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Despite the existence of guidelines for the safe handling of antineoplastic drugs¹⁻⁵ and changes in work practices^{6,7} in the early 1980s, studies continued to document the exposure of health care workers who handled these agents.⁸⁻¹⁷ Since the publication of the early guidelines, most organizations revised their guidelines as new information became available.¹⁸⁻²⁰ The Oncology Nursing Society has revised its guidelines,²¹ and the American Society of Health-System Pharmacists is currently revising its guidelines for handling these agents. During the past few years, several review articles have summarized the hazards associated with handling antineoplastic agents.²³⁻²⁶ Among the effects related to exposure to these agents, the adverse reproductive effects reported by Valanis et al.^{10,16} and the Dutch government in 1999¹⁷ are some of the more noteworthy. The increasing

number of patients receiving cancer chemotherapy and the use of high-dose, multiple-agent therapy may be some of the factors contributing to increased exposures.²⁷

Several key studies have shown that surface contamination occurs when antineoplastic agents are prepared in biological-safety cabinets (BSCs). A study conducted in 1993 in the United States examined the levels of surface contamination with cyclophosphamide in a limited number of wipe samples collected from the pharmacy and clinic areas.²⁸ In that

study, contamination with antineoplastic agents was detected in 18% of the pharmacy samples and 14% of the clinic samples. Several European studies have confirmed the extent of surface contamination in various settings, including pharmacies, treatment areas, and other locations.²⁹⁻³² A recent study demonstrated surface contamination in three U.S. and three Canadian treatment centers in both the pharmacy and administration areas.³³ BSCs, floors, carts, countertops, patient tables, and chairs used during infusions were sampled for cyclophosphamide, ifosfamide, and fluorouracil. The results showed that 75% of the locations sampled in the pharmacies and 65% in the treatment areas were contaminated with at least one of the three agents. Two studies performed in Italy demonstrated patterns of environmental contamination that were considerably higher than those described in other countries.^{34,35}

In a study evaluating the use of a closed-system device (PhaSeal, Carmel Pharma, Shelton, CT) without a BSC, Sessink and colleagues³⁶ reported virtually no surface contamination after using the system for one year in a Swedish hospital that prepared 3000 chemotherapy doses annually. Connor and coworkers³⁷ demonstrated that the introduction of the PhaSeal closed-system device resulted in signif-

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icant reductions in levels of ifosfamide surface contamination in a hospital pharmacy that handled a high volume of chemotherapy.

The present study evaluated the effectiveness of the PhaSeal system in reducing surface contamination in a pharmacy setting in which a high volume of chemotherapy was prepared in BSCs. Three high-usage agents served as indicators of contamination.

Methods. *Site description.* The study site was the i.v. preparation area in the pharmacy of an ambulatory care treatment center at a large cancer treatment center in the Southwest United States. The facility received approximately 51,000 and 60,000 outpatient visits in 1998 and 1999, respectively; typically, 50,000 doses of chemotherapy are prepared here each year. The pharmacy operates 17 hours a day on weekdays and 10 hours a day on weekends, and the i.v. preparation area is staffed by 10 technicians. The cleaning procedures that were in effect before and during the study included daily sweeping and mopping with a germicidal agent.

Pharmacy staff and equipment. Before the study, the pharmacy's i.v. preparation area had been remodeled and refitted. The new facility comprised a 465-square-foot room and an anteroom in which technicians changed into protective clothing before entering the preparation area. The new design incorporated six Class II, Type B3 BSCs, which are vented to the outside environment. The preparation area was maintained under negative pressure. All cabinetry, countertops, and tables were new. The floor, ceiling, and walls were the only remaining original parts of the pharmacy.

PhaSeal system. The PhaSeal system, which was designed to prevent the leakage of drugs into the environment during preparation and administration, has several components (Figure 1). The PhaSeal protector, which fits onto a drug vial, has an expansion chamber designed to pre-

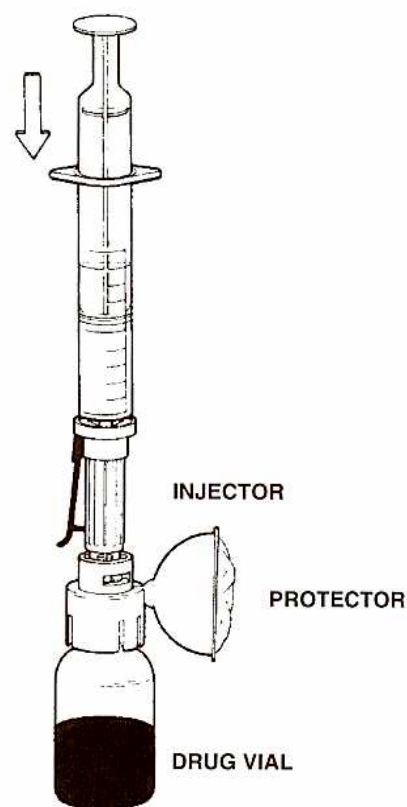
vent overpressure or a vacuum from occurring in the vial when air or diluent is injected or withdrawn. This feature is intended to prevent the release of drug aerosols and droplets during preparation. PhaSeal injectors and PhaSeal connectors use a double-membrane system designed to ensure leak-free drug transfers and disconnections. The injector is a syringe with a protected needle. The tip of the needle is never exposed when in use, so needle-stick injuries are avoided, and leakage from this source is prevented.

Training of technicians. All pharmacy technicians had been trained in the use of the PhaSeal system and had been using the system for several months before the study started, which allowed them to become adept with the new technique.

Study design. When the renovation of the pharmacy was completed and the new BSCs were installed, wipe samples were collected from 18 locations in the pharmacy area before drug preparation commenced. Thereafter, all doses of both cyclophosphamide and ifosfamide were routinely prepared using the PhaSeal system. As a control, all doses of fluorouracil were prepared using the standard method (without PhaSeal). After the baseline sampling, the 18 locations were sampled every four weeks for each of the three agents. Sampling continued for a period of 24 weeks, resulting in six postintervention sampling dates.

Sample collection. Surface-wipe samples were collected from BSCs, carts, tables, countertops, the transfer window and mats immediately in front of the BSCs, and the floor throughout the preparation area. Each area to be sampled was measured, and 20 mL of 0.03 M sodium hydroxide was applied to the location. The location was then wiped with two tissues (Scott 130 roll towels, Kimberly-Clark Corporation, Northrop, United Kingdom) until dry, and the tissues were placed in coded 175-mL plastic

Figure 1. The closed-system PhaSeal device comprises three components: a protector, an injector, and a connector. The protector has a flexible expansion bulb into which air can be transferred while filling the vial with diluent to dissolve the drug. The injector contains a needle, which is enclosed within a protective sleeve sealed by a membrane. The connector couples the injector to the syringe. An infusion adaptor provides a spike into the i.v. bag and a port through which drugs can be added, making a closed system (not shown). Reprinted with permission of Carmel Pharma AB.



screw-top bottles (Nalge Nunc, Rochester, NY).³³

Duplicate blanks were prepared on each sampling day by adding 20 mL of the sodium hydroxide solution to two tissues and placing them in a plastic container for analysis. All samples and blanks were assigned a random number so a blinded analysis could later be performed. Samples were immediately shipped on dry ice to Exposure Control in The Netherlands for analysis. The sam-

NOTE Cyclophosphamide and ifosfamide

ples were extracted and analyzed for fluorouracil by reverse-phase high-performance liquid chromatography (HPLC) and for cyclophosphamide and ifosfamide by gas chromatography with tandem mass spectroscopy (GC-MS-MS).³³ The analytical detection limit was 20 ng/mL for fluorouracil and 0.1 ng/mL for cyclophosphamide and ifosfamide. Results were reported in nanograms of drug recovered per square centimeter of surface area sampled, normalized to the amount of ifosfamide used per day.

Results. The mean \pm S.D. daily quantities of fluorouracil (5-g vials), cyclophosphamide (2-g vials), and ifosfamide (1- and 3-g vials) prepared were 18.0 ± 1.2 , 10.5 ± 1.4 , and 19.2 ± 5.0 g, respectively. At the beginning of the study there was fluorouracil contamination on some areas of the floor (Table 1). Thereafter, the levels of fluorouracil contamination increased for most locations, including the two BSCs and several areas on the

floor. Most values ranged between 1 and 10 ng/cm². Two particularly high values were detected: one on a mat in front of a BSC and one in an area where returned chemotherapy pumps were stored. For cyclophosphamide, most values were less than 3 ng/cm² except for one location by the window where the prepared i.v. bags were placed and an area on the floor where there were high levels initially that declined over the course of the study.

At the beginning of the study, some areas of the floor still had residual contamination with ifosfamide, but this declined during the study. On the final day of sampling, a high level of ifosfamide contamination was detected in the BSC. Other than this location and those locations with preexisting contamination, ifosfamide levels were less than 1 ng/cm².

Discussion. Changes in the procedures for the preparation and handling of antineoplastic agents during the 1980s led to a significant reduc-

tion in occupational exposures to these agents. The primary intervention responsible for reducing worker exposure was the change from horizontal laminar-flow hoods to Class II BSCs.^{6,7} However, the methods used to evaluate these exposures, such as urine mutagenicity, chromosomal aberrations, and sister chromatid exchanges, are relatively insensitive and nonspecific. New technology has increased the sensitivity and specificity of devices monitoring the exposure of health care workers to antineoplastic agents, which may be 1000-fold more sensitive than previous techniques.³⁸ HPLC and GC-MS-MS have been employed to identify and quantify specific antineoplastic agents found in the urine of pharmacists and nursing personnel and in surface samples, such as wipe samples.²⁸⁻³⁶ Studies in the United States and several other countries have demonstrated widespread surface contamination in i.v. preparation areas, even in those with BSCs.²⁸⁻³⁷

Table 1. Antineoplastic Drug Recovery from Various Sampling Locations

Drug and Sampling Location	Mean Amount Recovered (ng/cm ² per gram of drug) ^a with PhaSeal						
	Before PhaSeal	Day 28	Day 56	Day 84	Day 112	Day 140	Day 168
Fluorouracil							
BSC	0.01	1.20	6.49	2.73	4.16	4.39	4.63
Mat	0.01	0.62	1.06	0.76	1.17	34.2	8.56
Table	0.01	2.55	0.71	1.09	0.49	1.07	0.31
Window	0.01	1.40	2.02	2.68	0.60	0.01	0.01
Floor	4.78	1.38	1.78	2.01	0.56	7.96	3.28
Other	1.30	0.27	1.63	2.46	17.0 ^b	0.51	0.01
Cyclophosphamide							
BSC	1.83	5.87	11.9	0.54	0.40	0.26	0.15
Mat	0.01	4.52	3.83	1.88	0.46	0.15	0.22
Table	0.03	1.88	2.21	4.58	0.88	0.33	0.11
Window	0.01	1.06	1.42	34.6	1.28	0.18	0.09
Floor	1.61	32.0 ^c	18.1	21.2	4.89	3.84	1.45
Other	0.29	0.25	0.51	0.62	0.13	0.09	0.07
Ifosfamide							
BSC	<0.01	0.19	0.28	1.43	0.63	0.09	108
Mat	0.01	0.02	0.24	1.03	0.17	0.13	0.90
Table	0.01	0.17	0.05	0.22	0.10	0.18	0.81
Window	0.02	0.14	0.56	0.29	0.11	0.09	1.69
Floor	11.4	3.49	1.39	0.40	0.19	0.71	1.06
Other	0.88	0.10	0.13	0.40	0.19	0.11	0.18

^aTwo locations were sampled for the table, mat, and window; four locations were sampled for the BSC, floor, and other areas. BSC = biological-safety cabinet. Values were normalized to the amount of ifosfamide used per day.

^bThis value included an area where used i.v. pumps were returned to the pharmacy, and leakage from the pumps may have contributed to the high value.

^cContamination of the floor areas was probably the result of a documented breakage of a 2-g vial of cyclophosphamide in this area just before the 28-day sampling.

The results of the present study show that contamination inside a BSC is contained through the use of a closed-system device. However, because of the extreme sensitivity of the detection technique and the apparent ineffectiveness of the routine cleaning procedures, the issue becomes more complex than might have been expected.

The use of a sensitive technique to detect antineoplastic agents revealed some previously unsuspected aspects of surface contamination. For each of the drugs, there were a few high values that clearly stood out from the background contamination pattern. In most cases, these high values were related to spillage due to breakage or leakage or to preexisting contamination.

Following the renovation of the pharmacy area and the replacement of BSCs and other equipment, minimal baseline contamination with antineoplastic agents could have been expected. However, there were still detectable levels of fluorouracil and ifosfamide on some areas of the floor after two months of construction and cleaning. Before opening the renovated pharmacy, the wax on the floor was stripped, and the floor was cleaned and rewaxed. Once the i.v. preparation area had become operational again, the levels of fluorouracil contamination increased for most locations, including the two BSCs and several areas on the floor. One particularly high value was found outside of the pharmacy where returned chemotherapy pumps were routinely stored. Apparently, the pumps had been the source of this "hotspot" identified in the "other" category.

During the study, there was substantial cyclophosphamide contamination in two locations in the pharmacy. High levels were recorded on the floor in the center of the preparation area; this most likely resulted from the breakage of a 2-g vial early in the study. Although the values de-

clined during the course of the study, it was quite clear that they declined over a period of weeks rather than days, calling into question the efficacy of the floor-cleaning procedures. At the beginning of the study there was low-to-moderate ifosfamide contamination on several locations on the floor. This declined to a very low level by the end of the study. On the final sampling day, a high level of ifosfamide was detected in one of the two BSCs. While a spill was not documented, the high level may have been the result of the improper use or failure of the PhaSeal system, an unreported breakage, or contamination by some other means. This one possible failure represents 2 samples in one of the BSCs out of a total of 24 samples taken from the BSCs over the course of the study. However, several vials of ifosfamide were prepared daily in that particular BSC over a six-month period, and only one incidence of contamination was observed.

This study has added to our previous work in this area and appears to confirm the results of a similar, preliminary study that showed substantial reductions of ifosfamide contamination using the PhaSeal system.³⁷ In that study, a 60-fold reduction in surface contamination was seen in the BSCs and a threefold reduction was seen overall in the pharmacy area. In both studies, the PhaSeal system, used in conjunction with a BSC and conventional cleaning procedures, effectively contained antineoplastic agents during preparation and kept the working environment free from surface contamination. On the basis of our previous studies^{33,37} and other published values,^{28-32,34,35} preparing such large quantities of cyclophosphamide and ifosfamide (10.5 and 19.5 g/day, respectively) using standard techniques would typically result in substantial surface contamination.

The values in our study were somewhat elevated initially for cyclo-

phosphamide and very low on the last four sampling days. Levels of ifosfamide, which was prepared in quantities approximately twice those of cyclophosphamide, were even lower for most of the study, other than the obviously high level of contamination on the final sampling day. In our previous intervention study,³⁷ fluorouracil contamination levels of samples without using PhaSeal were similar to those seen in the current study. In that study, a before-and-after comparison with ifosfamide demonstrated a significant reduction in ifosfamide contamination when the PhaSeal system was used. Although fluorouracil may not be an ideal control for a study of this nature because of possible differences in stability and in the ease with which it may be effectively removed by cleaning procedures, the data from our earlier study suggest that it is a suitable control. Our results are supported by Sessink et al.,³⁶ who used the PhaSeal system without a BSC to prepare antineoplastic agents in a low-volume hospital in Sweden. After one year of drug preparation and administration, virtually no contamination was seen when cyclophosphamide and fluorouracil were used as indicators of contamination. Thus, it appears that the PhaSeal system can reduce the level of contamination with antineoplastic agents.

Given the continued potential for occupational exposure of health care workers who handle antineoplastic agents, it is prudent to reduce exposure as far as possible. The PhaSeal closed-system device may offer a solution to this problem and, combined with other safe handling practices, should make the work environment safer for health care personnel.

Conclusion. A closed-system device, in conjunction with the use of BSCs in an i.v. admixture area, appeared to contain surface contamination resulting from the preparation of cyclophosphamide and ifosfamide.

References

1. U.S. Department of Labor. Guidelines for cytotoxic (antineoplastic) drugs. Washington, DC: U.S. Occupational Health and Safety Administration, 1986; Publication no. 8-11.
2. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic drugs in hospitals. *Am J Hosp Pharm.* 1985; 42:131-7.
3. Cancer chemotherapy: guidelines and recommendations for nursing education and practice. Pittsburgh: Oncology Nursing Society; 1994.
4. American Medical Association Council on Scientific Affairs. Guidelines for handling parenteral antineoplastics. *JAMA.* 1985; 253:1590-2.
5. Recommendations for handling cytotoxic agents. Providence: National Study Commission on Cytotoxic Exposure; 1987 Sep.
6. Nguyen TV, Theiss JC, Matney TS et al. Exposure of pharmacy personnel to mutagenic antineoplastic drugs. *Cancer Res.* 1982; 42:4792-6.
7. Anderson RW, Puckett WH, Dana WJ. Risk of handling injectable antineoplastic agents. *Am J Hosp Pharm.* 1982; 39:1881-7.
8. Burgaz S, Karahalil B, Bayrak P et al. Urinary cyclophosphamide excretion and micronuclei frequencies in peripheral lymphocytes and in exfoliated buccal epithelial cells of nurses handling antineoplastics. *Mutat Res.* 1999; 439:97-104.
9. Ündeger U, Basaran N, Kars A et al. Assessment of DNA damage in nurses handling antineoplastic drugs by the alkaline COMET assay. *Mutat Res.* 1999; 439:277-85.
10. Valanis B, Vollmer W, Labuhn K et al. Occupational exposure to antineoplastic agents and self-reported infertility among nurses and pharmacists. *J Occup Environ Med.* 1997; 39:574-80.
11. Fuchs J, Hengstler JG, Jung D et al. DNA damage in nurses handling antineoplastic agents. *Mutat Res.* 1995; 342:17-23.
12. Bruman V, Horvat D. Work environment influence on cytostatics-induced genotoxicity in oncologic nurses. *Am J Ind Med.* 1996; 30:67-71.
13. DeMeó MP, Mérono S, DeBaille AD et al. Monitoring exposure of hospital personnel handling cytotoxic drugs and contaminated materials. *Int Arch Occup Environ Health.* 1995; 66:363-8.
14. Ensslin A, Stoll Y, Pethran A et al. Biological monitoring of cyclophosphamide and ifosfamide in urine of hospital personnel occupationally exposed to cytostatic drugs. *Occup Environ Med.* 1994; 51:229-33.
15. Ensslin A, Huber R, Pethran A et al. Biological monitoring of hospital pharmacy personnel occupationally exposed to cytostatic drugs: urinary excretion and cytogenetics studies. *Int Arch Occup Environ Health.* 1997; 70:205-8.
16. Valanis B, Vollmer WM, Steele P. Occupational exposure to antineoplastic agents: self-reported miscarriages and stillbirths among nurses and pharmacists. *J Occup Environ Med.* 1999; 41:632-8.
17. Peelen S, Roeleveld N, Heederik D et al. Toxic effects on reproduction in hospital personnel. Reproductie-toxische effecten bij ziekenhuispersoneel. Netherlands: Elsevier; 1999. In Dutch.
18. Fishman M, Mrozek-Orlowski M. Cancer chemotherapy guidelines and recommendations for practice. 2nd ed. Pittsburgh: Oncology Nursing Society; 1999.
19. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm.* 1990; 47:1033-49.
20. Occupational Safety and Health Administration. Controlling occupational exposure to hazardous drugs (section VI, chapter 2). In: OSHA technical manual. http://www.osha-slc.gov/dts/osta/otm/otm_vi/otm_vi_2.html (accessed 2001 Nov 21).
21. Brown KA, Esper P, Kelleher LO et al. Chemotherapy and biotherapy guidelines and recommendations for practice. Pittsburgh: Oncology Nursing Society; 2001.
22. Power L. Safe handling of cytotoxic drugs: current concerns and proposed changes to the ASHP technical assistance bulletin. Paper presented at ASHP Midyear Clinical Meeting, Las Vegas, NV; 2000 Dec 5.
23. Baker ES, Connor TH. Monitoring occupational exposure to cancer chemotherapy drugs. *Am J Health-Syst Pharm.* 1996; 53:2713-23.
24. Sorsa M, Anderson D. Monitoring of occupational exposure to cytostatic anticancer agents. *Mutat Res.* 1996; 355:253-61.
25. Bos RP, Sessink PJ. Biomonitoring of occupational exposure to cytostatic anticancer drugs. *Rev Environ Health.* 1997; 12:43-58.
26. Sessink PJ, Bos RP. Drugs hazardous to healthcare workers. *Drug Saf.* 1999; 20:347-59.
27. Cancer facts & figures 2000. Atlanta: American Cancer Society; 2000.
28. McDevitt JJ, Lees PS, McDiarmid MA. Exposure of hospital pharmacists and nurses to antineoplastic agents. *J Occup Med.* 1993; 35:57-60.
29. Sessink PJ, Boer KA, Scheefhals AP et al. Occupational exposure to antineoplastic agents at several departments in a hospital. *Int Arch Occup Environ Health.* 1992; 64:105-12.
30. Sessink PJ, Anzion RB, van den Broek et al. Detection of contamination with antineoplastic agents in a hospital pharmacy department. *Pharm Weekbl Sci.* 1992; 14:16-22.
31. Sessink PJ, de Roos JH, Pierik FH et al. Occupational exposure of animal caretakers to cyclophosphamide. *J Occup Med.* 1993; 35:47-52.
32. Pethran A, Hauff K, Hessel H et al. Biological, cytogenetic, and ambient monitoring of exposure to antineoplastic drugs. *J Oncol Pharm Pract.* 1998; 4:57. Abstract.
33. Connor TH, Anderson RW, Sessink PJ et al. Surface contamination with antineoplastic agents in six cancer treatment centers in Canada and the United States. *Am J Health-Syst Pharm.* 1999; 56:1427-32.
34. Minoia C, Turci R, Sottani C et al. Application of high performance liquid chromatography/tandem mass spectrometry in the environmental and biological monitoring of health care personnel occupationally exposed to cyclophosphamide and ifosfamide. *Rapid Commun Mass Spectrom.* 1998; 12:1485-93.
35. Rubino FM, Florida L, Pietropaolo AM et al. Measurement of surface contamination by certain antineoplastic drugs using high-performance liquid chromatography: applications in occupational hygiene investigations in hospital environments. *Med Lav.* 1999; 90:572-83.
36. Sessink PJ, Rolf M-AE, Rydén NS. Evaluation of the PhaSeal hazardous drug containment system. *Hosp Pharm.* 1999; 34:1311-7.
37. Connor TH, Anderson RW, Sessink PJ. Intervention study to reduce occupational exposure to antineoplastic agents in a pharmacy setting. Paper presented at ASHP Midyear Clinical Meeting, Orlando, FL; 1999 Dec 7.
38. Harrison BR. Exposure to hazardous drugs: time to reevaluate your program? *Am J Health-Syst Pharm.* 1999; 56:1403. Editorial.