Chemotherapy: Every Step You Take, Every Move You Make...

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This article describes sources of workplace contamination with hazardous drugs and how healthcare workers may be exposed to hazardous drugs during the course of their duties. For a description of some of the hazards associated with working with antineoplastic drugs in the pharmacy and discussion of some of the published recommendations for their safe handling, see the article by Roussel and Connor in the May 2013 issue of The Oncology Pharmacist.[1]

Measurement of surface contamination is currently the only indication of the amount of environmental contamination in areas where hazardous drugs are prepared, administered to patients, or otherwise handled (such as receiving areas, in transit throughout the facility, and waste storage areas) (**Table 1**). Although limited associations have been demonstrated between surface contamination and actual worker exposure,[2] surface contamination is the most commonly used metric for evaluation of the workplace for hazardous drugs (**Table 2**[2-12]). Workplace contamination with hazardous drugs in the United States and other countries has remained fairly constant over the past decade or more, indicating that worker exposure probably has not changed considerably over that time, despite efforts to reduce or eliminate environmental contamination. The introduction of Class II biological safety cabinets (BSCs) for the preparation of hazardous drugs in the 1980s substantially reduced the potential for worker exposure,[13] but BSCs did not prove to be as efficient at reducing contamination as first believed.[4] The recent use of isolators has not been widespread in the United States, nor have they proven to offer more protection to workers than do BSCs, as contamination from the inside surfaces of the isolator may be transferred to the outside of syringes and infusion bags.[14] Use of robotic systems to prepare hazardous drugs may reduce environmental contamination and worker exposure to these drugs; however, their high cost makes them prohibitive for all but large cancer centers.[15] The addition of closed-system drug transfer devices (CSTDs) for the preparation and administration of hazardous drugs has been shown to reduce surface contamination and possibly worker exposure, but they do not totally eliminate it.[5,6,10,11]

Table 1 Common Locations in the Pharmacy Where Antineoplastic Drugs Have Been Detected
Locations where high levels of contamination are seen:
Working surface of BSC
Surfaces inside the compounding isolator
Leading edge (airfoil) of BSC
Floor in front of BSC
Locations where lower levels of contamination are seen:
Floor in pharmacy
Countertops
Storage bins and trays
Storage shelves
Inside and outside pass-through windows
Waste containers
Keyboards
Door handles
Shoes of pharmacy employees
Employee telephones
Abbreviation: BSC, biological safety cabinet.

Table 1

Recent research has shown that even when all of these controls are used in healthcare settings, the potential for exposure to antineoplastic and other hazardous drugs cannot be completely eliminated.[2,10,11,16-22] Despite improvements in engineering controls and other attempts to reduce environmental contamination, hazardous drugs are still being released into the work environment and subsequently workers are being exposed to them. Therefore, for the foreseeable future, as the number of patients requiring treatment with hazardous drugs increases,[23,24] contamination of the workplace with hazardous drugs and/or worker exposure to hazardous drugs will be an issue that does not have an immediate solution.

Surface Contamination and Wipe Sampling for Hazardous Drugs

Wipe sampling for surface contamination has been used in many industrial settings to measure materials such as pesticides, lead, asbestos, etc. Sampling for hazardous drugs usually involves a battery of a small number of drugs for which sampling and analytic methods have been developed (**Table 3**). Methodology allows measurement as low as picogram amounts, but most values are reported as ng/cm2. The method for surface sampling typically follows this approach: an appropriate solvent is applied to a specified area; the surface is wiped with a swab; then the swab is extracted with a solvent and analyzed using either gas chromatography-tandem mass spectrometry or liquid chromatography-tandem mass spectrometry (GC-MS/MS or LC-MS/MS).25 Values typically seen in pharmacies range from <1 ng/cm2 to a few hundred ng/cm2 (**Table 2** provides specific contamination levels detected in studies from the US). Although there are no standards for surface contamination with hazardous drugs, and an action level has not been validated, <1 ng/cm2 is a value to aim for in the pharmacy.[26] **Table 3** also lists laboratories that provide analysis of hazardous drug wipe samples and the drugs that they can analyze. Some provide kits for sampling that can be shipped to the laboratory for analysis.

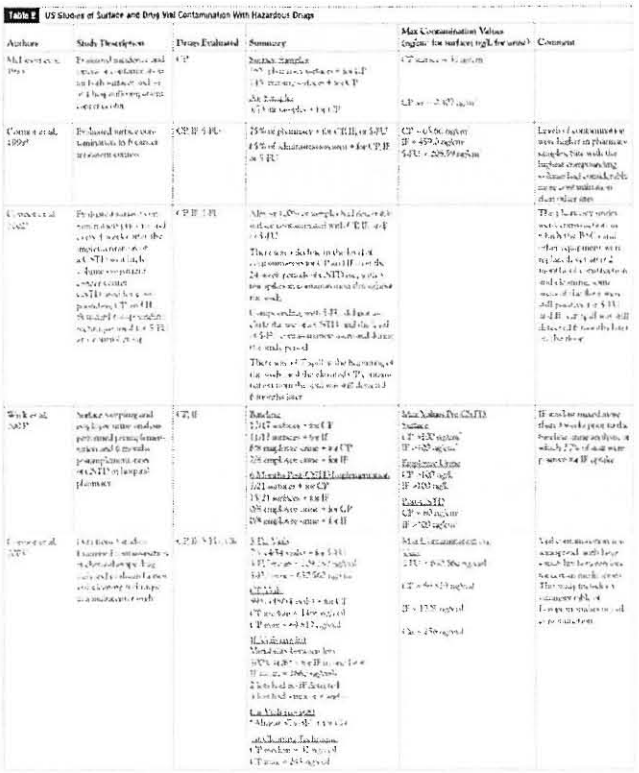

Table 2

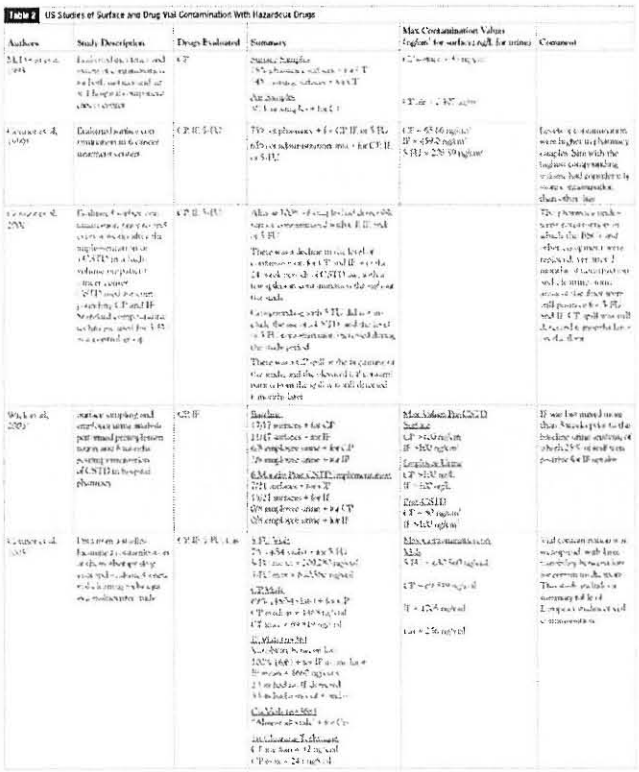

Table 2 (continued)

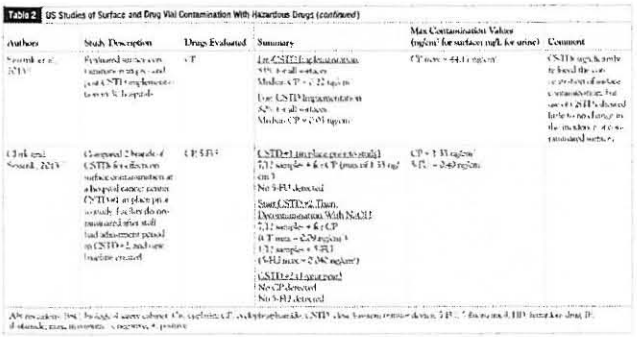

Table 2 (continued)

It is important for individual institutions to test their own workplace for hazardous drug contamination, rather than make assumptions about their facilities and staff. Pharmacy and other healthcare provider management may worry about the employee perception of these results or the risk incurred by searching for such data. It is not uncommon to question the point of testing, or the greater worry about what the action plan will be if contamination is detected and whether this opens up an institution to litigation. While standard assays and established acceptable levels of workplace contamination have yet to be formally established, the latest revision of USP Chapter 797 (2008) includes a recommendation that surface sampling for hazardous drugs be tested for at baseline and every 6 months or more frequently for larger-volume facilities.[26] It is recommended that surface sampling be conducted in a targeted manner, such as the surfaces of the BSC, floor beneath the BSC, counters adjacent to primary engineering controls, counters where final compounded hazardous drug products are placed, and patient administration areas. Evaluation of facility controls should include the type of engineering control in use and to what extent the device is vented to the outside, where exhausting 100% of the filtered air is most appropriate based on volume and the extent of contamination.[27] All employees' techniques and knowledge should be evaluated, and retraining should be conducted as appropriate. Poor technique by one individual can lead to an area of concentrated drug on a surface that can, in turn, lead to worker uptake weeks after that drug was originally mishandled. Workflow processes including waste disposal could also be a contributor to contamination. Each institution should consider a self-evaluation of its workflow. Following simple recommendations, such as discarding all waste including syringes into a sealable plastic bag within the BSC while compounding, can dramatically reduce contamination. Once the contaminated waste is contained, it can then be removed from the engineering control and put into chemotherapy disposal bins. Otherwise, if the waste is open (ie, used syringes) during the transfer process, small droplets can contaminate the gown of the compounder, the floor, and the lid of the chemotherapy disposal container.[28]

Drug Vial Contamination

The reporting of external contamination on drug vials is an important reminder that safe handling of hazardous drugs by healthcare workers begins with receiving. Studies in the United States,[7] France,[29] Germany,[30] Switzerland,[31] and Japan[32] all show the high frequency of external vial contamination, with more than one study reporting contamination on 100% of samples. Favier and colleagues detected 2.4 µg of hazardous drug on the external surface of a single vial and 1.5 µg of hazardous drug on the plastic overwrap of a 25-vial package.29 Connor and colleagues measured 12 µg (cisplatin), 69 µg (cyclophosphamide), and 630 µg (5-fluorouracil) on vials in a multicenter study.[7] Fleury-Souverain and colleagues detected traces of cytotoxic drugs different from the active ingredient in the vial on 35% of vials analyzed,[31] and Schierl and colleagues reported cross-contamination on 54% of the vials tested.[30] Connor, Fleury-Souverain, Schierl, and their respective colleagues all noted a reduction in contamination on the external surface of vials coated in plastic shrink-wrap.[7,30,31]

These studies highlight the importance of wearing gloves during handling of vials when performing noncompounding activities such as unloading shipping containers and managing stock. Vials become contaminated during manufacturing from lack of cleaning, incomplete cleaning, improper vial washing, contamination by broken vials during transportation, or contact with contaminated surfaces or employees' hands.[7] Globally, manufacturers must improve their procedures to provide the healthcare industry with products free from external contamination. If the external surfaces of drug vials are contaminated, the result is a continuous source of contamination, and it can be assumed that hazardous drug contamination can be spread to pharmacy surfaces, storage shelves, and bins, as well as employees' hands.

In light of external drug vial contamination, healthcare workers should consider the process of cleaning compounding supplies prior to entry into a cleanroom. USP Chapter 797 recommends sterile 70% isopropyl alcohol (IPA) delivered from a spray bottle or other suitable delivery method to compounding supplies prior to entering the buffering room; then transferred to a clean and properly sanitized metal cart.[26] However, the vials themselves should not be sprayed directly with alcohol, as this may produce an aerosol of the drug that could lead to inhalation, and excess contaminated disinfecting solution could then drip off the vials, thus transferring contamination to other surfaces. The best practice is to spray the wipe materials and then use them to wipe the vials. The contaminated wipes should then be disposed of as hazardous waste. Alcohol solubilizes hazardous drugs and is not known to decontaminate drugs through chemical degradation like bleach does. The use of alcohol to sanitize areas where chemotherapy is compounded has been shown to spread contamination.[28] Therefore, even cleaning procedures for these vials must be thoroughly evaluated to minimize the inadvertent spread of contamination.

Skin Absorption of Hazardous Drugs

Although the magnitude of surface contamination has yet to be proven to have a direct relationship with worker uptake of hazardous drugs, it is important to think about how workplace contamination leads to systemic exposure. Dermal absorption is a principal route of chemical exposure for nonvolatile chemicals, often exceeding respiratory exposure.[33] Nonvolatile antineoplastic drugs can persist for several weeks on work surfaces, functioning as sources of worker contamination for long periods of time.[5,6] In addition to a chemical's local effects on the skin, including contact dermatitis and irritation, skin exposure to chemicals can function as a pathway to the bloodstream for hazardous chemicals to enter the body.

The skin has 2 basic layers, the epidermis and the dermis, providing protection against chemical absorption.[33] Chemicals can diffuse passively across the stratum corneum, reaching the blood vessels in the dermis where significant dermal exposure can produce detectable blood levels. The rate and magnitude of skin absorption can be affected by many occupational factors. Organic solvents such as alcohol, as found in hand sanitizer, can "defat" the skin, damaging the external layer and allowing increased chemical absorption. Wearing gloves for extended periods of time can increase the water content of the stratum corneum, both from perspiration and trapping normal skin water evaporation, thus increasing absorption of hydrophilic chemicals. Frequent hand washing with strong detergents throughout the workday can also lead to skin damage in healthcare settings. Increased moisture, skin irritation, damage from exposure to harsh chemicals, small cuts, or skin tears alter the physical barrier function of the skin and allow for increased chemical permeability. If chemical penetration did occur through a glove, due to prolonged contact of the chemical on the external surface or from a tear in the glove, the glove would function as an occlusive dressing, increasing chemical absorption through increasing temperature, friction, and contact between the glove and skin.

Dermal uptake has been postulated to be the major route of exposure to antineoplastic drugs in workplace settings.[34-37] Inhalation appears to be the second most common route, with oral (hand-to-mouth) and accidental injection with sharps less common. Although a few antineoplastic drugs have been shown to have

the ability to produce vapors, most antineoplastic drugs have very low vapor pressures.[38,39] Numerous studies from the United States and countries around the world have documented surface contamination with antineoplastic drugs in areas where they are used.[40]

Table 3 Laboratories That Test for Hazardous Drugs and Some Commonly Tested Drugs

Laboratory	Drugs
Exposure Control B.V. www.exposurecontrol.nl	Cyclophosphamide, ifosfamide, 5-fluorouracil, methotrexate, etoposide, mitomycin C, platinum-containing compounds
RJ Lee Group www.rjlg.com	Cyclophosphamide, ifosfamide, 5-fluorouracil, methotrexate, cisplatin, carboplatin, oxaliplatin
ChemoGlo, LLC www.chemoglo.com	Cyclophosphamide, ifosfamide, 5-fluorouracil, paclitaxel, docetaxel
BVNA www.us.bureauveritas.com/labs/ChemoAlert	Cyclophosphamide, ifosfamide, 5-fluorouracil, paclitaxel, methotrexate, doxorubicin, daunorubicin, idarubicin, cisplatin, carboplatin, cytarabine, imatinib, capecitabine

Table 3

Uptake of Hazardous Drugs

As stated previously, it is difficult to directly relate worker exposure to surface contamination with hazardous drugs. However, Connor and colleagues were able to detect cyclophosphamide in the urine of 2 pharmacists working in an area that had high levels of surface contamination with this drug.[2] Both pharmacy and nursing personnel have been shown to have measurable amounts of antineoplastic drugs in their urine as a result of working where the drugs are handled. As with wipe samples, analysis is available for determining a battery of drugs in the urine of healthcare workers. Interestingly, in some studies, specific antineoplastic drugs have been measured in the urine of workers not directly involved with their preparation, suggesting indirect or incidental exposure from contact with contaminated surfaces. Uptake of these drugs by pharmacists and nurses has been well documented in more than 50 studies in the world literature.[40] Analysis of the urine for hazardous drugs is usually done strictly on a research basis, as there are no standards for the amount of drugs in the urine and what the consequences might be concerning workers' health. However, it does indicate that the workplace environment is contaminated with the drugs or that the worker may not have good technique, indicating the need for better engineering controls and cleaning procedures of the pharmacy and/or retraining of the worker. Although findings of hazardous drugs can be alarming to the worker, the OSHA Technical Manual states, "Results of biologic monitoring which have been voluntarily conducted by an employer should not be used as a basis for citations. In fact OSHA promotes the use of biologic monitoring of employees as a useful means of minimizing exposure and for evaluating effectiveness of control measures."[33]

Summary

Surface contamination with hazardous drugs, in particular, antineoplastic drugs, is usually present in pharmacies and all areas where the drugs are handled. Most work surfaces and drug vials have been demonstrated to be contaminated with antineoplastic drugs in numerous studies from the United States and internationally. Although other routes (inhalation, oral, needlesticks) may be factors in uptake of these drugs, the dermal route appears to be the most common. Uptake has been well documented by the presence of some antineoplastic drugs in the urine of healthcare workers. A prospective gap analysis of the work environment and compounding process, including surface analysis for hazardous drugs, is a good starting point. While appropriate facility design and proper equipment are critical, so is a strong employee training program with

continuing education. Components of employee education should include a hazard communication document, with didactic and demonstrative components and spill kit training. Access to proper personal protective equipment and a "safety culture" can promote employee compliance.[41]

Disclaimers

The findings and conclusions of this presentation have not been formally disseminated by NIOSH and should not be construed to represent any agency determination or policy.

Mention of company names or products does not constitute endorsement by the National Institute for Occupational Safety and Health.

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