

Introduction

Key Points

- Hazardous drugs (HDs) are toxic to genes, reproductive organs, and other body systems.
- Healthcare workers (HCWs) often are not aware of all sources of exposure to HDs.
- Nurses need to identify risks in their work settings and change practices that put themselves and colleagues at risk.

Many oncology nurses have a daily responsibility for preparing and administering drugs used in the treatment of cancer. Many of these drugs are HDs because they alter DNA or affect other intracellular processes that interfere with cancer cell growth. HDs are toxic to genes, reproductive organs, and other body systems. For patients, the benefits of treatment generally outweigh the risks. For HCWs, though, there are no benefits, and HD exposure should be avoided.

Most oncology nurses acknowledge the adverse effects associated with occupational exposure to HDs (Polovich & Clark, 2012). However, they may not know that they are potentially exposed during routine handling. Numerous studies demonstrate that work areas where HDs are prepared and administered are commonly contaminated with the drugs, which then become a source of HCW exposure (Berruyer, Tanguay, Caron, Lefebvre, & Bussi eres, 2015; Chu, Hon, Danyluk, Chua, & Astrakianakis, 2012; Connor et al., 2010; Yoshida et al., 2011). The evidence for environmental contamination, the adverse health outcomes associated with occupational HD exposure, and the fact that eight million HCWs in the United States are potentially exposed (U.S. Bureau of Labor Statistics, 2015) reinforces the need for safe handling.

Guidelines for the safe handling of HDs have been available in the United States since 1986, but 30 years of attention to the issue have not yet solved the problem of occupational HD exposure. There is, however, a steadily increasing awareness of the need for safe handling of HDs among HCWs, professional organizations, regulatory bodies, and even some state legislators. Progress in the past five years is evidenced by publication of updated guidance from the Occupational Safety and Health Administration (OSHA, 2016), the National Institute for Occupational Safety and Health (NIOSH, 2016), and the Oncology Nursing Society (ONS; Polovich, Olsen, & LeFebvre, 2014). At the time of this writing, legislation that provides for

HD safety currently exists in three states (California Legislative Information, 2013; North Carolina General Assembly, 2014; Washington State Department of Labor and Industries, n.d.) and is pending in others. Acceptance and implementation of HD safe handling precautions is increasing (Boiano, Steege, & Sweeney, 2014, 2015). The implementation of the U.S. Pharmacopeial Convention (USP) General Chapter 800 standards for HD safe handling (USP, 2016a) will represent an important step forward for nurses and other potentially exposed HCWs.

This manual is based on the recommendations of NIOSH, OSHA, ONS, the American Society of Health-System Pharmacists (ASHP), and USP. Its intent is to help to translate safe handling recommendations into practice for nurses who handle HDs in the delivery of care to patients. Nurse managers, nurse administrators, and nurses responsible for employee health and wellness also may find this content useful. Nurses are encouraged to critically examine their workplaces and work practices to identify activities that might result in HD exposure and to change practices that put themselves and their colleagues at risk.

In preparing the update to these guidelines, the authors searched the National Library of Medicine's PubMed database using the following search terms:

- "Occupational exposure"[MeSH] AND ("antineoplastic agents"[MeSH] OR "chemotherapy"[All Fields] OR "hazardous drugs"[All Fields]) AND ("pharmacists"[MeSH] OR "nurses"[MeSH] OR "healthcare workers"[All Fields]) AND ("humans"[MeSH Terms] AND English[lang])
- "Occupational exposure"[MeSH] AND ("antineoplastic agents"[MeSH] OR "chemotherapy"[All Fields] OR "hazardous drugs"[All Fields]) AND ("DNA damage" OR "chromosome aberration" OR "genotoxic" OR "cancer") AND ("humans"[MeSH Terms] AND English[lang])
- "Occupational exposure"[MeSH] AND ("antineoplastic agents"[MeSH] OR "chemotherapy"[All Fields] OR "hazardous drugs"[All Fields]) AND ("gloves" OR "gowns" OR "personal protective equipment" OR "PPE" OR "safe handling precautions" OR "closed system" OR "nurses" OR "pharmacist") AND ("humans"[MeSH Terms] AND English[lang])
- "Occupational exposure"[MeSH] AND ("antineoplastic agents"[MeSH] OR "chemotherapy"[All Fields] OR "hazardous drugs"[All Fields]) AND ("guidelines" OR "standards" OR "recommendations") AND ("humans"[MeSH Terms] AND English[lang])
- "Occupational exposure"[MeSH] AND ("antineoplastic agents"[MeSH] OR "chemotherapy"[All Fields] OR "hazardous drugs"[All Fields]) AND

- “administration” AND (“intravenous” OR “oral” OR “intraperitoneal” OR “intrathecal” OR “intracavitary” OR “intraperitoneal” OR “intraocular” OR “topical”) AND (“humans”[MeSH Terms] AND English[lang])
- (“Risk”[MeSH] OR “risk” OR “safety”) AND (“antineoplastic protocols”[MeSH] OR “immunotherapy”[MeSH] OR “chemotherapy” OR “immunotherapy” OR “antineoplastic” OR “antineoplastic” OR “antibodies, monoclonal”[mh] OR “monoclonal antibody” OR “monoclonal antibodies” OR “adalimumab” OR “bevacizumab” OR “certolizumab” OR “cetuximab” OR “denosumab” OR “natalizumab” OR “omalizumab” OR “palivizumab” OR “ranibizumab” OR “trastuzumab” OR “ustekinumab” OR “muromonab” OR “rituximab” OR “infliximab” OR “single-chain antibodies”) AND (“breast feeding”[MeSH] OR “breast feeding” OR “breastfeeding” OR “breast milk”)
 - (“Occupational exposure”[MeSH] OR “exposure” OR “personal protective equipment”[mh] OR “personal protective equipment” OR “PPE”) AND (“health personnel”[MeSH] OR “health-care workers” OR “health personnel” OR “nurses” OR “nurse”[tw] OR “pharmacist” OR “pharmacists”) AND (“antineoplastic agents”[MeSH] OR “antineoplastic” OR “chemotherapy” OR “anticancer” OR “anti-cancer”) AND (“epidemiologic studies”[MeSH] OR “case-control” OR “retrospective” OR “cohort” OR “follow-up study” OR “fol-

low-up studies” OR “prospective” OR “controlled study” OR “controlled trial” OR “descriptive study” OR “descriptive studies” OR “urinary” OR “urine” OR “buccal mucosa” OR “DNA damage” OR “chromosomal abnormalities”) AND “last 5 years”[PDat]

Articles were limited to those published in the English language in peer-reviewed journals from 2005 through 2015. Older publications considered classic references also were included.

Further searches of the medical literature also were conducted (based on initial findings, group feedback, and authors’ experience) to identify other relevant materials. In addition to searching peer-reviewed publications, the authors searched websites of known domestic or international regulatory agencies and professional societies involved in generating relevant materials (e.g., reports, white papers, official announcements) related to HD topics. The authors sought to identify literature leading to evidence-based practices and quality measures developed by healthcare organizations or specialty societies. Websites of the following organizations were searched:

- ASHP: www.ashp.org
- NIOSH: www.cdc.gov/niosh
- ONS: www.ons.org
- OSHA: www.osha.gov

Findings derived from these searches were used to generate additional searches for guidelines published in the United States and abroad.

Definition of Hazardous Drugs

Key Points

- All drugs are assessed for hazardous characteristics.
- Investigational agents and those with inadequate information should be considered hazardous.
- Organizations are required to develop a list of HDs used in the facility.

HDs require careful handling by healthcare personnel and others who come into contact with them to minimize exposure and the associated adverse health effects and to reduce contamination of the workplace with drug residue. A universally accepted definition of HDs is essential so that clinicians recognize the drugs for which safe handling recommendations apply. Drugs are classified as hazardous when they possess any one of the following six characteristics (ASHP, 2006; NIOSH, 2004a):

- **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
- **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

The sixth characteristic in 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. Organizations should evaluate the hazardous potential of all drugs, approved and investigational, when they are first introduced into a facility (ASHP, 2006; NIOSH, 2016).

The determination that a drug is hazardous is based on the characteristics in the aforementioned definition and not the chemical class to which the drug belongs. NIOSH evaluates newly approved agents and compares known characteristics of the drugs to the criteria in the definition. Older drugs with new warnings also are reviewed in this manner. Reviewers use infor-

mation from the official U.S. Food and Drug Administration (FDA)-approved prescribing information (www.accessdata.fda.gov/scripts/cder/daf/index.cfm), DailyMed (<https://dailymed.nlm.nih.gov/dailymed/index.cfm>), DrugBank (www.drugbank.ca), and drug-specific safety data sheets (SDSs) to determine if any drug should be classified as hazardous and added to the NIOSH list. The NIOSH review is hazard identification, not risk assessment. A full risk assessment requires a dose-response assessment of harm to human health, which is not available for most drugs, as it is for other chemicals. About half of the drugs listed as hazardous are antineoplastic agents, and the rest are non-antineoplastic agents. Rather than suggesting a different level of risk based on drug category, NIOSH recommends that if a drug “meets one or more of the criteria for hazardous drugs in the NIOSH definition, handle it as hazardous” (NIOSH, 2016, p. 5).

All investigational agents should 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, 2016). 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 International Agency for Research on Cancer (IARC) is part of the World Health Organization (WHO). IARC classifies agents as carcinogens (see Table 1). This agency has evaluated more than 900 substances for their cancer-causing potential. The 2012 IARC publication *Review of Human Carcinogens* includes six volumes developed by separate work groups: Pharmaceuticals; Biological Agents; Arsenic, Metals, Fibres, and Dust; Radiation; Personal Habits and Household Exposures; and Chemical Agents and Related Occupations (IARC, 2012).

In 2015, IARC convened a separate work group to conduct a systematic review of the literature. The group agreed on 10 key characteristics exhibited by human carcinogens to determine cancer hazard risk (Smith et al., 2015). The intent of this approach was to establish a more objective method to assess whether an agent is a potential human carcinogen by reviewing mechanistic data, which was not previously available. The 10 characteristics include the ability of an agent to

1. Act as an electrophile either directly or after metabolic activation.
2. Be genotoxic.

3. Alter DNA repair or cause genomic instability.
4. Induce epigenetic alterations.
5. Induce oxidative stress.
6. Induce chronic inflammation.
7. Be immunosuppressive.
8. Modulate receptor-mediated effects.
9. Cause immortalization.
10. Alter cell proliferation, cell death, or nutrient supply.

A comprehensive list of all drugs currently considered hazardous does not exist in the literature. NIOSH reviews new drugs approximately every two years and lists drugs identified as hazardous (NIOSH, 2017). Given the large number of new drug approvals each year, the NIOSH list will never be complete; therefore, organizations must have a process for evaluating the drugs they use to determine whether they are hazardous. Table 1 provides resources that will aid

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.
International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans	<p>This resource includes six volumes (A–F): Pharmaceuticals; Biological Agents; Arsenic, Metals, Fibres, and Dust; Radiation; Personal Habits and Household Exposures; and Chemical Agents and Related Occupations.</p> <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.
Safety data sheets (SDSs)	<p>SDSs are developed by manufacturers to describe the chemical properties of a product and communicate the hazards, including the following:</p> <ul style="list-style-type: none"> • Identification and labeling • Composition • First aid measures • Fire-fighting measures • Accidental release measures • Handling and storage • Exposure controls/personal protection • Physical and chemical properties • Stability and reactivity • Toxicologic information • Ecologic information • Disposal considerations • Transport information • Regulatory information
U.S. Department of Health and Human Services National Toxicology Program Report on Carcinogens, 14th edition	Carcinogens listed in this report are classified as either known human carcinogens or reasonably anticipated to be human carcinogens. The report can be obtained at https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html .
National Institute for Occupational Safety and Health List of Antineoplastic and Other Hazardous Drugs in Health-care Settings	This publication lists drugs that should be handled as hazardous. The hazardous drug list was updated in 2016 and can be found at www.cdc.gov/niosh/topics/antineoplastic/pdf/hazardous-drugs-list_2016-161.pdf .
Package inserts for specific pharmaceutical agents	<p>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 the following:</p> <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, 2016; International Agency for Research on Cancer, 2012; National Institute for Occupational Safety and Health, 2016; U.S. Department of Health and Human Services National Toxicology Program, 2016.

clinicians in evaluating whether a drug should be handled as hazardous.

In 2014, NIOSH divided its list of HDs into three groups:

- **Group 1: Antineoplastic drugs.** All drugs in this group belong to the American Hospital Formulary Service (2016) classification 10:00 antineoplastic agents, except for one drug, bacillus Calmette-Guérin (BCG), which belongs to the vaccine class. At the time of this publication, group 1 includes the monoclonal antibodies brentuximab vedotin, gemtuzumab ozogamicin, and pertuzumab, as well as 19 small molecules, such as afatinib and axitinib.
- **Group 2: Nonantineoplastic drugs.** This group includes drugs from multiple classes, such as immunosuppressants and antivirals. Examples of nonantineoplastic HDs are mycophenolate mofetil, tacrolimus, conjugated estrogens, and ganciclovir (NIOSH, 2016).
- **Group 3: Drugs that primarily pose a reproductive risk to men and women.** This group includes alitretinoin, fluconazole, oxytocin, and others.

This grouping is not meant to suggest that a different level of risk exists based on the group but rather

to assist in the development of a facility-specific list in organizations where antineoplastic agents are not used. NIOSH asserts that drugs meeting one or more of the criteria in the HD definition should be handled as hazardous (NIOSH, 2016).

USP General Chapter 800, which must be fully implemented by December 1, 2019, requires organizations to develop a list of HDs present in the facility (USP, 2016a). The organization-specific HD list should be comprehensive and must contain any drugs that are on the current NIOSH list. A list is an essential first step because it determines the drugs to which all other containment standards apply (e.g., receipt, storage, disposal). Once the organization creates a list of HDs, labeling must be applied to each drug dispensed to ensure proper identification and safe handling.

Because HDs are administered in multiple clinical settings, it is imperative that safe handling policies and training extend throughout the organization in both inpatient and ambulatory areas. HD safe handling should be a top priority in any organization. The handling of HDs and HD waste affects all employees who work in the healthcare setting.