D. Waste Disposal.

1. Equipment. Cytotoxic waste disposal sealable plastic or wire tie bags of 4-mil thick polyethylene or 2-mil polypropylene, labeled with a cytotoxic hazard label and colored differently from other hospital trash bags, should be used for the routine accumulation and collection of used containers, syringes, discarded gloves, gowns, goggles and any other disposable material. All CD-related wastes should be put into these bags, and nothing else.

a. Needles, syringes, and breakable items should be placed in a plastic vial or puncture proof box before they are placed into the bag; needles should not be clipped or capped nor syringes crushed. The bag should be kept inside a covered waste container clearly labeled "cytotoxic waste only."

b. At least one such receptacle should be located in every area where the drugs are prepared or administered so that the waste need not be moved from one area to another. The bag should be sealed when it is filled and the carton should be taped.

2. Handling. Housekeeping personnel must wear gowns and surgical latex gloves when handling the waste containers, and should be instructed on the necessity of handling this waste with care and on procedures governing spills and leaks.

3. Disposal. These wastes must be handled separately from other hospital trash, and must be regarded as toxic (hazardous) wastes and disposed of in accordance with applicable regulations, (See reference 57 and/or more recent publications.)

a. Disposal in a licensed sanitary landfill for toxic wastes is an acceptable alternative. If waste is to be picked up by a commercial disposal firm, the company must be licensed, and the waste must be held in a secure area in covered, labeled drums lined with 6.5-mil polyethelene liners.

b. Chemical inactivation of CDs is often ineffective and may produce by-products that are more mutagenic than the parent drug. (See reference 31.) Therefore, with the exception of nitrogen mustard, which can be safely inactivated by sodium thiosulfate, chemical inactivation should be avoided until safe chemical procedures are developed.

E. Spills.

1. General Procedures. Spills and breakages should be cleaned up immediately by a properly protected person trained in the appropriate procedures. Broken glass should be carefully removed. A spill should be identified with a warning sign so that other persons in the area will not be contaminated.

2. Personnel Contamination. Overt contamination of gloves or gowns, or direct skin or eye contact should be treated as follows:

a. Immediate removal of the gloves or gown;

b. Wash the affected skin area immediately with soap (not germicidal cleaner) and water. For eye exposure, immediately flood the affected eye with water or isotonic eyewash designated for that purpose for at least 5 minutes;

c. Obtain medical attention immediately.

3. Cleanup of Small Spills. Spills of less than 5 ml or 5 gm outside a hood should be cleaned immediately by personnel wearing gowns and double surgical latex gloves and eye protection.

a. Liquids should be wiped with absorbent gauze pads; solids should be wiped with wet absorbent gauze. The spill areas then should be cleaned (three times) using a detergent solution followed by clean water.

b. Any broken glass fragments should be placed in a small cardboard or plastic container and then into a CD disposal bag, along with the used absorbent pads and any noncleanable contaminated items.

c. Glassware or other contaminated reusable items should be placed in a plastic bag and washed in a sink with detergent by a trained employee wearing double surgical latex gloves.

4. Cleanup of Large Spills. For spills of amounts larger than 5 ml or 5 gm, spread should be limited by gently covering with absorbent sheets or spill-control pads or pillows or, if a powder is involved, with damp cloths or towels. Be sure not to generate aerosols. Access to the spill areas should be restricted.

a. Protective apparel should be used (See E.3.) with the addition of a respirator when there is any danger of airborne powder or an aerosol being generated. The dispersal of CD particles into surrounding air and the possibility of inhalation is a serious matter and should be treated as such.

b. Chemical inactivators, with the exception of sodium thiosulfate, which can be used safely to inactivate nitrogen mustard, may produce hazardous by-products (See reference 31.) and should not be applied to the absorbed drug.

c. All contaminated surfaces should be thoroughly cleaned with detergent solution and then wiped with clean water. All contaminated absorbents and other materials should be disposed of in the CD disposal bag.

5. Spills in Hoods. Decontamination of all interior hood surfaces may be required after the above procedures have been followed. If the HEPA filter of a hood is contaminated, the unit must be labeled "Do not use--contaminated," and the filter must be changed and disposed of properly as soon as possible by trained personnel wearing protective equipment. Protective goggles should be cleaned with an alcohol wipe after the cleanup.

6. Spill Kits. Spill kits, clearly labeled, should be kept in or near preparation and administrative areas. It is suggested that kits include a respirator, chemical splash goggles, two pairs of gloves, two sheets (12 x 12) of absorbent material, 250-ml and 1-liter spill control pillows and a small scoop to collect glass fragments. Absorbents should be incinerable. Finally, the kit should contain two large CD waste-disposal bags.

F. Medical Surveillance.

1. Routine Procedures.

a. All employees with potential exposure to CDs through preparation, administration, housekeeping, waste disposal, transport or storage of CDs in addition to being fully informed of all potential dangers and the need to take adequate precautions, should have a preplacement physical examination. Care should be taken to note any risk factors in the history, and a complete blood count including differential may be taken to provide a baseline.

b. At present, no techniques exist for screening individual employees that would indicate the level of exposure reliably, though group screening for urine mutagenesis or for the presence of certain CDs in the urine may be recommended by medical staff.

c. A registry of all staff who routinely prepare or administer CDs should be permanently maintained, with the number recorded of each drug the employee has prepared or administered if this is feasible.

2. Acute Exposures. After an acute exposure, the treatment procedure noted under section E. "Spills" should be followed, and the employee should receive a physical examination with particular attention to the eyes, buccal and nasal mucous membranes, and the skin. Acute exposures include needle-sticks from needles attached to syringes containing the drugs. However, needle-sticks received by laboratory personnel dealing with the blood of patients being treated with CDs do not constitute a special hazard and require only ordinary needle-stick procedures. Needle-sticks as with all other acute exposures should be recorded both on incident forms and in the employee's medical record.

3. Pregnancy. On the basis of the available evidence, it seems reasonable to assume that if appropriate procedures are followed, and proper equipment and protection are provided, reproductive hazards will be reduced.

a. Employees should be fully informed of the potential reproductive hazard and, if they so request, staff members who are pregnant or breast-feeding should be transferred to

comparable duties that do not involve handling CDs.

b. A similar policy covering male or female personnel who are actively trying to conceive a child should be established.

G. Storage and Transport.

1. Storage Areas. Access to areas where CDs are stored should be limited to authorized personnel. Such areas should be posted with a large warning sign, a list of all drugs covered by CD policies, and a sign detailing spill procedures. Facilities used for storing CDs, if possible, should not be used for other drugs, and should be designed to prevent containers from falling to the floor. Warning labels should be applied to all CD containers, as well as the shelves and bins where these containers are permanently stored.

2. Receiving Damaged CD Packages. Damaged cartons should be opened in an isolated area by an employee wearing the same protective equipment as is used in preparation (including a PAPR) without a hood.

a. Broken containers and contaminated packaging mats should be placed in a puncture-resistant receptacle and then in CD disposal bags, which should be closed and placed into appropriate receptacles, both of which are described under section D. "Waste Disposal."

b. The appropriate protective equipment and waste disposal materials should be kept in the area where shipments are received, and employees should be trained in their use and the risks of exposure to CDs.

3. Transport. Within the medical facility, drugs should be securely capped or sealed and packaged in impervious packing material for transport.

a. Personnel involved in transporting CDs should be cautioned and trained in the necessary procedures should a spill occur, including sealing off the contaminated area and calling for appropriate assistance.

b. All drugs should be labeled with a warning label and clearly identified as cytotoxics. Transport methods that produce stress on contents, such as pneumatic tubes, should not be used to transport CDs.

H. Training and Information Dissemination.

1. Training and Personnel. All personnel involved in any aspect of the handling of CDs (shipment-receiving personnel, physicians, nurses, pharmacists, housekeepers, employees involved in the transport or storage of drugs) must receive an orientation on CDs, including their known risks, relevant techniques and procedures for their handling, the proper use of protective equipment and materials, spill procedures, and medical policies (including those dealing with pregnancy and with staff actively trying to conceive children). Prospective temporary and permanent employees who will be required to work with CDs should receive notice of this requirement. Medical staff who are not hospital employees should be informed of hospital policies and of the expectation that they will comply with these policies.

2. Evaluation of Staff Performance. Knowledge and competence of personnel should be evaluated after the first orientation or training session, and then yearly, or more often if a need is perceived. Evaluation may involve direct observation of an individual's

performance on the job. In addition, non-CD solutions may be used for evaluation of preparation technique; quinine which will fluoresce under ultraviolet light, provides a easy mechanism for detection of clumsy technique.

3. Information. The pharmacy should maintain a loose-leaf, index card or computerized file containing information on the toxicity, acute exposure treatment, chemical inactivators, solubility and stability of CDs used in the institution. This file should be available to employees. (Any special instructions for the handling of specific drugs should be included in the orientation and training sessions.) If drugs are administered in a centralized area, such as an oncology floor, a copy of this file should be available there. Summaries of relevant procedures should be posted in the appropriate work areas. A complete policy and procedures manual should be made available to all employees.

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ANTINEOPLASTIC AGENTS 1/ _____

ALKYLATING AGENTS TRADE NAMES _____ _____

CIS-PLATIN (PLATINOL)

CYCLOPHOSPHAMIDE (CYTOXAN) (NEOSAR)

NITROGEN MUSTARD (MUSTARGEN)

TRIETHYLENE THIOPHOSPHORAMIDE (THIOTEPA)

CARMUSTINE (BiCNU)

STREPTOZOCIN (ZANOSAR)

BUSULFAN

CHLORAMBUCIL

CCNU BELUSTINE

MELPHALAN (ALKERAN)

MYLERAN

TEOSULFAN

URACIL MUSTARD URAMUSTINE

CHLORNAPHAZIN

DACARBAZINE DIC

1/ This is not a complete list and should be periodically updated.

ANTIMETABOLITES _____

CYTOSINE ARABINOSIDE (CYTOSAR-U)

FLUOROURACIL (ADRUCIL)

METHOTREXATE (MEXATE)(FOLEX)

MERCAPTOPURINE

AZATHIOPRIME

PROCARBAZINE MATULANE

ANTIBIOTICS _____

DOXORUBICIN (ADRIAMYCIN)

BLEOMYCIN (BLENOXANE)

DACTINOMYCIN (ACTINOMYCIN-D) (COSMEGEN)

DAUNORUBICIN (CERUBIDINE)

MITHRAMYCIN (MITHRACIN)

MITOMYCIN (MUTAMYCIN)

MITOTIC INHIBITORS (Vinca alkaloids) _____

VINCRISTINE (ONCOVIN)

VINBLASTINE (VELBAN)

ETOPOSIDE (VP-16-213) (VePESID)

MISCELLANEOUS

L-ASPARAGINASE (ELSPAR)

DACARBAZINE (DTIC)

INVESTIGATIONALS

AZACYTIDINE

AMSACRINE

MELPHALAN

VM-26

IFOSFAMIDE

MITOXANTRONE

VINDESINE

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Appendix B

Dear Health Care Professional:

The Occupational Safety and Health Administration (OSHA) is aware that health care professionals may inadvertently expose themselves to hazardous substances while administering antineoplastic drugs. The Agency has developed the enclosed document, suitable for direct distribution to your employees, describing the hazards of antineoplastic drugs, identifying the high-risk workers and recommending control work practice techniques that can be implemented to help prevent adverse health effects.

Local OSHA offices have recently assumed wider responsibilities for serving as a safety and health resource center for the communities they serve. Therefore, as your local OSHA contact, I am providing this document to you for the information of your employees. In addition, I would like to offer any assistance we might provide on any other safety and health topic of concern to you. Please feel free to contact me at:

(Regional/Area Office) (Address) (Telephone)

Sincerely,

(Name) (Title)

Enclosure

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