This Alert supersedes the previous prepublication version that was placed on the National Institute for Occupational Safety and Health Web site on March 25, 2004. This Alert was modified slightly based on public comments received since this date. The Alert is currently being edited and prepared for publication. If you have any further comments, please forward them to tconnor@cdc.gov , no later than July 6, 2004.

FOREWORD

This document is a prepublication version of the Alert from the National Institute for Occupational Safety and Health (NIOSH) entitled *Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Healthcare Settings*. This Alert was developed with input from the NIOSH Working Group on Hazardous Drugs. Two earlier drafts of the document were reviewed by external experts in healthcare, academia, government, labor, and industry. Their comments have been incorporated as appropriate.

The purpose of this Alert is to increase awareness among healthcare workers and their employers about the health risks posed by working with hazardous drugs and to provide them with measures for protecting their health. Healthcare workers who prepare or administer hazardous drugs or who work in areas where these drugs are used may be exposed to these agents in the air or on work surfaces, contaminated clothing, medical equipment, patient excreta, and other surfaces. Studies have associated workplace exposures to hazardous drugs with health effects such as skin rashes and adverse reproductive outcomes (including infertility, spontaneous abortions, and congenital malformations) and possibly leukemia and other cancers. The health risk is influenced by the extent of the exposure and the potency and toxicity of the hazardous drug. To provide workers with the greatest protection, employers should (1) implement necessary administrative and engineering controls and (2) assure that workers use sound procedures for handling hazardous drugs and proper protective equipment. The Alert contains a list of drugs that should be handled as hazardous drugs.

This Alert applies to all workers who handle hazardous drugs (e.g., pharmacy and nursing personnel, physicians, operating room personnel, environmental services workers, veterinary care workers, and shipping and receiving personnel). Although not all workers in these categories handle hazardous drugs, the number of exposed workers exceeds 5.5 million. The Alert does not apply to workers in the drug research and development and manufacturing sectors.

The production, distribution, and application of pharmaceutical medications are part of a rapidly growing field of patient therapy. New areas of pharmaceutical development will bring fundamental changes to methods for treating and preventing diseases. Both traditional medications and bio-engineered drugs can be hazardous to healthcare workers who must handle them. This NIOSH Alert will help make workers and employers more aware of these hazards and provide the tools for preventing exposures.

John Howard, M.D.
Director
National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention

Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Healthcare Settings

June 7, 2004

ORDERING INFORMATION

To receive documents or other information about occupational safety and health topics, contact the National Institute for Occupational Safety and Health (NIOSH) at

NIOSH—Publications Dissemination
4676 Columbia Parkway
Cincinnati, OH 45226-1998

Telephone: 1-800-35-NIOSH (1-800-356-4674)
Fax: 513-533-8573
E-mail: pubstaft@cdc.gov

Or visit the NIOSH Web site at www.cdc.gov/niosh

DHHS (NIOSH) Publication Number 2004-XXXdate

Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Healthcare Settings

Warning!

Healthcare workers who prepare or administer hazardous drugs or who work in areas where these drugs are used may be exposed to these agents in air or on work surfaces, contaminated clothing, medical equipment, patient excreta, or other sources. Studies have associated workplace exposures to hazardous drugs with health effects such as skin rashes and adverse reproductive events (including infertility, spontaneous abortions or congenital malformations) and possibly leukemia and other cancers. The health risk is influenced by the extent of the exposure and the potency and toxicity of the hazardous drug. Potential health effects can be minimized through sound procedures for handling hazardous drugs, engineering controls and proper use of protective equipment to protect workers to the greatest degree possible.

SCOPE

The purpose of this Alert is to warn healthcare workers of the potential hazards associated with working with *hazardous drugs*, and to alert them and their employers of appropriate measures for protecting their health. The term *hazardous drug*, as used throughout this Alert, refers to particular drugs that have been associated with or suspected of causing adverse health effects from workplace exposures. Appendix A includes examples of drugs that are considered hazardous by several sources. This Alert addresses workers in the healthcare setting who handle hazardous drugs, but not those in the drug manufacturing sector.

Employers of healthcare workers should:

- Ensure that written policies address medical surveillance of healthcare workers and all phases of hazardous drug handling including receipt and storage, preparation, administration, housekeeping, deactivation and cleanup and disposal of unused drugs and contaminated spills and patient wastes.

- Formally seek input from employees who handle drugs in developing a program for preventing exposure.
- Prepare a written inventory identifying all hazardous drugs used in the workplace and establish a procedure for regular review and update of the inventory.
- Make guidance documents, Material Safety Data Sheets (MSDSs) and other information available to those who handle hazardous drugs or work in an area where hazardous drugs are handled.
- Provide training to employees on the recognition, evaluation and control of hazardous drugs.
- Ensure that horizontal laminar flow workstations that move the air from the drug towards the worker are never used for the preparation of hazardous drugs.
- For hazardous drug preparation, provide and maintain ventilated cabinets designed for worker protection. Examples of these include biological safety cabinets (BSCs) and containment isolators that are designed to prevent hazardous drugs inside the cabinet from escaping into the surrounding environment. The exhaust from these cabinets should be HEPA-filtered and whenever feasible exhausted to the outdoors (away from air intake locations). Additional equipment, such as closed-system drug-transfer devices, glove bags and needle-less systems will further protect workers from exposures when used properly.
- Establish and oversee the implementation of appropriate work practices when hazardous drugs, patient wastes and contaminated materials are handled.
- Ensure training in and the availability and use of proper personal protective equipment (PPE) to reduce exposure via inhalation, ingestion, skin absorption,

and injection of hazardous drugs as required based on the results of a risk assessment and the OSHA PPE Standard. PPE includes chemotherapy gloves, low-lint, low-permeability disposable gowns and sleeve covers, and eye and face protection. NIOSH-certified respiratory protection is needed when equipment such as biological safety cabinets are not adequate to protect against inhalation exposure. Surgical masks do not provide adequate respiratory protection.

- Provide syringes and intravenous (IV) sets with Luer-lock™ fittings for preparing and administering hazardous drugs, as well as containers for their disposal. Closed-system, drug-transfer devices and needle-less systems should be considered to protect nursing personnel during drug administration.
- Complete a periodic evaluation of workplace hazardous drugs, equipment, training effectiveness, policies and procedures to reduce exposures to the greatest degree possible.
- Comply with all relevant U S Environmental Protection Agency/Resource Conservation and Recovery Act (USEPA/RCRA) regulations related to the handling, storage and transportation of hazardous waste.

Healthcare workers should:

- Participate in standardized training on the hazards of the drugs handled and equipment and procedures used to prevent exposure.
- Review guidance documents, MSDSs and other information resources for hazardous drugs handled.
- Be familiar with and be able to recognize sources of exposure to hazardous drugs.

- Prepare these agents in a dedicated area where access is restricted to authorized personnel only.
- Prepare these agents within a ventilated cabinet designed to protect workers and adjacent personnel from exposure and to provide product protection for all drugs that require aseptic handling.
- Use two pairs of powder-free, disposable chemotherapy gloves with the outer one covering the gown cuff whenever there is risk of exposure to hazardous drugs.
- Avoid skin contact by using a disposable gown made of a low-lint and low permeability fabric. The gown should have a closed front, long sleeves and elastic or knit closed cuffs and should not be reused.
- Wear a face shield to avoid splash incidents involving eyes, nose, or mouth when adequate engineering controls are not available.
- Wash hands with soap and water immediately before using and after removing personal protective clothing, such as disposable gloves and gowns.
- Use syringes and IV sets with Luer-lock™ fittings for preparing and administering these agents and place drug-contaminated syringes and needles in chemotherapy sharps containers for disposal.
- When additional protection is necessary, use closed-system, drug-transfer devices, glove bags and needle-less systems within the ventilated cabinet.
- Handle hazardous wastes and contaminated materials separately from other trash.
- Decontaminate work areas before and after each activity with hazardous drugs and at the end of each shift.

- Clean up spills immediately while using appropriate safety precautions and personal protective equipment (PPE) unless the spill is large enough to require an environmental services specialist.

Please tear out and post. Distribute copies to workers. See back of sheet to order complete Alert.

For additional information, see NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Healthcare Settings [DHHS (NIOSH) Publication No. 2004-xxx]. Single copies of the Alert are available from the following:

NIOSH–Publications Dissemination
4676 Columbia Pkwy.
Cincinnati, OH 45226-1998

Telephone: 1-800-35-NIOSH (1-800-356-4674)
Fax: 1-513-533-8573
E-mail: pubstaft@cdc.gov
Or visit the NIOSH Web site: www.cdc.gov/NIOSH
Department of Health and Human Services
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

TABLE OF CONTENTS

Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Healthcare Settings

INTRODUCTION

Pharmaceutical drugs are used with success to treat illnesses and injuries. The use of pharmaceutical agents is responsible for many of the advances in human medicine over the past century. Virtually all pharmaceutical agents have side effects, and, in addition to patients, workers who handle them are at risk of suffering an agent's known or unknown side effects. The term *hazardous drugs* was first used by the American Society of Hospital Pharmacists [ASHP 1990] and is used by the Occupational Safety and Health Administration (OSHA) in several documents [OSHA 1995, 1999]. Pharmaceutical agents are classified as hazardous drugs if studies in animals or humans indicate their potential to cause cancer, developmental or reproductive toxicity, or harm to organs (when it occurs at low doses). Many of the agents that are considered hazardous drugs are used to treat illnesses such as cancer or HIV infection [Galassi et al. 1996; McInnes and Schilsky 1996; Erlichman and Moore 1996]. A full discussion of criteria used to classify pharmaceutical agents as hazardous drugs, the definition of hazardous drugs, and examples of hazardous drugs are presented in Appendix A.

While the potential therapeutic benefits of these drugs outweigh the risks of unwanted side effects for ill patients, these same side effects may pose a hazard to healthcare workers. Occupational exposure can lead to: (1) acute effects, such as skin rashes [McDiarmid and Egan 1988; Valanis et al. 1993a,b; Krstev et al. 2003]; (2) chronic

effects, including adverse reproductive events [Selevan et al. 1985; Hemminki et al. 1985; Stücker et al. 1990; Valanis et al. 1997,1999; Peelen et al. 1999]; and (3) possibly cancer [Skov et al. 1992].

There are guidelines for handling hazardous drugs, but adherence to these guidelines has been reported to be sporadic [Valanis et al. 1991, 1992; Mahon et al. 1994; Nieweg et al. 1994]. In addition, measurable levels of some hazardous drugs have been documented in the urine of healthcare workers involved in the preparation or administration of drugs even after safety precautions had been employed [Ensslin et al. 1994, 1997; Sessink et al. 1992b; Sessink et al. 1994a; Sessink et al. 1994b; Sessink et al. 1997; Minoia et al. 1998; Wick et al. 2003]. Environmental studies of patient care areas have documented measurable levels of drug contamination even in those facilities thought to be following recommended handling guidelines [Minoia et al. 1998; Connor et al. 1999; Pethran et al. 2003].

Antineoplastic agents are increasingly used in the treatment of non-malignant rheumatologic and immunologic diseases [Baker et al. 1987; Moody et al. 1987; Chabner et al. 1996; Abel 2000], as well as in veterinary medicine for anti-cancer chemotherapy [Rosenthal 1996; Takada 2003], thus expanding the number and types of work environments where these drugs are used. This Alert summarizes the known health effects associated with occupational exposure to these agents and reviews elements of existing safe handling recommendations.

WORKERS AT RISK

Throughout the life cycle of a drug--from manufacture to transport and distribution, to use in actual healthcare or home care settings, to waste disposal--there are a number of drug handling operations that have the potential for worker exposure. The workers who have the potential to be exposed to hazardous drugs include: shipping and receiving personnel; pharmacists and pharmacy technicians; nursing personnel; physicians; operating room personnel; environmental services personnel; and personnel involved in veterinary practices where hazardous drugs are used. This Alert addresses all drug-handling workers including veterinary care workers, but not those workers in research and development and the drug manufacturing sector. Although not all workers in these categories handle hazardous drugs, the number of workers who may be exposed to hazardous drugs exceeds 5.5 million [U.S. Census Bureau 1997; BLS 1998, 1999; NCHS 1996].

Potential Exposure

Exposure to hazardous drugs may occur to clinical and non-clinical workers in the following settings:

- During reconstitution of powdered or lyophilized drugs and further dilution of either the reconstituted powder or concentrated liquid forms of hazardous drugs [Fransman et al. 2004].
- When aerosols are generated by expelling air from syringes filled with hazardous drugs or during the administration of drugs by intramuscular, subcutaneous or intravenous routes.

- When dust is generated through counting out individual uncoated oral doses and tablets from multi-dose bottles or unit-dosing uncoated tablets in a unit-dose machine, presenting a possible inhalation hazard.
- When crushing tablets to make oral liquid doses thus presenting potential inhalation and dermal exposure [Dorr and Alberts 1992; Shahsavarani et al. 1993; Harrison and Schultz 2000].
- When compounding potent powders into custom dosage capsules.
- When measurable levels of drugs are present on drug vial exteriors, work surfaces, floors, and final drug products (bottles, bags, cassettes, and syringes) and when airborne droplets of the drug are generated during reconstitution [McDevitt et al. 1993; Sessink et al. 1992a; Sessink et al. 1992b; Sessink et al. 1994b; Minoia et al. 1998; Connor et al. 1999, 2002; Schmaus et al. 2002].
- When aerosols are generated during the administration of drugs, either by direct IV push or by IV infusion.
- If priming the IV set with drug-containing solution at the patient bedside. (It is recommended that this procedure be done in the pharmacy.)
- When handling body fluids, clothing, dressings, linens and other materials contaminated with body fluids by hospital or home health personnel working with patients treated with hazardous drugs [Cass and Musgrave 1992; Kromhout et al. 2000].
- Through handling of contaminated waste generated at all steps of the preparation and administration process.

- When specialized procedures (intraoperative intraperitoneal chemotherapy) are performed in the operating room for some patients [White et al. 1996; Stuart et al. 2002].
- When handling unused hazardous drug waste, hazardous drug-contaminated waste, decontaminating and cleaning drug preparation or clinical areas, and transporting infectious, chemical or hazardous waste containers.
- When removing and disposing of PPE used during the handling of hazardous drugs or waste.

Exposure Routes

Exposures occur via inhalation, skin absorption, ingestion, and injection. Inhalation and skin exposure are the most likely, while unintentional ingestion from hand to mouth contact and unintentional injection through a needlestick or sharps injury are also possible [Duvall and Baumann 1980; Dorr 1983; Black and Presson 1997; Schreiber et al. 2003].

Several studies have attempted to measure concentrations of airborne antineoplastic drugs in healthcare settings [Kleinberg and Quinn 1981; Neal et al. 1983; McDiarmid et al. 1986; Pyy et al. 1988; McDevitt et al. 1993; Sessink et al.1992a; Nygren and Lundgren 1997; Stuart et al. 2002; Kiffmeyer et al. 2002; Larson et al. 2003]. In most cases, the percentage of samples demonstrating the presence of drug particulate was low and the concentration of the drugs, when present, was quite low. These low airborne concentrations may be attributed to the inefficiency of sampling and analytical techniques

employed in the past [Larson et al. 2003]. Both particulate and gaseous phases of one antineoplastic drug, cyclophosphamide, have been reported in two studies [Kiffmeyer et al. 2002; Larson et al. 2003].

Since the early 1990s, 14 studies have examined environmental contamination of drug preparation and administration areas in healthcare facilities in the U.S. and several other countries, Sessink et al. 1992a; Sessink et al. 1992b; McDevitt et al. 1993; Pethran et al. 1998; Minoia et al. 1998; Rubino et al. 1999; Sessink and Bos 1999; Connor et al. 1999; Micoli et al. 2001; Vandenbroucke et al. 2001; Connor et al. 2002; Kiffmeyer et al. 2002; Schmaus et al. 2002; Wick et al. 2003]. Using wipe samples, most studies measured detectable levels of one to five drugs in various locations such as: surfaces of BSCs; floors; counter tops; storage areas; tables and chairs in patient treatment areas; and locations adjacent to where the drugs were handled. All of the studies reported some level of contamination with at least one drug and several reported contamination with all the drugs for which assays were performed. Such widespread contamination of work surfaces makes highly probable the potential for dermal contact in both pharmacy and patient areas.

Evidence for Worker Exposure

There is evidence that workers are being exposed to hazardous drugs and that they are experiencing serious health consequences despite current work practice guidelines. Protection from exposure to hazardous drugs depends on safety programs established by the employer and adhered to by the employees. Factors that affect exposure include:

drug handling circumstances (preparation, administration, or disposal); amount of drug prepared; frequency and duration of handling the drugs; potential for absorption; and/or the use of ventilated cabinets[1]; personal protective equipment (PPE); and work practices. The likelihood of experiencing any of the adverse effects associated with hazardous drugs increases as the degree and frequency of exposure increases and when proper work practices are not implemented.

Workers' exposures have been assessed by studies on biological markers of exposure. No single biological marker has been found to be a good indicator of exposure to hazardous drugs or a good predictor of subsequent adverse health effects [Baker and Connor 1996]. Sessink and Bos [1999] noted that 11 of 12 studies detected cyclophosphamide in the urine of healthcare workers tested, indicating continued exposure despite safety precautions.

[1]Ventilated Cabinet: A type of engineering control designed for purposes of worker protection. Examples include biological safety cabinets and isolators designed to prevent hazardous drugs inside the cabinet from escaping into the surrounding environment. See Glossary of Terms and Abbreviations (Appendix B) for additional descriptions.

Harrison [2001] reported that six different drugs (cyclophosphamide, methotrexate, ifosfamide, epirubicin and cisplatin/carboplatin) were reported in the urine of healthcare workers in 13 of 20 investigations. Two recent studies have documented antineoplastic drugs in the urine of pharmacy and nursing personnel [Pethran et al. 2003; Wick et al. 2003]. Pethran and coworkers collected urine samples in 14 German hospitals over a three-year period. Cyclophosphamide, ifosfamide, doxorubicin, epirubicin and platinum (from cisplatin or carboplatin), but not daunorubicin or idarubicin, were identified in urine samples from many of the study participants. An investigation conducted in the U.S. demonstrated a reduction in both the percentage of urine samples with measurable levels of cyclophosphamide or ifosfamide present and the concentration of the drugs in the urine following use of a closed-system device for six months [Wick et al. 2003]. Hazardous drugs have also been documented in the urine of healthcare workers not handling the drugs but potentially exposed via fugitive aerosols or secondary contamination of work surfaces, clothing or drug containers [Sessink et al.1994b; Mader et al. 1996; Pethran et al. 2003].

Evidence for Health Effects in Workers who Handle Hazardous Drugs

By the 1970s, the carcinogenicity of several antineoplastic drugs in animals was well established [Shimkin et al. 1966; Weisberger 1975; Schmahl and Habs 1978]. Likewise, a number of researchers during this period linked the therapeutic use of alkylating agents in humans to subsequent leukemia and other cancers [Harris 1975, 1976; IARC 1979]. Many in healthcare began to question whether occupational exposure to these agents was hazardous [Ng 1970; Donner 1978; Johansson 1979].

Mutagenicity

A number of studies indicate that antineoplastic drugs may cause increased genotoxic effects in pharmacists and nurses exposed in the workplace [Falck et al. 1979; Anderson et al 1982.; Nguyen et al. 1982; Rogers and Emmett 1987; Oestricher et al. 1990; Fuchs et al. 1995; Ündeğer et al. 1999; Norppa et al. 1980; Nikula et al. 1984; McDiarmid et al. 1992; Sessink et al. 1994a; Burgaz et al. 1988]. Technical confounders and a lack of accurate sampling of exposed workers' urine or blood have been described as explanations for several other studies with negative genotoxic associations [Sorsa et al. 1985; McDiarmid et al. 1992]. Considering all the data, the weight of the evidence in occupationally exposed cohorts demonstrates an association between exposures to hazardous drugs and increases in various measures of genotoxicity [Sorsa and Anderson 1996; Baker and Connor 1996; Bos and Sessink 1997; Hewitt 1997; Sessink and Bos 1999; Harrison 2001].

Developmental and Reproductive Effects

A recent review of 14 investigations described the association between exposure to antineoplastic agents and adverse reproductive effects and reported nine studies showed some positive association [Harrison 2001]. The major reproductive effects found in these studies were increased fetal loss [Selevan et al. 1985; Stücker et al. 1990], congenital malformations depending on the length of exposure [Hemminki et al. 1990], low birth weight and congenital abnormalities [Peelen et al. 1999], and infertility [Valanis et. al. 1999].

Cancer

Several reports have addressed cancer occurrence related to exposures of healthcare workers to anticancer drugs. A significantly increased risk of leukemia has been reported among oncology nurses identified in the Danish cancer registry for 1943 to 1987 [Skov et al. 1992]. The same group [Skov et al. 1990] found an increased, but not significant, risk of leukemia in physicians employed for at least six months in a department where patients were treated with antineoplastic agents.

CASE REPORTS

The following case reports illustrate the range of health effects exhibited after exposure to antineoplastic drugs. These case reports are summarized journal articles.

Case 1

A female oncology nurse was exposed to a solution of carmustine when the complete tubing system fell out of an infusion bottle of carmustine and all of the solution poured down her right arm and leg and onto the floor [McDiarmid and Egan 1988]. Although she wore gloves, her right forearm was unprotected and the solution penetrated her clothing and stockings. Feeling no sensation on the affected skin areas, she immediately washed her arm and leg with soap and water, but did not change her clothing. A few hours later, while at work, she began to experience minor abdominal distress and profuse belching, followed by intermittent episodes of non-bloody diarrhea with cramping abdominal pain. Profuse vomiting occurred, after which she felt better. She went to the emergency room

where her vital signs and physical examination were normal, no specific therapy was prescribed. She felt better the following day. Carmustine is known to cause gastric upset, and the authors attributed her gastrointestinal distress to systemic absorption of carmustine.

Case 2

Levin et al. [1993] described the case of a 39-year-old pharmacist who presented with two episodes of painless hematuria and was found to have a grade II papillary transitional cell carcinoma. History revealed that twelve years prior to diagnosis she worked full time for 20 months in a hospital intravenous preparation area where she routinely prepared cytotoxic agents, including cyclophosphamide, fluorouracil, methotrexate, doxorubicin, and cisplatin. She used a horizontal laminar-flow hood that directed the airflow toward her. Since she was a non-smoker and had no other known occupational or environmental risk factors, her cancer was attributed to her work exposure to hazardous antineoplastic drugs, although a cause and effect relationship has not been established in the literature.

Case 3

Walusiak et al. [2002] reported a case of occupational asthma due to mitoxantrone. A 41-year old nurse who had worked on an oncology ward for 13 years suffered from rhinorrhea, dyspnea and cough attacks 1-2 hours after beginning work. During the third year, she developed dyspnea while away from work. The total IgE was low and specific IgE antibodies to common agents and skin prick tests to common allergens, including latex, were all negative. The patient was subjected to a number of single-blind bronchial

challenge tests with antineoplastic drugs and monitored by spirometry and peak expiratory flow measurements. Mitoxantrone produced 15 and 20 % falls in forced expiratory volume at 1 and 4 hours, respectively. The challenge with mitroxantrone was repeated one week later and bronchoalvelor lavage fluid was taken before and at 6 and 18 hours after provocation. Significant increases in lymphocytes and neutorophils were observed at 18 hours. There was also an eosinophil influx and a two-fold increase in the permeability index. Based on the clinical findings, the authors concluded that the evidence was consistent with mitroxantrone-induced allergic asthma.

Case 4

Kevekordes et al. [1998] reported on the effects of a malfunctioning BSC resulting in possible exposure of nursing personnel to a number of antineoplastic drugs that were prepared in the BSC. Blood samples from nurses were analyzed for genotoxic biomarkers two and nine months following replacement of the faulty BSC. At two months after replacement of the BSC, both sister chromatid exchanges (SCEs) and micronuclei were significantly elevated as compared to a matched control group. At nine months, the micronuclei levels were similar to the two-month controls. SCEs were not determined at nine months. The authors concluded that the elevation in the biomarkers had resulted from the malfunctioning of the BSC resulting in worker exposure to the antineoplastic drugs. They also concluded that the subsequent replacement with a new BSC contributed to the lowering of the effect seen with the micronucleus test at nine months.

Case 5

A 41-year-old patient care assistant working on the oncology floor developed a pruritic, disseminated rash approximately 30 minutes after emptying a commode of urine into a toilet [Kusnetz and Condon 2003]. She denied any direct contact with the urine, wore a protective gown and nitrile gloves, and followed hospital policy for the disposal of materials contaminated with antineoplastics. The rash subsided after one to two days. Three weeks later, a similar reaction occurred approximately one hour after performing the same procedure. Upon investigation, it was found that both hospital patients had been recently treated with vincristine and doxorubicin. The employee had no other signs or symptoms present, no changes in lifestyle and no history of allergies or recent infections. She was treated with diphenhydramine, intramuscular and oral corticosteroids and became asymptomatic. Although the cause could not be definitely confirmed, both vincristine and doxorubicin and their metabolites have been associated with allergic reactions when given to patients. The aerosolization of the drug present in the urine may have provided enough exposure for symptoms to develop.

CURRENT STANDARDS AND RECOMMENDATIONS

Current Occupational Safety and Health Administration (OSHA) standards and guidelines that address hazardous drugs include the *Hazard Communication Standard* [29 CFR* 1910.1200], the *Occupational Exposure to Hazardous Chemicals in Laboratories*

**Code of Federal Regulations.* See CFR in references.

Standard [29 CFR, 1910.1450], and the OSHA Technical Manual Guidelines, *Controlling Occupational Exposure to Hazardous Drugs* [OSHA 1999]. Main elements of the 1999 guidelines include:

- Categorization of drugs as hazardous
- Hazardous drugs as occupational risks
- Work area
- Prevention of employee exposure
- Medical surveillance
- Hazard communication
- Training and information dissemination
- Recordkeeping

Additional guidelines that address hazardous drugs or the equipment in which they are manipulated include:

- National Sanitation Foundation (NSF) and American National Standards Institute (ANSI) NSF/I 49-2002 Class II (Laminar Flow) Biosafety Cabinetry [NSF/ANSI 2002] Ann Arbor, MI, addresses classification and certification of Class II BSCs and provides a definition for Class III BSCs;
- Technical Report No. 34, *Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products*, a supplemental publication to the PDA Journal of Pharmaceutical Science and Technology [2001], provides definitions, design, and operation and testing guidance for types of isolators used in the healthcare product manufacturing industry;

- *Guidelines for Gloveboxes*, 2nd Edition, from the American Glovebox Society [AGS 1998], provides guidance on the design, testing, use, and decommissioning of glovebox containment systems;
- *Primary Containment for Biohazards* [CDC/NIH 2000], provides guidance on the selection, installation, testing and use of BSC's;
- *Recommendations for the Safe Handling of Cytotoxic Drugs* from the National Institutes of Health [CDC/NIH 1999], which includes recommendations for the safe preparation and administration of cytotoxic drugs;
- The American Society of Health-System Pharmacists (ASHP), *ASHP Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs* [1990], which is an informed discussion of the dangers and safe handling procedures for hazardous drugs; and
- The *Chemotherapy and Biotherapy Guidelines and Recommendations for Practice*, published by the Oncology Nursing Society [Brown et al. 2001] provides complete guidelines for the administration of antineoplastic drugs including safe handling guidelines.
- *Safe Handling of Hazardous Drugs*, published by the Oncology Nursing Society [Polovich 2003] includes proper handling guidelines for hazardous drugs.
- *Managing Hazardous Waste: A Guide for Small Businesses*, United States Environmental Protection Agency; EPA530-K-01-005; December, 2001.
- *RCRA Hazardous Waste Regulations*; 40 CFR Parts 260-279.

Currently, there are no NIOSH Recommended Exposure Limits (RELs), OSHA Permissible Exposure Limits (PELs) or American Conference of Government Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs®) for hazardous drugs. An ACGIH TLV® and an OSHA PEL exist for soluble platinum salts [ACGIH 2003; 29 CFR 1910.1450]. However, these are based on sensitization and not the potential to cause cancer. There is also a PEL, an REL and a TLV for inorganic arsenic compounds, which includes the antineoplastic drug, arsenic trioxide [ACGIH 2003; NIOSH 2004; 29 CFR 1910.1018]. Some pharmaceutical manufacturers develop risk-based occupational exposure limits (OELs) to be used in their own manufacturing settings, and this information may be available on some MSDSs or from the manufacturer [Sargent and Kirk 1988; Naumann and Sargent 1997; Sargent et al 2002].

RECOMMENDED PROTECTION PROCEDURES AND EQUIPMENT

An evaluation of the workplace to assess the hazard is recommended prior to anyone working with hazardous drugs. This evaluation should include an assessment of the total working environment, equipment (i.e. ventilated cabinets, closed system drug transfer devices, glovebags, needle-less systems and PPE) and the physical layout as well as the type of drugs being handled, the volume, frequency and form (tablet coated versus uncoated, powder versus liquid), maintenance of equipment, decontamination and cleaning and handling of waste. This evaluation should identify all hazards and reflect the range of potential exposure during work activity. It should also include potential exposures to other agents, such as blood borne pathogens and chemicals used to deactivate hazardous drugs or clean surfaces potentially contaminated with them. It

should address routine operations, spill response, waste disposal segregation and containment. The health and safety staff or an internal committee should regularly review the current inventory of hazardous drugs, equipment and practices with input from affected employees. Regular training reviews should be conducted with all potentially exposed workers in workplaces where hazardous drugs are used. On-going input from employees and other potentially exposed workers should be sought regarding the quality and effectiveness of the prevention program. Based upon employee input, management should provide the safest equipment and conditions to reduce healthcare worker exposure to the greatest degree possible. This is the only prudent public health approach as safe levels of occupational exposure for these agents have not been conclusively determined.

A written workplace safe handling program should be implemented and reviewed annually, based on the workplace evaluation of the area. Work policies and procedures specific to the handling of hazardous drugs should be established. They should include delineation of hazardous materials, labeling, storage, personnel issues (such as pregnancy) and spill control, as well as detailed procedures for preparation, administration, and disposal. In addition, workplace procedures should be developed for the use and maintenance of all equipment that functions to reduce exposure (ventilated cabinets, closed-system drug-transfer devices, needle-less systems, and PPE). Work practices relate not only to drug manipulation techniques but also to general hygiene practices, such as no eating or drinking in the drug handling areas (either pharmacy or clinic). General and specific safety training should be provided for handling hazardous drugs, all equipment, PPE, spills, and cleanup. Training should include information

about location and proper use of spill kits, that should be available in the immediate vicinity of potential sources of unintentional exposure. Training must conform to the requirements of the OSHA *Hazard Communication Standard* [29 CFR 1910.1200] and other relevant OSHA requirements. Procedures should also be established for cleaning and decontamination of the work areas and for proper waste handling and disposal of all contaminated materials, including patient waste.

Ventilated Cabinets

When mixing, preparing or otherwise manipulating hazardous drugs, including counting or crushing of tablets, compounding powders, or pouring of liquid drugs, these tasks should be conducted within a ventilated cabinet designed specifically to prevent hazardous drugs from being released into the surrounding environment. NIOSH recognizes that aseptic technique is an important requirement for many applications regarding hazardous drugs in order to protect then from possible contamination. These aseptic requirements are generally regulated by individual state boards of pharmacy [Thompson 2003]. While the need for asepsis is critical for many operations, this need should not require the sacrifice of worker safety and health. When asepsis is required or is the recommended work practice, the use of ventilated cabinets designed for both hazardous drug containment and aseptic processing is recommended.

The selection of ventilated cabinets intended to control exposures to hazardous drugs will depend upon the need for aseptic processing. When asepsis is not required, a Class I

BSC or an isolator intended for containment applications ("Containment Isolator") may be sufficient. When aseptic technique is required, the recommended ventilated cabinets include Class II (Type B2 preferred, Type A2 & B1 allowed under certain conditions) and Class III BSC's as well as isolators intended for asepsis and containment ("Aseptic Containment Isolators") [NSF/ANSI 2002; PDA 2001]. Regardless of type, each ventilated cabinet should be equipped with a continuous monitoring device to allow confirmation of adequate airflow prior to each use. The exhaust from these controls should be HEPA (High Efficiency Particulate Air) filtered and preferably exhausted 100% to the outside. **The outside exhaust should be installed to avoid re-entrainment by the building envelope or HVAC systems.** Fan placement should be downstream of the HEPA filter so that contaminated ducts are maintained under negative pressure. A ventilated cabinet with air recirculation, either within the cabinet or to the room environment, should only be used if the hazardous drug(s) in use will not volatilize during process manipulation or after capture by the HEPA filter. Information on volatilization should be based on information from the drug manufacturer (possibly in the MSDS) or from air sampling data.

Additional information regarding placement of the cabinet, exhaust system, and stack design may be found in NSF/ANSI 49 [2002] and should generally be incorporated regardless of which type of ventilated cabinet is selected. Additional engineering or process controls such as needle-less systems, glove bags and closed system drug transfer devices are not a substitution for ventilated cabinets although they may provide further

benefit in reducing the exposure potential during preparation and administration of hazardous drugs.

Ventilated cabinets require both routine and unscheduled maintenance by building facility personnel or outside contractors. All maintenance activities performed on ventilated cabinets and exhaust systems associated with hazardous drug procedures should be reviewed, in advance, by a health and safety representative familiar with the potential exposures and their associated hazards. A written safety plan should be developed for all routine maintenance activities performed on equipment potentially contaminated with hazardous drugs. Individuals performing the maintenance operations should be familiar with the applicable safety plans, warned of the potential hazards, and trained on the appropriate work techniques and PPE necessary to minimize exposure. Under most circumstances, all hazardous drugs and chemicals should be removed and the ventilated cabinet decontaminated prior to initiating the maintenance activity. Occupants in the affected areas should be warned immediately before the maintenance activity begins and warning signs placed on all equipment which may be affected. All applicable lock-out/tag-out procedures should be strictly followed. Equipment parts, removed for replacement or repair, should be decontaminated and bagged prior to their departure from the facility. Used filtration media should be sealed in plastic immediately upon removal and tagged for disposal as chemotherapy waste or as otherwise directed by the environmental health and safety office or applicable regulation.

Receiving and Storage

Control of exposure should begin at the point where the drugs enter the facility. The most significant risk for exposure during distribution and transport is from spills, resulting from damaged containers. PPE is generally not required when packaging is intact during routine activities. However, workers should be prepared for the possibility of spills during handling of containers. On the outside of containers, medical products should have labeling that is understandable to all levels of personnel who will be separating hazardous drugs from non-hazardous. Any person opening a container to unpack the drugs should wear chemotherapy gloves [ASTM 2004], protective clothing and eye protection because there is a possibility of spreading contamination if damaged containers are encountered. Chemotherapy gloves should also be worn when transporting the vial or syringe to the work area due to possible contamination. ASHP [1990] and other chemical safety standards recommend storing hazardous drugs separately from other drugs. Hazardous drugs should also be stored and transported in closed containers that minimize the risk of breakage. The storage area should have sufficient general exhaust ventilation to dilute and remove any airborne contaminants. Depending upon the physical nature and quantity of the stored drugs, consideration should be given to installing a dedicated emergency exhaust fan sufficient in size to quickly purge (to the outdoors) any airborne contaminants within the storage room and to prevent airborne contamination in adjacent areas in the event of a spill.

Drug Preparation and Administration

As part of the hazard assessment (described above), the entire process from drug preparation through drug administration should be evaluated and reviewed for possible unintentional releases of the drug into the work environment. The possibility of contamination on the outside of containers should always be considered [Ros et al. 1997; Hepp and Gentschew 1998; Delporte et al. 1999; Nygren et al. 2002; Favier et al. 2003; Mason et al. 2003]. Limiting access to an area designed for drug preparation protects persons not involved in that process. As a matter of practice, worker exposures are more effectively controlled when the tasks associated with the preparation and administration of hazardous drugs are coordinated.

During the preparation of hazardous drugs, a ventilated cabinet (as identified in the Ventilated Cabinet section of this document) should be used to reduce the potential for occupational exposure. Performance test methods and criteria for BSC's may be found in *Primary Containment for Biohazards: Selection, Installation and Use of Biological Safety Cabinets, 2nd Edition* [NCI 1978; CDC/NIH, 2000]. Where a class II BSC is used, it should be properly installed, maintained and routinely cleaned. Its performance should be field-certified upon installation, following relocation, after maintenance repairs to internal components, after HEPA filter replacement and every six months thereafter [NSF/ANSI 2002; OSHA 1999]. A current field-certification label should be prominently displayed on the ventilated cabinet [NFS/ANSI 49 2002]. Other types of ventilated cabinet should be treated similarly as to care and frequency of performance verification tests.

Selecting the appropriate performance and test methods for isolators will depend upon the type (containment-only or aseptic containment), the operating pressure (positive or negative and designed magnitude), and the toxicity of the hazardous drug being used. At a minimum, isolators should undergo a leak test and containment integrity test such as those described in Guidelines for Gloveboxes [AGS 1998]. Those isolators relying upon HEPA filtration for containment should also undergo the HEPA filter leak test described in NSF/ANSI 49 [2002]. Additional tests may be required by local and/or national jurisdictions to verify aseptic conditions. In addition to appropriate installation, maintenance, and operation of the ventilated cabinets, the safe use of any control is dependent upon proper work practices. While certification or performance testing assures the proper operation of the cabinet, it does not assure worker protection. Proper technique and use of equipment should also be practiced. All staff using ventilated cabinets must be well trained in the work practices established for their particular equipment. Initial and periodic assessments of technique should be included in the safety program [Harrison et al. 1996]. The technique used during drug administration should also be verified.

PPE, including double gloves and protective gowns, should be worn during drug reconstitution and admixture. Gloves should be specified as "Chemotherapy Gloves" and such information should be available on the box [ASTM 2004] or from the manufacturer. While a number of glove materials are suitable for protecting against exposure to antineoplastic drugs [Connor 1999; Singleton and Connor 1999; Klein et al. 2003], consideration must be given to the possibility of individuals who are sensitive to latex products [NIOSH 1997]. For those hazardous drugs that are not chemotherapy drugs or

for which no information is available, a chemotherapy glove should be considered for use. Double gloving is recommended for all activities involving hazardous drugs and the outer glove should extend over the cuff of the gown [Connor 1999; Brown et al. 2001]. Gloves should be inspected for physical defects before use. Hands should be washed with soap and water before donning protective gloves and immediately following removal. Gloves should be changed every 30 minutes or when torn, punctured or contaminated and discarded immediately in a yellow chemotherapy waste container [ASHP 1990; Brown et al. 2001]. Protective gowns should be disposable, low-lint, closed in the front, have tight fitting cuffs at the wrist and have low permeability to the agents being handled. Protective gowns must be disposed of after each use. Disposable sleeve covers can be used to effectively protect the wrist area by removing the covers after the task is completed. Polypropylene-based gown materials provide inadequate protection against many of the commonly used antineoplastic drugs. Polyethylene-coated materials provide better protection [Connor 1993; Harrison and Kloos 1999].

Following completion of drug preparation, the final product should be sealed in a plastic bag or other sealable container for transport out of the ventilated cabinet and to other areas. Outer gloves and sleeve covers (if used) should be removed and bagged for disposal inside the ventilated cabinet. All waste containers in the ventilated cabinet should be sealed and wiped prior to their removal from the cabinet. Workers involved in associated activities including opening drug packaging, handling vials or finished product, labeling hazardous drug containers or disposing of waste should wear protective

gloves and gowns. Hands should be washed with soap and water immediately following removal of gloves.

While ventilated cabinets should be used for the preparation of hazardous drugs, other devices (closed system transfer devices, glovebags, needle-less systems) may offer additional protection benefits for both the preparation and administration of these compounds.

Transfers from primary packaging such as vials to dosing equipment (i.e. infusion bags, bottles or pumps) should be carried out using closed systems whenever possible. Devices that contain the product within a closed system during drug transfers limit the potential for aerosol generation, as well as exposure to sharps. Evidence has documented a decrease in drug contaminants present within a Class II BSC when a closed system transfer device was used. [Sessink et al. 1999; Vandenbroucke and Robays 2001; Connor et al. 2002; Nygren et al. 2002; Spivey and Connor 2003; Wick et al. 2003]. However, a closed system transfer device is not an acceptable substitute for a ventilated cabinet and should only be used in conjunction with a ventilated cabinet. Regardless of whether a closed system is used, appropriate PPE and work practices should always be applied.

Safe drug administration includes the use of protective medical devices such as needle-less systems, closed-systems, and techniques like priming of IV tubing by pharmacy personnel in the ventilated cabinet or priming in-line with non-drug solutions. PPE, including double gloves, goggles, and protective gowns, should be worn for all activities

associated with drug administration—opening outer bag, assembly of delivery system, actual patient delivery and removal, and disposal of all equipment used in administration. Outer gloves and gowns should be removed and bagged for disposal in the yellow chemotherapy waste container at the site of administration. The chemotherapy waste should be double bagged before removal of the inner gloves. Hands should be washed with soap and water prior to leaving the site of administration.

Administration sets should be attached to the IV bag and primed prior to the addition of drug to the bag. Priming of IV tubing and syringes should be done by pharmacy personnel in the ventilated cabinet and never in the patient's room. Tubing should never be removed from an IV bag containing a hazardous drug. Tubing should not be disconnected at other points in the system until the tubing has been thoroughly flushed. When possible, the IV bag and tubing should be removed intact. Disposable items should be placed directly in a yellow chemotherapy waste container and lids to those containers should be closed. Double bagging should be considered for all contaminated equipment.

Routine Cleaning, Decontamination, Housekeeping and Waste Disposal

Work should be done in areas that are sufficiently ventilated to prevent build-up of airborne drug concentrations. Protocols should specify that unventilated areas such as storage closets not be used for drug storage or any tasks involving hazardous drugs. Work surfaces should be cleaned according to a cleaning protocol, which includes an appropriate deactivation (if available) and cleaning agent before and after each activity and at the end of the workday. Periodic cleaning routines should be established for all

work surfaces and equipment that may become contaminated, including administration carts and trays. At a minimum, safety glasses with side shields and protective gloves should be worn. Face shields should be worn if splashing or spraying is expected. Protective gloves should be selected by referring to the MSDS, to glove selection guidelines, or by conferring with the glove manufacturer. Gloves should be chemically resistant to the deactivation or cleaning agent and double gloving is recommended.

Personnel handling patient linens and excreta from patients who have received hazardous drugs within the last 48 hours, and in some cases up to seven days [Cass and Musgrave 1992] should be provided with and wear two pairs of appropriate gloves, and a disposable gown, to be discarded after each use or whenever contaminated. Face shields should be worn if splashing is possible. The outer gloves and gown should be removed by turning them inside out and placing them into the yellow chemotherapy waste container followed by removal of the inner gloves. Hands should be washed with soap and water after removal of gloves.

The preparation and administration of hazardous drugs generates various types of waste, including: partially filled vials; undispensed products; unused IVs; needles and syringes; gloves; gowns; underpads and materials from spill cleanups. Under USEPA/RCRA, hazardous waste is a specific category of wastes that must be managed following a strict set of regulatory requirements [40 CFR 260-279]. The RCRA list of hazardous waste, developed in 1976, included only about 30 pharmaceuticals, eight of which were antineoplastic drugs. Recent research has provided evidence that a number of drug

formulations exhibit hazardous waste characteristics [Smith 2002]. OSHA [1999] and ASHP [1990] recommend hazardous drug waste should be disposed of similar to RCRA-listed hazardous waste. This includes containers such as IV bags or drug vials that contain more than trace amounts of hazardous drugs and are not contaminated by blood or other potentially infectious waste.

Waste, such as needles, empty vials and syringes, gloves, gowns, and tubing that contain trace amounts of hazardous drugs, should be placed in separate containers (traditionally yellow chemotherapy waste containers). Soft trace contaminated items may be placed in chemotherapy bags; however, sharps such as needles, syringes and empty vials should be placed in chemotherapy waste containers designed to protect workers from injuries. Drug-contaminated sharps should not be included in red sharps containers that are used for infectious wastes since these are often autoclaved or microwaved and trace amounts of hazardous drugs can be disposed of by a regulated medical waste company through incineration [ASHP 1995; OSHA 1999; Smith 2002]. These recommendations are consistent with current knowledge of the toxicity of antineoplastic and other hazardous drugs, as defined in this Alert, that suggest bulk hazardous drugs (i.e., greater than 3% of the initial volume) not listed under RCRA be handled similarly to hazardous waste and disposed of in a RCRA-permitted hazardous waste incinerator.

Several authors have addressed the risk of potential respiratory exposure from volatile or micro-aerosolized drug [Connor et al 2000; Kiffmeyer et al 2002; Larson et al 2003]. Assuring containment of chemotherapy related waste in the proper disposal container addresses this concern.

Spill Control

Spills should be managed according to workplace hazardous drug spill policy and procedures. The size of the spill might determine both who is authorized to conduct the cleanup and decontamination and how that cleanup is managed. Whenever possible, cleanup of large spills should be handled by individuals who are trained in handling hazardous materials [29 CFR 1910.1200]. Spill kits and other cleanup materials should be located in the immediate vicinity of a potential, unintentional exposure. However, OSHA requires that persons who wear respirators such as those contained in some spill kits follow a complete respiratory protection program including fit-testing [29 CFR 1910.134]. The written program should address the protective equipment required for differing amounts spilled, the possible spreading of material, restricted access to hazardous drug spills, and signs to be posted. All spill cleanup materials should be disposed of in a hazardous chemical waste container in accordance with USEPA/RCRA regulations regarding hazardous waste, not in a chemotherapy waste or biohazard container.

Medical Surveillance

In addition to preventing exposure to hazardous drugs and careful monitoring of the environment, medical surveillance is an important part of a safe handling program. NIOSH recommends employees handling hazardous drugs are encouraged to participate in medical surveillance programs that are provided at their workplace. In the absence of an institutional medical surveillance program, workers handling hazardous drugs are encouraged to see their private healthcare provider for routine medical care, and

to inform their healthcare provider of their occupation and possible hazardous drug exposure.

The OSHA Technical Manual, TED 1-0.15A, Section VI Chapter 2 [OSHA 1999] currently recommends that workers handling hazardous drugs be monitored in a medical surveillance program that includes the taking of a medical and exposure history, physical examination and some laboratory measures. Professional organizations, including ASHP [1990] and the Oncology Nursing Society [Brown et al. 2001] recommend medical surveillance as the recognized standard of occupational health practice for hazardous drug handlers. The American College of Occupational and Environmental Medicine also recommends surveillance for these workers in their "Reproductive Hazard Management Guidelines" [ACOEM 1996].

Past exposure history of the employee may serve as a surrogate measure of the potential exposure intensity. The occupational health professional should ask questions that focus on those symptoms relating to organ systems that are targets for the hazardous drugs. For example, following acute exposure, such as a splash or other contact with skin or mucous membranes, the physical examination should focus on the exposed areas, and the clinician should look for signs of rash or irritation to those areas. Specific baseline and periodic laboratory tests should include a complete blood count with differential and a reticulocyte count may be helpful as an indicator of bone marrow reserve. Because several antineoplastic agents are known to cause bladder damage and hematuria in treated

patients, the urine of workers who handle these drugs should be monitored by means of a urine dipstick or a microscopic examination of the urine for blood [Brown et al. 2001]. Additionally, environmental sampling and/or biological monitoring may be beneficial where exposure is suspected or specific symptoms have been noted.

CONCLUSIONS AND RECOMMENDATIONS

Recent evidence summarized in this Alert documents that worker exposure to hazardous drugs is a persistent problem. Although most air sampling studies have not demonstrated significant airborne concentrations of these drugs, the methodology employed in the past has come into question [Larson et al 2003] and may not be a good indicator of environmental contamination of the workplace. All studies that examined surface wipe samples have determined that surface contamination of the workplace is common and widespread. A number of recent studies have documented the excretion of several indicator drugs in the urine of healthcare workers, thus showing their exposure to these drugs. Results from studies indicate that worker exposure to hazardous drugs in healthcare facilities may result in adverse health effects. Appropriately designed studies have begun and are continuing to characterize the extent and nature of health hazards incurred by these ongoing exposures. NIOSH is currently conducting studies to further identify potential sources of exposure and methods to reduce and/or eliminate worker exposure to these drugs. To minimize these potential acute (short-term) and chronic (long-term) health effects, NIOSH recommends that, at a minimum, employers and healthcare workers follow the recommendations described in this document.

ADDITIONAL INFORMATION

Additional information about exposure to hazardous drugs is available at 1-800-35-NIOSH (1-800-356-4674), fax: 1-513-533-8573, E-mail: pubstaft@cdc.gov, or Web site: www.cdc.gov/NIOSH.

Additional information on hazardous drug safety may be found at:

www.osha.gov.

ACKNOWLEDGEMENTS

Principle contributors to this Alert were G. Edward Burroughs, PhD, CIH[1]; Thomas Connor, PhD[1]; Barbara J. Coyle, BSN, RN COHN-S[2]; Duane R. Hammond, BS, ME[1]; Melissa Leone, RN, BSN[3]; Melissa McDiarmid, MD, MPH[4]; Kenneth Mead, M.S., P.E[1].; Marty Polovich, MN, RN, AOCN[5]; Luci Power, MS, RPh[6]; and Laurence Reed, M.S[1].

[1]NIOSH; [2]State of Wisconsin; [3]Apria Healthcare; [4]University of Maryland; [5]Oncology Nursing Society; [6]University of California

Contributions to this Alert were also made by members of the NIOSH Hazardous Drug Safe Handling working group. A complete listing of the agencies and organizations who contributed to this Alert is listed in Appendix C.

Support for the development of this Alert was provided by the National Occupational Research Agenda (NORA), Control Technology and Personal Protective Equipment Team and the NORA Reproductive Health Research Team.

Please direct comments, questions, or requests for additional information to:

Director, Division of Applied Research and Technology

National Institute for Occupational Safety and Health

4676 Columbia Pkwy.

Cincinnati, OH 45226-1998

Telephone: 1-513-533-8462 or 1-800-35-NIOSH

Reference verification by Anne Votaw and Teresa Lewis

REFERENCES

Abel EA [2000]. Immunosuppressant and cytotoxic drugs: Unapproved uses or indications. Clin Dermatol *18*: 95–101.

ACGIH [2003]. TLVs® and BEIs® based on the documentation of the Threshold Limit Values for chemical substances and physical agents & Biological Exposure Indices. Cincinnati, OH: American Conference of Government Industrial Hygienists.

ACOEM (American College of Occupational and Environmental Medicine) [1996]. Committee report: ACOEM reproductive hazard management guidelines. J Occup Environ Med. *38*(1):83–90.

AGS [1998]. Guidelines for gloveboxes second edition. Santa Rosa, CA: American Glovebox Society, AGS-G001-1998.

Anderson RW, Puckett WH Jr., Dana WJ, Nguyen TV, Theiss JC, Matney TS [1982]. Risk of handling injectable antineoplastic agents. Am J Hosp Pharm *39*:1881–1887.

Arrington DM, McDiarmid MA [1993]. Comprehensive program for handling hazardous drugs. Am J Hosp Pharm *50*:1170–1174.

ASHP (American Society of Hospital Pharmacists) [1990]. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. Am J Hosp Pharm *47*:1033–1049.

ASHP/AHFS DI (American Hospital Formulary Service Drug Information) [2003]. AHFS drug information—online updates. [http://www.ashp.org./ahfs/index.cfm]. Date accessed: March 4.

ASTM [in press, 2004]. Draft standard practice for assessment of resistance of chemotherapy gloves to permeation by chemotherapy drugs. West Conshohocken, PA: American Society for Testing and Materials.

Baker ES, Connor TH [1996]. Monitoring occupational exposure to cancer chemotherapy drugs. Am J Health-Syst Pharm *53*:2713–2723.

Baker GL, Kahl LE, Zee BC, Stolzer BL, Agarwal AK, Medsger TA Jr. [1987]. Malignancy following treatment of rheumatoid arthritis with cyclophosphamide. Long-term case-control follow-up study. Am J Med *83*(1):1–9.

Black LA, Presson AC [1997]. Hazardous Drugs. Occup Med: State of the Art Rev. *12*(4):669–685.

BLS [1998]. Bureau of Labor Statistics homepage: 1998 national industry-occupational employment matrix. Excludes hospital-based and public agencies. [http://stats.bls.gov]. Date accessed: 2001.

BLS [1999]. Bureau of Labor statistics homepage: 1999 national occupational employment and wage estimates. [http://stats.bls.gov]. Date accessed: 2001.

Bos RP, Sessink PJM [1997]. Biomonitoring of occupational exposure to cytostatic drugs. Rev Environ Health *12*(1):43–58.

Brown KA, Esper P, Kelleher LO, O'Neill JEB, Polovich M, White JM [2001]. Chemotherapy and biotherapy guidelines and recommendations for practice. Pittsburgh, PA: Oncology Nursing Society.

Burgaz S, Özdamar YN, Karakaya AE [1988]. A signal assay for the detection of genotoxic compounds: application of the urines of cancer patients on chemotherapy and of nurses handling cytotoxic drugs. Human Toxicol *7*:557–560.

Cass Y, Musgrave CF [1992] Guidelines for the safe handling of excreta contaminated by cytotoxic agents. Am J Hosp Pharm *49*(8):1957–1958.

CDC/NIH [1999]. Biosafety in microbiological and biomedical laboratories (BMBL). 4th ed. Washington, DC: U.S. Department of Health and Human Services, Centers for

Disease Control and Prevention and National Institutes of Health. [http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4toc.htm]. Date accessed: March 2004.

CDC/NIH [2000]. Primary containment for biohazards: selection, installation and use of biological safety cabinets. 2nd ed. Washington, DC: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention and National Institutes of Health. [www.cdc.gov/od/ohs/biosfty/bsc/bsc.htm]. Date accessed: March 2004.

CFR. Code of Federal regulations. Washington, DC: U.S. Government Printing Office, Office of the Federal Register.

Chabner BA, Allegra CJ, Curt GA, Calabresi P [1996]. Antineoplastic agents. In: Hardman JG and Limbird LE, eds. Goodman and Gilman's the pharmacological basis of therapeutics. 9th ed. New York, NY: McGraw-Hill, pp1233–1287.

Connor TH [1993]. An evaluation of the permeability of disposable polypropylene-based protective gowns to a battery of cancer chemotherapy drugs. Appl Occup Environ Hyg. *8*(9):785–789.

Connor TH [1999]. Permeability of nitrile rubber, latex, polyurethane, and neoprene gloves to 18 antineoplastic drugs. Am J Health-Syst Pharm. *56*:2450–2453.

Connor TH, Anderson RW, Sessink PJ, Broadfield L, Power LA [1999]. Surface contamination with antineoplastic agents in six cancer treatment centers in Canada and the United States. Am J Health-Syst Pharm *56*:1427–1432.

Connor TH, Shults M, Fraser MP [2000]. Determination of the vaporization of solutions of mutagenic antineoplastic agents at 23 and 37º C using a desiccator technique. Mutat Res *470*:85–92.

Connor TH, Anderson RW, Sessink PJ, Spivey SM [2002]. Effectiveness of a closed-system device in containing surface contamination with cyclophosphamide and ifosfamide in an i.v. admixture area. Am J Health-Syst Pharm *59*:68–72.

Delporte JP, Chenoix P, Hubert Ph [1999]. Chemical contamination of the primary packaging of 5-fluorouracil RTU solutions commercially available on the Belgian market. Eur Hosp Pharm *5*(3):119–121.

Donner AL [1978]. Possible risk of working with antineoplastic drugs in horizontal laminar flow hoods [letter to the editor]. Am J Hosp Pharm. *35*:900.

Dorr RT [1983]. Practical techniques for preparation and administration of cytotoxic agents. Presented at Practical approaches to safe handling of anticancer products. Mayaguez, Puerto Rico, Nov 2–5.

Dorr RT, Alberts DS [1992]. Topical absorption and inactivation of cytotoxic anticancer agents in vitro. Cancer *70*(4)(Suppl):983–987.

Duvall E, Baumann B [1980]. An unusual accident during the administration of chemotherapy. Cancer Nurs *3*(4):305–306.

Ensslin AS, Stoll Y, Pethran A, Pfaller A, Römmelt H, Fruhmann G [1994]. Biological monitoring of cyclophosphamide and ifosfamide in urine of hospital personnel occupationally exposed to cytostatic drugs. Occup Environ Med *51*:229–233.

Ensslin AS, Huber R, Pethran A, Römmelt H, Schierl R, Kulka U, Fruhmann G [1997]. Biological monitoring of hospital pharmacy personnel occupationally exposed to cytostatic drugs: urinary excretion and cytogenetics studies. Int Arch Occup Environ Health *70*:205–208.

Erlichman C, Moore MJ [1996]. Carcinogenesis: a late complication of cancer chemotherapy. In: Chabner BA and Longo DL eds. Cancer chemotherapy and biotherapy: principles and practice. 2nd ed. Philadelphia, PA: Lippincott-Raven, pp 45–58.

Falck K, Gröhn P, Sorsa M, Vainio H, Heinonen E, Holsti LR [1979]. Mutagenicity in urine of nurses handling cytostatic drugs. Lancet *1*(8128):1250–1251.

Favier B, Gilles L, Ardiet C, Latour JF [2003]. External contamination of vials containing cytotoxic agents supplied by pharmaceutical manufacturers. J Oncol Pharm Practice *9*:15–20.

Fransman W, Vermeulen R, Kromhout H [2004]. Occupational dermal exposure to cyclophosphamide in Dutch hospitals: a pilot study. Ann Occup Hyg *48* (3):237–244.

Fuchs J, Hengstler JG, Jung D, Hiltl G, Konietzko J, Oesch F [1995]. DNA damage in nurses handling antineoplastic agents. Mutat Res *342*:17–23.

Galassi A, Hubbard SM, Alexander HR, Steinhaus E [1996]. Chemotherapy administration: practical guidelines. In: Chabner BA and Longo DL eds. Cancer chemotherapy and biotherapy: principles and Practice. 2nd ed. Philadelphia, PA. Lippincott-Raven, pp 529–551.

Harris CC [1975]. Immunosuppressive anticancer drugs in man: their oncogenic potential. Radiol *114*(1):163–166.

Harris CC [1976]. The carcinogenicity of anticancer drugs: a hazard to man. Cancer. *37*(2)(Suppl):1014–1023.

Harrison BR, Godefroid RJ, Kavanaugh EA [1996]. Quality-assurance testing of staff pharmacists handling cytotoxic agents. Am J Health-Syst Pharm *53*:402–407.

Harrison BR, Kloos MD [1999]. Penetration and splash protection of six disposable gown materials against fifteen antineoplastic drugs. J Oncol Pharm Practice. *5*(2):61–66.

Harrison BR, Schultz CD [2000]. Determination of tablet trituration dust in work zone air. J Oncol Pharm Pract *6*(1):23.

Harrison BR [2001]. Risks of handling cytotoxic drugs. In: Perry MC ed., The chemotherapy source book. 3rd ed. Philadelphia, PA: Lippincott, Williams and Wilkins, pp 566–582.

Hemminki K, Kyyrönen P, Lindbohm M-L [1985]. Spontaneous abortions and malformations in the offspring of nurses exposed to anesthetic gases, cytostatic drugs, and other potential hazards in hospitals, based on registered information of outcome. J Epidemiol Community Health *39*:141–147.

Hepp R, Gentschew G [1998]. External contamination of commercially available cytotoxic drugs (in German). Krankenhauspharmazie *19*(1):22–27.

Hewitt JB [1997]. Health effects of occupational exposure to antineoplastic drugs: an integrative research approach. Ontario, Canada: Ministry of Labour, Industrial Disease Panel.

IARC [1979]. IARC monographs: chemicals and industrial processes associated with cancer in humans: 20 Vols. Lyons, France: World Health Organization, International Agency for Research on Cancer, pp. 1–70.

IARC [2004]. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Lyons, France: World Health Organization, International Agency for Research on Cancer. [http://www.iarc.fr.]. Date accessed: March 2004.

Johansson H [1979]. How hazardous are cytotoxic agents to personnel? (in Swedish). Vardfacket *3*(1):10–16.

Kevekordes S, Gebel TW, Hellwig M, Dames W, Dunkelberg H [1998]. Human effect monitoring in cases of occupational exposure to antineoplastic drugs: a method comparison. Occup Environ Med *55*: 145–149.

Kiffmeyer TK, Kube C, Opiolka S, Schmidt KG, Schöppe G, Sessink PJM [2002]. Vapor pressures, evaporation behaviour and airborne concentrations of hazardous drugs: implications for occupational safety. Pharmeaceut J *268*:331–337.

Klein M, Lambov N, Samev N, Carstens G [2003]. Permeation of cytotoxic formulations through swatches from selected medical gloves. Am J Health-Syst Pharm *60*:1006–1011.

Kleinberg ML, Quinn MJ [1981]. Airborne drug levels in a laminar-flow hood. Am J Hosp Pharm *38*:1301-1303.

Kolmodin-Hedman B, Hartvig P, Sorsa M, Falck K [1983]. Occupational handling of cytostatic drugs. Arch Toxicol *54*: 25–33.

Kromhout H, Hoek F, Uitterhoeve R, Huijbers R, Overmars RF, Anzion R, Vermeulen R [2000]. Postulating a dermal pathway for exposure to antineoplastic drugs among hospital workers. Applying a conceptual model to the results of three workplace surveys. Ann Occup Hyg *44*(7):551–560.

Krstev S, Peruničić B, Vidaković A [2003]. Work practice and some adverse health effects in nurses handling antineoplastic drugs. Med Lav *94* (5):432-439.

Kusnetz E, Condon M [2003]. Acute effects from occupational exposure to antineoplastic drugs in a para-professional health care worker. Am J Ind Med *44*:107–109.

Larson RR, Khazaeli MB, Dillon HK [2003]. A new monitoring method using solid sorbent media for evaluation of airborne cyclophosphamide and other antineoplastic agents. Appl Occup Environ Hyg *18*(2): 120–131.

Levin LI, Holly EA, Seward JP [1993]. Bladder cancer in a 39-year-old female pharmacist. J Natl Cancer Inst *85*(13):1089–1091.

McDevitt JJ, Lees PSJ, McDiarmid MA [1993]. Exposure of hospital pharmacists and nurses to antineoplastic agents. J Occup Med *35*(1):57–60.

McDiarmid M, Egan T [1988]. Acute occupational exposure to antineoplastic agents. J Occup Med *30*(12):984–987.

McDiarmid MA, Egan T, Furio M, Bonacci M, Watts S [1986]. Sampling for airborne fluorouracil in a hospital drug preparation area. Am J Hosp Pharmacy *4*3:1942–1945.

McDiarmid MA [1990]. Medical surveillance for antineoplastic-drug handlers. Am J Hosp Pharm *47*:1061–1066.

McDiarmid MA, Gurley HT, Arrington D [1991]. Pharmaceuticals as hospital hazards: managing the risks. J Occup Med *33*(2):155–158.

McDiarmid MA, Kolodner K, Humphrey F, Putman D, Jacobson-Kram D [1992]. Baseline and phosphoramide mustard-induced sister-chromatid exchanges in pharmacists handling anti-cancer drugs. Mutat Res *279*:199–204.

McInnes S, Schilsky RL [1996]. Infertility following cancer chemotherapy. In: Chabner BA and Longo DL eds. Cancer chemotherapy and biotherapy: principles and practice. 2nd ed. Philadelphia, PA: Lippincott-Raven, pp 31–44.

Mader RM, Rizovski B, Steger GG, Wachter A, Kotz R, Rainer H [1996]. Exposure of oncologic nurses to methotrexate in the treatment of osteosarcoma. Arch Environ Health *51*(4): 310–314.

Mahon SM, Casperson DS, Yackzan S, Goodner S, Hasse B, Hawkins J, Parham J, Rimkus C, Schlomer M, Witcher V [1994]. Safe handling practices of cytotoxic drugs: the results of a chapter survey. Oncol Nurs Forum *21*(7):1157–1165.

Mason HJ, Morton J, Garfitt SJ, Iqbal S, Jones K [2003]. Cytotoxic drug contamination on the outside of vials delivered to a hospital pharmacy. Ann Occup Hyg. *47*(8):681–685.

Micoli G, Turci R, Arpellini M, Minoia C [2001]. Determination of 5-fluorouracil in environmental samples by solid-phase extraction and high-performance liquid chromatography with untraviolet detection. J Chromatogr B *750*:25–32.

Minoia C, Turci R, Sottani C, Schiavi A, Perbellini L, Angeleri S, Draicchio F, Apostoli P [1998]. Application of high performance liquid chromatography/tandem mass spectrometry in the environmental and biological monitoring of healthcare personnel occupationally exposed to cyclophosphamide and ifosfamide. Rapid Commun Mass Spectrom *12*:1485–1493.

Moody DJ, Kagan J, Liao D, Ellison GW, Myers LW [1987]. Administration of monthly-pulse cyclophosphamide in multiple sclerosis patients. Effects of long-term treatment on immunologic parameters. J Neuroimmunol *14*(2):161–173.

Naumann BD, Sargent EV [1997]. Setting occupational exposure limits for pharmaceuticals. Occup Med: State of the Art Rev *12*(1):67–80.

NCHS (National Center for Health Statistics [1996]. Vital and health statistics: the national home and hospice care survey, 1996 summary. Series 13: data from the National Health Care Survey No. 141. [http://www.cdc.gov/nchs/fastats/homehosp.htm]. Date accessed: 2001.

NCI [1978]. Laboratory safety monograph: a supplement to the NIH guidelines for recombinant DNA research. Bethesda, MD: National Cancer Institute.

Neal AdW, Wadden RA, Chlou WL [1983]. Exposure of hospital workers to airborne antineoplastic agents. Am J Hosp Pharm *40*:597–601.

Ng LM, Jaffe N [1970]. Possible hazards of handling antineoplastic drugs. Pediatrics *46*(4):648–649.

Nguyen TV, Theiss JC, Matney TS [1982]. Exposure of pharmacy personnel to mutagenic antineoplastic drugs. Can Res *42*:4792–4796.

Nieweg RMB, de Boer M, Dubbleman RC, Gall HE, Hesselman GM, Lenssen PCHP, van Maanen LWGM, Majoor PWFM, Ouwerkerk J, Slegt JH. [1994]. Safe handling of antineoplastic drugs. Cancer Nurs *17*:501–511.

NIH [2002]. 1999 recommendations for the safe handling of cytotoxic drugs. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, NIH Publication No. 92-2621. [http://www.nih.gov/od/ors/ds/pubs/cyto]. Date accessed March 28.

Nikula E, Kiviniitty K, Leisti J, Taskinen PJ [1984]. Chromosomal aberrations in lymphocytes of nurses handling cytostatic agents. Scand J Work Environ Health *10*:71–74.

NIOSH [1989]. Comments of the National Institute for Occupational Safety and Health on the Occupational Safety and Health Administration's proposed rule on health standards; methods of compliance, October 2, 1989, 29 CFR Part 1910, Docket No. H–160. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

NIOSH [2004]. Arsenic. In: NIOSH pocket guide to chemical hazards. Washington, DC: U.S. Department of Health and Human Services. Centers for Disease Control and

Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 97-140.

NIOSH [1997]. NIOSH alert: preventing allergic reactions to natural rubber latex in the workplace. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 97-135.

Norppa H, Sorsa M, Vainio H, Gröhn P, Heinonen E, Holsti L, Nordman E [1980]. Increased sister chromatid exchange frequencies in lymphocytes of nurses handling cytostatic drugs. Scand J Work Environ Health *6*:299–301.

NSF/ANSI [2002]. Class II (laminar flow) biosafety cabinetry: NSF International standard/American National standard for biosafety cabinetry. Ann Arbor, MI: National Sanitation Foundation and American National Standards Institute, NSF/ANSI 49-2002. [http://www.nsf.org/biohazard/bio_standards.html]. Date accessed: March 28.

Nygren O, Lundgren C [1997]. Determination of platinum in workroom air and in blood and urine from nursing staff attending patients receiving cisplatin chemotherapy. Int Arch Occup Environ Health *70*:209–214.

Nygren O, Gustavsson B, Ström L, Friberg A [2002]. Cisplatin contamination observed on the outside of drug vials. Ann Occup Hyg *46*(6):555–557.

Oestreicher U, Stephan G, Glatzel M [1990]. Chromosomal and SCE analysis in peripheral lymphocytes of persons occupationally exposed to cytostatic drugs handled with and without use of safety covers. Mutat Res *242*:271–277.

OSHA [1986]. Guidelines for cytotoxic (antineoplastic) drugs. Washington, DC: Department of Labor, Occupational Safety and Health Administration, Office of Occupational Medicine Publication No. 8-1.1.

OSHA [1995]. OSHA Instruction TED (training and education directive), 1.15 directorate of technical support: controlling occupational exposure to hazardous drugs. Washington, DC: Occupational Safety and Health Administration.

OSHA [1999]. OSHA technical manual, TED 1-0.15A, Sec VI, Chapt II: Categorization of drugs as hazardous. [http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html#2]. Date accessed: Jan 20.

PDA [2001]. Technical report no. 34: design and validation of isolator systems for the manufacturing and testing of health care products. PDA J Pharm Sci Technol *55*(5)(Suppl).

PDR.net [2004]. Physician's desk reference for drug interactions. Montvale, NJ: Thomson Healthcare. [http://www.pdr.net/pdrnet]. Date accessed: March 9.

Peelen S, Roeleveld N, Heederik D, Krombout H, de Kort W [1999]. Toxic effects on reproduction in hospital personnel (in Dutch). Reproductie-toxische effecten bij ziekenhuispersonel. Netherlands: Elsivier.

Pethran A, Hauff K, Hessel H, Grimm C-H [1998]. Biological, cytogenetic, and ambient monitoring of exposure to antineoplastic drugs. J Oncol Pharm Practice *4*:57.

Pethran A, Schierl R, Hauff K, Grimm C-H, Boos K-S, Nowak D [2003]. Uptake of antineoplastic agents in pharmacy and hospital personnel. Part 1: monitoring of urinary concentrations. Int Arch Occup Environ Health. *76*: 5–10.

Polovich M, ed. [2003] Safe handling of hazardous drugs. Pittsburgh, PA: Oncology Nursing Society.

Pyy L, Sorsa M, Hakala E [1988]. Ambient monitoring of cyclophosphamide in manufacture and hospitals. Am Ind Hyg Assoc J *49*(6):314–317.

REPROTOX [2003]. Reproductive Toxicology Center, Colombia Hospital for Women Medical Center, Washington, DC. [http://reprotox.org]. Date accessed: Feb. 2004.

Rogers B, Emmett EA [1987]. Handling antineoplastic agents: Urine mutagenicity in nurses. IMAGE: J Nurs Scholarsh *19*:108–113.

Ros JJW, Simons KA, Verzijl JM, de Bijl GA, Pelders MG [1997]. Practical applications of a validated method of analysis for the detection of traces of cyclophosphamide on injection bottles and at oncological outpatient center (in Dutch). Ziekenhuisfarmacie *13*:168–171.

Rosenthal RC [1996]. Multimodality therapy: using the best available treatments together rationally. Vet Clin North Am Small Anim Pract *26*(1):1–8.

Rubino FM, Floridia L, Pietropaolo AM, Tavazzani M, Colombi A [1999]. Measurement of surface contamination by certain antineoplastic drugs using high-performance liquid chromatography: applications in occupational hygiene investigations in hospital environments. Med Lav *90*(4):572–583.

Sargent EV, Kirk GD [1988]. Establishing airborne exposure control limits in the pharmaceutical industry. Am Ind Hyg Assoc J *49*(6): 309–313.

Sargent EV, Naumann BD, Dolan DG, Faria EC, Schulman L [2002]. The importance of human data in the establishment of occupational exposure limits. Hum Ecol Risk Assess *8*(4): 805–822.

Schardein, JL [2000]. Chemically induced birth defects. 3rd rev. ed. New York, NY: Marcel Deckker, Inc.

Schmahl D, Habs M [1978]. Experimental carcinogenesis of antitumor drugs. Cancer Treat Rev *5*(4):175–184.

Schmaus G, Schierl R, Funck S [2002]. Monitoring surface contamination by antineoplastic drugs using gas chromatography-mass spectrometry and voltammetry. Am J Health-Syst Pharm *59*: 956–961.

Schreiber C, Radon K, Pethran A, Schierl R, Hauff K, Grimm C-H, Boos K-S, Nowak D. [2003]. Uptake of antineoplastic agents in pharmacy personnel. Part 2: study of work-related risk factors. Int Arch Occup Environ Health *76*: 11–16.

Selevan SG, Lindbohm M-L, Hornung RW, Hemminki K [1985]. A study of occupational exposure to antineoplastic drugs and fetal loss in nurses. N Engl J Med *313*(19):1173–1178.

Sessink PJM, Anzion RBM, van der Broek PHH, Bos RP [1992a]. Detection of contamination with antineoplastic agents in a hospital pharmacy department. Pharm Week Sci *14*:16–22.

Sessink PJM, Boer KA, Scheefhals APH, Anzion RBM, Bos RP [1992b]. Occupational exposure to antineoplastic agents at several departments in a hospital: environmental

contamination and excretion of cyclophosphamide and ifosfamide in urine of exposed workers. Int Arch Occup Environ Health *64*:105–112.

Sessink PJM, Bos RP [1999]. Drugs hazardous to healthcare workers: evaluation of methods for monitoring occupational exposure to cytostatic drugs. Drug Saf *20*(4):347–359.

Sessink PJM, Cerná M, Rössner P, Pastorková A, Bavarová H, Franková K, Anzion RBM, Bos RP [1994a]. Urinary cyclophosphamide excretion and chromosomal aberrations in peripheral blood lymphocytes after occupational exposure to antineoplastic agents. Mutat Res *309*:193–199.

Sessink PJM, Kroese ED, van Kranen HJ, Bos RP [1995]. Cancer risk assessment for health care workers occupationally exposed to cyclophosphamide. Int Arch Occup Environ Health *67*:317–323.

Sessink PJM, Rolf M-AE, Ryden NS [1999]. Evaluation of the *PhaSeal* hazardous drug containment system. Hosp Pharm *34*:1311–1317.

Sessink PJM, van der Kerkhof MCA, Anzion RBM, Noordhoek J, Bos RP [1994b]. Environmental contamination and assessment of exposure to antineoplastic agents by determination of cyclophosphamide in urine of exposed pharmacy technicians: Is skin absorption an important exposure route? Arch Environ Health *49*(3):165–169.

Sessink PJM, Wittenhorst BCJ, Anzion RBM, Bos RP [1997]. Exposure of pharmacy technicians to antineoplastic agents: reevaluation after additional protective measures. Arch Environ Health *52*(3):240–244.

Shahsavarani S, Godefroid RJ, Harrison BR [1993]. Evaluation of occupational exposure to tablet trituration dust. 28th Annual ASHP Midyear Clinical Meeting, Atlanta, GA.

Shepard, TH [2001]. Catalog of teratogenic agents. 10th ed. Baltimore, MD: Johns Hopkins University Press. [http://www.depts.washington.edu/~terisweb]. Date accessed: Feb. 2004.

Shimkin MB, Weisburger JH, Weisburger EK, Gubareff N, Suntzeff V [1966]. Bioassay of 29 alkylating chemicals by the pulmonary-tumor response in strain A mice. J Natl Cancer Inst *36*:915–935.

Shortridge LA, Lemasters GK, Valanis B, Hertzberg V [1995]. Menstrual cycles in nurses handling antineoplastic drugs. Cancer Nurs *18*(6):439–444.

Singleton LC, Connor TH [1999]. An evaluation of the permeability of chemotherapy gloves to three cancer chemotherapy drugs. Oncol Nurs Forum *26*(9):1491–1496.

Skov T, Lynge E, Maarup B, Olsen J, Rørth M, Winthereik H [1990]. Risk for physicians handling antineoplastic drugs. The Lancet *336*:1446.

Skov T, Maarup B, Olsen J, Rørth M, Winthereik H, Lynge E [1992]. Leukaemia and reproductive outcome among nurses handling antineoplastic drugs. Br J Ind Med *49*:855–861.

Smith CA [2002]. Managing pharmaceutical waste: What pharmacists should know. J Pharm Soc Wis (Nov/Dec):17–22.

Sorsa M, Anderson D [1996]. Monitoring of occupational exposure to cytostatic anticancer agents. Mutat Res *355*:253-261.

Sorsa M, Hemminki K, Vainio H [1985]. Occupational exposure to anticancer drugs—potential and real hazards. Mutat Res *154*:135–149.

Sotaniemi EA, Sutinen S, Arranto AJ, Sutinen S, Sotaniemi KA, Lehtola J, Pelkonen RO [1983]. Liver damage in nurses handling cytostatic agents. Acta Med Scand *214*:181–189.

Spivey S, Connor TH [2003]. Determining sources of workplace contamination with antineoplastic drugs and comparing conventional IV drug preparation with a closed system. Hosp Pharm *38*(2):135–139.

Stuart OA, Stephens AD, Welch L, Sugerbaker PH [2002]. Safety monitoring of the coliseum technique for heated intraoperative intraperitoneal chemotherapy with mitomycin C. Ann Surg Oncol *9*(2):186–191.

Stücker I, Caillard J-F, Collin R, Gout M, Poyen D, Hémon D [1990]. Risk of spontaneous abortion among nurses handling antineoplastic drugs. Scand J Work Environ Health *16*:102–107.

Sweetman SC, ed. [2002]. Martindale: the complete drug reference.33rd ed. London, UK: The Royal Pharmaceutical Society of Great Britain. E-mail: [jmcglashan@rpsgb.org.uk].

Takada S [2003]. Principles of chemotherapy safety procedures. Clin Tech Small Anim Pract *18*(2):73–74.

Thompson CA [2003]. USP publishes enforceable chapter on sterile compounding. Am J Health-Syst Pharm *60*:1814–1817.

Ündeğer Ü, Başaran N, Kars A, Güç D [1999]. Assessment of DNA damage in nurses handling antineoplastic drugs by the alkaline COMET assay. Mutat Res *439*:277–285.

U.S. Census Bureau [1997]. U.S. Census Bureau homepage: 1997 economic census data. [http://www.census.gov]. Date accessed: March 2004.

USEPA (Environmental Protection Agency) [1986]. Guidelines for mutagenicity risk assessment. Federal Register 51(185):34006–34012.

USEPA (Environmental Protection Agency) [1991]. Guidelines for developmental toxicity risk assessment Federal Register 56 (234) 63798–63826.

USEPA (Environmental Protection Agency) [1996a]. Guidelines for reproductive toxicity risk assessment. Federal Register 61 (212):56274–56322.

USEPA (Environmental Protection Agency) [1996b] Proposed guidelines for carcinogen risk assessment. Federal Register 61(79):17960–18011.

Valanis B, McNeil V, Driscoll K [1991]. Staff members' compliance with their facility's antineoplastic drug handling policy. Onc Nurs Forum *18*(3):571-576.

Valanis BG, Vollmer WM, Labuhn KT, Glass AG [1993a]. Acute symptoms associated with antineoplastic drug handling among nurses. Cancer Nurs *16*(4):288–295.

Valanis BG, Vollmer WM, Labuhn KT, Glass AG [1993b]. Association of antineoplastic drug handling with acute adverse effects in pharmacy personnel. Am J Hosp Pharm *50*:455–462.

Valanis B, Vollmer W, Labuhn K, Glass A [1997]. Occupational exposure to antineoplastic agents and self-reported infertility among nurses and pharmacists. J Occup Environ Med *39*(6):574–580.

Valanis B, Vollmer WM, Labuhn K, Glass A, Corelle C [1992]. Antineoplastic drug handling protection after OSHA guidelines: comparison by profession, handling activity, and work site. J Occup Med *34*: 149–155.

Valanis B, Vollmer WM, Steele P [1999]. Occupational exposure to antineoplastic agents: Self-reported miscarriages and stillbirths among nurses and pharmacists. J Occup Environ Med *41*(8):632–638.

Vandenbroucke J, Robays H [2001]. How to protect environment and employees against cytotoxic agents, the UZ Ghent experience. J Oncol Pharm Practice *6*(4):146–152.

Venitt S C-S C, Hunt J, Speechley V, Briggs K [1984]. Monitoring exposure of nursing and pharmacy personnel to cytotoxic drugs: urinary mutation assays and urinary platinum as markers of absorption. Lancet *1*(8368): 74–77.

Walusiak J, Wittczak T, Ruta U, Palczynski C [2002]. Occupational asthma due to mitoxantrone. Allergy *57*(5):461.

Weisburger JH, Griswold DP, Prejean JD, Casey AE, Wood HB, Weisburger EK [1975]. The carcinogenic properties of some of the principal drugs used in clinical cancer chemotherapy. Recent Results Cancer Res *52*:1–17.

White SK, Stephens AD, Dowjat B, Sugarbaker PH [1996]. Safety constiderations [sic] in the use of intraoperative intraperitoneal chemotherapy. Cancer Treat Res *82*:311–316.

Wick C, Slawson MH, Jorgenson JA; Tyler LS [2003]. Using a closed-system protective device to reduce personnel exposure to antineoplastic agents. Am J Health-Syst Pharm *60*:2314–2320.

APPENDIX A

DRUGS CONSIDERED HAZARDOUS

This Alert presents a "Standard Precautions" or “Universal Precautions” approach to handling hazardous drugs safely. As such, no attempt has been made to perform drug risk assessments or propose exposure limits. The area of new drug development is rapidly evolving as unique approaches are being taken to treat cancer and other serious diseases. The definition of hazardous drugs employed in this Alert is based on an ASHP definition that was originally developed in 1995 and, therefore, may not accurately reflect the toxicity criteria associated with the newer generation of pharmaceuticals that are entering the healthcare setting. Bio-engineered drugs target specific sites in the body and, although they may be toxic to the patient, some may not pose a risk to healthcare workers. NIOSH and other organizations are still gathering data on potential toxicity and health effects related to highly potent drugs and bio-engineered drugs. Therefore, when working with all hazardous drugs, “Standard Precautions” should be followed along with any recommendations included in the manufacturer’s MSDSs. This appendix presents useful criteria and sources for determining whether a drug is hazardous. When a drug of concern has been judged to be hazardous, the various precautions outlined in this Alert should be applied as appropriate to the handling of that drug. This appendix also includes a list of drugs that should be handled as

hazardous based on a compilation of lists from four healthcare institutions and one healthcare organization.

Each organization should generate an individual list of drugs considered to be hazardous. Guidance is given in this appendix for making a facility-specific list. Once made, newly purchased drugs should be evaluated against the organization's hazardous drug criteria and, if deemed hazardous, added to the list.

Some organizations may have inadequate resources for determining their own list of hazardous drugs. In these cases, the sample listing of hazardous drugs in this appendix (current only to the printing date of this document) will aid employers and workers to determine when precautions are needed. However, reliance on such a published list is a concern because it quickly becomes outdated since new drugs continually enter the market while drugs on the list may be removed based on additional information becoming available. To fill this knowledge gap, NIOSH will update an internet list at regular intervals, adding new drugs considered to be hazardous or removing those that require re-classification. This hazardous drug list will be posted on the NIOSH website <http://www.cdc.gov/niosh> under the topic page for Healthcare Workers.

Determining Whether a Drug Should Be Considered Hazardous

Many hazardous drugs used to treat cancer bind to or damage DNA (e.g. alkylating agents). Other antineoplastic drugs, some antivirals, antibiotics, and bio-engineered drugs interfere with cell growth, or proliferation, or DNA synthesis. In some cases, the

non-selective action of these drugs disrupts the growth and function of healthy as well as diseased cells, resulting in toxic side effects for treated patients. This same lack of drug selectivity can also cause adverse effects in healthcare workers who are inadvertently exposed to hazardous drugs.

Early concerns about occupational exposure to potent drugs that involved anti-cancer or antineoplastic agents first appeared in the 1970s. While the antineoplastic drugs remain the principal focus of this Alert, other drugs may be considered hazardous, also, because they are potent (small quantities produce a physiological effect) or cause irreversible effects. As use and number of these potent drugs increase, so do opportunities for hazardous exposure among healthcare workers. For example, antineoplastic drugs, e.g., cyclophosphamide, have immunosuppressant effects proven beneficial for treating non-malignant diseases, such as rheumatoid arthritis and multiple sclerosis [Baker et al. 1987; Moody et al. 1987; Chabner et al. 1996; Abel 2000].

Definition of Hazardous Drugs

The American Society of Health-System Pharmacists (ASHP) defines hazardous drugs in the 1990 revision of *Technical Assistance Bulletin on Handling Hazardous Drugs* [ASHP 1990]. The bulletin gives criteria to identify potentially hazardous drugs that should be handled in accordance with an established safety program [McDiarmid et al. 1991; Arrington and McDiarmid 1993]. The criteria are prioritized to reflect the hierarchy of potential toxicity described below. As the hazardous drugs covered by this Alert were designed as human prophylactic agents, human toxicity profiles should be considered

superior to any data from animal models or *in vitro* systems. Additional guidance for the determination of hazardous drugs may be found in the following citations: carcinogenicity [USEPA 1996b; IARC 2004]; teratogenicity [USEPA 1991]; developmental toxicity [USEPA 1991]; and reproductive toxicity [USEPA 1996a]. Physical characteristics of the agents (such as liquid versus solid, or water versus lipid solubility) also need to be considered in determining the potential for occupational exposure.

The 1990 ASHP definition of hazardous drugs[1] was revised by the NIOSH Working Group on Hazardous Drugs for this Alert. Drugs considered hazardous include those that exhibit one, or more, of the following six characteristics in humans or animals:

1. Carcinogenicity
2. Teratogenicity or other developmental toxicity[2]
3. Reproductive toxicity[2]
4. Organ toxicity at low doses[2]
5. Genotoxicity[3]
6. Structure and toxicity profiles of new drugs, which mimic existing drugs as determined hazardous by the above criteria.

---

[1] ASHP (1990) definition of hazardous drugs:

1. Genotoxicity (i.e., mutagenicity and clastogenicity in short-term test systems)
2. Carcinogenicity in animal models, in the patient population, or both as reported by the International Agency for Research on Cancer (IARC)
3. Teratogenicity or fertility impairment in animal studies or in treated patients

4. Evidence of serious organ or other toxicity at low doses in animal models or treated patients.

[2] All drugs have toxic side effects, but some exhibit toxicity at low doses. The level of toxicity reflects a continuum from relatively non-toxic to production of toxic effects in patients at low doses (e.g., a few milligrams or less). For example, a daily therapeutic dose of 10 mg/day or a dose of 1 mg/kg/day in laboratory animals that produces serious organ toxicity, developmental toxicity or reproductive toxicity has been used by the pharmaceutical industry to develop occupational exposure levels (OELs) of less than 10 $\mu g/m^3$ after applying appropriate uncertainty factors [Sargent and Kirk 1988; Naumann and Sargent 1997; Sargent et al. 2002]. OELs in this range are typically established for potent or toxic drugs in the pharmaceutical industry. Under all circumstances, an evaluation of all available data should be conducted to protect healthcare workers from possible adverse effects.

---

[3] In the evaluation of mutagenicity for potentially hazardous drugs, responses from multiple test systems are needed before precautions can be required for handling that agent. The USEPA evaluations include the type of cells affected and *in vitro* versus *in vivo* testing. [USEPA 1986].

Where to Find Information Related to a Drug's Toxicity

The *OSHA Hazard Communication Standard* (HCS) [29 CFR 1910.1200] requires employers to develop a workplace-appropriate hazard communication program. An essential part of this requirement is the identification of all hazardous drugs that employees may contact in their workplace. Compliance with the HCS entails (1) evaluating in-house medications that meet the criteria of one or more of the hazardous drug definitions and (2) informing employees of needed precautions when handling those medications. Practice-specific lists of hazardous drugs (usually developed by pharmacy or nursing departments) should be comprehensive, including all hazardous medications routinely used or very likely to be used by a local practice. Some of the resources that employers can use to evaluate a drug's hazard potential include, but are not limited to:

- Material Safety Data Sheets.
- U.S. Food and Drug Administration approved product labeling (package inserts).
- Special health warnings from drug manufacturers, the FDA and other professional groups and organizations.
- Reports and case studies published in medical and other healthcare profession journals.
- Evidence-based recommendations from other facilities that meet the criteria defining hazardous drugs.

How to Generate Your Own List of Hazardous Drugs

The HCS requires employers to develop a hazard communication program appropriate for their unique workplace. An essential part of the program is the identification of all hazardous drugs an employee may encounter in the facility. Compliance with the HCS entails evaluating whether these medications meet one or more of the criteria that define hazardous drugs and posting the hazardous medications to ensure employee safety. Institutions may wish to compare their lists to the sample listing in this document or on the NIOSH website.

It is not probable that every healthcare provider or facility will use all medications that have received FDA approval, and the HCS does not mandate evaluation of every marketed medication. Instead, compliance with the HCS requires practice-specific

assessments for drugs used at any one time by a facility. However, hazardous drug evaluation is a continual process. Local hazard communication programs should provide assessment for new drugs as they enter the marketplace, and when appropriate, reassessment for addition of or removal from their hazardous drug lists as toxicological data becomes available to support re-categorization. Often toxicological data are incomplete or unavailable for investigational drugs. However, if the mechanism of action suggests that there may be a concern, it is prudent to handle them as hazardous drugs until adequate information becomes available to exclude them.

Some drugs defined as hazardous may not pose a significant risk of direct occupational exposure due to their dosage formulation, such as coated tablets or capsules (i.e. solid, intact medications that are administered to patients without modifying the formulation). However, they may pose a risk if solid drug formulations are altered, such as by crushing tablets or making solutions from them outside of a ventilated cabinet.

Examples of Hazardous Drugs

Below is a sample listing of major hazardous drugs compiled using information from four institutions that have generated lists of hazardous drugs for their respective facilities and one based on the American Hospital Formulary Service (AHFS) Drug information monographs [ASHP 2003] and several other sources. The HCS requires drugs categorized as hazardous to be handled using special precautions. The mandate applies not only to healthcare professionals who provide direct patient care but also to others who support patient care by participating in product acquisition, storage, transportation,

housekeeping and waste disposal. Institutions may want to adopt this list or compare theirs to the listing on the NIOSH website.

INSERT or Tear-out

XX,XX, 2004

Examples of some Drugs Currently Considered as Hazardous

The insert contains a sample list of drugs that should be considered hazardous. These should be handled with special precautions not only by the healthcare professionals who provide direct patient care, but also by others who support patient care by participating in product acquisition, storage, transportation, housekeeping, and waste disposal.

Caution

Drugs purchased and used by a facility may have entered the marketplace after the list below was assembled and, as such, this list may not be all-inclusive!

If you use a drug that is not included in the list of examples, check the available literature to see if the unlisted drug should be treated as if it is hazardous. Check the Material Safety Data Sheet (MSDS), the proper handling section of the package insert, or check with other institutions that might be using the same drug. If any of the documents mention carcinogenicity, genotoxicity, teratogenicity, reproductive, or developmental toxicity, you should use the precautions stipulated in this Alert. If a drug meets one or more of the criteria for hazardous drugs listed in this Alert, it should be handled as hazardous.

The listing below is a sample of what will be available on the NIOSH website <http://www.cdc.gov/niosh> and this list will be updated annually.

Sample List of Drugs that should be Handled as Hazardous*

Drug	Source	AHFS Pharmacologic-Therapeutic Classification
Aldesleukin	4,5	10:00 Antineoplastic Agents
Alemtuzumab	1,3,4,5	10:00 Antineoplastic Agents
Alitretinoin	3,4,5	84:36 Miscellaneous Skin and Mucous Membrane Agents (Retinoid)
Altretamine	1,2,3,4,5	Not in AHFS (Antineoplastic Agent)
Amsacrine	3,5	Not in AHFS (Antineoplastic Agent)
Anastrozole	1,5	10:00 Antineoplastic Agents
Arsenic Trioxide	1,2,3,4,5	10:00 Antineoplastic Agents
Asparaginase	1,2,3,4,5	10:00 Antineoplastic Agents
Azacitidine	3,5	Not in AHFS (Antineoplastic Agent)
Azathioprine	2,3,5	92:00 Unclassified Therapeutic Agents (Immunosuppressant)
Bacillus Calmette Guerin	1,2,4	80:12 Vaccines
Bexarotene	2,3,4,5	10:00 Antineoplastic Agents
Bicalutamide	1,5	10:00 Antineoplastic Agents
Bleomycin	1,2,3,4,5	10:00 Antineoplastic Agents

Drug	Source	AHFS Pharmacologic-Therapeutic Classification
Busulfan	1,2,3,4,5	10:00 Antineoplastic Agents
Capecitabine	1,2,3,4,5	10:00 Antineoplastic Agents
Carboplatin	1,2,3,4,5	10:00 Antineoplastic Agents
Carmustine	1,2,3,4,5	10:00 Antineoplastic Agents
Cetrorelix Acetate	5	92:00 Unclassified Therapeutic Agents (GnRH Antagonist)
Chlorambucil	1,2,3,4,5	10:00 Antineoplastic Agents
Chloramphenicol	1,5	8:12 Antibiotics
Choriogonadotropin alfa	5	68:18 Gonadotropins
Cidofovir	3,5	8:18 Antivirals
Cisplatin	1,2,3,4,5	10:00 Antineoplastic Agents
Cladribine	1,2,3,4,5	10:00 Antineoplastic Agents
Colchicine	5	92:00 Unclassified Therapeutic Agents (Mitotic Inhibitor)
Cyclophosphamide	1,2,3,4,5	10:00 Antineoplastic Agents
Cytarabine	1,2,3,4,5	10:00 Antineoplastic Agents
Cyclosporin	1	92:00 Immunosuppressive Agents
Dacarbazine	1,2,3,4,5	10:00 Antineoplastic Agents
Dactinomycin	1,2,3,4,5	10:00 Antineoplastic Agents
Daunorubicin HCl	1,2,3,4,5	10:00 Antineoplastic Agents
Denileukin	3,4,5	10:00 Antineoplastic Agents
Dienestrol	5	68:16.04 Estrogens
Diethylstilbestrol	5	Not in AHFS (Nonsteroidal Synthetic Estrogen)
Dinoprostone	5	76:00 Oxytocics
Docetaxel	1,2,3,4,5	10:00 Antineoplastic Agents
Doxorubicin	1,2,3,4,5	10:00 Antineoplastic Agents
Dutasteride	5	92:00 Unclassified Therapeutic Agents (5-alpha reductase inhibitor)
Epirubicin	1,2,3,4,5	10:00 Antineoplastic Agents
Ergonovine/Methylergonovine	5	76:00 Oxytocics
Estradiol	1,5	68:16.04 Estrogens
Estramustine phosphate sodium	1,2,3,4,5	10:00 Antineoplastic Agents
Estrogen-Progestin Combinations	5	68:12 Contraceptives
Estrogens, Conjugated	5	68:16.04 Estrogens
Estrogens, Esterified	5	68:16.04 Estrogens
Estrone	5	68:16.04 Estrogens
Estropipate	5	68:16.04 Estrogens

Drug	Source	AHFS Pharmacologic-Therapeutic Classification
Etoposide	1,2,3,4,5	10:00 Antineoplastic Agents
Exemestane	1,5	10:00 Antineoplastic Agents
Finasteride	1,3,5	92:00 Unclassified Therapeutic Agents (5-alpha reductase inhibitor
Floxuridine	1,2,3,4,5	10:00 Antineoplastic Agents
Fludarabine	1,2,3,4,5	10:00 Antineoplastic Agents
Fluorouracil	1,2,3,4,5	10:00 Antineoplastic Agents
Fluoxymesterone	5	68:08 Androgens
Flutamide	1,2,5	10:00 Antineoplastic Agents
Fulvestrant	5	10:00 Antineoplastic Agents
Ganciclovir	1,2,3,4,5	8:18 Antiviral
Ganirelix Acetate	5	92:00 Unclassified Therapeutic Agents (GnRH Antagonist)
Gemcitabine	1,2,3,4,5	10:00 Antineoplastic Agents
Gemtuzumab ozogamicin	1,3,4,5	10:00 Antineoplastic Agents
Gonadotropin, Chorionic	5	68:18 Gonadotropins
Goserelin	1,2,5	10:00 Antineoplastic Agents
Hydroxyurea	1,2,3,4,5	10:00 Antineoplastic Agents
Ibritumomab tiuxetan	3	10:00 Antineoplastic Agents
Idarubicin	1,2,3,4,5	Not in AHFS (Antineoplastic Agent)
Ifosfamide	1,2,3,4,5	10:00 Antineoplastic Agents
Imatinib mesylate	1,3,4,5	10:00 Antineoplastic Agents
Interferon alfa-2a	1,2,4,5	10:00 Antineoplastic Agents
Interferon alfa-2b	1,2,4,5	10:00 Antineoplastic Agents
Interferon alfa-n1	1,5	10:00 Antineoplastic Agents
Interferon alfa-n3	1,5	10:00 Antineoplastic Agents
Irinotecan HCl	1,2,3,4,5	10:00 Antineoplastic Agents
Leflunomide	3,5	92:00 Unclassified Therapeutic Agents (Antineoplastic Agent)
Letrozole	1,5	10:00 Antineoplastic Agents
Leuprolide acetate	1,2,5	10:00 Antineoplastic Agents
Lomustine	1,2,3,4,5	10:00 Antineoplastic Agents
Mechlorethamine	1,2,3,4,5	10:00 Antineoplastic Agents
Megestrol	1,5	10:00 Antineoplastic Agents
Melphalan	1,2,3,4,5	10:00 Antineoplastic Agents
Menotropins	5	68:18 Gonadotropins
Mercaptopurine	1,2,3,4,5	10:00 Antineoplastic Agents
Methotrexate	1,2,3,4,5	10:00 Antineoplastic Agents
Methyltestosterone	5	68:08 Androgens

Drug	Source	AHFS Pharmacologic-Therapeutic Classification
Mifepristone	5	76:00 Oxytocics
Mitomycin	1,2,3,4,5	10:00 Antineoplastic Agents
Mitotane	1,4,5	10:00 Antineoplastic Agents
Mitoxantrone HCl	1,2,3,4,5	10:00 Antineoplastic Agents
Mycophenolate mofetil	1,3,5	92:00 Immunosuppressive Agents
Nafarelin	5	68:18 Gonadotropins
Nilutamide	1,5	10:00 Antineoplastic Agents
Oxaliplatin	1,3,4,5	10:00 Antineoplastic Agents
Oxytocin	5	76:00 Oxytocics
Paclitaxel	1,2,3,4,5	10:00 Antineoplastic Agents
Pegaspargase	1,2,3,4,5	10:00 Antineoplastic Agents
Pentamidine isethionate	1,2,3,5	8:40 Miscellaneous Anti-infectives
Pentostatin	1,2,3,4,5	10:00 Antineoplastic Agents
Perphosphamide	3,5	Not in AHFS (Antineoplastic Agent)
Pipobroman	3,5	Not in AHFS (Antineoplastic Agent)
Piritrexim isethionate	3,5	Not in AHFS (Antineoplastic Agent)
Plicamycin	1,2,3,5	Not in AHFS (Antineoplastic Agent)
Podoflilox	5	84:36 Miscellaneous Skin and Mucous Membrane Agents (Mitotic Inhibitor)
Podophyllum Resin	5	84:36 Miscellaneous Skin and Mucous Membrane Agents (Mitotic Inhibitor)
Prednimustine	3,5	Not in AHFS (Antineoplastic Agent)
Procarbazine	1,2,3,4,5	10:00 Antineoplastic Agents
Progesterone	5	68:32 Progestins
Progestins	5	68:12 Contraceptives
Raloxifene	5	68:16.12 Estrogen Agonists-Antagonists
Raltitrexed	5	Not in AHFS (Antineoplastic Agent)
Ribavirin	1,2,5	8:18 Antiviral
Streptozocin	1,2,3,4,5	10:00 Antineoplastic Agents

Drug	Source	AHFS Pharmacologic-Therapeutic Classification
Tacrolimus	1,5	92:00 Unclassified Therapeutic Agents (Immunosuppressant)
Tamoxifen	1,2,5	10:00 Antineoplastic Agents
Temozolomide	3,4,5	10:00 Antineoplastic Agents
Teniposide	1,2,3,4,5	10:00 Antineoplastic Agents
Testolactone	5	10:00 Antineoplastic Agents
Testosterone	5	68:08 Androgens
Thalidomide	1,3,5	92:00 Unclassified Therapeutic Agents (Immunomodulator)
Thioguanine	1,2,3,4,5	10:00 Antineoplastic Agents
Thiotepa	1,2,3,4,5	10:00 Antineoplastic Agents
Topotecan	1,2,3,4,5	10:00 Antineoplastic Agents
Toremifene citrate	1,5	10:00 Antineoplastic Agents
Tositumomab	3,5	Not in AHFS (Antineoplastic Agent)
Tretinoin	1,2,3,5	84:16 Cell Stimulants and Proliferants (Retinoid)
Trifluridine	1,2,5	52:04.06 Antivirals
Trimetrexate glucuronate	5	8:40 Miscellaneous Anti-Infectives (Folate Antagonist)
Triptorelin	5	10:00 Antineoplastic Agents
Uracil Mustard	3,5	Not in AHFS (Antineoplastic Agent)
Valganciclovir	1,3,5	8:18 Antiviral
Valrubicin	1,2,3,5	10:00 Antineoplastic Agents
Vidarabine	1,2,5	52:04.06 Antivirals
Vinblastine sulfate	1,2,3,4,5	10:00 Antineoplastic Agents
Vincristine sulfate	1,2,3,4,5	10:00 Antineoplastic Agents
Vindesine	1,5	Not in AHFS (Antineoplastic Agent)
Vinorelbine tartrate	1,2,3,4,5	10:00 Antineoplastic Agents
Zidovudine	1,2,5	8:18:08 Antiretroviral Agents

[1]The National Institutes of Health Clinical Center, Bethesda, MD (Revised 8/2002)
The National Institutes of Health Clinical Center Hazardous Drug (HD) List is part of the NIH Clinical Center's hazard communication program. It was developed in compliance with the *Hazard Communication Standard* [29 CFR 1910.1200] as it applies to hazardous drugs used in the workplace. The list is continually revised and represents the diversity of medical practice at the NIH Clinical Center; however, its content does not reflect an

exhaustive review of all FDA-approved medications that may be considered hazardous and it is not intended for use outside the NIH.
[2]The Johns Hopkins Hospital, Baltimore, MD (Revised 9/2002)
[3]The Northside Hospital, Atlanta, GA (Revised 8/2002)
[4]The University of Michigan Hospitals and Health Centers, Ann Arbor, MI (Revised 2/2003)

[5]This sample listing of hazardous drugs was compiled by the Pharmaceutical Research and Manufacturers of America (PhRMA) using information from the American Hospital Formulary Service (AHFS) Drug Information monographs published by ASHP in selected AHFS Pharmacologic-Therapeutic Classification categories [ASHP/AHFS DI 2003] and by applying the definition for hazardous drugs. The list also includes drugs from other sources [PDR 2003; Sweetman (Martindale) 2002; Shepard 2001; Schardein 2000; REPROTOX 2003] that satisfy the definition for hazardous drugs. Newly approved drugs that have structures or toxicological profiles that mimic the drugs on this list should also be included. (Revised 12/2004)

*These lists were used with permission of the institutions that provided them and were adapted for use by NIOSH. The sample lists are intended to guide healthcare providers in diverse practice settings and should not be construed as complete representations of all of the hazardous drugs used at the referenced institutions. Some drugs defined as hazardous may not pose a significant risk of direct occupational exposure due to their dosage formulation, such as coated tablets or capsules (i.e., solid, intact medications that are administered to patients without modifying the formulation). However, they may pose a risk if solid drug formulations are altered (e.g., tablets are crushed or dissolved, capsules are pierced or opened) outside of a ventilated cabinet.

APPENDIX B

GLOSSARY OF TERMS AND ABBREVIATIONS

ACGIH American Conference of Government Industrial Hygienists

ACOEM American College of Occupational and Environmental Medicine

AHFS American Hospital Formulary Service

AGS American Glovebox Society

Antineoplastic Drug A chemotherapeutic agent that controls or kills cancer cells. Drugs used in the treatment of cancer are cytotoxic but are generally more damaging to dividing cells than to resting cells.

Aseptic Free of living pathogenic organisms or infected materials.

ASHP American Society of Health-System Pharmacists (formerly the American Society of Hospital Pharmacists)

Barrier System An open system that can exchange unfiltered air and contaminants with the surrounding environment.

Barrier Isolator This is a term with varying interpretations, especially as they pertain to hazard containment and aseptic processing. For this reason, it has been intentionally omitted from this Alert.

Biohazard Infectious agents or hazardous biological materials that present a risk or potential risk to the health of humans or the environment. Biohazards include tissue, blood or body fluids and materials such as needles or other equipment contaminated with these agents or materials.

Biomarker A biological, biochemical or structural event that may serve as an indicator of potential damage to cellular components, whole cells, tissues or organs.

BSC Biological Safety Cabinet [CDC/NIH 1999; NSF/ANSI 2002]

Class I A Class I BSC provides personnel and environmental protection, but no product protection. It is a negative-pressure, ventilated cabinet usually operated with an open front and a minimum face velocity at the work opening of at least 75 ft/min. It is similar in design to chemical fume hood except all of the air from the cabinet is exhausted through a HEPA filter (either into the laboratory or to the outside).

Class II A ventilated cabinet for personnel, product, and environmental protection having an open front with inward airflow for personnel protection, downward HEPA-filtered laminar airflow for product protection, and HEPA-filtered exhausted air for environmental protection.

Type A1 (formerly, Type A) These cabinets maintain a minimum inflow velocity of 75 ft/min, have HEPA-filtered downflow air that is a portion of the mixed downflow and inflow air from a common plenum, may exhaust HEPA-filtered air back into the laboratory or to the environment through an exhaust canopy, and may have positive pressure contaminated ducts and plenums that are not surrounded by negative pressure plenums. They are not suitable for use with volatile toxic chemicals and volatile radionucleotides.

Type A2 (formerly, Type B3) These cabinets maintain a minimum inflow velocity of 100 ft/min, have HEPA-filtered downflow air that is a portion of the mixed downflow and inflow air from a common exhaust plenum, may exhaust HEPA-filtered air back into the laboratory or to the environment through an exhaust canopy, and

have all contaminated ducts and plenums under negative pressure or surrounded by negative pressure ducts and plenums. If these cabinets are used for minute quantities of volatile toxic chemicals and tracer amounts of radionucleotides, they must be exhausted through properly functioning exhaust canopies.

Type B1 These cabinets maintain a minimum inflow velocity of 100 ft/min, have HEPA-filtered downflow air composed largely of uncontaminated recirculated inflow air, exhaust most of the contaminated downflow air through a dedicated duct exhausted to the atmosphere after passing it through a HEPA filter, and have all contaminated ducts and plenums under negative pressure or surrounded by negative pressure ducts and plenums. If these cabinets are used for work involving minute quantities of volatile toxic chemicals and tracer amounts of radionucleotides, the work must be done in the direct exhausted portion of the cabinet.

Type B2 (total exhaust) These cabinets maintain a minimum inflow velocity of 100 ft/min, have HEPA-filtered downflow air drawn from the laboratory or the outside, exhaust all inflow and downflow air to the atmosphere after filtration through a HEPA filter without recirculation in the cabinet or return to the laboratory, and have all contaminated ducts and plenums under negative pressure or surrounded by directly exhausted negative pressure ducts and plenums. These cabinets may be used with volatile toxic chemicals and radionucleotides.

Class III A totally enclosed, ventilated cabinet of gas-tight construction in which operations are conducted through attached rubber gloves and observed through a non-opening view window. It is maintained under negative pressure of at least 0.50 inches of water gauge, and air is drawn into the cabinet through HEPA filters. The

exhaust air is treated by double HEPA filtration or single HEPA filtration/incineration. Passage of materials in/out of the cabinet is generally performed through a dunk tank (accessible through the cabinet floor) or a double-door pass through box (such as an autoclave) that can be decontaminated between uses. [Abbreviated definition. For a more thorough description, refer to the September 2000 CDC/NIH document, Primary Containment for Biohazards: Selection, Installation and Use of Biological Safety Cabinets, 2nd Edition available at http://www.cdc.gov/od/ohs/biosfty/bsc/bsc.htm]

CDC Centers for Disease Control and Prevention

Chemotherapy Drug A chemical agent used to treat diseases. The term usually refers to a drug used to treat cancer.

Chemotherapy Glove A medical glove that has been approved by the FDA for use when handling antineoplastic drugs. It should conform to the ASTM Standard XXXX.

Chemotherapy Waste Discarded items such as gowns, gloves, masks, IV tubing, empty bags, empty drug vials, needles and syringes and other items generated in the preparation and administration of antineoplastic agents.

Closed System A device that does not exchange unfiltered air or contaminants with the adjacent environment.

Closed System Drug Transfer Device A drug transfer device which mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system.

Cytotoxic A pharmacologic compound that is detrimental or destructive to cells within the body.

Decontamination Inactivation, neutralization or removal of toxic agents, usually by chemical means.

Engineering Controls Devices designed to eliminate or reduce worker exposures to chemical, biological, radiological, ergonomic or physical hazards. Examples include laboratory fume hoods, glove bags, retracting syringe needles, sound-dampening materials to reduce noise levels, safety interlocks, and radiation shielding.

FDA Food and Drug Administration

Genotoxic Capable of damaging the DNA leading to mutations.

Glove Box A controlled environment work enclosure providing a primary barrier from the work area. The operations are performed through sealed gloved openings to protect the worker, the ambient environment, and/or the product.

Glove Bag A glove box made from a flexible plastic film. The operations are performed through sealed gloved openings to protect the worker, the ambient environment, and/or the product.

Hazardous Drug Any drug that is identified by at least one of the following six criteria: carcinogenicity; teratogenicity or developmental toxicity; reproductive toxicity in humans; organ toxicity at low doses in humans or animals; genotoxicity; or new drugs that mimic existing hazardous drugs in structure or toxicity.

Hazardous Waste Any waste that is a RCRA listed hazardous waste [40 CFR 261.30–33] or meets a RCRA characteristic of ignitability, corrosivity, reactivity or toxicity as defined in 40 CFR 261.21-24.

Healthcare Settings All hospitals, medical clinics, outpatient facilities, physicians' offices, retail pharmacies and similar facilities dedicated to the care of patients.

Healthcare Worker All employees who are involved in the care of patients. These include: pharmacists; pharmacy technicians; nurses (RNs, LPNs, nurses aids etc); physicians; home healthcare personnel; and environmental services personnel (housekeeping, laundry, waste disposal)

HEPA Filter High Efficiency Particulate Air Filter, rated 99.97% efficient in capturing 0.3 micron-diameter particles.

Horizontal Laminar Flow Hood (Horizontal Laminar Flow Clean Bench) A device that protects the work product and the work area by supplying HEPA-filtered air to the rear of the cabinet, flowing horizontally across the work area and out towards the worker.

IARC International Agency for Research on Cancer.

Isolator An isolator is sealed or is supplied with air through a microbially retentive filtration system (HEPA minimum) and may be reproducibly decontaminated. When closed, it uses only decontaminated (where necessary) interfaces or Rapid Transfer Ports (RTPs) for materials transfer. When open, it allows for the ingress and/or egress of materials through defined openings that have been designed and validated to preclude the transfer of contaminants or unfiltered air with adjacent environments. It can be used for aseptic processing activities, containment of potent compounds, or simultaneously for both asepsis and containment. Some isolator designs allow operations within the isolator to be conducted through attached rubber gloves without compromising asepsis and/or containment.

Aseptic Isolator: A ventilated isolator designed to exclude external contamination from entering the critical zone inside the isolator.

Aseptic Containment Isolator: A ventilated isolator designed to meet the requirements of both an Aseptic Isolator and a Containment Isolator.

Containment Isolator: A ventilated isolator designed to prevent the toxic materials processed inside the isolator from escaping to the surrounding environment.

Lab Coat A disposable or reusable open-front coat usually made of cloth or other permeable material.

MSDS Material Safety Data Sheet. Summaries provided by the manufacturer that describe the chemical properties and hazards of specific chemicals and ways in which the workers can protect themselves from exposure to these chemicals.

Mutagenic Capable of increasing the spontaneous mutation rate by causing changes in the DNA.

NIH National Institutes of Health

NIOSH National Institute for Occupational Safety and Health

NSF National Sanitation Foundation

OEL Occupational Exposure Limit. An industry or other non-government exposure limit usually based on scientific calculations of levels of materials in air considered to be acceptable for healthy workers.

ONS Oncology Nursing Society

OSHA Occupational Safety and Health Administration

PDA Formally the Parenteral Drug Association. An international trade association serving pharmaceutical science and technology

PEL Permissible Exposure Limit An OSHA established permissible concentration in air of a substance to which nearly all workers may be repeated exposed 8 hours a day, 40 hours a week, for 30 years without adverse effects.

PPE Personal Protective Equipment Items such as gloves, gowns, respirators, goggles, face shields, and others that protect the individual worker from coming into contact with hazardous physical or chemical exposures.

RCRA Resource Conservation and Recovery Act

REL Recommended Exposure Limit

Respirator A type of PPE that prevents harmful materials from entering the respiratory system usually by filtering hazardous agents from the workroom air. A surgical mask does not offer respiratory protection.

Risk Assessment The characterization of the potential adverse health effects of human exposure to environmental or occupational hazards. It can be divided into five major steps: hazard identification; dose-response assessment; exposure assessment; risk characterization; and risk communication.

Sister Chromatid Exchange The exchange of segments of DNA between sister chromatids.

Standard Precautions (formerly Universal Precautions) Describes the practice in healthcare of treating every patient as if they were infected with HIV or other similar diseases by using barriers to avoid known means of transmission of infectious agents. These barriers can include nonporous gloves, goggles and face shields. Careful handling and disposal of sharps or the use of needle-less systems are also important.

TLV® Threshold Limit Value An exposure level established by the ACGIH under which most people can work consistently for 8 hours a day, day after day, with no harmful effects.

Ventilated Cabinet A type of engineering control designed for purposes of worker protection (as used in this document). These devices are designed to minimize employee exposures by controlling emissions of airborne contaminants through: (1) The full or partial enclosure of a potential contaminant source and (2) The use of airflow capture velocities to capture and remove airborne contaminants near their point of generation, and/or air pressure relationships that define the direction of airflow in/out of the cabinet. Examples include biological safety cabinets, containment isolators, or laboratory fume hoods.

APPENDIX C

NIOSH HAZARDOUS DRUG SAFETY WORKING GROUP

The following individuals and organizations were members of the NIOSH Hazardous Drug Safety Working Group that provided information and recommendations for this document:

Tito Aldape, Microflex Corporation; Roger Anderson, DrPH, University of Texas M.D. Anderson Cancer Center; Britton Berek, Joint Commission on Accreditation of Healthcare Organizations; Stephen Brightwell, G. Edward Burroughs, PhD, CIH, Thomas Connor, PhD, NIOSH; Barbara J. Coyle, BSN, RN COHN-S, State of Wisconsin; Gayle DeBord, PhD, NIOSH; Robert DeChristoforo, MS, National Institutes of Health; Phillup C. Dugger, Dori Greene, US Oncology, Inc; Duane R. Hammond, BS, ME, NIOSH; Bruce Harrison, MS, RPh, BCOP, Department of Veterans Affairs; Hye-Joo Kim, Food and Drug Administration; L.D. King, International Academy of Compounding

Pharmacists; Nancy Kramer, RN, BSN, Coram Healthcare; R. David Lauper, PharmD, SuperGen, Inc; Melissa Leone, RN, BSN, Apria Healthcare; Chiu S. Lin, PhD, Food and Drug Administration; Barbara MacKenzie, Charlene Maloney, NIOSH; Melissa McDiarmid, MD, MPH, University of Maryland; Kenneth Mead, M.S., P.E, NIOSH; CDR Martha T. O'Lone, Jerry Phillips, Food and Drug Administration; Marty Polovich, MN, RN, AOCN, Oncology Nursing Society; Luci Power, MS, RPh, University of California; Angela C. Presson, MD, MPH, US Occupational Safety and Health Administration; Hank Rahe, Containment Technologies Group, Inc; Laurence Reed, M.S, Anita L. Schill, PhD, MPH, Teresa Schnorr, PhD, Doug Sharpnack, DVM, NIOSH; Charlotte A. Smith, MS, RPh, PharmEcology Associates, LLC; Sandi Yurichuk

American Federation of State, County and Municipal Employees; American Nurses Association; American Society of Health-System Pharmacists; Oncology Nursing Society; Pharmaceutical Research and Manufacturers of America; Service Employees International Union; US Environmental Protection Agency

Baxa Corporation; Nuaire, Inc; The Baker Company, Inc