NIOSH ALERT

Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings
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Foreword

The purpose of this Alert is to increase awareness among health care workers and their employers about the health risks posed by working with hazardous drugs and to provide them with measures for protecting their health. Health care 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 (for example, pharmacy and nursing personnel, physicians, operating room personnel, environmental services workers, workers in research laboratories, 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 manufacturing sector.

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 bioengineered drugs can be hazardous to health care 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.

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Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings

Warning!
Working with or near hazardous drugs in health care settings may cause skin rashes, infertility, miscarriage, birth defects, and possibly leukemia or other cancers.

The National Institute for Occupational Safety and Health (NIOSH) requests assistance in preventing occupational exposures to antineoplastic drugs (drugs used to treat cancer) and other hazardous drugs in health care settings. Health care workers who work with or near hazardous drugs may suffer from skin rashes, infertility, miscarriage, birth defects, and possibly leukemia or other cancers.

Workers may be exposed to hazardous drugs in the air or on work surfaces, clothing, medical equipment, and patient urine or feces. The term hazardous drugs, as it is used in this Alert, includes drugs that are known or suspected to cause adverse health effects from exposures in the workplace. They include drugs used for cancer chemotherapy, antiviral drugs, hormones, some bioengineered drugs, and other miscellaneous drugs. The health risk depends on how much exposure a worker has to these drugs and how toxic they are. Exposure risks can be greatly reduced by (1) making sure that engineering controls such as a ventilated cabinet are used and (2) using proper procedures and protective equipment for handling hazardous drugs.

This Alert warns health care workers about the risks of working with hazardous drugs and recommends methods and equipment for protecting their health. The Alert addresses workers in health care settings, veterinary medicine, research laboratories, retail pharmacies, and home health care agencies; it does not address workers in the drug manufacturing sector. Included in the Alert are five case reports of workers who suffered adverse health effects after being exposed to antineoplastic drugs.

NIOSH requests that employers, editors of trade journals, safety and health officials, and unions bring the recommendations in this Alert to the attention of all workers who are at risk.
BACKGROUND

Drugs have a successful history of use in treating illnesses and injuries, and they are responsible for many of our medical advances over the past century. However, virtually all drugs have side effects associated with their use by patients. Thus, both patients and workers who handle them are at risk of suffering these effects. In addition, it is known that exposures to even very small concentrations of certain drugs may be hazardous for workers who handle them or work near them.

The term hazardous drugs was first used by the American Society of Hospital Pharmacists (ASHP) [ASHP 1990] and is currently used by the Occupational Safety and Health Administration (OSHA) [OSHA 1995, 1999]. Drugs are classified as hazardous if studies in animals or humans indicate that exposures to them have a potential for causing cancer, developmental or reproductive toxicity, or harm to organs. Many 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]. See Appendix A for examples of hazardous drugs and a full discussion of criteria used to define and classify them as hazardous.

Although the potential therapeutic benefits of hazardous drugs outweigh the risks of side effects for ill patients, exposed health care workers risk these same side effects with no therapeutic benefit. Occupational exposures to hazardous drugs 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; Stückter et al. 1990; Valanis et al. 1997, 1999; Peelen et al. 1999]; and (3) possibly cancer [Skov et al. 1992].

Guidelines have been established 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 concentrations of some hazardous drugs have been documented in the urine of health care workers who prepared or administered them—even after safety precautions had been employed [Ensslin et al. 1994, 1997; Sessink et al. 1992b, 1994a,b, 1997; Minoia et al. 1998; Wick et al. 2003]. Environmental studies of patient-care areas have documented measurable concentrations of drug contamination, even in facilities thought to be following recommended handling guidelines [Minoia et al. 1998; Connor et al. 1999; Pethran et al. 2003].

The numbers and types of work environments containing antineoplastic drugs are expanding as these agents are used increasingly for nonmalignant rheumatologic and immunologic diseases [Baker et al. 1987; Moody et al. 1987; Chabner et al. 1996; Abel 2000] and for chemotherapy in veterinary medicine [Rosenthal 1996; Takada 2003]. This Alert summarizes the health effects associated with occupational exposure to these agents and provides recommendations for safe handling.

POTENTIAL FOR WORKER EXPOSURE

Workers may be exposed to a drug throughout its life cycle—from manufacture to...
transport and distribution, to use in health care or home care settings, to waste disposal. 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]. These workers include shipping and receiving personnel, pharmacists and pharmacy technicians, nursing personnel, physicians, operating room personnel, environmental services personnel, and workers in veterinary practices where hazardous drugs are used. This Alert addresses workers in health care settings, veterinary medicine, research laboratories, retail pharmacies, and home health care agencies; it does not address workers in the drug manufacturing sector.

.conditions for exposure

Both clinical and nonclinical workers may be exposed to hazardous drugs when they create aerosols, generate dust, clean up spills, or touch contaminated surfaces during the preparation, administration, or disposal of hazardous drugs. The following list of activities may result in exposures through inhalation, skin contact, ingestion, or injection:

- Reconstituting powdered or lyophilized drugs and further diluting either the reconstituted powder or concentrated liquid forms of hazardous drugs [Fransman et al. 2004]
- Expelling air from syringes filled with hazardous drugs
- Administering hazardous drugs by intramuscular, subcutaneous, or intravenous (IV) routes
- Counting out individual, uncoated oral doses and tablets from multidose bottles
- Unit-dosing uncoated tablets in a unit-dose machine
- Crushing tablets to make oral liquid doses [Dorr and Alberts 1992; Shahsavaran et al. 1993; Harrison and Schultz 2000]
- Compounding potent powders into custom-dosage capsules
- Contacting measurable concentrations of drugs present on drug vial exteriors, work surfaces, floors, and final drug products (bottles, bags, cassettes, and syringes) [McDevitt et al. 1993; Sessink et al. 1992a,b, 1994b; Minoia et al. 1998; Connor et al. 1999, 2002; Schmaus et al. 2002]
- Generating aerosols during the administration of drugs, either by direct IV push or by IV infusion
- Priming the IV set with a drug-containing solution at the patient bedside (this procedure should be done in the pharmacy)
- Handling body fluids or body-fluid-contaminated clothing, dressings, linens, and other materials [Cass and Musgrave 1992; Kromhout et al. 2000]
- Handling contaminated wastes generated at any step of the preparation or administration process
- Performing certain specialized procedures (such as intraoperative intraperitoneal chemotherapy) in the operating room [White et al. 1996; Stuart et al. 2002]
Handling unused hazardous drugs or hazardous-drug-contaminated waste

Decontaminating and cleaning drug preparation or clinical areas

Transporting infectious, chemical, or hazardous waste containers

Removing and disposing of personal protective equipment (PPE) after handling hazardous drugs or waste

**EXPOSURE ROUTES**

Exposures to hazardous drugs may occur through inhalation, skin contact, skin absorption, ingestion, or injection. Inhalation and skin contact/absorption are the most likely routes of exposure, but 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].

A number of studies have attempted to measure airborne concentrations of antineoplastic drugs in health care settings [Kleinberg and Quinn 1981; Neal et al. 1983; McDiarmid et al. 1986; Py 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 air samples containing measurable airborne concentrations of hazardous drugs was low, and the actual concentrations of the drugs, when present, were quite low. These results may be attributed to the inefficiency of sampling and analytical techniques used 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 areas where hazardous drugs are prepared and administered at health care facilities in the United States 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 investigators measured detectable concentrations of one to five hazardous drugs in various locations such as biological safety cabinet (BSC) surfaces, floors, counter tops, storage areas, tables and chairs in patient treatment areas, and locations adjacent to drug-handling areas. 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 the potential for skin contact highly probable in both pharmacy and patient areas.

**EVIDENCE FOR WORKER EXPOSURE**

Evidence indicates that workers are being exposed to hazardous drugs and are experiencing serious health effects despite current work practice guidelines. Protection from hazardous drug exposures depends on safety programs established by employers.
and followed by workers. Factors that affect worker exposures include the following:

- Drug handling circumstances (preparation, administration, or disposal)
- Amount of drug prepared
- Frequency and duration of drug handling
- Potential for absorption
- Use of ventilated cabinets*
- PPE
- Work practices

The likelihood that a worker will experience adverse effects from hazardous drugs increases with the amount and frequency of exposure and the lack of proper work practices.

Worker exposures have been assessed by studies of 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 adverse health effects [Baker and Connor 1996]. Sessink and Bos [1999] noted that 11 of 12 studies reported cyclophosphamide in the urine of health care workers tested, indicating continued exposure despite safety precautions.

Harrison [2001] reported that six different drugs (cyclophosphamide, methotrexate, ifosfamide, epirubicin and cisplatin/carboplatin) were detected in the urine of health care workers by 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 3-year period. Cyclophosphamide, ifosfamide, doxorubicin, and epirubicin (but not daunorubicin or idarubicin) and platinum (from cisplatin or carboplatin) were identified in urine samples from many of the study participants. A U.S. investigation demonstrated that use of a closed-system device for 6 months reduced both the concentration of cyclophosphamide or ifosfamide in the urine of exposed health care workers and the percentage of samples containing these drugs [Wick et al. 2003]. Hazardous drugs have also been documented in the urine of health care workers who did not handle hazardous drugs but were potentially exposed through 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**

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 leukemias and other cancers [Harris 1975, 1976; IARC 1979]. Many health care professionals began to question the safety of occupational exposure to these agents [Ng and Jaffe 1970; Donner 1978; Johansson 1979].

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*Ventilated cabinet is a type of engineering control designed to protect workers. Examples include BSCs and isolators designed to prevent hazardous drugs inside the cabinet from escaping into the work environment. See the Glossary in Appendix B for additional descriptions of engineering controls.
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]. Several studies that have not linked genotoxic effects with worker exposures may be explained by technical confounders and a lack of accurate blood and urine sampling in exposed workers [Sorsa et al. 1985; McDiarmid et al. 1992]. When all the data are considered, the weight of evidence associates hazardous drug exposures at work with increased genotoxicity [Sorsa and Anderson 1996; Baker and Connor 1996; Bos and Sessink 1997; Hewitt 1997; Sessink and Bos 1999; Harrison and Schulz 2001].

Developmental and Reproductive Effects

A recent review of 14 studies described an association between exposure to antineoplastic drugs and adverse reproductive effects, and 9 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 [Hemmingi et al. 1985], low birth weight and congenital abnormalities [Peelen et al. 1999], and infertility [Valanis et al. 1999].

Cancer

Several reports have addressed the relationship of cancer occurrence to health care workers' exposures to antineoplastic drugs. A significantly increased risk of leukemia has been reported among oncology nurses identified in the Danish cancer registry for the period 1943–1987 [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 6 months in a department where patients were treated with antineoplastic drugs.

CURRENT STANDARDS AND RECOMMENDATIONS

Currently, no NIOSH recommended exposure limits (RELS), OSHA permissible exposure limits (PELs), or American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (TLVs®) have been established for hazardous drugs in general. An OSHA PEL and an ACGIH TLV have been established for soluble platinum salts [29 CFR 1910.1000; ACGIH 2003]. However, these standards are based on sensitization and not on the potential to cause cancer. A PEL, an REL, and a TLV have also been established for inorganic arsenic compounds, which include the antineoplastic drug arsenic trioxide [29 CFR 1910.1018; NIOSH 2004; ACGIH 2003]. A workplace environmental exposure level (WEEL) has been established for some antibiotics, including chloramphenicol (AIHA 2002). 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 material safety data sheets (MSDSs) or from the manufacturer [Sargent and Kirk 1988; Naumann and Sargent 1997; Sargent et al. 2002].

U.S. Environmental Protection Agency (EPA) regulations under the Resource Conservation and Recovery Act (RCRA) [42 USC1 6901–6992] apply to the management of hazardous wastes, which include nine antineoplastic drugs [40 CFR 260–279].

OSHA

OSHA originally published guidelines for antineoplastic drugs in 1986 [OSHA 1986]. Current OSHA standards and guidelines that address hazardous drugs include the following:

- Hazard communication standard [29 CFR 1910.1200]
- Occupational exposure to hazardous chemicals in laboratories standard [29 CFR 1910.1450]
- *OSHA Technical Manual; Section VI, Chapter 2: Controlling Occupational Exposure to Hazardous Drugs* [OSHA 1999]. Main elements of these 1999 OSHA guidelines include the following:
  - 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

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EPA

EPA/RCRA regulations require that hazardous waste be managed by following a strict set of regulatory requirements [40 CFR 260–279]. The RCRA list of hazardous wastes was developed in 1976 and includes only about 30 pharmaceuticals, 9 of which are antineoplastic drugs. Recent evidence indicates that a number of drug formulations exhibit hazardous waste characteristics [Smith 2002]. OSHA [1999] and ASHP [1990] recommend that hazardous drug waste be disposed of in a manner similar to that required for RCRA-listed hazardous waste. Hazardous drug waste includes partially filled vials, undispensed products, unused IVs, needles and syringes, gloves, gowns, underpads, contaminated materials from spill cleanups, and 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. Published EPA guidelines are as follows:


Additional Guidelines

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

- Centers for Disease Control (CDC) and National Institutes of Health (NIH). *Primary Containment for Biohazards* [CDC/NIH 2000]. Provides guidance on the selection, installation, testing, and use of BSCs.

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*United States Code. See USC in references.*
NIH. Recommendations for the Safe Handling of Cytotoxic Drugs [NIH 2002]. Includes recommendations for the safe preparation and administration of cytotoxic drugs.


Oncology Nursing Society. Chemotherapy and Biotherapy Guidelines and Recommendations for Practice [Brown et al. 2001]. Provides complete guidelines for the administration of antineoplastic drugs, including safe handling guidelines.

Oncology Nursing Society. Safe Handling of Hazardous Drugs [Polovich 2003]. Includes proper handling guidelines for hazardous drugs.

United States Pharmacopeia. Chapter <797> Pharmaceutical Compounding—Sterile Preparations [USP 2004]. Details the procedures and requirements for compounding sterile preparations and sets standards applicable to all settings in which sterile preparations are compounded.

National Sanitation Foundation (NSF) and American National Standards Institute (ANSI). NSF/ANSI 49–2002 Class II (Laminar Flow) Biosafety Cabinetry [NSF/ANSI 2002]. Addresses classification and certification of Class II BSCs and provides a definition for Class III BSCs.


CASE REPORTS

The following cases illustrate the range of health effects reported after exposure to antineoplastic drugs:

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 nonbloody diarrhea with cramping abdominal pain. Profuse vomiting occurred, after which she felt better. The nurse 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

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cause gastric upset, and the investigators attributed her gastrointestinal distress to systemic absorption of carmustine.

Case 2

A 39-year-old pharmacist suffered two episodes of painless hematuria (blood in the urine) and was found to have cancer (a grade II papillary transitional cell carcinoma) [Levin et al. 1993]. Twelve years before her diagnosis, she had worked full time for 20 months in a hospital IV 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. Because she was a nonsmoker and had no other known occupational or environmental risk factors, her cancer was attributed to her antineoplastic drug exposure at work—though a cause and effect relationship has not been established in the literature.

Case 3

A 41-year-old nurse who had worked on an oncology ward for 13 years suffered from nasal discharge, difficult breathing, and attacks of coughing 1 to 2 hours after beginning work [Walusiak et al. 2002]. During the third year of her employment on the ward, she developed difficult breathing while away from work. Her 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 she was monitored by spirometry and peak expiratory flow measurements. On the basis of clinical findings, the investigators concluded that the evidence was consistent with a diagnosis of allergic asthma.

Case 4

A malfunctioning BSC resulted in possible exposure of nursing personnel to a number of antineoplastic drugs that were prepared in the BSC [Kevekordes et al. 1998]. Blood samples from the nurses were analyzed for genotoxic biomarkers 2 and 9 months after replacement of the faulty BSC. At 2 months, both sister chromatid exchanges (SCEs) and micronuclei were significantly elevated compared with those of a matched control group. At 9 months, the micronuclei concentrations were similar to those of the 2-month controls. SCEs were not determined at 9 months. The investigators concluded that the elevation in biomarkers had resulted from the malfunctioning of the BSC, which resulted in worker exposure to the antineoplastic drugs. They also concluded that the subsequent replacement with a new BSC contributed to the reduced effect seen with the micronucleus test at 9 months.

Case 5

A 41-year-old patient-care assistant working on an oncology floor developed an itchy 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 antineoplastic drugs. The rash subsided after 1 to 2 days. Three weeks later, she had a similar reaction approximately 1 hour after performing the same procedure for another patient. Upon investigation, it was found that both hospital patients had recently been treated with vincristine and doxorubicin. The patient-care assistant had no other signs or symptoms and reported no changes in lifestyle.
and no history of allergies or recent infections. After treatment with diphenhydramine (intramuscular) and oral corticosteroids, her symptoms disappeared. Although the cause could not be definitely confirmed, both vincristine and doxorubicin 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.

**CONCLUSIONS**

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 sampling methods used in the past have come into question [Larson et al. 2003] and may not be a good indicator of contamination in the workplace. In all studies involving examination of surface wipe samples, researchers have determined that surface contamination of the workplace is common and widespread. Also, a number of recent studies have documented the excretion of several indicator drugs in the urine of health care workers. Results from studies indicate that worker exposure to hazardous drugs in health care facilities may result in adverse health effects.

 Appropriately designed studies have begun and are continuing to characterize the extent and nature of health hazards associated with these ongoing exposures. NIOSH is currently conducting studies to further identify potential sources of exposure and methods to reduce or eliminate worker exposure to these drugs. To minimize these potentially acute (short-term) and chronic (long-term) effects of exposure to hazardous drugs at work, NIOSH recommends that at a minimum, employers and health care workers follow the recommendations presented in this Alert.

**RECOMMENDATIONS**

**Summary of Recommended Procedures**

1. Assess the hazards in the workplace.

   - Evaluate the workplace to identify and assess hazards before anyone begins work with hazardous drugs. As part of this evaluation, assess the following:
     - Total working environment
     - Equipment (i.e., ventilated cabinets, closed-system drug transfer devices, glovebags, needleless systems, and PPE)
     - Physical layout of work areas
     - Types of drugs being handled
     - Volume, frequency, and form of drugs handled (tablets, coated versus uncoated, powder versus liquid)
     - Equipment maintenance
     - Decontamination and cleaning
     - Waste handling
     - Potential exposures during work, including hazardous drugs, bloodborne pathogens, and chemicals used to deactivate hazardous drugs or clean drug-contaminated surfaces
     - Routine operations

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Hazardous Drugs in Health Care Settings
— Spill response
— Waste segregation, containment, and disposal

- Regularly review the current inventory of hazardous drugs, equipment, and practices, seeking input from affected workers. Have the safety and health staff or an internal committee perform this review.

- Conduct regular training reviews with all potentially exposed workers in workplaces where hazardous drugs are used. Seek ongoing input from workers who handle hazardous drugs and from other potentially exposed workers regarding the quality and effectiveness of the prevention program. Use this input from workers to provide the safest possible equipment and conditions for minimizing exposures. This approach is the only prudent public health approach, since safe concentrations for occupational exposure to hazardous drugs have not been conclusively determined.

2. Handle drugs safely.

- Implement a program for safely handling hazardous drugs at work and review this program annually on the basis of the workplace evaluation. Establish work policies and procedures specific to the handling of hazardous drugs. These policies and procedures should address and define the following:
  — Presence of hazardous drugs
  — Labeling
  — Storage
  — Personnel issues (such as exposure of pregnant workers)
  — Spill control
  — Detailed procedures for preparing, administering, and disposing of hazardous drugs

- Establish procedures and provide training for handling hazardous drugs safely, cleaning up spills, and using all equipment and PPE properly. Inform workers about the location and proper use of spill kits. Make these kits available near all potential sources of exposure. Make sure that training conforms to the requirements of the OSHA hazard communication standard [29 CFR 1910.1200] and other relevant OSHA requirements such as the PPE standard [29 CFR 1910.132]. In addition, establish procedures for cleaning and decontaminating work areas and for proper waste handling and disposal of all contaminated materials, including patient waste.

- Establish work practices related to both drug manipulation techniques and to general hygiene practices—such as not permitting eating or drinking in areas where drugs are handled (the pharmacy or clinic).

3. Use and maintain equipment properly.

- Develop workplace procedures for using and maintaining all equipment that functions to reduce exposure—such as ventilated cabinets, closed-system drug-transfer devices, needleless systems, and PPE.

Detailed Recommendations

Receiving and Storage

- Begin exposure control when hazardous drugs enter the facility. The most significant exposure risk during distribution
and transport is from spills resulting from damaged containers.

- Prepare workers for the possibility that spills might occur while they are handling containers (even when packaging is intact during routine activities), and provide them with appropriate PPE.

- Make sure that medical products have labeling on the outsides of containers that will be understood by all workers who will be separating hazardous from nonhazardous drugs.

- Wear chemotherapy gloves [ASTM in press], protective clothing, and eye protection when opening containers to unpack hazardous drugs. Such PPE protects workers and helps prevent contamination from spreading if damaged containers are found.

- Wear chemotherapy gloves to prevent contamination when transporting the vial or syringe to the work area.

- Store hazardous drugs separately from other drugs, as recommended by ASHP [1990] and other chemical safety standards.

- Store and transport hazardous drugs in closed containers that minimize the risk of breakage.

- Make sure the storage area has sufficient general exhaust ventilation to dilute and remove any airborne contaminants.

- Depending on the physical nature and quantity of the stored drugs, consider installing a dedicated emergency exhaust fan that is large enough to quickly purge airborne contaminants from the storage room in the event of a spill and prevent contamination in adjacent areas.

**Drug Preparation and Administration**

**Initial steps**

- As part of the hazard assessment described earlier, evaluate and review the entire drug preparation and administration process to identify points at which drugs might be released into the work environment. Always consider the possibility of contamination on the outside of containers [Ros et al. 1997; Hepp and Gentschew 1998; Delporte et al. 1999; Nygren et al. 2002; Favier et al. 2003; Mason et al. 2003].

- Limit access to areas where drugs are prepared to protect persons not involved in drug preparation.

- Coordinate tasks associated with preparing and administering hazardous drugs for most effective control of worker exposures.

**Preparing hazardous drugs**

- Use a ventilated cabinet designed to reduce worker exposures while preparing hazardous drugs (see following section entitled *Ventilated Cabinets*).

- Train all staff who use ventilated cabinets to employ work practices established for their particular equipment. The safe use of any control depends on proper work.

- Practice proper technique and use of equipment.

- Include initial and periodic assessments of technique in the safety program [Harrison et al. 1996], and verify technique during drug administration.

- Wear protective gloves and gowns if you are involved in preparation activities such as opening drug packaging, handling vials or finished products, labeling.
hazardous drug containers, or disposing of waste.

- Wear PPE (including double gloves and protective gowns) while reconstituting and admixing drugs:
  - Make sure that gloves are labeled as chemotherapy gloves and make sure such information is available on the box [ASTM in press] or from the manufacturer.
  - Consider latex-sensitive workers [NIOSH 1997] and remember that a number of glove materials are suitable for protecting workers from antineoplastic drugs [Connor 1999; Singleton and Connor 1999; Klein et al. 2003].
  - Consider using chemotherapy gloves for hazardous drugs that are not chemotherapy drugs or for which no information is available.
  - Use double gloving for all activities involving hazardous drugs. Make sure that the outer glove extends over the cuff of the gown [Connor 1999; Brown et al. 2001].
  - Inspect gloves for physical defects before use.
  - Wash hands with soap and water before donning protective gloves and immediately after removal.
  - Change gloves every 30 minutes or when torn, punctured, or contaminated. Discard them immediately in a yellow chemotherapy waste container [ASHP 1990; Brown et al. 2001].
  - Use disposable gowns made of polyethylene-coated polypropylene (which is nonlinting and nonabsorbent). These gowns offer better protection than polypropylene gowns against many of the antineoplastic drugs [Connor 1993; Harrison and Kloos 1999]. Make sure gowns have closed fronts, long sleeves, and elastic or knit closed cuffs.
  - Dispose of protective gowns after each use.
  - Use disposable sleeve covers to protect the wrist area and remove the covers after the task is complete.

- When drug preparation is complete, seal the final product in a plastic bag or other sealable container for transport before taking it out of the ventilated cabinet.

- Seal and wipe all waste containers inside the ventilated cabinet before removing them from the cabinet.

- Remove all outer gloves and sleeve covers and bag them for disposal while you are inside the ventilated cabinet.

- Wash hands with soap and water immediately after removing gloves.

- Consider using devices such as closed-system transfer devices, glovebags, and needleless systems when transferring hazardous drugs from primary packaging (such as vials) to dosing equipment (such as infusion bags, bottles, or pumps). Closed systems limit the potential for generating aerosols and exposing workers to sharps. Evidence documents a decrease in
drug contaminants inside a Class II BSC when a closed-system transfer device is 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].

- Remember that a closed-system transfer device is not an acceptable substitute for a ventilated cabinet and should be used only within a ventilated cabinet.
- Use appropriate PPE and work practices even when you are using a closed system.

- Have pharmacy personnel prime the IV tubing and syringes inside the ventilated cabinet, or prime them in-line with non-drug solutions—never in the patient’s room.

**Administering hazardous drugs**

- Administer drugs safely by using protective medical devices (such as needleless and closed systems) and techniques (such as priming of IV tubing by pharmacy personnel inside a ventilated cabinet or priming in-line with non-drug solutions).
- Wear PPE (including double gloves, goggles, and protective gowns) for all activities associated with drug administration—opening the outer bag, assembling the delivery system, delivering the drug to the patient, and disposing of all equipment used to administer drugs.
- Attach drug administration sets to the IV bag, and prime them before adding the drug to the bag.
- Never remove tubing from an IV bag containing a hazardous drug.

- Do not disconnect tubing at other points in the system until the tubing has been thoroughly flushed.
- Remove the IV bag and tubing intact when possible.
- Place disposable items directly in a yellow chemotherapy waste container and close the lid.
- Remove outer gloves and gowns, and bag them for disposal in the yellow chemotherapy waste container at the site of drug administration.
- Double-bag the chemotherapy waste before removing the inner gloves.
- Consider double bagging all contaminated equipment.
- Wash hands with soap and water before leaving the drug administration site.

**Ventilated Cabinets**

**Use of cabinets**

- Mix, prepare, and otherwise manipulate, count, crush, compound powders, or pour liquid hazardous drugs inside a ventilated cabinet designed to prevent hazardous drugs from being released into the work environment.
- Do not use supplemental engineering or process controls (such as needleless systems, glove bags, and closed-system drug transfer devices) as a substitution for ventilated cabinets, even though such controls may reduce the potential for exposure when preparing and administering hazardous drugs.

**Selection**

- Consult the following document for performance test methods and selection

- Select a ventilated cabinet depending on the need for aseptic processing. Aseptic technique is important for protecting hazardous drugs from possible contamination. However, it is also important to consider worker protection and to assure that worker safety and health is not sacrificed. Therefore, when asepsis is required or recommended, use ventilated cabinets designed for both hazardous drug containment and aseptic processing. Aseptic requirements are generally regulated by individual State boards of pharmacy [Thompson 2003; USP 2004].

- When asepsis is not required, a Class I BSC or an isolator intended for containment applications (a “containment isolator”) may be sufficient.

- When aseptic technique is required, use one of the following ventilated cabinets:
  - Class II BSC (Type B2 is preferred, but Types A2 and B1 are allowed under certain conditions)
  - Class III BSC
  - Isolators intended for asepsis and containment (aseptic containment isolators) [NSF/ANSI 2002; PDA 2001]

**Air flow and exhaust**

- Regardless of type, equip each ventilated cabinet with a continuous monitoring device to confirm adequate air flow before each use.

- Use a high-efficiency particulate air filter (HEPA filter) for the exhaust from these controls, and where feasible, exhaust 100% of the filtered air to the outside.

- Install the outside exhaust so that the exhausted air is not pulled back into the building by the heating, ventilating, and air conditioning (HVAC) systems or by the windows, doors, or other points of entry.

- Place fans downstream of the HEPA filter so that contaminated ducts are maintained under negative pressure.

- Do not use a ventilated cabinet that recirculates air inside the cabinet or exhausts air back into the room environment unless the hazardous drug(s) in use will not volatilize (evaporate) while they are being handled or after they are captured by the HEPA filter. Information about volatilization should be supplied by the drug manufacturer (possibly in the MSDS) or by air-sampling data.

- Seek additional information about placement of the cabinet, exhaust system, and stack design from NSF/ANSI 49–2002 [NSF/ANSI 2002]. Incorporate their recommendations regardless of the type of ventilated cabinet selected.

**Maintenance**

- Identify a safety and health representative familiar with potential drug exposures and their hazards. Ask that person to review in advance all maintenance activities performed on ventilated cabinets and exhaust systems associated with hazardous drug procedures.

- Develop a written safety plan for all routine maintenance activities performed on equipment that could be contaminated with hazardous drugs.
- Properly install and maintain and routinely clean any Class II BSC.
  - Field-certify its performance (1) after installation, relocation, maintenance repairs to internal components, and HEPA filter replacement, and (2) every 6 months thereafter [NSF/ANSI 2002; OSHA 1999].
  - Prominently display a current field-certification label on the ventilated cabinet [NSF/ANSI 2002].
- Treat other types of ventilated cabinets similarly with regard to care and frequency-of-performance verification tests.
- Select the appropriate performance and test methods for isolators, depending on the type (containment-only or aseptic containment), the operating pressure (positive or negative and designed magnitude), and the toxicity of the hazardous drug:
  - At a minimum, provide isolators with a leak test and a containment integrity test such as those described in Guidelines for Gloveboxes [AGS 1998].
  - Perform a HEPA filter leak test (described in NSF/ANSI [2002]) for isolators that rely on HEPA filtration for containment.
  - Perform additional tests as required by local and/or national jurisdictions to verify aseptic conditions.
- Make sure that workers performing maintenance are
  - familiar with applicable safety plans,
  - warned about hazards, and
  - trained in appropriate work techniques and PPE needed to minimize exposure.
- Remove all hazardous drugs and chemicals, and decontaminate the ventilated cabinet before beginning maintenance activities.
- Warn occupants in the affected areas immediately before the maintenance activity begins, and place warning signs on all equipment that may be affected.
- Strictly follow all applicable lockout/tagout procedures [29 CFR 1910.147].
- Decontaminate and bag equipment parts removed for replacement or repair before they are taken outside the facility.
- Seal used filtration media in plastic immediately upon removal, and tag it for disposal as chemotherapy waste; or dispose of it as otherwise directed by the environmental safety and health office or applicable regulation.

Routine Cleaning, Decontaminating, Housekeeping, and Waste Disposal

Cleaning and decontaminating
- Perform cleaning and decontamination work in areas that are sufficiently ventilated to prevent buildup of hazardous airborne drug concentrations. Develop protocols prohibiting the use of unventilated areas such as storage closets for drug storage or any tasks involving hazardous drugs.
- Clean work surfaces with an appropriate deactivation agent (if available) and cleaning agent before and after each activity and at the end of the work shift.
- Establish periodic cleaning routines for all work surfaces and equipment that may become contaminated, including administration carts and trays.

- At a minimum, wear safety glasses with side shields and protective gloves for cleaning and decontaminating work.

- Wear face shields if splashing is possible.

- Wear protective double gloves for decontaminating and cleaning work.
  - Select them by referring to the MSDS, glove selection guidelines, or information from the glove manufacturer.
  - Make sure the gloves are chemically resistant to the decontamination or cleaning agent used.

**Waste disposal**

- Be aware of the various types of waste generated by preparing and administering hazardous drugs: partially filled vials, undispensed products, unused IVs, needles and syringes, gloves, gowns, under-pads, and contaminated materials from spill cleanups.

- Place trace wastes (those that contain less than 3% by weight of the original quantity of hazardous drugs)—such as needles, empty vials and syringes, gloves, gowns, and tubing—in yellow chemotherapy waste containers. Assuring that drug-contaminated waste is properly contained will protect workers from respiratory exposure to volatile or micro-aerosolized drugs [Connor et al. 2000; Kifmeyer et al. 2002; Larson et al. 2003].
  - Place soft trace items (those that are contaminated with trace amounts of hazardous drugs) in yellow chemotherapy bags for disposal by incineration at a regulated medical waste facility.
  - Place empty vials and sharps such as needles and syringes in chemotherapy waste containers designed to protect workers from injuries and dispose of them by incineration at a regulated medical waste facility.

- Do not place hazardous drug-contaminated sharps in red sharps containers that are used for infectious wastes, since these are often autoclaved or microwaved [ASHP 1990; OSHA 1999; Smith 2002].

- Dispose of P-listed arsenic trioxide and its containers and any bulk amounts of U-listed drugs [40 CFR 261.33] in

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**Housekeeping**

- Wear two pairs of protective gloves and a disposable gown if you must handle linens, feces, or urine from patients who have received hazardous drugs within the last 48 hours—or in some cases, within the last 7 days [Cass and Musgrave 1992].

- Dispose of the gown after each use or whenever it becomes contaminated.

- Wear face shields if splashing is possible.

- Remove the outer gloves and the gown by turning them inside out and placing them into the yellow chemotherapy waste container. Repeat the procedure for the inner gloves.

- Wash hands with soap and water after removing the gloves.

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hazardous waste containers at a RCRA-permitted incinerator. Nine hazardous drugs in Appendix A are listed as hazardous waste by EPA.

- Consider disposing of other bulk hazardous drugs (that is, expired or unused vials, ampoules, syringes, bags, and bottles of hazardous drugs or solutions of any other items with more than trace contamination) in a manner similar to that required for RCRA-defined hazardous wastes as recommended by ASHP [1990] and OSHA [1999].

**Spill Control**

- Manage hazardous drug spills according to the established, written policies and procedures for each workplace.

- Be aware that the size of the spill might determine who is authorized to conduct the cleanup and decontamination and how the cleanup is managed.

- Assure that the written policies and procedures address the protective equipment required for various spill sizes, the possible spreading of material, restricted access to hazardous drug spills, and signs to be posted.

- Assure that cleanup of a large spill is handled by workers who are trained in handling hazardous materials [29 CFR 1910.120].

- Locate spill kits and other cleanup materials in the immediate area where exposures may occur.

- As required by OSHA, follow a complete respiratory protection program, including fit-testing, if you wear respirators such as those contained in some spill kits [29 CFR 1910.134]. Use NIOSH-certified respirators [42 CFR 84]. **Surgical masks do not provide adequate protection.**

- Dispose of all spill cleanup materials in a hazardous chemical waste container, in accordance with EPA/RCRA regulations regarding hazardous waste—not in a chemotherapy waste or biohazard container.

**Medical Surveillance**

- In addition to preventing exposure to hazardous drugs and carefully monitoring the environment, make medical surveillance an important part of any safe handling program for hazardous drugs.

- If you handle hazardous drugs, participate in medical surveillance programs provided at your workplace.

- If you handle hazardous drugs but have no medical surveillance program at work, see your private health care provider for routine medical care. Be sure to inform him or her about your occupation and possible exposures to hazardous drugs.

- Refer to the **OSHA Technical Manual: Controlling Occupational Exposure to Hazardous Drugs**, Section VI Chapter 2 [OSHA 1999]. This document 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 tests.

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1Arsenic trioxide is a P-listed hazardous waste. Chlorambucil, cyclophosphamide, daunorubicin HCl, diethylstilbestrol, melphalan, mitomycin, streptozocin, and uracil mustard are U-listed hazardous wastes. See 40 CFR 261.33.
Refer to the guidelines of professional organizations such as the ASHP [1990] and the Oncology Nursing Society [Brown et al. 2001], which recommend medical surveillance as the recognized standard of occupational health practice for hazardous drug handlers. The American College of Occupational and Environmental Medicine (ACOEM) also recommends surveillance for these workers in their Reproductive Hazard Management Guidelines [ACOEM 1996].

Use a worker's past exposure history as a surrogate measure of potential exposure intensity.

If you are an occupational health professional who is examining a drug-exposed worker, ask questions that focus on the worker's symptoms relating to the organ systems that are known targets for the hazardous drugs.

— For example, after an acute exposure such as a splash or other drug contact with skin or mucous membranes, focus the physical examination on the exposed areas and the clinical signs of rash or irritation to those areas.

— Include a complete blood count with differential and a reticulocyte count in the baseline and periodic laboratory tests. These may be helpful as an indicator of bone marrow reserve.

Monitor the urine of workers who handle hazardous drugs with a urine dipstick or a microscopic examination of the urine for blood [Brown et al. 2001]. Several antineoplastic agents are known to cause bladder damage and blood in the urine of treated patients.

Conduct environmental sampling and/or biological monitoring when exposure is suspected or symptoms have been noted.

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: pubstaff@cdc.gov, or Web site: www.cdc.gov/NIOSH.

Additional information about hazardous drug safety is available at www.osha.gov.

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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. Anne C. Hamilton, Vanessa Becks, Susan Afanuh, Jane Weber, Andre Allen, Anne Votaw, and Teresa Lewis provided editorial and production services.

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APPENDIX A
DRUGS CONSIDERED HAZARDOUS

General Approach to Handling Hazardous Drugs

In this Alert, NIOSH presents a standard precautions or universal precautions approach to handling hazardous drugs safely: that is, NIOSH recommends that all hazardous drugs be handled as outlined in this Alert. Therefore, 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.

Defining Hazardous Drugs

Hazardous drugs include those used for cancer chemotherapy, antiviral drugs, hormones, some bioengineered drugs, and other miscellaneous drugs. The definition of hazardous drugs used in this Alert is based on an ASHP definition that was originally developed in 1990 [ASHP 1990]. Thus the definition may not accurately reflect the toxicity criteria associated with the newer generation of pharmaceuticals entering the health care setting. For example, bioengineered drugs target specific sites in the body; and although they may or may not be toxic to the patient, some may not pose a risk to health care workers.

NIOSH and other organizations are still gathering data on the potential toxicity and health effects related to highly potent drugs and bioengineered drugs. Therefore, when working with any hazardous drug, health care workers should follow a standard precautions approach along with any recommendations included in the manufacturer's MSDSs.

ASHP Definition of Hazardous Drugs

The ASHP defines hazardous drugs in their 1990 revision of Technical Assistance Bulletin on Handling Hazardous Drugs [ASHP 1990]. The bulletin gives criteria for identifying potentially hazardous drugs that should be handled in accordance with an established safety program [McDiamid et al. 1991; Arrington and McDiamid 1993]. The criteria are prioritized to reflect the hierarchy of potential toxicity described below. Since the hazardous drugs covered by this Alert were designed as therapeutic agents for humans, human toxicity profiles should be considered superior to any data from animal models or in vitro systems. Additional guidance for defining hazardous drugs is available in the following citations: carcinogenicity [61 Fed. Reg. 17960–18011 (1996b); IARC 2004], teratogenicity [56 Fed. Reg. 63798–63826 (1991)], developmental toxicity [56 Fed. Reg. 63798–63826 (1991)], and reproductive toxicity [61 Fed. Reg. 56274–56322]
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.

NIOSH Revision of ASHP Definition

The 1990 ASHP definition of hazardous drugs 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
3. Reproductive toxicity
4. Organ toxicity at low doses

5. Genotoxicity
6. Structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the above criteria.

Determining Whether a Drug is Hazardous

Many hazardous drugs used to treat cancer bind to or damage DNA (for example, alkylating agents). Other antineoplastic drugs, some antivirals, antibiotics, and bioengineered drugs interfere with cell growth or proliferation, or with DNA synthesis. In some cases, the nonselective actions of these drugs disrupt the growth and function of both healthy and diseased cells, resulting in toxic side effects for treated patients. These nonselective actions can also cause adverse effects in health care workers who are inadvertently exposed to hazardous drugs.

Early concerns about occupational exposure to antineoplastic drugs first appeared in the 1970s. Although the antineoplastic drugs remain the principal focus of this Alert, other drugs may also be considered hazardous because they are potent (small quantities produce a physiological effect) or cause irreversible effects. As the use and number of these potent drugs increase, so do opportunities for hazardous exposures among health care workers. For example, antineoplastic drugs such as cyclophosphamide have immunosuppressant effects that proved beneficial for treating nonmalignant

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diseases such as rheumatoid arthritis and multiple sclerosis [Baker et al. 1987; Moody et al. 1987; Chabner et al. 1996; Abel 2000].

This appendix presents criteria and sources of information for determining whether a drug is hazardous. When a drug has been judged to be hazardous, the various precautions outlined in this Alert should be applied when handling that drug. Also included is a list of drugs that should be handled as hazardous. This list is based on a compilation of lists from four health care facilities and one drug manufacturers' organization.

In addition to using the list of hazardous drugs presented here, each organization should create its own list of drugs considered to be hazardous. This appendix presents guidance for making such a facility-specific list (see section entitled How to Generate your own List of Hazardous Drugs). Once this list is made, newly purchased drugs should be evaluated against the organization’s hazardous drug criteria and added to the list if they are deemed hazardous.

Some organizations may have inadequate resources for determining their own list of hazardous drugs. If so, the sample list of hazardous drugs in this appendix (current only to the printing date of this document) will help employers and workers to determine when precautions are needed. However, reliance on such a published list is a concern because it quickly becomes outdated as new drugs continually enter the market or listed drugs are removed when additional information becomes available. To fill this knowledge gap, NIOSH will update an internet list annually, adding new drugs considered to be hazardous and removing those that require reclassification. This hazardous drug list will be posted on the NIOSH Web site at www.cdc.gov/niosh.

How to Generate Your Own List of Hazardous Drugs

The OSHA hazard communication standard [29 CFR 1910.1200] 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 a worker may encounter in the facility. Compliance with the OSHA hazard communication standard entails (1) evaluating whether these drugs meet one or more of the criteria for defining hazardous drugs and (2) posting a list of the hazardous drugs to ensure worker safety. Institutions may wish to compare their lists to the sample listing in this document or on the NIOSH Web site.

It is not likely that every health care provider or facility will use all drugs that have received U.S. Food and Drug Administration (FDA) approval, and the OSHA hazard communication standard does not mandate evaluation of every marketed drug. Instead, compliance 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 for assessment of new drugs as they enter the marketplace, and when appropriate, reassessment of their presence on hazardous drug lists as toxicological data become available to support recategorization. Toxicological data are often 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 because of their dosage formulation (for example, coated tablets or capsules—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 a ventilated cabinet.

**Where to Find Information Related to Drug Toxicity**

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 the hazard potential of a drug include, but are not limited to, the following:

- MSDSs
- Product labeling approved by the U.S. FDA (package inserts)
- Special health warnings from drug manufacturers, FDA, and other professional groups and organizations
- Reports and case studies published in medical and other health care profession journals
- Evidence-based recommendations from other facilities that meet the criteria defining hazardous drugs

**Examples of Hazardous Drugs**

The following list contains a sampling of major hazardous drugs. The list was compiled from information provided by (1) four institutions that have generated lists of hazardous drugs for their respective facilities, (2) the American Hospital Formulary Service Drug Information (AHFS DI) monographs [ASHP/AHFS DI 2003], and (3) several other sources. The OSHA hazard communication standard requires hazardous drugs to be handled using special precautions. The mandate applies not only to health care 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 with the list on the NIOSH Web site.

_Caution: Drugs purchased and used by a facility may have entered the marketplace after the list below was assembled. Therefore, 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 whether the unlisted drug should be treated as hazardous. Check the MSDS or 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, or reproductive or developmental toxicity, use the precautions stipulated in this Alert. If a drug meets one or more of the criteria for hazardous drugs listed in this Alert, handle it as hazardous.

The listing below is a sample of what will be available on the NIOSH Web site [www.cdc.gov/niosh], and this list will be updated annually.
### Sample list of drugs that should be handled as hazardous*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Source</th>
<th>AHFS Pharmacologic-Therapeutic Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldeleukin</td>
<td>4,5</td>
<td>10:00 Antineoplastic agents</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>1,3,4,5</td>
<td>10:00 Antineoplastic agents</td>
</tr>
<tr>
<td>Alitretinoin</td>
<td>3,4,5</td>
<td>84:36 Miscellaneous skin and mucous membrane agents (Retinoid)</td>
</tr>
<tr>
<td>Altretamine</td>
<td>1,2,3,4,5</td>
<td>Not in AHFS (Antineoplastic agent)</td>
</tr>
<tr>
<td>Amsacrine</td>
<td>3,5</td>
<td>Not in AHFS (Antineoplastic agent)</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>1,5</td>
<td>10:00 Antineoplastic agents</td>
</tr>
<tr>
<td>Arsenic trioxide</td>
<td>1,2,3,4,5</td>
<td>10:00 Antineoplastic agents</td>
</tr>
<tr>
<td>Asparaginase</td>
<td>1,2,3,4,5</td>
<td>10:00 Antineoplastic agents</td>
</tr>
<tr>
<td>Azacitidine</td>
<td>3,5</td>
<td>Not in AHFS (antineoplastic agent)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>2,3,5</td>
<td>92:00 Unclassified therapeutic agents (immunosuppressant)</td>
</tr>
<tr>
<td>Bacillus Calmette-Guerin</td>
<td>1,2,4</td>
<td>80:12 Vaccines</td>
</tr>
<tr>
<td>Bexarotene</td>
<td>2,3,4,5</td>
<td>10:00 Antineoplastic agents</td>
</tr>
<tr>
<td>Bicalutamide</td>
<td>1,5</td>
<td>10:00 Antineoplastic agents</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>1,2,3,4,5</td>
<td>10:00 Antineoplastic agents</td>
</tr>
<tr>
<td>Busulfan</td>
<td>1,2,3,4,5</td>
<td>10:00 Antineoplastic agents</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>1,2,3,4,5</td>
<td>10:00 Antineoplastic agents</td>
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<tr>
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<tr>
<td>Cetorelix acetate</td>
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<td>Chlorambucil</td>
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<td>Colchicine</td>
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*See footnotes at end of table*
### Sample list of drugs that should be handled as hazardous* (Continued)

<table>
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<td>Cyclosporin</td>
<td>1</td>
<td>92:00 Immunosuppressive agents</td>
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<td>Denileukin</td>
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<td>Diethylstilbestrol</td>
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<td>Estrogen-progestin combinations</td>
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<tr>
<td>Estrogens, conjugated</td>
<td>5</td>
<td>68:16.04 Estrogens</td>
</tr>
<tr>
<td>Estrogens, esterified</td>
<td>5</td>
<td>68:16.04 Estrogens</td>
</tr>
<tr>
<td>Estrone</td>
<td>5</td>
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<td>Etoposide</td>
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<td>Finasteride</td>
<td>1,3,5</td>
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<td>Flouxuridine</td>
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*See footnotes at end of table*
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<td>Fluoxymesterone</td>
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</tr>
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<td>Flutamide</td>
<td>1,2,5</td>
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<td>Fulvestrant</td>
<td>5</td>
<td>10:00 Antineoplastic agents</td>
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<tr>
<td>Ganciclovir</td>
<td>1,2,3,4,5</td>
<td>8:18 Antiviral</td>
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<tr>
<td>Ganirelix acetate</td>
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<td>92:00 Unclassified therapeutic agents (GnRH antagonist)</td>
</tr>
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<td>Gemcitabine</td>
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<td>Gemtuzumab ozogamicin</td>
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<td>Gonadotropin, chorionic</td>
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<td>Goserein</td>
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<td>Hydroxyurea</td>
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<td>Idarubicin</td>
<td>1,2,3,4,5</td>
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<td>Interferon alfa-2b</td>
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<td>Interferon alfa-n3</td>
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<td>Letrozole</td>
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<td>Leuprolide acetate</td>
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<td>Lomustine</td>
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<tr>
<td>Melphalan</td>
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(See footnotes at end of table)
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<td>1,2,3,4,5</td>
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<td>Methyltestosterone</td>
<td>5</td>
<td>68:08 Androgens</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>5</td>
<td>76:00 Oxytocics</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>1,2,3,4,5</td>
<td>10:00 Antineoplastic agents</td>
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<td>Mitotane</td>
<td>1,4,5</td>
<td>10:00 Antineoplastic agents</td>
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<td>Mitoxantrone HCl</td>
<td>1,2,3,4,5</td>
<td>10:00 Antineoplastic agents</td>
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<tr>
<td>Mycophenolate mofetil</td>
<td>1,3,5</td>
<td>92:00 Immunosuppressive agents</td>
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<td>Nafarelin</td>
<td>5</td>
<td>68:18 Gonadotropins</td>
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<td>Pipobroman</td>
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<td>Plicamycin isethionate</td>
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<td>Podophyllum resin</td>
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<td>68:32 Progestins</td>
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<td>Progestins</td>
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<td>68:12 Contraceptives</td>
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(See footnotes at end of table)
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<th>Source</th>
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<tr>
<td>Raloxifene</td>
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<td>Raltitrexed</td>
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<td>Streptozocin</td>
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<td>Thioguanine</td>
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<td>84:16 Cell stimulants and proliferants (retinoid)</td>
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<td>Trifluridine</td>
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<td>52:04.06 antivirals</td>
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<td>Trimetrexate glucuronate</td>
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<td>Uracil mustard</td>
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<td>1,2,5</td>
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(See footnotes at end of table)
Sample list of drugs that should be handled as hazardous* (Continued)

<table>
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<th>Drug</th>
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<td>Vincristine sulfate</td>
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<td>Vinodesine</td>
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<td>Vinorelbine tartrate</td>
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<tr>
<td>Zidovudine</td>
<td>1,2,5</td>
<td>8:18:08 Antiretroviral agents</td>
</tr>
</tbody>
</table>

*These lists of hazardous drugs were used with the permission of the institutions that provided them and were adapted for use by NIOSH. The sample lists are intended to guide health care 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 because of their dosage formulation (for example, intact medications such as coated tablets or capsules that are administered to patients without modifying the formulation). However, they may pose a risk if solid drug formulations are altered outside a ventilated cabinet (for example, if tablets are crushed or dissolved, or if capsules are pierced or opened).

1The NIH Clinical Center, Bethesda, MD (Revised 8/2002).
2The NIH 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 OSHA 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.
3The John Hopkins Hospital, Baltimore, MD (Revised 9/2002).
4The Northside Hospital, Atlanta, GA (Revised 8/2002).
5The University of Michigan Hospitals and Health Centers, Ann Arbor, MI (Revised 2/2003).

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

## ABBREVIATIONS AND GLOSSARY

### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACGIH</td>
<td>American Conference of Governmental Industrial Hygienists</td>
</tr>
<tr>
<td>ACOEM</td>
<td>American College of Occupational and Environmental Medicine</td>
</tr>
<tr>
<td>AHFS</td>
<td>American Hospital Formulary Service</td>
</tr>
<tr>
<td>AHFS DI</td>
<td>American Hospital Formulary Service Drug Information</td>
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<td>AGS</td>
<td>American Glovebox Society</td>
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<td>ANSI</td>
<td>American National Standards Institute</td>
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<tr>
<td>ASHP</td>
<td>American Society of Health-System Pharmacists (before 1995, American Society of Hospital Pharmacists)</td>
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<tr>
<td>BSC</td>
<td>Biological safety cabinet</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
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<tr>
<td>ft</td>
<td>foot (feet)</td>
</tr>
<tr>
<td>HEPA</td>
<td>high-efficiency particulate air</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HVAC</td>
<td>heating, ventilating, and air conditioning</td>
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<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
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<td>IV</td>
<td>intravenous</td>
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<tr>
<td>kg</td>
<td>kilogram(s)</td>
</tr>
<tr>
<td>LPN</td>
<td>licensed practical nurse</td>
</tr>
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<td>m³</td>
<td>cubic meter(s)</td>
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<tr>
<td>mg</td>
<td>milligram(s)</td>
</tr>
<tr>
<td>min</td>
<td>minute (s)</td>
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<td>MSDS</td>
<td>material safety data sheet</td>
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<td>National Institutes of Health</td>
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Hazardous Drugs in Health Care Settings
Glossary

**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.

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

**Barrier isolator**: This term has various interpretations, especially as they pertain to hazard containment and aseptic processing. For this reason, it has been omitted from this Alert.

**Biohazard**: An infectious agent or hazardous biological material that presents a 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 infectious agents or hazardous biological materials.

**Biomarker**: A biological, biochemical or structural change that serves as an indicator of potential damage to cellular components, whole cells, tissues, or organs.

**BSC (biological safety cabinet)**: A BSC may be one of several types, as described here [CDC/NIH 1999; NSF/ANSI 2002]:

**Class I BSC**: A BSC that protects personnel and the work environment but does not protect the product. 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. A Class I BSC 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 BSC:** A ventilated BSC that protects personnel, product, and the work environment. A Class II BSC has 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 Class II BSCs 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 Class II BSCs 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 trace amounts of radionucleotides, they must be exhausted through properly functioning exhaust canopies.

**Type B1:** These Class II BSCs 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 trace amounts of radionucleotides, the work must be done in the directly exhausted portion of the cabinet.

**Type B2 (total exhaust):** These Class II BSCs 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 inside 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 BSC:** A BSC with a totally enclosed, ventilated cabinet of gas-tight construction in which operations are conducted through attached rubber gloves and observed through a nonopening view window. This BSC is maintained under negative pressure of at least 0.50 inch 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 and 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. For a more detailed description, refer to CDC/NIH [2000], *Primary Containment for Biohazards: Selection, Installation and Use of Biological Safety Cabinets*, 2nd edition. [www.cdc.gov/od/ohs/iosafety/bsc/bsc.htm].

**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.

**Chemotherapy waste:** Discarded items such as gowns, gloves, masks, IV tubing, empty bags, empty drug vials, needles and syringes, and other items generated while preparing and administering 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 that 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.

**Deactivation:** Treating a chemical agent (such as a hazardous drug) with another chemical, heat, ultraviolet light, or other agent to create a less hazardous agent.

**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.

**Genotoxic:** Capable of damaging the DNA and leading to mutations.

**Glove box:** A controlled environment work enclosure providing a primary barrier from the work area. 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. Operations are performed through sealed gloved openings to protect the worker, the work environment, and/or the product.

**Hazardous drug:** Any drug 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 that meets a RCRA characteristic of ignitability, corrosivity, reactivity, or toxicity as defined in 40 CFR 261.21–24.

**Health care settings:** All hospitals, medical clinics, outpatient facilities, physicians' offices, retail pharmacies, and similar facilities dedicated to the care of patients.

**Health care worker:** All workers who are involved in the care of patients. These include pharmacists, pharmacy technicians, nurses (registered nurses [RNs], licensed practical nurses [LPNs], nurses aids, etc.), physicians, home health care workers and environmental services workers (housekeeping, laundry, and 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 and producing a horizontal flow across the work area and out toward the worker.

**Isolator:** A device that is sealed or is supplied with air through a microbiologically retentive filtration system (HEPA minimum) and may be reproducibly decontaminated. When closed, an isolator uses only decontaminated interfaces (when necessary) 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 to adjacent environments. An isolator can be used for aseptic processing, for containment of potent compounds, or for simultaneous 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 it 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. These sheets contain summaries provided by the manufacturer to describe the chemical properties and hazards of specific chemicals and ways in which workers can protect themselves from exposure to these chemicals.

**Mutagenic:** Capable of increasing the spontaneous mutation rate by causing changes in the DNA.
**OEL**: Occupational exposure limit. An industry or other nongovernment exposure limit usually based on scientific calculations of airborne concentrations of a substance that are considered to be acceptable for healthy workers.

**PDA**: An international trade association serving pharmaceutical science and technology. Formerly known as the Parenteral Drug Association.

**PEL**: OSHA permissible exposure limit: The time-weighted average concentration of a substance to which nearly all workers may be exposed for up to 8 hours per day, 40 hours per week for 30 years without adverse effects. A PEL may also include a skin designation.

**PPE**: Personal protective equipment. Items such as gloves, gowns, respirators, goggles, face shields, and others that protect individual workers from hazardous physical or chemical exposures.

**REL**: NIOSH recommended exposure limit: An occupational exposure limit recommended by NIOSH as being protective of worker health and safety over a working lifetime. The REL is frequently expressed as a time-weighted average exposure to a substance for up to a 10-hour workday during a 40-hour work week.

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

**Risk assessment**: Characterization of potentially adverse health effects from human exposure to environmental or occupational hazards. Risk assessment 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)**: The practice in health care of treating all patients as if they were infected with HIV or other similar diseases by using barriers to avoid known means of transmitting infectious agents [CDC 1987, 1988]. These barriers can include nonporous gloves, goggles, and face shields. Careful handling and disposal of sharps or the use of needleless systems are also important.

**TLVs**: Threshold limit values. These values are exposure limits established by the ACGIH. They refer to airborne concentrations of chemical substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed, day after day, over a working lifetime, without adverse health 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 worker exposures by controlling emissions of airborne contaminants through the following:

- The full or partial enclosure of a potential contaminant source
- The use of airflow capture velocities to capture and remove airborne contaminants near their point of generation
- The use of air pressure relationships that define the direction of airflow into the cabinet
Examples of ventilated cabinets include BSCs, containment isolators, and laboratory fume hoods.

**WEEL (workplace environmental exposure level):** Occupational exposure limits developed by the American Industrial Hygiene Association as a chemical concentration to which nearly all workers may be repeatedly exposed for a working lifetime without adverse health effects.
APPENDIX C

NIOSH HAZARDOUS DRUG SAFETY WORKING GROUP

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