Evaluation of Antineoplastic Drug Exposure of Health Care Workers at Three University-Based US Cancer Centers

Thomas H. Connor, PhD, D. Gayle DeBord, PhD, Jack R. Pretty, PhD, Marc S. Oliver, MPH, RN, MBA, Tracy S. Roth, RN, MS, Peter S. J. Lees, PhD, Edward F. Krieg, Jr., PhD, Bonnie Rogers, DrPH, COHN-S, LNCC, Carmen P. Escalante, MD, Christine A. Toennis, BS, John C. Clark, Belinda C. Johnson, and Melissa A. McDiarmid, MD, MPH, DABT

Objective: This study evaluated health care worker exposure to antineoplastic drugs. **Methods:** A cross-sectional study examined environmental samples from pharmacy and nursing areas. A 6-week diary documented tasks involving those drugs. Urine was analyzed for two specific drugs, and blood samples were analyzed by the comet assay. **Results:** Sixty-eight exposed and 53 nonexposed workers were studied. Exposed workers recorded 10,000 drug-handling events during the 6-week period. Sixty percent of wipe samples were positive for at least one of the five drugs measured. Cyclophosphamide was most commonly detected, followed by 5-fluorouracil. Three of the 68 urine samples were positive for one drug. No genetic damage was detected in exposed workers using the comet assay. **Conclusions:** Despite following recommended safe-handling practices, workplace contamination with antineoplastic drugs in pharmacy and nursing areas continues at these locations.

The carcinogenic, mutagenic, and adverse reproductive outcomes in patients treated with antineoplastic agents are well known.[1,2] A growing number of antineoplastic drugs are identified by the International Agency for Research on Cancer as known or suspected human carcinogens.[3] Many antineoplastic drugs are also teratogenic or produce other adverse reproductive effects in patients and have demonstrated similar effects in health care workers.[4,5] Adding to the public health impact of hazardous drug exposure is a new forecast predicting that, by 2050, an aging US population will see the number of cancer cases double, resulting in an increase in the use of antineoplastic drugs.[6] Currently, an estimated 8 million US health care workers are potentially exposed to hazardous drugs, which include most of the antineoplastic drugs.[7] With the increasing use of antineoplastic agents in treating cancer and nonmalignant diseases and their use in veterinary oncology, it is reasonable to expect an increase in the number of health care workers potentially exposed to these drugs.

The risk to health care workers resulting from this exposure was first identified >30 years ago and drove research attempting to characterize exposure intensity and to document early effects on health. In addition to the contamination of the work environment with antineoplastic drugs,[2,8] health care worker exposure to these drugs has been documented in many studies that used either biological monitoring for uptake of a specific drug[8] or biomarkers of genotoxic exposure and early effects of drug exposure in workers.[5,9–11] Multiple environmental sampling studies have documented work area contamination, and a majority of the biomarker studies have demonstrated an association with antineoplastic drugs, indicating effects in workers.[2,5,9–11] When differences in biomarker study results have occurred, factors such as use of safe-handling procedures, complexities of different laboratory methodologies, confounders for the outcomes of interest, drug-handling history, workload, and many other technical issues have been described.[2,12]

Reports of occupational exposure to antineoplastic drugs have appeared in the world literature since the late 1970s. In the United States, McDevitt et al[13] first reported surface contamination with cyclophosphamide in a hospital pharmacy and nursing/patient areas, and Connor et al[14] demonstrated widespread contamination with cyclophosphamide, ifosfamide, and 5-fluorouracil in pharmacy and patient treatment areas in six North American hospitals, despite adherence to currently recommended handling procedures. Among the numerous published reports dealing with workplace contamination issues, a series of reports by Sessink et al,[15–18] in The Netherlands described various determinants of potential worker exposure in the 1990s. Studies in varied health care settings examined surface and glove contamination, air samples, and drugs in the urine of nursing and pharmacy personnel, which documented environmental contamination and worker exposure. Similar studies have described work area contamination and worker exposure issues in facilities that reported using recommended engineering controls and safe-handling procedures. A series of reports from German researchers evaluated the environmental contamination, the measurement of drugs in the urine of workers, and the factors that affect exposure in 14 German hospitals.[19–21] Nevertheless, most of the published reports have been limited in either the number of drugs examined or the evaluation of the range of work practices and other factors that may result in environmental contamination with antineoplastic drugs and subsequent worker exposure. Therefore, the authors of this study undertook a more comprehensive evaluation of multiple factors that can result in contamination of the work environment and worker exposure by a selected group of antineoplastic drugs. To evaluate the entire workplace, a multifaceted strategy was developed that included 1) a comprehensive health and work history questionnaire for potentially exposed workers; 2) information on the use of personal protective equipment (PPE) such as gloves, gowns, respiratory, and

From the Division of Applied Research and Technology (Dr Connor, Dr DeBord, Dr Pretty, Dr Krieg, Ms Toennis, Mr Clark, Ms Johnson), National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, Ohio; Occupational Health Program (Mr Oliver, Ms Roth, Dr McDiarmid), University of Maryland School of Medicine, Baltimore, Md; North Carolina Occupational Safety and Health and Education and Research Center and OHN Program (Dr Rogers), University of North Carolina School of Public Health, Chapel Hill, NC; Department of General Internal Medicine, Ambulatory Treatment and Emergency Care (Dr Escalante), Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, Tex; and Department of Environmental Health Sciences (Dr Lees), Johns Hopkins Bloomberg School of Public Health, Baltimore, Md.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health. Mention of company names and/or products does not constitute endorsement by the National Institute for Occupational Safety and Health.

Address correspondence to: Thomas H. Connor, PhD, Division of Applied Research and Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, MS C-23, 4676 Columbia Parkway, Cincinnati, OH 45226; E-mail: tmc6@cdc.gov.

DOI: 10.1097/JOM.0b013e3181f72b63

eye protection by these workers; 3) a diary describing frequency of drug-handling events (individual tasks performed with specific drugs); 4) measurement of antineoplastic drugs that were common to the three university-based cancer treatment centers using surface wipe, fixed-location, and personal breathing zone air samples; 5) measurement of two of the drugs in the urine of workers; and 6) use of a biomarker of genetic damage.

MATERIALS AND METHODS

Study Design

Study participants were selected from three university hospital-based cancer centers in different areas of the United States. Each center followed current recommendations for safe-handling practices in preparing (compounding) and administering cancer chemotherapy agents as recommended by National Institute for Occupational Safety and Health (NIOSH).[5] All sites used class II biological safety cabinets (BSCs) to prepare drugs, but the type (A2 and B2) and venting characteristics varied. In addition, the pharmacy designs varied for the different sites, ranging from basic rooms to clean rooms with anterooms. One of the three sites used a closed-system transfer device (CSTD) for preparing of antineoplastic drugs.

Study subjects potentially exposed to antineoplastic drugs were employed in an oncology pharmacy or oncology nursing unit. The comparison population consisted of nonexposed pharmacy and nursing personnel from the same hospitals, frequency matched for gender and age within 5 years. Inclusion criteria required that the exposed individuals had been working with antineoplastic drugs (eg, actively handling) for the previous 6 months and in the week before assessment, must have worked 24 hours handling drugs. Nonexposed subjects had a similar current job (in nursing or pharmacy) but were not involved with handling of antineoplastic drugs or working in areas where they were handled.

The study included 68 participants who handled antineoplastic drugs and 53 nonexposed controls (Table 1). The mean age for the exposed workers was 38.5 (SD, 10.5) years and 39.9 (SD, 10.4) years for the nonexposed workers. Eighty-three percent of the exposed and 75% of the nonexposed workers were women.

Workers currently smoking, receiving chemotherapy, or who had previously received chemotherapy or radiation therapy were excluded as subjects. Also excluded were those who used other genotoxic pharmaceuticals (eg, isotretinoin and metronidazole) and males undergoing hormonal therapy in the past 6 months. All participants gave their informed consent to study participation, and the study protocol was approved by the University of Maryland Institutional Review Board and the NIOSH Human Subjects Review Board. In addition, Institutional Review Board approval was obtained for each of the study sites.

All study participants completed questionnaires describing medical history, employment history, personal medications, second-hand tobacco smoke exposure, radiation or chemical exposure, and other social habits. Exposed workers also included detailed history of work practices used, including PPE and work policy specific to their duties. The study participants who handled antineoplastic drugs also completed a daily diary for a 6-week period, preceding on-site exposure measurements. For each drug-related activity, this diary included the name of the antineoplastic drug handled, the manner of use, and the use of protective apparel or equipment (such as gloves, gowns, eye, or respiratory protection). Details of drug preparation activity (eg, prepared, checked, primed tubing, and whether a spill or splash occurred) and administration method (eg, infusion, intravenous [IV] push, primed tubing, and whether a spill or splash occurred) were also collected.

For each participant, drug-handling events were tallied for the 6-week diary period before environmental and biological sample collection. Drug-handling events were also stratified by drug class (alkylating agent, antibiotics, anthracyclines, antimetabolites, etc) and for the five drugs for which environmental sampling was done. For nine nursing technicians, it was not possible to quantify their handling events adequately because of the variability of the tasks they performed and the inability to identify the drugs they may have been handling. Therefore, the nursing technicians could not be included in data analyses that required the individual number of handling events as an exposure variable.

TABLE 1. Demographic Characteristics of Study Population

Total	All (121)	Exposed (68)	Nonexposed (53)
Gender			
Male	21	8	13
Female	100	60	40
Ethnicity			
Hispanic	3	2	1
Race			
Asian	19	16	3
African-American	26	15	11
Native Hawaiian/Pacific Islander	1	0	1
White	74	37	36
Not identified	1	0	2
Job status			
Nurse	80	47	33
Pharmacist	21	9	12
Pharmacy technician	10	8	2
Nurse assistant	10	4	6
Location			
Site 1	42	29	13
Site 2	42	21	21
Site 3	37	18	19

Environmental Measures of Exposure to Antineoplastic Drugs

Surface Wipe Samples

Wipe Sampling Strategy. Surface wipe samples were collected in pharmacy and nursing areas to evaluate the magnitude of surface contamination by antineoplastic drugs that were generally used in all three institutions. The sampling was performed by the same individual at all three locations. Sampling locations in the pharmacy and nursing areas were selected according to the physical characteristics of each location such as size, number of BSCs, by the work practices of personnel, and by published reports that examined wipe sampling in health care settings.[8] Wipe samples were collected from the work surfaces and airfoils of the BSCs, the floor directly in front of the BSCs, waste containers, countertops and/or carts where the drugs were placed to be checked by the pharmacist, inside and outside of any pass-through windows, trays for carrying or storing drugs, and several other locations on counters and floors. Each location was sampled one time. Wipe samples were collected from areas where the drugs arrived at the nursing stations, carts and trays for transporting or storing drugs, areas where IV bags were hung before use, chairs, tables, and floors in patient rooms, floors in patient restrooms, waste containers, and utility rooms. Similar locations were sampled in the three institutions. The wipe samples were analyzed for five drugs: cyclophosphamide, ifosfamide, pac-

litaxel, 5-fluorouracil, and cytarabine. The drugs, except for ifosfamide, were chosen based on the frequency of usage in the three institutions. Because the analytical method used to quantify the field samples enables the simultaneous detection of cyclophosphamide and ifosfamide, all wipe and air samples were also analyzed for ifosfamide.

Wipe Sampling Procedure. Surface-wipe samples were collected using the method of Larson et al.[22] A 10-cm × 10-cm plastic template was used for sampling most locations. For some locations, such as airfoils of BSCs where the template was not appropriate, an area of 100 cm^2 was measured for the sampling procedure. The surface to be sampled was wetted with 250 μL of solvent (10% acetonitrile, 25% methanol, and 65% Milli-Q water buffered to pH 6.0) dispensed with an automatic pipette. The area was then wiped in a standard pattern using a 55-mm filter paper disc (Fisher Scientific, Pittsburgh, PA), and the filter paper was placed in a 125-mL widemouthed, screw top, polypropylene jar (Fisher Scientific, Pittsburgh, PA) for storage and shipping. Wiping was repeated with another 250 μL of solvent and a second filter paper that was stored with the first sample. The samples were placed in a freezer at −20°C and shipped on dry ice to the laboratory where they were stored at −70°C until they were analyzed.

Extraction of Wipe Samples. Samples were extracted according to the procedure of Pretty et al.[23] Hexamethylphosphoramide (Sigma-Aldrich, St. Louis, MO) was used as an internal standard at a final concentration of 10 ng/mL.

Analysis of Wipe Samples. Wipe samples were analyzed for antineoplastic drug content at NIOSH except for 5-fluorouracil content, which was determined by Bureau Veritas North America (Novi, MI). All quantitative analyses for drugs followed the method of Pretty et al[23] based on high-performance liquid chromatography-tandem mass spectrometry using ions produced via collision-induced fragmentation, with the exception of cytarabine that was analyzed using infusion-MS/MS. Calibration plots were generated, and samples were quantified using the ratio of elution peak heights for the analyte and internal standard. All LC-MS/MS analyses were reported as the mean result of triplicate injections.

Area and Personal Air Samples

Air Sampling Strategy. Air samples were collected in various pharmacy and nursing/patient areas close to where antineoplastic drugs were handled in the three institutions to determine if airborne concentrations of the drugs were present as vapors or particulates. Personal air samples were collected from both pharmacy and nursing personnel who were potentially exposed to antineoplastic drugs as were samples from a number of the nonexposed controls.

Air Sampling Procedure. Area and personal air sampling was based on the method of Larson et al[24] with some modifications.[23] OSHA Versatile Sampler sorbent tubes (SKC, Eighty Four, PA) containing 200 mg of Anasorb 108 were used for both personal and area air sampling. The sorbent tubes were connected to an Air-Check 2000 Pump (SKC) and sampled at 1 L/min. Sample was collected on each sorbent tube for ~4 hours, and multiple sorbent tubes were used to span an 8- or 12-hour shift. After sampling, the sorbent tubes were capped and placed in 15-mL centrifuge tubes and sealed. The samples were placed in a freezer at −20°C and then shipped on dry ice to the laboratory where they were stored at −70°C until they were analyzed.

Extraction of Air Samples. Sorbent tubes were extracted using the method of Pretty et al.[23] When multiple sorbent tubes were used to collect vapor or particulate or both from a single location, tubes were processed individually, and the final extracts were analyzed separately.

Analysis of Air Samples. The air samples were analyzed for cyclophosphamide, ifosfamide, paclitaxel, and 5-fluorouracil using the method described by Pretty et al.[23] Because of the low volume of cytarabine observed in wipe samples, selected air samples were screened for this drug. Analyses were performed at NIOSH except for 5-fluorouracil that was performed by Bureau Veritas North America.

Biological Measures of Worker Exposure to Antineoplastic Drugs

Urine Samples

Urine Collection Strategy. Urine specimens were collected from all participants in the study for the analysis of cyclophosphamide and paclitaxel. Participants were asked to collect each void for the last 4 hours of the work shift and for the first 4 hours after the end of the shift. The sampling time was selected to maximize the amount of drug in the urine while not diluting it by collecting 24-hour samples.

Urine Sampling Procedure. Each specimen void was collected in 500-mL bottles (Nalgene; Fisher Scientific, Pittsburgh, PA) and stored on ice until they were placed on dry ice and shipped to the laboratory for analysis. The samples were stored at −20°C until they were analyzed. For each participant, aliquots of the voided samples from the last 4 hours of the work shift were pooled, and aliquots from the 4 hours after the end of the work shift were pooled, resulting in two samples for analysis. Each of these two samples was analyzed separately.

Analysis of Urine Samples. The urine samples were analyzed for cyclophosphamide and paclitaxel by high performance liquid chromatography-tandem mass spectrometry at the Duke Comprehensive Cancer Center, Clinical Research PK/PD Laboratory, Durham, NC, using the method described by Pretty et al.[23]

Comet Assay

Sampling. The comet assay, which detects DNA damage in single cells, was carried out according to the method of Toraason et al.[25] Blood was collected in an ethylenediaminetetraacetic acid-treated tube (Becton, Dickinson and Company, Franklin Lakes, NJ), and the tube was inverted 8 to 10 times. After aliquoting into 2-mL cryovials, the tubes were shipped on dry ice to NIOSH and stored at −80°C until they were shipped to the University of Washington, Seattle, WA, on dry ice for comet analysis.

Slide Preparation and Analysis. Slides were prepared and stained according to the procedure of Toraason et al.[25] One hundred leukocytes from each blood sample were analyzed using VisComet image analysis software (Impulse Bildanalyse GmbH, Gilching, Germany) and a CCD camera CV272 (JAI Corporation, Kanagava, Japan) attached to a DMLB epifluorescent microscope (Leica, Germany) with excitation at 490 nm, dichroic at 500 nm, and emission at 515 nm. Comet tail (Olive) moment was calculated by multiplying average tail length in pixels (distance between the center of the head and the center of tail) by the fraction of DNA in the tail. The mean tail moment and the percent of DNA in the tail from analysis of 100 leukocytes per subject were used in the subsequent statistical analysis.

Statistical Methods

Summary statistics were used to characterize drug handling and to analyze the wipe sample data. Linear models were used to test for relationships between the outcomes of the comet assay and the measures of exposure adjusted for covariates. A separate model was run for each combination of assay outcome and exposure measure. The outcome measures for the comet assay were percent tail DNA and tail (Olive) moment. The measures of exposure were

TABLE 2. Number of Antineoplastic Drug Handling Events by Site, Location, and Drug

	Site 1		Site 2		Site 3*		
Drug	Pharmacy Areas	Nursing/ Patient Areas	Pharmacy Areas	Nursing/ Patient Areas	Pharmacy Areas	Nursing/ Patient Areas	Total
Cyclophosphamide	78	24	122	24	341	51	640
Ifosfamide	9	3	53	9	77	38	189
Paclitaxel	198	114	249	1	840	80	1,482
5-Fluorouracil	33	23	71	0	479	68	674
Cytarabine	62	29	94	42	58	12	297
Total 5 drugs	380	193	589	76	1,795	249	3,282
Other antineoplastic drugs	778	501	1,512	179	2,787	723	6,480
Total handling for all antineoplastic drugs	1,158	694	2,101	255	4,582	972	
Total by site	1,852		2,356		5,554		9,762

*One pharmacy at site 3 did not have any study participants who worked in that area, so the number of handling events is not known for that pharmacy.

TABLE 3. Type of Antineoplastic Drug Handling Events by Task and Site

	Site 1	Site 2	Site 3	Total
Prepare*	607	393	2,974	3,974
Check*	502	1,667	1,340	3,509
Infusion†	525	118	836	1,479
Prime tubing‡	556	50	507	1,113
IV push†	99	14	73	186
Urine exposure†	0	112	0	112
Spill‡	20	3	0	23
Splash‡	5	1	0	6
Vomit exposure†	0	0	0	0
Total	2,314	2,358	5,730	10,402

*Pharmacy areas only.
†Nursing/patient areas only.
‡Pharmacy areas and/or nursing/patient area.

exposure status (exposed and nonexposed), job classification, lifetime number of exposure hours as calculated from the questionnaire, total number of handling events, number of handling events for the five drugs sampled for in the work environment, number of handling events for mutagenic drugs, and drug class.

The covariates considered were study site location, subject age at the time of the sampling and the number of genotoxic drugs taken that might affect the comet assay, and glove usage. All calculations were made using SAS (version 9.2; SAS Institute, Inc, Cary, NC).

RESULTS

Study Population

It was not possible to document the 6-week drug-handling diary information for the three nursing technicians who handled antineoplastic drugs, so these three exposed subjects and six nonexposed nursing technicians were not included in the data analyses, which required use of drug-handling history because there were no quantifiable measures of their exposure for the exposed group. In the drug-exposed group, two individuals did not provide blood samples for the biomarker assay, and one nonexposed individual was dropped out of the study.

Drug-Handling Diary

Overall, there were 9762 handling events recorded for all drugs during the 6-week period (Table 2). Of these, 3282 involved one of the five drugs that were the focus of this study, whereas 6480 events involved handling of the other antineoplastic drugs. Paclitaxel had the most handling events, followed by 5-fluorouracil, cyclophosphamide, cytarabine, and ifosfamide. For both pharmacy and nursing personnel, the number of handling events for site 3 was greater than that for sites 1 and 2 combined. Overall, the most common handling event was drug preparation followed by the checking of the final product by the pharmacist and administration of the drug infusion (Table 3). The most common events by site were site 1 (drug preparation), site 2 (checking the final product), and site 3 (drug preparation). Note that there is not a one-to-one relationship between the number of drugs handled and the number of handling events by task because a single drug could have multiple tasks associated with it (eg, one drug preparation vs the preparation, the administration spill, and a splash).

Surface-Wipe Samples

Overall, 7 separate pharmacies and 10 nursing/patient areas were assessed at the end of the 6-week diary collection period. The number of wipe samples by site and location (pharmacy and nursing areas) for each site is listed in Table 4. Sites 1 and 2, each had two separate pharmacies where antineoplastic drugs were prepared, and site 3 had three pharmacies. Site 1 had two separate nursing areas, nursing stations, or patient treatment areas where antineoplastic drugs were handled, and sites 2 and 3 had four each. In most cases, the individual pharmacy and nursing areas were in separate buildings at each institution. Eighty-one wipe samples were collected in the pharmacy areas. Sixty-two wipe samples were collected in the nursing/patient areas. The 143 wipe samples represent 715 separate analyses for the 5 drugs. At least one of the five drugs was present above the limit of detection (LOD) in 60% of the wipe samples, and 32% of the samples had more than one drug present.

Although recovery efficiencies have been shown to be $<$100% for some drug/surface combinations,[12,23] corrections were not made to the surface concentrations (eg, the amount of drug residue on each surface) as reported in this study. In this study, recovery efficiencies for the drugs ranged from as low as 20% (vinyl flooring) to 100% (Formica [plastic laminate] and stainless steel). Therefore, values for most surfaces are accurate estimates of actual contamination values, but values for floors underestimate the actual concentrations.

TABLE 4. Summary of Wipe Sample Results by Site and Location*

Site	Location	No. Samples	Cyclophosphamide (ng/cm^2), Mean (SD)	Ifosfamide (ng/cm^2), Mean (SD)	Paclitaxel (ng/cm^2), Mean (SD)	5-Fluorouracil (ng/cm^2), Mean (SD)	Cytarabine (ng/cm^2), Mean (SD)
1	Pharmacy areas	25	0.71 (1.73)	0.08 (0.29)	<LOD	0.18 (0.44)	1.28 (4.62)
	Nursing/patient areas	22	0.01 (0.03)	0.05 (0.27)	<LOD	0.08 (0.37)	<LOD
2	Pharmacy areas	23	16.00 (34.70)	0.65 (1.35)	0.15 (0.30)	0.13 (0.42)	0.53 (1.94)
	Nursing/patient areas	14	0.12 (0.39)	0.01 (0.05)	<LOD	<LOD	<LOD
3	Pharmacy areas	33	0.47 (1.69)	0.14 (0.43)	0.08 (0.12)	0.53 (1.09)	<LOD
	Nursing/patient areas	26	0.07 (0.11)	0.85 (3.87)	0.01 (0.05)	35.44 (178.4)	<LOD

*Samples with values <LOD were assigned a value of zero.
LODs were 0.10 ng/cm^2 for cyclophosphamide and ifosfamide; 0.07 ng/cm^2 for paclitaxel; 0.06 ng/cm^2 for 5-fluorouracil; and 0.13 ng/cm^2 for cytarabine.

TABLE 5. Summary of Wipe Sample Results for Five Drugs by Location at Three Study Sites Combined*

Location	No. Samples	Cyclophos-Phamide (ng/cm^2), Mean (SD) % >LOD	Ifosfamide (ng/cm^2), Mean (SD) % >LOD	Paclitaxel (ng/cm^2), Mean (SD) % >LOD	5-Fluororacil (ng/cm^2), Mean (SD) % >LOD	Cytarabine (ng/cm^2), Mean (SD) % >LOD
Pharmacy areas						
BSC	8	18.1 (51) 25	<LOD	0.04 (0.08) 25	0.03 (0.08) 13	<LOD
Airfoil of BSC	9	11.8 (30.4) 89	0.8 (2.0) 44	0.2 (0.4) 44	0.5 (0.9) 44	4.6 (7.5) 33
Floor by BSC	13	4.4 (7.9) 62	0.3 (0.7) 31	0.1 (0.2) 23	0.3 (0.9) 38	<LOD
Floors	12	2.1 (3.6) 75	0.1 (0.2) 33	0.02 (0.05) 8	0.07 (0.07) 17	<LOD
Counters	13	4.0 (13.0) 62	0.3 (0.5) 46	0.07 (0.11) 31	0.1 (0.3) 23	0.2 (0.6) 16
Checking area	4	1.7 (3.2) 50	0.06 (0.1) 25	0.04 (0.07) 25	0.6 (1.2) 50	<LOD
Pass-through	9	0.2 (0.2) 56	0.5 (0.9) 44	0.1 (0.1) 44	0.8 (1.5) 33	<LOD
Miscellaneous	13	0.5 (1.3) 25	0.01 (0.03) (8)	0.01 (0.03) 17	0.2 (0.6) 33	<LOD
Nursing/patient areas						
Counter	18	0.03 (0.05) 22	0.01 (0.03) 6	<LOD	0.1 (0.2) 33	<LOD
Floor	17	0.4 (0.4) 29	0.1 (0.2) 23	0.01 (0.06) 18	0.1 (0.2) 23	<LOD
Cart	5	<LOD	<LOD	<LOD	<LOD	<LOD
Drug storage	7	0.04 (0.07) 29	0.2 (0.5) 29	<LOD	1.4 (1.8) 43	<LOD
Waste	5	0.08 (0.1) 40	4.0 (8.8) 60	<LOD	182 (407) 20	<LOD
Miscellaneous	10	<LOD	<LOD	<LOD	0.01 (0.04) 8	<LOD

*Samples with values <LOD were assigned a value of zero.
LODs were 0.10 ng/cm^2 for cyclophosphamide and ifosfamide; 0.07 ng/cm^2 for paclitaxel; 0.06 ng/cm^2 for 5-fluorouracil; and 0.13 ng/cm^2 for cytarabine.

Surface concentrations for the five drugs ranged from below the LOD (0.07 to 0.10 ng/cm^2) up to 910 ng/cm^2. Eighty-nine percent of the samples that were >LOD were in the range of 0.1 to 10 ng/cm^2 with eight samples >10 ng/cm^2. The highest concentration (910 ng/cm^2) was measured on the lid of a hazardous waste container in a nursing area at site 3 for 5-fluorouracil. For all areas combined, the drug detected most often in the wipe samples was cyclophosphamide (43%), followed by 5-fluorouracil (26%), ifosfamide (24%), paclitaxel (16%), and cytarabine (3%). For the three sites combined, the mean paclitaxel concentration was statistically significantly correlated with the number of handling events for paclitaxel. The mean concentration of paclitaxel on surfaces increased as the number of handling events increased.

For site 2, the mean drug concentration of the wipe samples of paclitaxel was statistically significantly correlated with the number of handling events for paclitaxel. In addition, the mean drug concentrations for ifosfamide, 5-fluorouracil, and cytarabine were significantly positively correlated with the handling events for each drug.

At site 1, three of eight samples from pharmacy 1-A were positive for cyclophosphamide (mean, 0.79 ng/cm^2; summarized in Tables 4 and 5). Also, six of these eight samples had measurable levels of 5-fluorouracil (mean, 0.42 ng/cm^2). In pharmacy 1-B, all the seven samples had measurable levels of cyclophosphamide (mean, 1.42 ng/cm^2).

The pharmacy areas at site 2 demonstrated the overall highest levels of surface contamination. In pharmacy 2-A, all the nine samples were positive for cyclophosphamide (mean, 1.22 ng/cm^2) and ifosfamide (mean, 1.64 ng/cm^2). In pharmacy 2-B, 9 of 10 samples were positive for cyclophosphamide (mean, 34.5 ng/cm^2). Three of the samples collected in the room adjacent to pharmacy 2-B, through which the drugs left the preparation area, demonstrated measurable levels of cyclophosphamide (mean, 3.85 ng/cm^2). In both pharmacies at site 2, contamination with some of the other drugs that were measured was also noted in the wipe samples.

For site 3, wipe samples in pharmacies 3-A and 3-C demonstrated relatively low surface contamination for the five drugs measured. Only pharmacy 3-B had surface wipes that demonstrated widespread contamination. Most of the eight wipe samples demonstrated levels of four of the drugs, cyclophosphamide, ifosfamide, paclitaxel, and 5-fluorouracil above the LOD.

Wipe sample results for the nursing areas generally revealed lower levels of contamination, and the proportion of wipe samples that had measurable values were also lower when compared with the pharmacy areas. At site 1 nursing areas, only three locations had concentrations of drugs above the LOD, and at site 2, only four areas demonstrated surface wipes above the LOD for the five drugs tested (summarized in Tables 4 and 5).

Site 3 had the most wipe samples for which multiple drugs were detected on the wipe. Three of the four locations had four drugs detected in the wipes, and the fourth had three drugs with concentrations above the LOD.

Area and Personal Air Samples

A total of 67 area air samples and 60 personal air samples (48 exposed individuals and 12 nonexposed) were collected in pharmacy and nursing areas where the drugs were handled. All area air sample concentrations were below the LOD (3.1 to 6.9 ng/m^3) for all five drugs. One personal air sample demonstrated a concentration of cyclophosphamide of 84.5 μg/m^3 for one of the nursing personnel at site 3. All other personal air samples were below the LOD. None of the personal air samples from the nonexposed individuals demonstrated the presence of any of the five drugs. There were no measurable concentrations of ifosfamide, paclitaxel, 5-fluorouracil, or cytarabine in any of the area or personal air samples.

Urine Samples

In total, 119 urine samples were analyzed for the presence of cyclophosphamide and paclitaxel, including 67 samples from exposed individuals and 52 from nonexposed individuals. None of the urine samples from the nonexposed individuals demonstrated concentrations of either drug greater than the LOD. Two of the urine samples from the exposed pharmacists demonstrated concentrations of cyclophosphamide above the LOD (0.015 ng/mL), and one pharmacy technician demonstrated a concentration of paclitaxel just at the LOD (0.015 ng/mL). The two pharmacists from site 2, who prepared drugs, had concentrations of cyclophosphamide in their urine (0.043 and 0.079 ng/L), and the pharmacy technician from site 1 had a concentration of paclitaxel of 0.01 ng/L.

Comet Assay

The results for the comet assay are listed in Table 6. Neither the percent tail DNA nor the tail (Olive) moment differed significantly between the exposed and the nonexposed groups. Additional analyses considered different exposure variables used to assess association with the comet outcomes. These included number of drug-handling events, handling events for the five drugs that were measured, lifetime handling of antineoplastic drugs, job classification (pharmacy and nursing), and class of drugs (alkylating, antimetabolites, etc). No significant associations were observed.

TABLE 6. Values for Comet Assay

Measure	*N*	Percent Tail DNA*	Comet Tail (Olive) Moment†
Control, mean (SD)	52	53.12 (7.50)	2,518 (715)
Exposed, mean (SD)	66‡	53.06 (7.32)	2,540 (652)
P (unadjusted)		0.9639	0.8574
P (adjusted)		0.2628	0.3992

*Percent tail DNA is the fraction of DNA in the tail multiplied by 100.

†Comet tail (Olive) moment was calculated by multiplying average tail length in pixels (distance between the center of the head and center of tail) by the fraction of DNA in the tail.

‡Two participants did not provide blood samples for the comet assay.

DISCUSSION

Since the 1990s, even after the publication of safe-handling practices for antineoplastic drugs advanced by both occupational health agencies and professional practice organizations,[5,26–28] many studies have continued to document contamination of the health care environment with these drugs along with associated worker exposure. Specifically, during this period, numerous reports have documented surface contamination,[8] including contamination of the exterior of vials with the vial contents.[29–31] Although the majority of the early studies originated in Europe,[8,15–21] two studies in North America documented contamination of the work environment with these drugs.[13,14] More recent studies in the United States reported surface contamination or the measurement or both of drugs in the urine of health care workers during studies that evaluated the use of a CSTD.[32–35] Similar studies continue to be reported from many countries around the world.[36–41] Typically, a small number of drugs are used to evaluate workplace contamination by means of wipe sample analysis. Some studies have used a single drug with little background information documenting drug usage, work practices, PPE, etc, whereas others have measured several drugs and have attempted to document other parameters in the work environment related to possible contamination.[21] Still, others have examined intervention techniques and used wipe sampling to evaluate their effectiveness.[32–35,42–47] Every published surface contamination study has identified at least one drug present by wipe sample analysis.

This study used environmental wipe samples to evaluate the prevalence and intensity of surface contamination by five commonly used antineoplastic drugs. The drugs were selected based on the usage patterns of the three institutions. Wipe samples collected in the pharmacy and nursing/patient areas indicated that surface contamination was evident in most locations. In general, surface drug concentrations in the pharmacies were higher than those in the nursing areas, and the pharmacies in site 2 had both a higher percentage of wipe samples with multiple drugs present on the same wipe and relatively higher levels of the drugs measured from the wipes. Both pharmacies at site 2 and pharmacy B at site 1 were open to the adjoining room, which served as an office area. With the exception of these pharmacies, the other pharmacies conformed to a clean room design, incorporating proper airflow and quality, and anterooms between the preparation area and the adjacent areas with pass-through windows for the completed drug product to leave the preparation area.

One of the nursing areas at site 3 had the highest measured concentration of any drug (5-fluorouracil at 910 ng/cm^2) present on the lid of a hazardous waste container located at one of the nursing stations. This could have resulted from spilling droplets of the drug as waste was being placed in the container or touching the lid with contaminated gloves. Two other locations in this area had increased concentrations of 5-fluorouracil (3.65 and 4.11 ng/cm^2). The ifosfamide concentration was also high on the waste container (19.8 ng/cm^2). The finding of several high values suggests a breakdown in the safe handling of discarded drugs or contaminated equipment or a lack of sufficient cleaning.

There were no correlations between the number of handling events for the five drugs studied and the percentage of wipe samples that had measurable levels of each drug. These drugs compromised over 3,000 handling events (out of almost 10,000 total events as shown in Table 2). Table 7 displays the relative frequency of each of the five drugs sampled for in a rank order. The rank order of the handling event frequency is not reflected in the percent of wipe samples with values >LOD. This implies that the frequency of handling is not the only driver of surface contamination. For instance, paclitaxel had more than twice the number of handling events of any drug, but it was detected in only 16% of the samples.

TABLE 7. Relationship Between the Number of Drug Handling and Levels of Surface Contamination

Drug	No. Handling Events (All Sites)	Percent Samples >LOD
Paclitaxel	1,482	16
5-Fluorouracil	674	26
Cyclophosphamide	640	43
Cytarabine	297	3
Ifosfamide	189	24
Total	3,282	

This discordant finding does not seem to be the result of recovery efficiency, storage stability, or analytical issues[23] but may be the result of the protective sleeve used on most paclitaxel vials.[30,31] Nevertheless, the mean concentration of paclitaxel in wipe samples was significantly correlated with the total number of all drugs handled, the number of handling events for the five drugs combined, and for handling events of paclitaxel alone. Cyclophosphamide was detected most frequently by wipe sampling (43% of the samples >LOD), whereas 5-fluorouracil was the second most frequently measured drug (26%; Table 7). Conversely, ifosfamide had the lowest number of handling events at 189, but it was present in 24% of the wipe samples. This may be because ifosfamide, similar to cyclophosphamide, remains on surfaces for extended periods of time.[32,48] For site 2, mean wipe sample concentrations of ifosfamide, 5-fluorouracil, and cytarabine were significantly correlated with the number of handling events for each drug.

This study confirmed findings from other published studies that contamination is generally widespread.[8,11–16,18,19,32–37,41–43,48–54] In this study, it was more common and in higher concentrations in pharmacy areas than in nursing areas. Even with the use of BSCs and, in most cases, clean room design, workplace contamination was widespread. In an earlier study,[14] in which three drugs were measured in six hospitals, 75% of the pharmacy samples and 65% of the nursing samples demonstrated contamination with at least one drug. In this study, almost 10 years later, for five drugs measured at three hospitals, 75% of the pharmacy samples and 43% of the nursing samples demonstrated the presence of at least one drug. The apparent improvement in the nursing areas could result from one (site 2) of the three sites in this study being an inpatient area where there was a very low number of drugs handled when compared with the outpatient areas (Table 2).

The reported results of drug sampling in air have proven generally as poor exposure assessment tools, although some studies have documented airborne contamination with antineoplastic drugs.[8] Typically, very large air volumes have been collected to measure concentrations of the drugs, indicating very low airborne drug concentrations due, in part, to their low vapor pressures.[55,56] Our results corroborate these findings and suggest that air sampling does not play a significant role in exposure assessment for these drugs.

The measurement of antineoplastic drugs in the urine of health care workers has been used as an integrating dosimeter of workplace exposure across all exposure routes. Workers may be exposed through dermal contact with contaminated surfaces, by inhaling particulates or vapors, and by hand-to-mouth contact. Occasionally, accidental injection by needle sticks or other sharps may be an additional route of exposure.[5,21] Most studies that have examined the urine of health care workers for the presence of antineoplastic drugs have reported at least one drug in the urine. Some studies have reported as high as 40% to 100% of the workers tested to have one or more drugs in their urine, whereas others have reported a low percentage of workers with drugs in their urine or have not detected any drugs present.[8,20,47] Importantly, several studies have reported the presence of specific drugs in the urine of health care workers when they were not actively handling these drugs.[20,33,57,58]

In this study, only 3 of 68 exposed workers had measurable concentrations of cyclophosphamide or paclitaxel in their urine. The most commonly detected drug, cyclophosphamide, was found in the urine of two pharmacists who worked in a pharmacy area that was open to an office area. The concentration of cyclophosphamide in wipe samples in this area was high with a maximum of 143 (mean, 34.5; SD, 47.7) ng/cm^2. Based on the small number of urine specimens (2 of 67) that contained measurable levels of cyclophosphamide, it is not possible to statistically assess the contribution of surface contamination to cyclophosphamide in the urine of exposed workers. Favier et al[59] reported no correlation between the amount of cyclophosphamide handled and urinary excretion of cyclophosphamide.

Approximately 13% of unchanged cyclophosphamide is excreted in the urine, but the range has been reported to vary from 3% to 36% based on individual differences in metabolism.[37] The plasma half-life has been reported to be ~5 hours in patients.[60] The two urine samples that contained cyclophosphamide were collected during the last 4 hours of the work shift and are in line with the reported half-life. The high level of environmental contamination of the two participants' work environment is consistent with these biomonitoring findings.

Urinary excretion of unchanged paclitaxel is ~9% after IV administration,[61,62] and only one of the urine specimens from the exposed workers had a concentration of unchanged drug that reached the LOD. The specimen that contained paclitaxel was collected during the 4-hour postshift period. No measurable concentration of paclitaxel was found in the area where this individual worked.

Although it would seem that the uptake of cyclophosphamide by the pharmacists at site 2 was correlated with the very high levels of surface contamination in that area, no other significant uptake of either of the two drugs measured in the urine was seen. Nevertheless, there were some relatively high levels of surface contamination with these drugs in other areas. This may be the result of lack of sufficient sensitivity in the assay to detect lower concentrations of the drugs in the urine, proper use of PPE and containment equipment, good work practices and technique, or a combination of these factors. In addition, collection times and individual differences in drug metabolism could affect these urinary measures.

Several types of biomarkers of exposure or effects or both have been used to evaluate health care worker exposure to these drugs. Because most of these drugs are mutagenic or clastogenic or both, endpoints that measure genetic damage are often used to assess worker exposure. Urine mutagenicity, chromosomal aberrations, sister chromatid exchange, micronuclei induction, DNA damage (comet assay and others), hypoxanthine-guanine phosphoribosyltransferase mutations, thioether excretion, and other assays have all been used in various studies of workers to assess exposure.[63]

This study used the comet assay that detects single-strand DNA breaks and has been used in several studies evaluating antineoplastic drug exposures. Eight of nine studies using the comet assay as a biomarker of exposure have reported a significant difference usually between workers exposed to antineoplastic drugs and nonexposed control groups, but typically when work environments did not include the safe-handling practices used at the three study sites.[64–72] In this study, there were no overall significant differences between the two endpoints that were determined for the comet assay, and no correlations were seen with any of the potential exposure variables that were examined. Based on the urinary measurement of the two more commonly used drugs, it seems that uptake was minimal and, thus, not sufficient to be detected by the

comet assay. Some wipe sample values for 5-fluorouracil were also very high, but this drug was not included in the drugs analyzed in the urine.

Although the majority of observations in this study focused on routine drug handling, each participant's spill experience was also included in the 6-week handling diary. Site 3 that reported 2974 drug preparations did not report an observable spill, whereas sites 1 and 2 combined had 23 spills for 845 drug preparations. Site 3 was the only site where a CSTD was used for drug preparation. This outcome is in agreement with published reports that CSTDs can reduce the level of contamination in the workplace.[32–35,42–47]

The use of a diary to record drug-handling tasks has been used in previous studies as an exposure measure and has some advantages and disadvantages when compared with tallying the number of drug preparations or total grams of drug per location.[73] A single drug preparation may be handled by more than one individual as it moves from the pharmacy to the nursing area, then to the patient and/or one individual may handle it more than one time. The use of a diary documents each handling event by each individual, thus producing a more accurate metric for individual exposure estimation. Nevertheless, if all the individuals in a work area did not take part in this study, the total number of drug events for that area could be underestimated. Therefore, this approach is an accurate measure for individual exposure, but it may underestimate total area contamination.

In summary, based on the five drugs used to evaluate surface contamination, all three sites had measurable levels of surface contamination demonstrating persistent contamination and worker exposure opportunity. Although airborne contamination for these drugs was not detected under the current conditions, it is likely that airborne sampling is not a sensitive measure or appropriate method to characterize exposure because of generally low vapor pressure for these drugs. We presumed skin absorption to be an important primary exposure route for these drugs. High levels of surface contamination, possibly in combination with pharmacy design, most likely contributed to measurable concentration of one of the drugs in the urine of two pharmacists. Nevertheless, these environmental conditions were not sufficient to elicit DNA damage as measured by the comet assay.

Despite following recommended safe-handling practices and, in most cases, the use of proper engineering controls, workplace contamination with antineoplastic drugs in pharmacy and nursing areas continues at all three locations. Vigilant use of safe work practices and adherence to a comprehensive approach to safe handling of these drugs are necessary to prevent contamination of the workplace with these drugs and subsequent worker exposure to them.

ACKNOWLEDGMENT

We thank Mark Toraason, Susan Reutman, Ivan Spasojevic, Jeff McLaurin, Patty Mathias, Shirley Robertson, Debbie Sammons, Paula Patterson, Susan Spivey, Katie Slavin, Evelyn Galvin, and Sheila Williams.

REFERENCES

1. Erlichman C, Moore MJ. Carcinogenesis: a late complication of cancer chemotherapy. In: Chabner BA, Longo DL, eds. *Cancer Chemotherapy and Biotherapy: Principles and Practice.* 2nd ed. Philadelphia, PA: Lippincott–Raven; 1996:45–58.
2. Connor TH, McDiarmid MA. Preventing occupational exposures to antineoplastic drugs in health care settings. *CA Cancer J Clin*. 2006;56:354–365.
3. IARC. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Lyons, France: World Health Organization, International Agency for Research on Cancer; 2009.
4. McInnes S, Schilsky RL. Infertility following cancer chemotherapy. In: Chabner BA, Longo DL, eds. *Cancer Chemotherapy and Biotherapy: Principles and Practice*. 2nd ed. Philadelphia, PA: Lippincott–Raven; 1996:31–44.
5. NIOSH. *NIOSH Alert: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Healthcare Settings*. DHHS (NIOSH) Publication No. 2004–165. Cincinnati, OH: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health; 2004.
6. Edwards BK, Howe HL, Ries LA, et al. Annual report to the nation on the status of cancer, 1973–1999, featuring implications of age and aging on U.S. cancer burden. *Cancer*. 2002;94:2766–2792.
7. US Bureau of Labor Statistics. *May 2006 National and Occupational Employment and Wage Estimates*. Washington, DC: United States Department of Labor, Bureau of Labor Statistics; 2007. Available at: http://146.142.422/oeshome.htm#overview. Accessed December 14, 2007.
8. Turci R, Sottani C, Spagnoli G, Minoia C. Biological and environmental monitoring of hospital personnel exposed to antineoplastic agents: a review of analytical methods. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2003;789:169–209.
9. Baker ES, Connor TH. Monitoring occupational exposure to cancer chemotherapy drugs. *Am J Health Syst Pharm*. 1996;53:2713–2723.
10. Sorsa M, Anderson D. Monitoring of occupational exposure to cytostatic anticancer agents. *Mutat Res*. 1996;355:253–261.
11. Sessink PJ, Bos RP. Drugs hazardous to healthcare workers. Evaluation of methods for monitoring occupational exposure to cytotoxic drugs. *Drug Safety.* 1999;20:347–359.
12. Hedmer M, Jönsson BA, Nygren O. Development and validation of methods for environmental monitoring of cyclophosphamide in workplaces. *J Environ Monit*. 2004;6:979–984.
13. McDevitt JJ, Lees PS, McDiarmid MA. Exposure of hospital pharmacists and nurses to antineoplastic agents. *J Occup Med*. 1993;35:57–60.
14. Connor TH, Anderson RW, Sessink PJ, Broadfield L, Power LA. Surface contamination with antineoplastic agents in six cancer treatment centers in Canada and the United States. *Am J Health Syst Pharm*. 1999;56:1427–1432.
15. Sessink PJ, Anzion RB, Van den Broek PH, Bos RP. Detection of contamination with antineoplastic agents in a hospital pharmacy department. *Pharm Weekbl Sci*. 1992;14:16–22.
16. Sessink PJ, Boer KA, Scheefhals AP, Anzion RB, Bos RP. Occupational exposure to antineoplastic agents at several departments in a hospital. Environmental contamination and excretion of cyclophosphamide and ifosfamide in urine of exposed workers. *Int Arch Occup Environ Health*. 1992;64:105–112.
17. Sessink PJ, Friemèl NS, Anzion RB, Bos RP. Biological and environmental monitoring of occupational exposure of pharmaceutical plant workers to methotrexate. *Int Arch Occup Environ Health*. 1994;65:401–403.
18. Sessink PJ, Wittenhorst BC, Anzion RB, Bos RP. Exposure of pharmacy technicians to antineoplastic agents: reevaluation after additional protective measures. *Arch Environ Health*. 1997;52:240–244.
19. Schmaus G, Schierl R, Funck S. Monitoring surface contamination by antineoplastic drugs using gas chromatography—mass spectrometry and voltammetry. *Am J Health Syst Pharm*. 2002;59:956–961.
20. Pethran A, Schierl R, Hauff K, Grimm CH, Boos KS, Nowak D. Uptake of antineoplastic agents in pharmacy and hospital personnel. Part I: monitoring of urinary concentrations. *Int Arch Occup Environ Health*. 2003;76:5–10.
21. Schreiber C, Radon K, Pethran A, et al. Uptake of antineoplastic agents in pharmacy personnel. Part II: study of work-related risk factors. *Int Arch Occup Environ Health*. 2003;76:11–16.
22. Larson RR, Khazaeli MB, Dillon HK. Monitoring method for surface contamination caused by selected antineoplastic agents. *Am J Health Syst Pharm*. 2002;59:270–277.
23. Pretty JR, Connor TH, Spasojevic I, et al. Sampling and mass spectrometric analytical methods for six antineoplastic drugs in the healthcare environment. *J Onc Pharm Pract*. In press.
24. Larson RR, Khazaeli MB, Dillon HK. A new monitoring method using solid sorbent media for evaluation of airborne cyclophosphamide and other antineoplastic agents. *Appl Occup Environ Hyg*. 2003;18:120–131.
25. Toraason M, Lynch DW, DeBord DG, et al. DNA damage in leukocytes of workers occupationally exposed to 1-bromopropane. *Mutat Res*. 2006;603:1–14.
26. OSHA. OSHA technical manual, TED 1–0.15A, Sec VI, Chapt II: Categorization of drugs as hazardous. Available at: www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html#2. Accessed February 4, 2010.
27. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm.* 2006;63:1172–1193.
28. Polovich M, Whitford JM, Olsen M, eds. *Chemotherapy and Biotherapy*

Guidelines and Recommendations for Practice. 3rd ed. Pittsburgh, PA: Oncology Nursing Society; 2009.

29. Connor TH. Hazardous anticancer drugs in health care: environmental exposure assessment. *Ann N Y Acad Sci*. 2006;1076:615–623.
30. Connor TH, Sessink PJ, Harrison BR, et al. Surface contamination of chemotherapy drug vials and evaluation of new vial-cleaning techniques: results of three studies. *Am J Health Syst Pharm*. 2005;62:475–484.
31. Schierl R, Herwig A, Pfaller A, Groebmair S, Fischer E. Surface contamination of antineoplastic drug vials: comparison of unprotected and protected vials. *Am J Health Syst Pharm*. 2010;67:428–429.
32. Connor TH, Anderson RW, Sessink PJ, Spivey SM. Effectiveness of a closed-system device in containing surface contamination with cyclophosphamide and ifosfamide in an i.v. admixture area. *Am J Health Syst Pharm*. 2002;59:68–72.
33. Wick C, Slawson MH, Jorgenson JA, Tyler LS. Using a closed-system protective device to reduce personnel exposure to antineoplastic agents. *Am J Health Syst Pharm*. 2003;60:2314–2320.
34. Harrison BR, Peters BG, Bing MR. Comparison of surface contamination with cyclophosphamide and fluorouracil using a closed-system drug transfer device versus standard preparation techniques. *Am J Health Syst Pharm*. 2006;63:1736–1744.
35. Nyman H, Jorgenson J, Slawson MH. Workplace contamination with antineoplastic agents in a new cancer hospital using a closed-system drug transfer device. *Hosp Pharm*. 2007;42:219–225.
36. Bussières JF, Théorêt Y, Prot-Labarthe S, Larocque D. Program to monitor surface contamination by methotrexate in a hematology—oncology satellite pharmacy. *Am J Health Syst Pharm*. 2007;64:531–535.
37. Hedmer M, Tinnerberg H, Axmon A, Jönsson BA. Environmental and biological monitoring of antineoplastic drugs in four workplaces in a Swedish hospital. *Int Arch Occup Environ Health*. 2008;81:899–911.
38. Ikeda K, Yagi Y, Tkegami M, Lu Y, Morimoto K, Kurokawa N. Efforts to ensure safety of hospital pharmacy personnel occupationally exposed to antineoplastic drugs during a preparation task. *Hosp Pharm*. 2007;42:209–218.
39. Kromhout H, Hoek F, Uitterhoeve R, et al. Postulating a dermal pathway for exposure to anti-neoplastic drugs among hospital workers. Applying a conceptual model to the results of three workplace surveys. *Ann Occup Hyg*. 2000;44:551–560.
40. Hedmer M, Georgiadi A, Bremberg ER, Jönsson BA, Eksborg S. Surface contamination of cyclophosphamide packaging and surface contamination with antineoplastic drugs in a hospital pharmacy in Sweden. *Ann Occup Hyg*. 2005;49:629–637.
41. Siderov J, Kirsa S, McLauchlan R. Surface contamination of cytotoxic chemotherapy preparation areas in Australian hospital pharmacy departments. *J Pharm Pract Res*. 2009;39:117–121.
42. Nygren O, Gustavsson B, Strom L, Eriksson R, Jarneborn L, Friberg A. Exposure to anti-cancer drugs during preparation and administration. Investigations of an open and a closed system. *J Environ Monit*. 2002;4:739–742.
43. Nygren O, Gustavsson B, Eriksson R. A test method for assessment of spill and leakage from drug preparation systems. *Ann Occup Hyg*. 2005;49:711–718.
44. Sessink PJ, Rolf M-AE, Ryden NS. Evaluation of the PhaSeal hazardous drug containment system. *Hosp Pharm*. 1999;34:1311–1317.
45. Tans B, Willems L. Comparative contamination study with cyclophosphamide, fluorouracil and ifosfamide: standard versus a proprietary closed-handling system. *J Oncol Pharm Pract*. 2004;10:217–223.
46. Vandenbroucke J, Robays H. How to protect environment and employees against cytotoxic agents: the UZ Ghent experience. *J Oncol Pharm Pract*. 2001;6:146–152.
47. Yoshida J, Tei G, Mochizuki C, Masu Y, Koda S, Kumagai S. Use of a closed system device to reduce occupational contamination and exposure to antineoplastic drugs in the hospital work environment. *Ann Occup Hyg*. 2009;53:153–160.
48. Schierl R, Böhlandt A, Nowak D. Guidance values for surface monitoring of antineoplastic drugs in German pharmacies. *Ann Occup Hyg.* 2009;53:703–711.
49. Fransman W, Vermeulen R, Kromhout H. Occupational dermal exposure to cyclophosphamide in Dutch hospitals: a pilot study. *Ann Occup Hyg*. 2004;48:237–244.
50. Fransman W, Vermeulen R, Kromhout H. Dermal exposure to cyclophosphamide in hospitals during preparation, nursing and cleaning activities. *Int Arch Occup Environ Health*. 2005;78:403–412.
51. Touzin K, Bussières JF, Langlois É, Lefebvre M. Evaluation of surface contamination in a hospital hematology—oncology pharmacy. *J Oncol Pharm Pract*. 2009;15:53–61.
52. Mason HJ, Blair S, Sams C, et al. Exposure to antineoplastic drugs in two UK hospital pharmacy units. *Ann Occup Hyg*. 2005;49:603–610.
53. Spivey S, Connor TH. Determining sources of workplace contamination with antineoplastic drugs and comparing conventional IV drug preparation with a closed system. *Hosp Pharm*. 2003;38:135–139.
54. Crauste-Manciet S, Sessink PJ, Ferrari S, Jomier JY, Brossard D. Environmental contamination with cytotoxic drugs in healthcare using positive air pressure isolators. *Ann Occup Hyg*. 2005;49:619–628.
55. Connor TH, Shults M, Fraser MP. Determination of the vaporization of solutions of mutagenic antineoplastic agents at 23 and 37 degrees C using a desiccator technique. *Mutat Res.* 2000;470:85–92.
56. Kiffmeyer TK, Kube C, Opiolka S, Schmidt KG, Schoppe G, Sessink PJ. Vapor pressures, evaporation behavior and airborne concentrations of hazardous drugs: implications for occupational safety. *Pharmaceut J*. 2002;268:331–337.
57. Sessink PJ, Van der Kerkhof MC, Anzion RB, Noordhoek J, Bos RP. Environmental contamination and assessment of exposure to antineoplastic agents by determination of cyclophosphamide in urine of exposed pharmacy technicians: is skin absorption an important exposure route? *Arch Environ Health*. 1994;49:165–169.
58. Mader RM, Rizovski B, Steger GG, Wachter A, Kotz R, Rainer H. Exposure of oncologic nurses to methotrexate in the treatment of osteosarcoma. *Arch Environ Health*. 1996;51:310–314.
59. Favier B, Gilles L, Gesage M, Latour JF. Analysis of cyclophosphamide in the urine of antineoplastic drug handlers. *Bull Cancer*. 2003;90:905–909.
60. Busse D, Busch FW, Bohnenstengel F, et al. Dose escalation of cyclophosphamide in patients with breast cancer: consequences for pharmacokinetics and metabolism. *J Clin Oncol*. 1997;15:1885–1896.
61. Malingré MM, Schellens JH, van Tellingen O, et al. Metabolism and excretion of paclitaxel after oral administration in combination with cyclosporine A and after i.v. administration. *Anticancer Drugs*. 2000;11:813–820.
62. Hempel G, Rübe C, Mosler C, et al. Population pharmacokinetics of low-dose paclitaxel in patients with brain tumors. *Anticancer Drugs*. 2003;14:417–422.
63. NIOSH. *NIOSH Safety and Health Topic: Occupational Exposure to Antineoplastic Agents*. Cincinnati, OH: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. Available at: http://www.cdc.gov/niosh/topics/antineoplastic/. Accessed January 28, 2010.
64. Undeğer U, Başaran N, Kars A, Güç D. Assessment of DNA damage in nurses handling antineoplastic drugs by the alkaline COMET assay. *Mutat Res.* 1999;439:277–285.
65. Maluf SW, Erdtmann B. Follow-up study of the genetic damage in lymphocytes of pharmacists and nurses handling antineoplastic drugs evaluated by cytokinesis-block micronuclei analysis and single cell gel electrophoresis assay. *Mutat Res*. 2000;471:21–27.
66. Kopjar N, Garaj-Vrhovac V. Application of the alkaline comet assay in human biomonitoring for genotoxicity: a study on Croatian medical personnel handling antineoplastic drugs. *Mutagenesis*. 2001;16:71–78.
67. Laffon B, Teixeira JP, Silva S, et al. Genotoxic effects in a population of nurses handling antineoplastic drugs, and relationship with genetic polymorphisms in DNA repair enzymes. *Am J Ind Med*. 2005;48:128–136.
68. Ursini CL, Cavallo D, Colombi A, Giglio M, Marinaccio A, Iavicoli S. Evaluation of early DNA damage in healthcare workers handling antineoplastic drugs. *Int Arch Occup Environ Health*. 2006;80:134–140.
69. Yoshida J, Kosaka H, Tomioka K, Kumagai S. Genotoxic risks to nurses from contamination of the work environment with antineoplastic drugs in Japan. *J Occup Health*. 2006;48:517–522.
70. Sasaki M, Dakeishi M, Hoshi S, Ishii N, Murata K. Assessment of DNA damage in Japanese nurses handling antineoplastic drugs by the comet assay. *J Occup Health*. 2008;50:7–12.
71. Rekhadevi PV, Sailaja N, Chandrasekhar M, Mahboob M, Rahman MF, Grover P. Genotoxicity assessment in oncology nurses handling anti-neoplastic drugs. *Mutagenesis*. 2007;22:395–401.
72. Rombaldi F, Cassini C, Salvador M, Saffi J, Erdtmann B. Occupational risk assessment of genotoxicity and oxidative stress in workers handling antineoplastic drugs during a work week. *Mutagenesis*. 2009;24:143–148.
73. Cloak MM, Connor TH, Stevens KR, et al. Occupational exposure of nursing personnel to antineoplastic agents. *Oncol Nurs Forum.* 1985;12:33–39.

