Chapter 12

# Hazardous Drugs as Compounded Sterile Preparations

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## Introduction

Concern regarding the safety of workers handling hazardous drugs (HDs), specifically the antineoplastics, initially surfaced in the 1970s when reports of second cancers in patients treated with these agents were coupled with the discovery of mutagenic substances in nurses who handled these drugs and cared for treated patients.[1-3] The nonspecific nature of the cytotoxic action of these drugs renders all cells at risk of DNA damage, patient and caregiver alike.

### *Evidence of Exposure and Adverse Effects*

Exposure to these drugs in the workplace has been associated with acute and short-term reactions. Anecdotal reports in the early literature ranged from malaise and flu-like symptoms to hair loss, nail damage, and mucosal sores.[4-7] Reproductive studies on healthcare workers have shown increases in fetal abnormality, fetal loss, and fertility impairment.[8-12] Increased learning disabilities in offspring resulting from occupational exposure to these potent drugs have also been reported.[13] An extensive study published in 2012 documented increased spontaneous abortions in nurses exposed to HDs in the workplace.[14]

Increased incidence of cancers for these exposed groups has been investigated with varying success.[15,16] The small number of individuals available for study presents a dilemma for the statistician. Two recent and related studies, however, described evidence of drug uptake (drug being incorporated into workers' bodies) and chromosomal changes in oncology workers exposed to workplaces contaminated with HD residue.[17,18] 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. As signature lesions in chromosomes 5, 7, and 11 have been shown to be associated with chemotherapy treatment–related myelodysplastic syndrome and acute myeloid leukemia, these results

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provide additional evidence for harmful effects from occupational exposure to HDs.[19,20]

Much research has been done in healthcare workers on biomarkers of HD exposure (intact HD or a metabolite measured in the body, usually in urine samples) or biomarkers of effect (a measurable biochemical alteration within an organism; for HDs usually related to the genotoxic properties of these drugs).[21-23] An early review noted none of the then currently available biological and analytical methods was sufficiently reliable or reproducible for routine monitoring of HD exposure in the workplace.[21] A more recent review of studies extending through 2010, advocated using combinations of selected markers to possibly validate protective measures and safety guidelines used in reducing exposure to HDs in healthcare workers.[23] Both reviews advocate more research on the important issue of healthcare worker exposure to HDs.

## Early Interventions

In the 1990s, ASHP and the Oncology Nursing Society (ONS), whose members are most directly impacted by the handling of HDs, updated U.S. guidance to encourage safe handling of HDs.[24,25] The Occupational Safety and Health Administration (OSHA) followed with extensive guidance in 1995.[26] Although the guidelines differ in some respects, the general principles and goals are very similar: To establish and maintain stringent work practices within a framework of engineering controls and personal protective equipment (PPE) to reduce the amount of drug released into the environment during manipulation. Subsequently, this reduction in available drug will reduce the potential exposure to personnel as well. Considerable research on HD exposure in healthcare settings was done primarily in Europe in the 1980s and 1990s.[22] HD contamination has been found on HD vials, work surfaces where HDs are compounded or administered, gloves used in handling HDs, and on the final products.[27-29]

### The 2004 NIOSH HD Alert and USP Chapter <797> 2008 Revision

A landmark multisite study published in 1999 was done in six cancer treatment centers in the United States and Canada to examine workplace contamination with HDs as compared to European sites.[30] This study found that 75% of compounding areas and 65% of patient administration areas were contaminated with measurable amounts of the marker HDs cyclophosphamide, fluorouracil, and ifosfamide (U.S. centers only). Substantial levels of contamination from the sampled HDs were detected on a variety of surfaces in pharmacy drug preparation areas and drug administration areas. The results were similar for U.S. and Canadian centers and similar to European sites reported in the literature. This study prompted the National Institute for Occupational Safety and Health (NIOSH), as part of the Centers for Disease Control and Prevention (CDC), to assemble a Hazardous Drug Working Group in 2000 to study the HD contamination in the healthcare setting, assess possible health risks, and provide better guidance in safe handling. The Working Group published the 2004 NIOSH Alert: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs.[31] The alert included an extensive literature background, detailed recommendations, modified HD criteria, and Appendix A, which was a compilation of lists of HDs contributed by various parties.[31]

The 2004 NIOSH HD Alert has become an influential document in the area of HD exposure and appropriate safe handling procedures. ASHP updated its guidance on HDs in 2006 to harmonize with the 2004 HD Alert.[32] ONS modified its chemotherapy and biotherapy guidelines in 2009 (and again for 2014) and updated the book *Safe Handling of Hazardous Drugs* in 2011.[33-35]

As many of the HDs in the healthcare setting are sterile, injectable drugs, the proposed equipment and work practices in the HD guidelines must be compatible with those for sterile compounding. The U.S. Pharmacopeial Convention (USP) recognized this need and revised USP Chapter <797> Pharmaceutical Compounding—Sterile Preparations in 2007.[36] This revision of the earlier USP Chapter <797> was harmonized with the NIOSH HD Alert and became effective June 1, 2008. It established many of the NIOSH recommendations as enforceable requirements. The standards set by USP Chapter <797> are applicable