It is well known that many drugs, while providing beneficial treatment, also pose a health risk themselves. The American Society of Health Systems Pharmacists (ASHP) and the National Institute of Occupational Safety and Health (NIOSH) have defined a drug to be “hazardous” if it exhibits one or more of the following characteristics in humans or animals: 1,2

- Carcinogenicity
- Teratogenicity or other developmental toxicity
- Reproductive toxicity
- Genotoxicity
- Organ toxicity
- Structure and toxicity profile for new drugs mimics existing hazardous drugs

Customize Your Drug List
While NIOSH has provided an initial list of drugs that may be considered hazardous, it is up to each organization to refine and customize this list to define which drugs in their own practice setting are hazardous. An obvious place to start is with chemotherapy agents, as these drugs can produce both acute and long-term negative effects in healthcare workers through regular occupational exposure.

While we know that these agents can cause acute and long-term side effects in patients, it is important to note that exposure patterns between patients and healthcare workers are markedly different. Cancer patients receive large doses of finite numbers of drugs over a relatively short period of time. In contrast, healthcare workers are exposed to multiple drugs in low doses over long periods of time. The key question is whether these differing exposure patterns create a real health risk for healthcare workers.

In examining the acute effects of these drugs in healthcare workers it is clear that there is sufficient documentation in the literature to establish this connection. There are numerous reports of neuropathies, hemorrhagic cystitis, memory and concentration loss, nausea, vomiting, headache, dizziness, hair loss, mucosal sores and transient liver enzyme changes in healthcare workers exposed to chemotherapy agents in the course of their normal job duties. Of greater concern is the potential for long-term effects due to this continual low dose exposure pattern. There is mounting evidence in each of the ASHP/NIOSH-defined elements for a hazardous drug that low dose exposure to chemotherapy drugs over long periods of time is an area of concern.

Reproductive Risk
Numerous peer reviewed studies document the relationship between exposure to chemotherapy agents and adverse effects on reproduction, making it clear that there is a direct cause and effect relationship between low dose chemotherapy exposure and negative reproductive system sequelae. These studies document statistically significant differences between healthcare workers exposed to chemotherapy drugs and the general population as well as healthcare workers who were not exposed to chemotherapy. Higher rates of infertility, spontaneous abortion, stillbirth, premature labor, and congenital abnormalities are associated with hazardous drug exposure in healthcare workers. 3

Teratogenic/Developmental Risk
Multiple studies have demonstrated a statistically significant difference in low birth weight infants, birth defects, and learning disabilities in children born to healthcare workers exposed to chemotherapy drugs during their pregnancy. There appears to be conflicting data regarding the hazards of exposure during the second and third trimesters. Regardless, it seems clear that the greatest health risk is associated with exposure in the first trimester. This is important since often a healthcare worker may not yet know they are pregnant while they continue to work and handle chemotherapy. The United States Pharmacopeia (USP) felt so strongly regarding reproductive, teratogenic, and developmental risks that it was addressed in the most recent Chapter 〈797〉 review. The resultant statement requires healthcare workers of childbearing age to sign a document acknowledging that they have been trained and understand the hazards associated with these drugs before they are allowed to work with these agents. 4

Genetic Effects
While reproductive and teratogenic risks are predominantly associated with female healthcare workers, genetic damage is a concern for both males and females. Genetic damage secondary to chemotherapy exposure has been
noted in healthcare workers. Studies in this area point to length of exposure rather than dose as the primary risk factor. Given the long term, low dose healthcare worker exposure pattern, this should be of great concern. Several peer-reviewed published studies have shown increased rates of single strand DNA breaks and sister chromatid exchanges in healthcare workers exposed to chemotherapy drugs as opposed to non-exposed workers.7

End Organ Damage
Most of the documented reports of organ damage involve the “filter” organs: liver and kidney. There are several reports of liver and kidney damage in oncology nurses.8 Although concerning, the literature in this area still needs further development to establish the same strength of evidence that is present in the previous categories.

Cancer
It is well documented that secondary cancers attributed to chemotherapy treatment have been identified in surviving cancer patients.9,10 There is increasing evidence that long term, low dose exposure to these agents may be associated with an increased cancer risk in healthcare workers. Given the number of variables that would need to be controlled and the length of time required for a study, it would be very difficult, if not impossible, to design a statistically valid study demonstrating a definite cause and effect relationship between low dose, long-term exposure and the development of cancer. However, it is hard to ignore the increasing body of evidence that is trending in this direction. The International Agency for Research on Cancer (IARC) has designated twelve drugs and drug combinations as Group 1 Human Carcinogens. These drugs include: azathioprine, cyclophosphamide, busulfan, thiotapec, tamoxifen, etoposide, chlorambucil, cyclosporine, and melphalan.11 Given enough time and exposure, these drugs will cause cancer. There are nine drugs listed in Group 2A as Probable Carcinogens and ten drugs listed in Group 2B as Possible Carcinogens, giving us over thirty drugs and drug combinations with the potential themselves to cause cancer.11 It is important to note these are just the tested agents. With the rapidity that new drugs and drug combinations are introduced, many of the drugs and combinations currently in use have yet to be tested. It is also significant to note that during the normal course of work in a large cancer treatment venue a nurse, pharmacist or pharmacy technician may be exposed to twenty or thirty different agents. The long term effects of this type of low dose “cocktail” are unknown.

Safe Handling Practices
With this serious health risk facing our organizations, what can be done to decrease our risk profile and increase our healthcare worker safety? The International Society of Oncology Pharmacy Practitioners (ISOPP) in their most recent standards release has introduced an excellent hierarchical approach based on an industrial hygiene model for safe handling of hazardous drugs.12 Using this approach, a program would work from the safest methods down to the least safe. Level 1 protection measures involve elimination, substitution, or replacement of the hazardous product. Level 2 involves isolation of the hazardous product. Level 3 involves generating controls or proper ventilation to dilute the hazardous product. Level 4 involves organizing workflow to reduce exposure. Finally, level 5 protection measures involve personal protective equipment. Unfortunately, in the USA and Canada the general approach seems to be just the opposite where organizations start with the least safe options and work up to the most safe. While a complete review of all of the elements in the ISOPP hierarchy is beyond the scope of this article, we do want to highlight three key elements in level 4 Administrative Controls that can help improve the overall safety profile for an organization. Specifically we would like to address the receipt and storage of these drugs, the education and training for handling these drugs and the internal surveillance programs for monitoring these drugs.

Receipt and Storage
Multiple studies have demonstrated that chemotherapy vials come to us directly from the manufacturer with the external surfaces of the vials contaminated.12,13 Therefore, an effective safe handling program should start as soon as the drugs enter the organization. These drugs should be shipped from the wholesaler in separate totes that clearly identify the contents as hazardous chemotherapy and provide extra cushioning to protect from breakage. All workers handling the drugs should wear protective gloves to reduce contact with possible contaminants. The drug, where possible, should be in a sealed over wrap such as a plastic zipper storage bag to help contain any breakage or overt external contamination on the packaging. These totes should be carefully inspected upon receipt by the organization for any visible signs of breakage or leaks. The drugs should be unpacked in a designated area away from the normal work area. Consideration should be given to the external contamination present on the surface of the vials. Some organizations at this point remove the vials from their boxes and dispose of the box and package insert as trace chemotherapy waste. The vials should be contained in a sealed over-wrap system or decontaminated with a dilute bleach solution before being placed in storage. Ideally, storage for these hazardous drugs should be in an
area separated from normal drug stores that is negative pressure with at least twelve air exchanges per hour and vented to the external atmosphere.15

**Education and Training**

The cornerstone of an effective safe handling program is a strong educational component. USP requires annual documentation of training for all personnel who compound hazardous drugs.7 Proper training must include a didactic review of hazardous drugs and the risks associated with them, as well as proper aseptic and negative pressure techniques. Personnel must also be trained on proper cleanup procedures, procedures should a spill occur or if personal exposure to hazardous drugs occurs.

**Surveillance/Monitoring Programs**

NIOSH, USP and ISOPP all recommend surveillance and monitoring programs for chemotherapy drugs and the personnel who routinely work with them. A comprehensive program should include an environmental monitoring program as well as a medical surveillance program for healthcare workers. Numerous studies have demonstrated the presence of these drugs in the workplace.8 Most frequently, tests for cyclophosphamide, ifosfamide, methotrexate, cisplatin and fluorouracil have been conducted. A regular program of environmental monitoring should be established to look for the presence of one or more of these agents. Based on observed levels of contamination, a program to identify and correct the source(s) of exposure should be established. USP suggests conducting a baseline test, followed by an every six month testing schedule (more frequently if needed based on levels).9 Consideration should also be given to the establishment of a formal medical surveillance program to monitor the health status of workers regularly in contact with these drugs or acutely exposed to these drugs through a break or spill. A sample template for such a policy is included in Appendix 1 (see page 8).

At the most basic level, a questionnaire focused on reproductive and overall health can be developed and administered to healthcare workers as part of their annual performance review process. Their history can be monitored and any obvious changes highlighted and additional medical follow-up suggested. A more comprehensive approach including physical examination and laboratory tests can also be added. A baseline and regular physical exam focused on those systems—such as lymph, skin, mucous membranes, hair and skin—that may display early warning signs for cancer should be considered. ISOPP suggests laboratory tests, such as a complete blood count, liver function tests, and urinalysis to be conducted at baseline and annually thereafter.10 While the majority of programs currently in practice are voluntary, rather than mandated, for employees, nonetheless, they can contribute to an overall risk reduction strategy for the organization and provide an important addition to the employees’ health history data. This data should be made available to the employee should they leave the organization so they can keep a complete history at their next site of employment.

**Conclusion**

There is mounting evidence that regular, low dose exposure to hazardous medications poses a real health risk for employees as well as a potential litigation risk for employer organizations. Consideration should be given to the development of a comprehensive safe handling program that addresses each of the levels in the hierarchy identified in the ISOPP standards in order to minimize the risk potential to the greatest extent possible. ■

---

**REFERENCES**


5. Hemminki K, Kyrönen P, Lindbohm ML. Spontaneous abortions and malformations in the offspring of nurses exposed to anesthetic gases, cytostatic drugs, and other...


The safe path to unit dose bar coding

**mPrint** v3
Bar Code Labeling Software
- First DataBank Database
- 23,000 Drug Images
- clearTag Labels
- 2-D Bar Codes
- Any Label, Any Printer

**safeSealRX**
Unit Dose Peel-Price
- Solid & Liquid Blister
- Digital Temperature Control
- Timed Auto-Release
- Use with mPrint Software

**iPack T60**
Single Use Flexible Packaging
- Packages Oral Solids
- Liquid Doses Up to 25ml
- Multiple Blister Sizes
- Powered by mPrint Software


These three factors have made MMI Systems the leading supplier of superior performing pharmacy systems for pharmacies across the world.

- 20 years experience supplying the needs of pharmacy facilities nationwide
- USP <797> assistance
- Personalized, one-on-one service
- Turn-key process — planning, design, manufacture and installation

Contact us today for more information.

**ASHP - Booth #313**

Also see our products in the following booths:

**swisslog**
Booth #228

**mPrint**
Booth #1163

**DIGITRAX**
Booth #584

Pearson Medical Technologies
SAFE AND EFFICIENT UNIT DOSE SOLUTIONS
866.640.3603
pearsonmedical.com

For more information, circle #105 on the Reader Service Card
Appendix 1

Draft Policy Template For Medical Surveillance of Employees with Occupational Exposure To Hazardous Drugs

PURPOSE
Hazardous drugs (such as chemotherapy) pose special hazards for workers handling these agents. This policy establishes the guidelines and procedures for surveillance of employees with routine exposure to hazardous drugs.

POLICY
Employees who handle hazardous drugs (such as chemotherapy) on a routine basis according to their work assignment may participate in a medical surveillance program designed to monitor their health.

Employees who experience acute exposure (spills, puncture wounds, etc) to hazardous drugs shall have a focused health assessment at the time of exposure.

__________________________________________________________________________ is responsible for performing the focused health assessments.

PROCEDURE
All employees with potential exposure to hazardous drugs will be informed of the potential risks and the need to follow the procedures related to the handling of these drugs. Training in the policies will be provided as appropriate for the department involved.

Employees who work with hazardous drugs on a routine basis and have a high risk for exposure will be offered a baseline medical surveillance exam within 6 months of implementation of this policy, after hire, or upon assignment to an area that requires routine handling of hazardous drugs. After the baseline exam, employees will then be scheduled for periodic medical surveillance exams at 2 year intervals as recommended by OSHA.

The following are examples of employees who would have routine, high risk exposure:

- Nursing personnel who work in areas that administer hazardous drugs on a routine basis, including inpatient oncology units and outpatient infusion clinics that administer chemotherapy drugs
- Pharmacists and pharmacy technicians who prepare and dispense hazardous drugs
- Environmental services personnel who routinely handle hazardous drug waste

A focused health assessment shall be performed by ____________. The results will be documented as part of the employee’s personal records and remain confidential. The exam shall include:

- Physical exam
- Urinalysis
- Complete Blood Count with differential
- Comprehensive Metabolic Panel

The provider will send the employee’s supervisor a letter indicating only that the employee has completed their focused health assessment. The supervisor shall retain this letter as part of the employee’s department personnel file.

Employees will be informed by their department of the potential reproductive hazards and if they so request, staff members who are pregnant or breast-feeding, will be transferred to comparable duties that do not involve handling hazardous drugs.

Employees who experience an acute exposure to hazardous drugs shall have a focused health assessment within two working days of the exposure. This assessment will be performed by ______________. The provider will assess the patient, obtain the history of exposure, and based on that information determine what needs to be included in the focused health assessment. The provider will then determine the plan for follow-up. Examples of acute exposure include needlesticks, cuts, spills, or splashes to the eye, skin or mucous membranes.

Acute exposure incidents should be handled like any other work-related injury. A workers compensation first report of injury is completed by the employee and his or her supervisor and the injured employee is directed to seek the designated medical care at_______________________________.

This draft template can be downloaded at www.pppmag.com