Antineoplastics Declared Occupational Hazard

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BETHESDA, MD, 07 May 2004 — A federal science-based group recently urged health care workers, employers, and safety professionals to take immediate action to reduce the risks from a "newly identified" occupational hazard: exposure to antineoplastics and other hazardous drugs.

The alert, issued in prepublishation form on March 25 by the National Institute for Occupational Safety and Health (NIOSH), part of the Centers for Disease Control and Prevention, warns pharmacy personnel and other health care staff of the potential dangers from working with hazardous drugs (see box) and describes appropriate measures that can be taken to protect employees' health.

NIOSH's Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Healthcare Settings comes 19 years after the American Society of Health-System Pharmacists (ASHP), then known as the American Society of Hospital Pharmacists, issued its first technical assistance bulletin on handling hazardous drugs.

NIOSH and its better-known cousin. NIOSH was established by the Occupational Safety and Health Act of 1970, which simultaneously created the Occupational Safety and Health Administration (OSHA) in the Department of Labor. The law also placed a general duty on employers to provide their employees with a safe work environment: Each employer "shall furnish to each of his employees employment and a place of employment which are free from recognized hazards that are causing or are likely to cause death or serious physical harm to his employees."

To help employers meet this obligation, the law charged NIOSH with creating recommended occupational safety and health standards and conducting research and educational and training programs.

A NIOSH alert, by definition, briefly presents new information on an occupational hazard and urgently requests employers' and workers' assistance in taking protective measures. But an alert is not transmitted as a formal publication to OSHA for use in promulgating legal standards. NIOSH itself lacks regulatory authority.

A spokesman for the Joint Commission on Accreditation of Healthcare Organizations indicated in an e-mail that the accrediting group does not require NIOSH alerts to be posted at work sites. But, he added, several of the group's standards relate to employee safety and the need for facilities to maintain a safe environment and manage their hazardous materials.
**Actions recommended.** The 93-page prepublication version of the NIOSH alert contains, on pages 4-8, a warning box and bulleted lists of actions that health care workers and their employers should take to prevent exposure to antineoplastics and other hazardous drugs.

NIOSH spokesman Fred Blosser said that those pages will be formatted in the final document as a double-sided page that the group recommends employers tear out and post at locations of maximum visibility for employees who may be exposed to hazardous drugs at the workplace.

Blosser said NIOSH recommends employers similarly tear out and post the sample list of drugs currently considered hazardous.

The 138-drug list, part of Appendix A of the NIOSH alert, is a compilation of lists from four hospitals and the Pharmaceutical Research and Manufacturers of America, which used information from *AHFS Drug Information*. Additional references were used by the alert's developers to identify other drugs whose descriptions mentioned carcinogenicity, genotoxicity, teratogenicity, or reproductive or developmental toxicity.

According to the 1994 OSHA Hazard Communication Standard, employers must develop an inventory of all the hazardous chemicals in the workplace.

The remainder of the NIOSH alert describes how health care workers can be exposed to hazardous drugs in the workplace, the dangers of exposure, case reports from the medical literature, current standards and recommendations, and recommended protection procedures and equipment, along with references and a glossary of terms.

**Biological-safety cabinet versus isolator.** Luci Power, pharmacy manager of the i.v. additive service at the University of California (UC) pharmaceutical services in San Francisco, said NIOSH's recommendations for employers "leave a lot up to the individual to choose," including the protective procedures and equipment.

Power was a principal contributor to the NIOSH alert and heads the team rewriting the 1990 ASHP technical assistance bulletin on handling hazardous drugs.

For the preparation of hazardous drugs, the NIOSH alert recommends that employers provide ventilated cabinets designed for worker protection. Biological-safety cabinets and containment isolators are named as examples of suitable protective equipment.

But studies since the early 1990s, Power said, have revealed an "increasingly alarming pattern of contamination" when pharmacy personnel used only a class II biological-safety cabinet, which has an open front and vertical-laminar-airflow through a high-efficiency particulate air (HEPA) filter.

A six-site study involving Power detected substantial amounts of hazardous drugs on the work surfaces and floors of the drug preparation and administration areas, despite the use of class II biological-safety cabinets. Subsequent research not involving Power indicated that the addition of a closed-system drug transfer device to the drug preparation process in a class II biological-safety cabinet could contain the surface contamination.

A closed-system drug transfer device mechanically prevents the escape of hazardous drug solution or vapor and the entry of environmental contaminants.

"The bottom line is that you're going to see a lot more isolator technology" in pharmacies, Power said.

Hank Rahe, technical director for Containment Technologies Group Inc., said isolators are gaining in popularity in health care settings after two decades in the pharmaceutical industry.

"The concept behind the barrier isolator is it protects both the product and the person," he said. Personnel work through glove ports or half suits. "The product itself cannot
contaminate the pharmacist or the technician" because of the physical barriers, he said.

Rahe was a member of the NIOSH Hazardous Drug Safety Working Group, which assisted the principal contributors in developing the alert. He entered the isolator industry after retiring from Eli Lilly and Company, where he headed the group that dealt with technologies for advanced sterile processing and the handling of hazardous drugs.

An isolator, he explained, has four basic physical components: the structure or shell; the air-handling system, which maintains a low burden of particles by moving air in and out through HEPA filters; the transfer system, or pass-through, for moving material in and out; and the access system, such as glove ports or half suits, for interacting with the drugs and support material.

Said Power: "If you're using an isolator, the concept is that inside the isolator, the microenvironment—because of the filtration and because of the ventilation—does not allow anything from the operator's body to get on to the product or from the product to contaminate the operator's body. That, unfortunately, is theoretical."

An isolator's pass-through, she noted, "only works 100% if you never put anything in or take anything out."

A need for new equipment? "I am just at the point where I'm considering isolators for chemo, because I can do it without impacting my practice too greatly," Power said.

UC San Francisco Medical Center operates a comprehensive cancer center and an ambulatory care facility, both of which prepare chemotherapy and other infusible formulations for outpatients, she said. The sterile-drug preparation areas at these two sites have a small horizontal-laminar-airflow workbench for regular aseptic processing and a three- or four-foot-wide biological-safety cabinet, which is vented or not vented, depending on the facility.

Power surmised that everyone involved in compounding sterile antineoplastics is "in a quandary" about simultaneously achieving the goals of the NIOSH alert, which calls for negative air pressure in the critical drug-preparation area relative to adjacent areas, and the United States Pharmacopeia (USP) chapter on sterile compounded preparations, which wants positive air pressure. USP general chapter 797 only briefly mentions hazardous drugs (as "chemotoxic agents") and offers no firm instruction on worker protection.

A goal of Power's work in rewriting the ASHP technical assistance bulletin is to mesh the NIOSH alert with USP chapter 797.

"If you put chemo into a positive-pressure environment and you spill the chemo, it's going to blow everywhere, not just [at] you," she said. Furthermore, based on the studies that revealed contamination of surfaces near open-front biological-safety cabinets, she cautioned against positioning one of those cabinets alongside a horizontal-laminar-airflow workbench used for regular aseptic processing. "You're just looking for trouble," she said.

Power described her solution to the main medical center pharmacy's NIOSH–USP dilemma: "I am actually going to design a positive-pressure cleanroom on the left side, with an anteroom in the center between the two rooms, and put my chemo room under negative pressure as it should be." The chemotherapy preparation room will have isolators, or microenvironments. She said the design "will still meet all of the [USP] criteria except for that one that says positive pressure" in the room for making sterile drug preparations, including chemotherapy.

Not much of a surprise, Patrick E. Parker, director of the pharmacy, i.v. therapy, and oncology departments at Lawrence Memorial Hospital in Lawrence, Kansas, said the content of the NIOSH alert did not surprise him at all.

"ASHP, I think, has done a good job of letting people know that most of this was coming," he said.
Parker said the NIOSH alert offers some good safety procedures that he had not previously considered, such as requiring staff to wear protective apparel when opening shipping containers of hazardous drugs. Already scheduled, he said, is a meeting to identify the gaps between the hospital's current hazardous-drug protection procedures and recommendations in the prepublication version of NIOSH alert.

"My suspicion is that there is going to be a handful of things that are touch-point pieces that we're going to want to go ahead and make standard in our own program," he said.

Parker said he had been fortunate, when planning the sterile-drug preparation areas, to have a hospital administration "that was extraordinarily supportive in enabling us to make this a high-quality area."

Built a number of years ago, the oncology pharmacy has a sterile-drug preparation area consisting of three defined spaces: a support area, a negative-pressure room in which the hazardous drugs are stored and from which the air is vented outdoors, and, inside this room, a negative-pressure class II biological-safety cabinet that is vented outdoors. He said the main pharmacy's sterile-drug preparation area has a receiving area, a positive-pressure room with horizontal-laminar-airflow workbenches, and, inside that room, a sealed-off negative-pressure room for the hazardous drugs and the class II biological-safety cabinet that is vented outdoors.

In addition to the bulleted recommendations in the NIOSH alert, Parker said he would examine the sample list of hazardous drugs for possible additions to the hospital's list. That list, he said, is routinely updated after the pharmacy and therapeutics committee reviews a new product for the formulary and decides that the drug should be handled as a hazardous substance.

Several drugs, such as colchicine, chloramphenicol, and conjugated estrogens, are on the NIOSH list but not Lawrence Memorial's, Parker said. To reconcile this, he intends to check NIOSH's reference source to compare its evidence with the way the medication is used and stored at the hospital.

Oxytocin, he said, is a good example of a drug whose real risk "is probably not for the general population." But it is a risk, he said, for a pregnant technician who is unpacking glass vials of the uterine-muscle contracting agent. "That is one of the things that we've told our pregnant staff that they shouldn't be handling."

**Protection when unpacking.** The potential danger from shipments of hazardous drugs may not be limited to broken vials, however.

Collaborators Robert DeChristoforo, deputy chief of the Clinical Center Pharmacy Department at the National Institutes of Health, and Thomas H. Connor, an NIOSH senior service fellow, followed up on research conducted in Europe, where investigators found outer-surface contamination on unused chemotherapy vials.

DeChristoforo said the cyclophosphamide and ifosfamide vials used for the U.S. study were part of routine orders placed over several months by the pharmacy department and intended for patient care. The pharmacy's prime vendor, he said, routinely places the hazardous drugs in resealable plastic bags in rigid shipping containers separate from other pharmaceuticals.

On arrival of each shipment, DeChristoforo took the sealed bags to a biological-safety cabinet in a laboratory separate from where chemotherapy doses are routinely prepared. He said a chemist wearing personal protective equipment and experienced in sampling techniques removed the drug packages from the bags and the vials from their cardboard containers, then wiped the outside surface of the vials with solvent-moistened filter-paper discs in accordance with a standard protocol for preparing wipe samples. These surface-wipe samples were immediately placed in a −80 degree C freezer and then shipped on dry ice to Connor, who performed the analysis.

DeChristoforo said the analysis revealed "consistent" contamination on the vials. "Not a huge amount, and it certainly wasn't visible," he said, but the wipe samples definitely
indicated there had been drug residue on the vials.

Discovery of drug residue on the outside of cyclophosphamide and ifosfamide vials, however, does not mean that the outside surface of all antineoplastic drug vials or even their cardboard boxes are contaminated, DeChristoforo cautioned.

After filing a report with FDA's MedWatch program, DeChristoforo said he and Connor contacted one of the manufacturers, who indicated it would change the drug's material safety data sheet to warn workers that the outside surface of the finished vials could be a source of exposure.

The collaborators said they are preparing a manuscript about their study for submission to a peer-reviewed journal.


—Cheryl A. Thompson