

Definition of Hazardous Drugs

HDs require careful handling by healthcare personnel and others who come in contact with them to minimize the adverse health effects of exposure and reduce contamination of the workplace. A definition of HDs is essential so that clinicians recognize the drugs for which the safe handling recommendations apply. Drugs are classified as hazardous when they possess any one of the following six characteristics (ASHP, 1990, 2006; National Institute for Occupational Safety and Health [NIOSH], 2004).

- **Genotoxicity**, or the ability to cause a change or mutation in genetic material; a mutagen.
- **Carcinogenicity**, or the ability to cause cancer in humans, animal models, or both; a carcinogen. The International Agency for Research on Cancer (IARC) classifies agents as carcinogens if they are capable of increasing the incidence of cancers, reducing the latency period before cancer development, or increasing the severity of growth of a malignancy. In some cases, an agent's ability to induce benign tumors was also evidence used to classify an agent as a carcinogen (IARC, 2006).
- **Teratogenicity**, or the ability to cause defects in fetal development or fetal malformation; a teratogen.
- **Fertility impairment or reproductive toxicity.**
- **Serious organ toxicity at low doses** in humans or animal models.
- **Chemical structure and toxicity profile that mimic existing drugs determined to be hazardous** by the five previous criteria. This additional criterion to the definition of HDs was first published by NIOSH in 2004 and serves as a reminder that new drugs should be critically evaluated using existing information and extrapolating data from similar agents. ASHP (2006) recommends that organizations evaluate the hazardous potential for all drugs, approved and investigational, when they are first introduced into the facility.

HDs may include antineoplastic or cytotoxic agents, biologic agents, antiviral agents, immunosuppressive agents, and drugs from other classes. OSHA (1995) recommends that all investigational agents be regarded as potentially hazardous until information establishing their safety becomes available. In the event that data provided to the principal investigator about an investigational agent are insufficient to make a decision, it is prudent to handle the agent as though it is hazardous (ASHP, 2006; NIOSH, 2004). ASHP (2006) specifies that all drugs should be considered hazardous if the information obtained about the drug is insufficient to make an informed decision as to whether it is hazardous. Certainly, healthcare providers must recognize that erring on the side of caution is essential to protecting workers' health and safety and the safety of the work environment.

The first step for organizations in creating an environment that is safe from HD exposure is to determine what HDs are used in the setting. Organizations should develop a list of all HDs used and ensure that a method is in place to regularly review and update the list. A comprehensive list of all drugs currently considered hazardous does not exist in the literature. Given the large number of new drug approvals each year, organizations must have a process for evaluating the medications they use to determine whether they are hazardous. Table 1 provides resources that will aid clinicians in evaluating whether a pharmaceutical agent should be handled as hazardous.

Clinicians should be aware that many drug classifications include medications that are hazardous. Examples of HDs in addition to traditional chemotherapy include thalidomide, interferon alpha, conjugated estrogens, and ganciclovir (NIOSH,

Table 1. Resources for Developing a List of Hazardous Drugs

Resource	Description
American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification System	The AHFS Pharmacologic-Therapeutic Classification System is a widely accepted system for classification of drugs into categories based on mechanism of action. The system designates all antineoplastic agents as category 10; all category 10 drugs are hazardous.
IARC Monographs on the Evaluation of Carcinogenic Risks to Humans	Monographs categorize the drugs, viruses, and other substances as <ul style="list-style-type: none"> • Group 1: The agent is carcinogenic to humans. • Group 2A: The agent is probably carcinogenic to humans. • Group 2B: The agent is possibly carcinogenic to humans. • Group 3: The agent is not classifiable as to its carcinogenicity to humans. • Group 4: The agent is probably not carcinogenic to humans.
Material safety data sheets (MSDS)	MSDS are developed by manufacturers to describe the chemical properties of a product, including <ul style="list-style-type: none"> • Health effects and first aid for exposure • Storage, handling, and disposal information • Personal protection • Procedures for cleaning in the event of a spill. Manufacturers are required to provide MSDS for all drugs that are deemed hazardous or contain hazardous components.
National Toxicology Program's Report on Carcinogens	Carcinogens listed in this report are classified either as known human carcinogens or reasonably anticipated to be human carcinogens. The report can be obtained at http://ntp.niehs.nih.gov/go/roc .
NIOSH	Appendix A of <i>Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings</i> contains a table with a sample list of drugs that should be handled as hazardous. The hazardous drug list was updated in 2010 and can be found at www.cdc.gov/niosh/docs/2010-167/pdfs/2010-167.pdf .
Package inserts for specific pharmaceutical agents	Package inserts for all U.S. Food and Drug Administration–approved medications contain information to assist clinicians in determining whether a drug should be classified as hazardous, including <ul style="list-style-type: none"> • Drug classification • Pregnancy category and reproductive toxicity • Organ toxicities • Secondary cancers that may develop with exposure • Drug warnings.

Note. Based on information from American Society of Health-System Pharmacists, 2010; International Agency for Research on Cancer, 2006; National Institute for Occupational Safety and Health, 2004; U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, 2010.

2004). Because HDs are administered in multiple clinical areas, it is imperative that safe handling training extend beyond the oncology unit. HD safe handling is an organizational issue.

Adverse Effects of Hazardous Drug Exposure

The adverse effects of HDs in treated patients are well known and generally seen as outweighed by the benefits of treatment, and measures are implemented to prevent or minimize these hazardous effects. The adverse effects of occupational exposure to HDs in HCWs, on the other hand, have no associated benefit. Precautions that will prevent or minimize occupational exposure to HDs are recommended in the literature. However, despite the existence of published research studies, guidelines, and recommendations, HCWs do not always follow measures to reduce HD exposure. This lack of action places HCWs at risk for myriad adverse effects. Adverse effects of occupational HD exposure are listed by system in Table 2.

Adverse effects of HD exposure can be categorized as either biologic or health effects. The consequences of HD exposure have been reported for more than 30 years. Although biologic effects have not always been linked to changes in health at the time of the studies, those identified have been associated with adverse health outcomes. For example, chemotherapy-related malignancies (myelodysplastic syndrome and acute myeloid leukemia) are known to be associated with specific alterations in chromosomes 5, 7, and 11. These chromosomal changes have occurred in patients receiving alkylating agents for the treatment of cancer.

The following section describes the biologic effects of HDs and is followed by evidence of adverse health outcomes of exposure. Table 3 summarizes studies since 1990 reporting the biologic and health effects of occupational HD exposure.

Biologic Effects of Hazardous Drug Exposure

The most frequently reported biologic effects of occupational HD exposure are genetic damage, chromosomal aberrations, DNA damage, and urinary mutagenicity. Various research studies indicate that nurses who were occupationally exposed to HDs sustained measurable genetic damage, which may be related to increased long-term health effects such as an increased incidence of cancer (Testa et al., 2007). For example, in a recent NIOSH study, the DNA of exposed workers showed a statistically significant increased frequency of damage to chromosome 5 or 7 and an increased frequency of damage to chromosome 5 alone using fluorescence in situ hybridization (McDiarmid, Oliver, Roth, Rogers, & Escalante, 2010).

Deng et al. (2005) found DNA damage, chromosomal damage, and housekeeping gene mutation in 21 workers who were occupationally exposed to methotrexate. These changes were detected by three assays and demonstrated a significant increase compared to unexposed controls. Burgaz et al. (2002) found cyclophosphamide in the urine of nurses, as well as increased genetic damage, following occupational HD handling. The authors emphasized that HD exposure should be kept to a minimum until the long-term effects of chronic low-dose occupational exposure are more fully understood. Not all studies have reported biologic effects of HD exposure, however. Monitoring methods and differences in safe handling precaution use may be an explanation for the different findings.

Adverse Health Outcomes of Occupational Hazardous Drug Exposure

The most frequently reported adverse health outcomes of work-related HD exposure are the occurrence of acute symptoms and reproductive effects. Evidence also has shown an increase in cancer occurrence in occupationally exposed workers.

Table 2. Adverse Health Effects of Occupational Exposure to Hazardous Drugs

System Affected by Hazardous Drug Exposure	Adverse Health Effect of the Exposure
Malignancies	Leukemia Non-Hodgkin lymphoma Bladder cancer Liver cancer
Reproductive	Infertility Prolonged time to conception Premature delivery Low birth weight Ectopic pregnancy Spontaneous abortions; miscarriages Stillbirths Learning disabilities in offspring
Integumentary and mucosal	Skin irritation/contact dermatitis Mouth and nasal sores Hair thinning, partial alopecia
Neurologic	Headaches Dizziness
Gastrointestinal	Nausea Vomiting Abdominal pain
Respiratory	Dyspnea
Allergic	Allergic asthma Eye irritation

Note. Based on information from Fransman, Roeleveld, et al., 2007; Martin, 2005b; Petralia et al., 1999; Saurel-Cubizolles et al., 1993; Skov et al., 1990, 1992; Valanis et al., 1993a, 1999; Walusiak et al., 2002.

Table 3. Hazardous Drug Exposure: Biologic and Health Effects

Study	Purpose	Design	Sample	Measurement	Results
Krepinsky et al., 1990	Evaluate possible genetic damage caused by HD exposure and to compare the effectiveness of three methods of detection	Matched case-controlled	10 exposed and 10 unexposed nurses and 10 patients with cancer receiving chemotherapy in Canada	CAs and SCEs in PBLs. Ames test for mutagenicity in urine. Samples collected before and after exposure. PPE use was not monitored.	SCE assay detected treated patients and 2 nurses who smoked. Ames test detected treated patients but not smokers. CAs detected in 4 out of 9 patients (data missing for 1 patient) and in exposed nurses after several days, which was not likely due to exposure.
Oestreicher et al., 1990	Evaluate possible genetic damage caused by HD exposure	Matched case-controlled	8 nurses handling HDs without protection for years, 8 exposed pharmacy personnel using precautions, 8 unexposed nurses	CAs and SCEs in PBLs	CAs significantly increased in exposed nurses when compared to unexposed nurses and pharmacists using precautions ($p < 0.01$). SCEs not significantly different between groups.
Stücker et al., 1990	Analyze relationship between SAs and occupational exposure to HDs among nurses	Matched case-controlled	4 French hospitals 466 women, 534 pregnancies	Questionnaire	26% SA in 139 pregnancies in exposed women 15% SA in 357 pregnancies in unexposed women OR = 1.7 (95% CI 1.2–2.8)
Cooke et al., 1991	Determine the occurrence of CAs in nurses and pharmacists exposed to HDs in United Kingdom	Case-controlled	50 pharmacists, 11 nurses, 12 controls, and 6 patients	Analysis of blood for CAs in PBLs	No significant differences between exposed pharmacists or nurses compared to controls No correlation between amount of drugs handled and CAs
Thiringer et al., 1991	Determine the relationship between urine mutagenicity, urinary thioethers, SCEs, and micronuclei and occupational exposure to HDs	Matched case-controlled	60 Swedish nurses exposed to HDs and 60 unexposed controls	Analysis of urine for mutagenicity and thioethers and blood for SCEs and micronuclei in PBLs	For urine mutagenicity, there was a significant difference between exposed and unexposed workers ($p < 0.01$). For SCEs, there was a significant difference between exposed and unexposed workers ($p < 0.05$). No significant difference for thioethers and micronuclei
Goloni-Bertollo et al., 1992	Determine the relationship between CAs and SCEs and occupational exposure to HDs	Matched case-controlled	15 nurses and nurse aides in Brazil preparing and administering HDs Controls: 15 nurses on nononcology wards and 15 office workers	Analysis of blood for SCEs and micronuclei in PBLs	Significantly more frequent CAs and SCEs in exposed nurses compared to controls
Harris et al., 1992	Determine the relationship between CAs and micronuclei and occupational exposure to HDs	Matched case-controlled	64 nurses in United States (24 low exposure, 21 medium exposure, 19 high exposure) and 15 patients with cancer	Analysis of blood for CAs and micronuclei in PBLs	No association between exposure classification and CAs or micronuclei CAs and micronuclei significantly associated with glove use of less than 100% of time compared to 100% use

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Table 3. Hazardous Drug Exposure: Biologic and Health Effects (Continued)

Study	Purpose	Design	Sample	Measurement	Results
Skov et al., 1992	Describe the risk for cancer and adverse reproductive outcomes among Danish nurses handling HDs	Descriptive, retrospective record review	1,282 female nurses from Danish hospitals preparing or administering HDs and 2,572 unexposed nurses working in the same hospitals	Danish health records (1973–1987) Hospital employment records	Significantly increased relative risk for leukemia. Overall risk estimates were not increased for adverse reproductive outcomes. The study included the time before as well as the time after implementation of safe handling measures.
Stücker et al., 1993	Determine the relationship between birth weight and exposure to HDs during and before pregnancy	Matched case-controlled	4 French hospitals 466 women; 420 live births, 298 births to unexposed women, 107 births to nurses exposed during and before pregnancy	Questionnaire	Birth weight of infants of exposed mothers was 85 g less than that of infants of unexposed mothers but was not statistically significant. Exposure data missing for 15.
Valanis et al., 1993a	Determine the relationship between occupational exposure to HDs and acute symptoms among nursing personnel	Descriptive, cross-sectional	1,932 nurses and 152 nurse aides from more than 200 healthcare facilities currently handling HDs	Questionnaire (handling activities, use of PPE, and symptoms experienced in the previous three months)	Handling HDs increased the number of symptoms. Use of protection decreased the number of reported symptoms. Skin contact while cleaning up spills or handling patient excreta was a predictor of symptoms.
Valanis et al., 1993b	Determine the relationship between occupational exposure to HDs and acute symptoms among pharmacy personnel	Descriptive, cross-sectional	533 pharmacists and technicians currently handling HDs and 205 pharmacists and technicians who never mixed HDs	Questionnaire (handling activities, use of PPE, and symptoms in the previous three months)	Diarrhea and chronic cough were increased in exposed study subjects over controls. Self-reported skin contact was a predictor of symptoms.
Hansen & Olsen, 1994	Determine cancer incidence among HD handlers	Archived data analysis	Female Danish pharmacy technicians identified in cancer registry	Comparison of Danish cancer registry data to expected cancer incidence rates	1.5-fold elevated risk of nonmelanoma skin cancer; 3.7-fold increased risk for non-Hodgkin lymphoma
Sessink et al., 1994	Compare urinary CP excretion and CAs in four groups of hospital workers with various levels of HD exposure	Descriptive	17 Dutch and 11 Czech hospital workers handling HDs, and 35 Dutch and 23 Czech workers not handling HDs	Analysis of urine for CP and blood for CAs in PBLs	The percentage of aberrant cells was increased in exposed Dutch and Czech workers. Results suggest additive effect of exposure and smoking. CP was detected in urine samples of 3 out of 11 Dutch workers and 8 out of 11 Czech workers handling HDs.
Fuchs et al., 1995	Determine the occurrence of DNA damage in nurses handling antineoplastic agents	Descriptive	91 nurses from four hospitals in Germany who handled chemotherapy and 54 unexposed controls	Blood samples for DNA single-strand breaks and alkali labile sites in PBLs Questionnaire and demographic data	A 50% higher level of DNA strand breaks and alkali labile sites were detected in nurses not using precautions as compared to controls. After implementing recommended safety precautions, strand breaks decreased to the level of controls.

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Table 3. Hazardous Drug Exposure: Biologic and Health Effects (Continued)

Study	Purpose	Design	Sample	Measurement	Results
Oesch et al., 1995	Determine the occurrence of DNA damage in nurses handling HDs	Case-controlled	German nurses handling HDs without proper safety equipment, nurses handling HDs with proper equipment, and unexposed controls	DNA strand breaks in PBLs	DNA strand breaks were greater in nurses without proper equipment compared to those with proper equipment ($p < 0.005$) and greater than in unexposed controls
Sessink et al., 1995	Calculate cancer risk for healthcare workers occupationally exposed to CP	Mathematical calculation	Data from an animal study Dose-response data on primary and secondary tumors in CP-treated patients Data on urinary excretion of CP	Dose-response data Estimated mean total CP uptake	For a 70 kg (154 pound) person working 200 days per year for 40 years: cancer risks obtained from both animal and patient data were the same and ranged from 1.4–10 per million per year for CP exposure.
Shortridge et al., 1995	Determine whether HD handling increases the prevalence of menstrual dysfunction in nurses	Descriptive	982 ONS members who handled HDs and 897 ANA members not exposed to HDs All were menstruating, non-pregnant females 46 years of age or younger	Questionnaire	Menstrual dysfunction differed among exposure groups, with the highest rate among study subjects currently handling HDs. Menstrual dysfunction was greatest for study subjects older than age 30.
Valanis et al., 1997	Analyze the relationship between infertility and occupational exposure to HDs among nurses and pharmacists	Descriptive, matched case-controlled	405 subjects reporting infertility and 1,215 matched controls	Questionnaire	Women had a significantly elevated OR (1.5, 95% CI) for infertility associated with HD handling prior to onset of infertility. A similar effect was found in men.
Garaj-Vrhovac & Kopjar, 1998	Determine the relationship between micronuclei and occupational exposure to HDs using three types of staining methods	Matched case-controlled	10 Croatian nurses exposed to HDs and 10 unexposed without adequate protection when preparing and administering HDs	Analysis of blood for micronuclei in PBLs	With the three staining methods, there was a significant difference between the exposed and controls ($p < 0.05$).
Labuhn et al., 1998	Analyze internal and external exposure to HDs	Descriptive	23 pharmacists who prepared HDs, 28 nurses who prepared and administered HDs, 32 nurses who administered HDs, and 35 controls who never handled HDs	Drug-handling log, 24-hour urine for mutagenicity, industrial hygiene (fluorescent) scans for doxorubicin contamination	15% of the urine samples were positive for mutagenicity; reported skin exposure predicted positive urine tests. 13% of scans were positive for worker contamination. More contamination occurred during HD administration than during preparation. Reported PPE use was 27% among nurses who handled HDs.
Valanis et al., 1999	Determine the effect of HD exposure on pregnancy loss among nurses and pharmacists	Descriptive	7,094 pregnancies among 2,976 pharmacy and nursing staff	Questionnaire	Exposure of the mother to HDs directly before or during pregnancy was associated with a significantly increased risk of SA and/or stillbirth.

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Table 3. Hazardous Drug Exposure: Biologic and Health Effects (Continued)

Study	Purpose	Design	Sample	Measurement	Results
Maluf & Erdtmann, 2000	Part 1: Analyze the relationship between micronuclei and occupational exposure to HDs among nurses and pharmacists	Matched case-controlled	10 Brazilian pharmacists and nurses exposed to HDs and 10 unexposed workers	Analysis of blood for micronuclei in PBLs	Significant difference between exposed workers and controls ($p = 0.038$)
	Part 2: Analyze the relationship between micronuclei and comet assay and modifications to work schedules among nurses and pharmacists	Matched case-controlled following reduction in work hours	12 Brazilian pharmacists and nurses exposed to HDs and 12 controls	Analysis of blood for micronuclei and comet assay in PBLs	No difference between exposed workers and controls for micronuclei Significant difference between exposed workers and controls for comet assay ($p = 0.0006$)
Burgaz et al., 2002	Determine frequency of CAs in PBLs of nurses exposed to HDs	Matched case-controlled	20 nurses handling HDs and 18 controls	CAs in PBL; CP excreted in urine	2.5-fold increase in CAs, including chromatid breaks, gaps, and acentric fragments for nurses handling HDs as compared to controls ($p < 0.05$) CP excretion rate for 12 nurses was 1.63 mcg/24 hours, indicating exposure.
Cavallo et al., 2005	Evaluate genotoxic effects of antineoplastic exposure	Laboratory analysis	25 exposed nurses, 5 pharmacy technicians, and 30 unexposed controls from administrative offices in a large Italian hospital	Micronuclei test and analysis of CAs with lymphocytes and exfoliated buccal cells	No difference between exposed study subjects and controls for micronuclei in lymphocytes Higher values for micronuclei in exfoliated buccal cells of exposed workers CAs were 2.5–5-fold higher in exposed groups.
Martin, 2005b	Determine the effects of chemotherapy handling among nurses and their offspring	Descriptive, correlational	2,427 nurses who reported handling 3 or more doses of HDs per day for at least one year and reported giving birth within 10 years of exposure Total of 3,399 offspring	Questionnaire	HD handling before age 25 increased odds of infertility. More years of HD handling resulted in higher rate of miscarriage. Handling 9 or more doses per day increased preterm labor and preterm birth. Learning disabilities increased in offspring of nurses who rarely wore gloves during HD handling. Increased cancer occurrence existed among exposed nurses.
Yoshida et al., 2006	Analyze the relationship between DNA damage and occupational HD exposure in nurses and pharmacists	Case-controlled	37 nurses in a hospital in Japan: 18 unexposed and 19 exposed nurses	Analysis of blood for comet assay, tail length	Tail length, 5.1 mcm in unexposed and 8.5 mcm in exposed study subjects Significant difference, $p = 0.004$

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Table 3. Hazardous Drug Exposure: Biologic and Health Effects (Continued)

Study	Purpose	Design	Sample	Measurement	Results
Fransman, Roeleveld, et al., 2007	Determine reproductive effects of HD exposure	Survey	4,393 exposed and unexposed nurses	Estimated HD exposure based on self-reported tasks Reproductive outcomes	Nurses highly exposed to HDs took longer to conceive than unexposed nurses. Exposure was associated with premature delivery and low birth weight.
Ikeda et al., 2007	Analyze the relationship between SCEs and occupational exposure to HDs among mixed population Determine epirubicin in urine and plasma of mixed population	Case-controlled; laboratory analysis	Pharmacists, nurses, and physicians in Japan with rotating duties SCE: 11 exposed workers and 2 controls Urine and plasma analysis: 13 exposed workers and 3 controls	SCEs in peripheral blood Epirubicin in urine and plasma	No correlation was found between hours worked per week and SCEs. No epirubicin was detected in urine or plasma.
Testa et al., 2007	Determine the incidence of CAs in PBLs of nurses occupationally exposed to HDs	Case-controlled	76 oncology nurses occupationally exposed to HDs and 72 controls from two hospitals in Italy	CAs in PBLs	Mean total number of CAs for exposed nurses was 3.7 times (11.2 versus 3.04) that of controls ($p < 0.0001$). Chromatid- and chromosome-type aberrations were 3.4 and 4.16 times that of controls.

ANA—American Nurses Association; CA—chromosomal aberration; CI—confidence interval; CP—cyclophosphamide; DNA—deoxyribonucleic acid; HD—hazardous drug; ONS—Oncology Nursing Society; OR—odds ratio; PBLs—peripheral blood lymphocytes; PPE—personal protective equipment; SA—spontaneous abortion; SCE—sister chromatid exchanges

Several studies have documented the adverse reproductive outcomes of occupational exposure. Fransman, Roeleveld, et al. (2007) compared outcomes in 4,393 exposed and unexposed (control) nurses in the Netherlands. Exposure to antineoplastic drugs was estimated using dermal measurements based on handling tasks. Nurses who were highly exposed, defined as 0.74 mcg/week exposure, took longer to conceive, had infants with lower birth weight, and had a higher incidence of preterm labor. Similarly, Martin (2005b) reported an inverse relationship between compliance with HD handling guidelines and adverse reproductive outcomes among nurses surveyed. Significant findings in exposed versus unexposed nurses included infertility in those who handled chemotherapy before age 25; miscarriages, preterm birth, and preterm labor in nurses who administered more than nine doses per day; and an increase in learning disabilities in offspring, which correlated to glove use. When a Danish study of exposed versus unexposed nurses found a similar risk of fetal malformations, miscarriages, low birth weight, or preterm delivery, the researchers concluded that a well-protected setting (e.g., one with proper safe handling precautions) reduces occupational HD exposure (Skov et al., 1992).

Valanis, Vollmer, Labuhn, and Glass (1993a) reported the occurrence of acute symptoms of HD exposure in 2,084 nurses and nurse aides. These included cardiac, gastrointestinal, neurologic, allergic, infectious, and systemic symptoms. The researchers found that skin contact with HDs, especially during spill cleanup, was associated with less use of personal protective equipment (PPE) and more acute symptoms, leading the authors to conclude that skin contact is a major source of exposure.

Several studies have found an increase in the occurrence of cancer in HD-exposed HCWs compared to unexposed HCWs. For instance, Skov et al. (1992) found a higher relative risk for acute leukemia in female Danish nurses handling chemotherapy. Hansen and Olsen (1994) reported that long-term pharmacy dispensers of HDs were 3.7 times more likely than the general population to develop non-Hodgkin lymphoma. Martin (2005b) found that HD-exposed nurses had a higher occurrence of cancer and that the cancer occurred at a younger age than expected according to National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results data.

Recent studies document genetic changes in HD handlers and fewer acute side effects experienced by HD-exposed HCWs when compared to earlier studies. This is likely due to both improved use of safe handling precautions and the availability of more sensitive measures of HD exposure. The effects of low-dose, chronic HD exposure are not well documented, but several recognized consequences of exposure exist. While overall exposure is lower than in years past, HCWs are still potentially exposed. Publications from around the world indicate that adherence to HD safe handling guidelines is lower than what is recommended. Nurses must recognize deficiencies in their systems, individual practices, and PPE use and make corrections to avoid the adverse biologic and health effects of HD exposure.

Evidence for Occupational Hazardous Drug Exposure

Occupational HD exposure is not as easy to measure as radiation exposure. In clinical settings, workers who have the potential for radiation exposure wear a film badge or dosimeter that records exposure as it occurs. The measuring devices are evaluated on a regular basis, and the HCW is notified when a predetermined level of exposure is exceeded. Individuals are counseled to then avoid exposure for a period of time. Currently, no reliable method exists for biologic monitoring of occupational exposure to HDs (Baker & Connor, 1996). Several methods (Ames test, sister chromatid exchanges, chromosomal aberrations, micronucleus assay, and urinary thioether excretion) have been found to correlate poorly with HD exposure. For this and other reasons, no recommendations have been made for routine testing for HD exposure.

Biologic Monitoring

HD exposure in HCWs occurs through various routes, including dermal absorption, absorption through mucous membranes, and inadvertent ingestion, inhalation, or injection. When HD exposure occurs, the drugs are absorbed, metabolized, and excreted. Assays have been developed for directly measuring specific HDs or their metabolites. Detecting these drugs in the urine of HCWs is one method of determining HD exposure.

In three studies by Sessink and colleagues, urine samples were analyzed using sensitive and specific high-performance liquid chromatography and gas chromatography-mass spectrometry (Sessink, Boer, Scheefhals, Anzion, & Bos, 1992; Sessink, Van de Kerkhof, Anzion, Noordhoek, & Bos, 1994; Sessink, Wittenhorst, Anzion, & Bos, 1997). HDs were detected in the urine of workers, including workers not directly involved in preparation or administration of the specific drugs. The authors concluded that routine handling of HDs results in contamination of the work environment and that dermal exposure is an impor-

tant route for uptake of these drugs. This is supported by an earlier report that detected cyclophosphamide both in the urine of volunteers who had the drug applied to their skin and in two nurses who prepared and administered cyclophosphamide without respiratory protection or PPE (Hirst, Tse, Mills, Levin, & White, 1984).

Additional studies using assays indicated exposure, uptake, and metabolism of HDs during routine work activities even when no obvious source of exposure was identified. Nygren and Lundgren (1997) detected increased platinum (from platinum-containing HDs such as cisplatin) in the blood of staff nurses (those involved in patient care) but not in graduate nurses (those involved in HD handling) or pharmacists. They concluded that exposure most likely occurred during routine care of treated patients rather than during HD preparation or administration, where PPE use was more likely. Pethran et al. (2003) found HDs in the urine of 40% of study participants despite the use of biologic safety cabinets (BSCs).

Environmental Monitoring for Hazardous Drug Exposure

Early support for precautions while handling HDs focused on the biologic effects in exposed individuals. Following the implementation of HD safe handling guidelines in most settings, pharmacists and nurses continued to demonstrate evidence of exposure despite the use of precautions such as BSCs, gloves, and gowns. The most plausible source of exposure is an environment that is contaminated with HDs.

Exposure From Contaminated Surfaces

One method of measuring environmental contamination with HDs is surface wipe sampling. Surfaces in work areas where HDs are handled are evaluated for the presence of HD residue. The sample areas are measured, moistened with 0.03 M sodium hydroxide, and wiped with paper towels until dry. The towels are placed in plastic containers and sent for analysis for the presence of several drugs (Connor, Anderson, Sessink, & Spivey, 2002).

Minoia et al. (1998) analyzed surface wipe samples, pads placed on gowns, air samples, and gloves of 24 workers involved in HD preparation and administration for the presence of cyclophosphamide and ifosfamide. In addition to positive air and urine samples, many of the wipe samples taken from inside and outside of the BSC, including the floor and door handles, were contaminated with the two drugs. Many of the pads and gloves were also contaminated. The authors concluded that inadequate performance of the BSC may result in worker contamination. They suggested that using a plastic-backed paper liner inside the BSC may interfere with airflow and affect BSC performance. No subsequent studies have evaluated the effect of BSC liners on airflow. The study further demonstrated that gloves are routinely contaminated during HD handling and should be changed periodically. Guidelines recommend that gloves be discarded after no more than 30 minutes of use.

In a multisite study in the United States and Canada, surface contamination with three cytotoxic agents was measured by more than 200 wipe samples (Connor, Anderson, Sessink, Broadfield, & Power, 1999). The results revealed that 75% of wipe samples from drug preparation areas and 65% of samples from drug administration areas had measurable levels of one or more of the drugs. The investigators concluded that surface contamination with HDs is common and that workers who are not directly involved in HD handling may be exposed to drug residue on these

surfaces. Other investigators have reported similar findings with cyclophosphamide (Kiffmeyer et al., 2002) and platinum (from cisplatin and/or carboplatin) in addition to ifosfamide (Mason et al., 2005; Nygren & Aspman, 2004; Schmaus, Schierl, & Funck, 2002).

Fransman, Vermeulen, and Kromhout (2004, 2005) evaluated workers' potential and actual dermal exposure to cyclophosphamide during the performance of common hospital tasks in two studies. The investigators placed pads on several body locations of nurses, pharmacy technicians, and cleaning personnel. They also analyzed gloves worn during handling activities, hand-wash water used after handling activities, patient body fluids, and linens from patients who had received cyclophosphamide. The gloves were commonly contaminated. Nurses were found to have skin contamination under gloves, especially following handling of patients' urine. These findings confirmed dermal exposure during normal patient care activities and led the authors to conclude that hands are a common site of HD exposure for HCWs.

Several studies have detected drug contamination on the outside of drug vials when delivered by the manufacturers (Connor et al., 2005; Nygren, Gustavsson, Strom, & Friberg, 2002; Sessink et al., 1992). Cyclophosphamide, fluorouracil, ifosfamide, and platinum have all been detected on vial exteriors using various wipe sampling and washing techniques. These findings indicate that nurses and pharmacists are at risk for skin exposure if they do not wear PPE while handling unopened drug vials.

Results from the many environmental monitoring studies demonstrate that the work areas where HDs are prepared and administered are commonly contaminated with the drugs. Workers who normally wear PPE for direct drug-handling activities can be exposed when touching unknowingly contaminated surfaces with unprotected hands. Every study measuring environmental contamination using surface wipe sampling found evidence of surface contamination (see Table 4).

Inhalation Exposure

Several investigators have identified low levels of HDs in air samples collected in areas where the drugs are handled (Kiffmeyer et al., 2002; Kromhout et al., 2000; Mason et al., 2005). Although this exposure route is less likely for workers who use a BSC, the risk is high for drug preparation outside of a primary engineering control (PEC), including inhalation of aerosols during the crushing of tablets (Dorr & Alberts, 1992). In addition, some authors have reported vaporization of several antineoplastic drugs (Connor, Shults, & Fraser, 2000; Kiffmeyer et al., 2002). A few authors have proposed that inhalation exposure may be higher than previously thought because earlier methods used to measure air samples were not sufficiently sensitive (Hedmer, Jonsson, & Nygren, 2004; Larson, Khazali, & Dillon, 2003b). Therefore, workers should consider inhalation as a possible route of HD exposure and avoid performing any drug preparation activities outside of a BSC.

To summarize, ongoing evidence shows that occupational HD exposure can and does occur. Few laboratories in the United States perform the assays described in this section, which makes routine monitoring impractical. In the absence of measured contamination in the workplace, nurses should consider the possibility of environmental contamination. Because a safe level of HD exposure does not exist, HCWs must take steps to minimize their exposure. Additional studies are needed that evaluate the magnitude of HD exposure of HCWs who consistently use safe handling precautions.

Table 4. Hazardous Drug Exposure: Environmental Monitoring

Study	Purpose	Design	Sample	Measurement	Results
Sessink et al., 1992	Measure surface contamination and air concentrations with 4 HDs	Laboratory studies	Pharmacy and nursing areas in a hospital in the Netherlands	Analysis of air samples and wipe samples for CP, IF, 5-FU, and MTX	Floors, hood, drug vials, sinks, cleaned urinals, gloves, and other objects > LOD for one or more HD. CP or IF detected in urine of 8 of 25 pharmacy technicians and nurses, including 6 not directly involved in handling.
McDevitt et al., 1993	Measure surface contamination and air concentrations with HDs	Laboratory studies	Pharmacy and nursing areas in a U.S. hospital 76 wipe samples and 73 air samples	Analysis of air samples and wipe samples for CP	Pharmacy, 34 wipe samples, 18% > LOD; air samples, 3/34 > LOD Nursing, 42 wipe samples, 14% > LOD; air samples, 0 of 39 > LOD
Minoia et al., 1998	Evaluate the occupational exposure of hospital personnel handling HDs	Laboratory studies	10 workers involved in HD preparation and 14 workers involved in administration of CP and IF in 2 Italian hospitals	Analysis of air samples, wipe samples, pads, and gloves Urinary excretion of CP and IF measured using HPLC/tandem mass spectrometry	Urine samples were positive for 12 of 24 workers for CP and 2 of 24 workers for IF. 3 of 24 air samples were positive, and wipe samples of surfaces as well as gloves were positive. A plastic-backed liner in the BSC was shown to compromise its containment properties.
Connor et al., 1999	Measure surface contamination with 3 HDs in pharmacy and nursing areas	Laboratory studies	More than 200 locations, including pharmacies and HD administration areas	Surface wipe samples analyzed for IF, CP, and 5-FU Duplicate blanks prepared for every surface sample.	75% of samples from drug preparation areas and 65% of samples from drug administration areas had measurable levels of HDs.
Rubino et al., 1999	Measure surface contamination with 4 HDs in pharmacy areas	Laboratory studies	8 oncology departments in 2 Italian hospitals	139 surface wipe samples for MTX, 5-FU, cytarabine, and gemcitabine measured at various distances from drug preparation area	Percent of samples with contamination: 83% > LOD in safety cabinet 53% > LOD < 1 M from safety cabinet 47% > LOD > 1 M from safety cabinet
Kromhout et al., 2000	Evaluate the potential for dermal exposure to HDs	Observation, simulation, and laboratory studies	Patient treatment areas in 3 hospitals in the Netherlands	Visual scoring of fluorescent tracer found on workers and work surfaces Air sampling for airborne particles of HDs using gas chromatography/tandem mass spectrometry	Leakage detected at connection sites of IV equipment. Leakage highest at the IV spike connection and lowest at Luer-lock connections. Floors, toilets, and soles of nurses' shoes were contaminated. CP was found in 16% of samples taken in patient treatment areas.

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Table 4. Hazardous Drug Exposure: Environmental Monitoring (Continued)

Study	Purpose	Design	Sample	Measurement	Results
Favier et al., 2001	Measure environmental contamination with HDs in BSCs and isolators	Laboratory analysis	6 French pharmacies, 3 with BSCs and 3 with isolators	Measurement of 5-FU on work surfaces in BSCs and isolators and several other locations	Comparable samples from the 3 BSCs, 1 of 6 > LOD Samples from isolators, 5 of 6 > LOD Values post-cleaning were lower. 25 of 30 preps in isolator > LOD 1 of 30 preps in BSCs > LOD Some other glove and environmental contamination was reported.
Kiffmeyer et al., 2002	Measure environmental contamination with HDs	Laboratory analysis	HD preparation areas	Measurement of carmustine, cisplatin, CP, etoposide, and 5-FU in air samples Measurement of CP in wipe samples and urine of workers who prepared CP.	Particulate CP was found in the air of 6 of 20 preparation sites. Gaseous CP was found in 7 of 15 sites. CP was present on 17 of 26 surfaces. No CP was found in the urine of 3 tested workers.
Nygren et al., 2002	Measure external vial contamination with HDs	Laboratory analysis	6 vials of platinum-containing drugs from 3 different manufacturers in Sweden	Wipe sample analysis using adsorptive voltammetry	Drug vials were contaminated on the outside when delivered by the manufacturer.
Schmaus et al., 2002	Measure environmental contamination with HDs	Laboratory analysis	7 standard locations in each of 14 hospital pharmacies in Germany	Wipe sample analysis using gas chromatography-mass spectrometry and voltammetry for CP, IF, 5-FU, and platinum	100% of samples tested positive for platinum, which has a low limit of detection. 0%–25% tested positive for CP and IF; 40%–80% tested positive for 5-FU. Volume of drugs prepared did not predict the amount of contamination. Work practices in some settings reduced contamination.
Favier et al., 2003	Measure external vial contamination	Laboratory analysis	739 vials tested for 6 drugs from several manufacturers Drug packaging tested for 5-FU and etoposide	Vials immersed in solvent with rotation for 30 seconds in water HPLC used for 5-FU, etoposide, doxorubicin, and docetaxel Gas chromatography used for CP and IF	100% of vials were contaminated 0.5–2,447 ng/vial. 5-FU drug packaging was contaminated. No contamination was seen on etoposide packaging.
Larson et al., 2003a	Method development	Laboratory analysis	Development of a method for detecting 5-FU, IF, CP, doxorubicin, and paclitaxel in air samples	Air samples collected and filtered with Anasorb® 708 (SKC, Inc.) solid sorbent tube	Greater than 90% recovery for both CP and ifostamide; 5-FU, doxorubicin, and paclitaxel were detected and measured. All 5 agents of interest were detected at minimal LOD of 0.5 mcg/ml.

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Table 4. Hazardous Drug Exposure: Environmental Monitoring (Continued)

Study	Purpose	Design	Sample	Measurement	Results
Larson et al., 2003b	Validate a new monitoring method for evaluation of airborne HDs	Laboratory analysis	Filters and sorbent tubes used for recovering CP, IF, and 5-FU from air samples	Air monitoring for HDs using reverse-phase HPLC/mass spectrometry	CP was recovered from filters and then evaporated, becoming gaseous. HEPA filters trap particles but not vapors. Recirculating BSCs may result in worker exposure.
Fransman et al., 2004	Evaluate dermal exposure to CP	Laboratory analysis	Pharmacy technicians, oncology nurses, and cleaning personnel in 3 Dutch hospitals during the performance of 5 tasks	Analysis of cotton pads attached to body surfaces Analysis of wipe samples of foreheads Assays of used gloves, wash water, wash cloths, towels, and bed-sheets for CP	CP was detected on pads, gloves, wipe samples, wash cloths, and bed linens. CP was found on foreheads of technicians and nurses. Cleaning personnel had CP on their gloves. Contamination of hand-wash samples was highest during handling of urine.
Hedmer et al., 2004	Validation of methods for detecting CP on surfaces and in the air	Laboratory analysis	Air and surface samples	Wipes made of different materials to clean up CP Several filter types for recovering CP from air	LOD for CP was 0.02 ng per sample for wipes and 0.03 ng for air samples.
Nygren & Aspman, 2004	Validation of x-ray fluorescence as a method for assessment of aerosol distribution	Laboratory analysis	Surfaces in a drug preparation room of an oncology clinic	Wipe samples analyzed for platinum	Platinum was recovered from every wipe sample except from a corridor outside the preparation room. The level of platinum was highest in the BSC and decreased with increasing distance from the BSC.
Connor et al., 2005	3 studies evaluating external vial contamination with HDs	Laboratory analysis	Unopened vials of HDs	Study 1: wipe sampling for CP and IF Study 2: wipe sampling for CP and 5-FU Study 3: analysis for cisplatin using two vial washing techniques and polymer sleeves	Surface contamination was detected on most commercially available drug vials tested. Improved decontamination in combination with sleeves reduced contamination by 90%.
Fransman et al., 2005	Measure dermal exposure to CP during various handling activities	Laboratory analysis	Personnel handling HDs or caring for people who receive HDs	Analysis of cotton pads attached to body surfaces Analysis of wipe samples of foreheads Assays of used gloves, wash water, wash cloths, towels, and bed-sheets for CP	CP was detected on pads, gloves, wipe samples, wash cloths, and bed linens. Most CP was found on hands. Nurses who wore gloves had skin contamination of their hands, most often after handling urine.

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Table 4. Hazardous Drug Exposure: Environmental Monitoring (Continued)

Study	Purpose	Design	Sample	Measurement	Results
Mason et al., 2005	Evaluate the effectiveness of negative and positive pressure isolators	Laboratory analysis	Air, urine, and surface samples from two hospital pharmacies in the United Kingdom	Analysis of air samples and urine samples Surface wipe sample to measure floor and glove contamination	Measurable amounts of HDs were detected on floors and on gloves of staff preparing HDs. Low levels of platinum were found in the urine, with significantly higher amounts in workers using negative pressure isolators. Personal air samples were mostly undetectable.
Zeedijk et al., 2005	Method development	Laboratory analysis	Method development for detecting residue of CP, IF, 5-FU, and MTX, pre- and post-cleaning of surfaces	Wipe samples tested using HPLC for 5-FU TDx FLx Immunology Analyzer for MTX Gas chromatography/mass spectrometry for CP and IF	4 drugs can be measured from one wipe sample. Pre-cleaning over 3 days, 15 of 15 > LOD Post-cleaning over 3 days, 10 of 14 > LOD
Bussieres et al., 2007	Measure environmental contamination with HDs	Laboratory study	Develop method for measuring MTX in a Canadian pharmacy	MTX from wipe samples using HPLC over 40 sampling times	5 of 198 wipe samples > LOD
Fransman, Huizer, et al., 2007	Measure environmental contamination with HDs	Laboratory study	Measurement of 8 drugs in air and on gloves, hands, and bed linens in a Dutch laundry	Air sample collected in linen handling area Linen strips and gloves tested for 8 drugs using triple quadrupole mass spectrometer	Before pre-wash, 5 of 15 sheets > LOD 3, CP; 2, IF; 1, 5-FU After pre-wash, 0 of 15 > LOD
Ikeda et al., 2007	Measure environmental contamination with HDs	Laboratory study	Develop method for measuring epirubicin in a Japanese pharmacy	Wipe samples measured from 11 different surfaces with HPLC	14 of 59 > LOD

BSC—biologic safety cabinet; CP—cyclophosphamide; 5-FU—fluorouracil; HD—hazardous drug; HEPA—high-efficiency particulate air; HPLC—high-performance liquid chromatography; IF—ifosfamide; LOD—level of detection; MTX—methotrexate