Ann. Occup. Hyg., Vol. 52, No. 8, pp. 765–771, 2008

doi:10.1093/annhyg/men050

Cyclophosphamide Contamination Observed on the External Surfaces of Drug Vials and the Efficacy of Cleaning on Vial Contamination

KARINE TOUZIN[1]*, JEAN-FRANÇOIS BUSSIÈRES[1], ÉRIC LANGLOIS[2], MICHEL LEFEBVRE[2] and CLAUDE GALLANT[3]

[1]Pharmaceutical Practice Research Unit, Department of Pharmacy, CHU Sainte-Justine, 3175, chemin de la Côte Sainte-Catherine, Montreal, Quebec H3T 1C5, Canada; [2]Clinical Laboratory Unit, Department of Human Toxicology, Institut National de Santé Publique du Québec, Quebec City, Canada; [3]Association pour la Santé et la Sécurité au Travail, Secteur Affaires Sociales, Montreal, Quebec, Canada

Received 15 April 2008; in final form 19 June 2008; published online 28 July 2008

Objective: Evaluate contamination on the external surfaces of cyclophosphamide vials available on the Canadian market during storage in pharmacy departments and the efficacy of decontaminating the external surfaces of vials using various cleaning techniques.

Methods: The study consisted of three phases: the quantification of cyclophosphamide on the external surfaces of 10 vials of Procytox and 10 vials of Cytoxan available on the Canadian market with or without prewashing (Phases I and II) and the quantification of cyclophosphamide on the surfaces of 30 deliberately contaminated empty sterile vials cleaned using three different washing techniques (Phase III). The quantification of cyclophosphamide was conducted using ultra performance liquid chromatography with tandem mass spectrometry.

Results: In Phase I, we observed that 9 of 10 vials of Procytox and 4 of 10 vials of Cytoxan had traces of cyclophosphamide. The average concentration of cyclophosphamide measured on the vials was higher for Procytox than it was for Cytoxan . In Phase II, we observed that simply by washing vials with water we could effectively eliminate the presence of contamination on 6 of 10 Procytox vials and on 10 of 10 Cytoxan vials. Phase III demonstrated the efficacy of using a cloth soaked in soapy water to clean the contaminated vials.

Conclusion: This pilot study demonstrates the presence of contamination on the external surfaces of cyclophosphamide vials from two manufacturers on the Canadian market. It suggests that cleaning vials from manufacturers and wholesalers may help to reduce the risk of occupational exposure. There is a need for a pilot study to establish guidelines on decontamination agents and cleaning process to eliminate the presence of contamination on vial surfaces.

Keywords: cyclophosphamide; decontamination; external contamination; quantification; sampling; vial

INTRODUCTION

While hazardous drugs are widely used in healthcare facilities, this use has significant consequences, as most agents have a carcinogenic, teratogenic or mutagenic potential and may be toxic to various organs or reproduction. Over the past two decades, a number of studies have documented the presence of hazardous drugs in the urine of pharmacy personnel and healthcare workers engaged in direct patient care, particularly in the hematology–oncology sector (Ensslin et al., 1994; Sessink et al., 1994; Minoia et al., 1998; Pethran et al., 2003; Turci et al., 2003). Several studies have revealed the presence of contaminated hazardous drugs on work surfaces used for preparing and storing these products (Vandenbrouke and Robays, 2001; Schmaus et al., 2002; Hedmer et al., 2004; Acampora et al., 2005; Connor et al., 2005; Crauste-Manciet et al., 2005). The publication of these findings prompted regulatory bodies, health agencies and occupational health and safety boards as well as professional associations to draft guidelines, policies and procedures to control

*Author to whom correspondence should be addressed.
Tel: þ1-514-345-4931; fax: þ1-514-345-4820;
e-mail: karine.touzin.hsj@ssss.gouv.qc.ca

the use of hazardous drugs and reduce the risk of occupational exposure (ASHP, 1990; USP, 2003; NIOSH, 2004; ASHP, 2006). In Quebec, in 2008, the Association for Health and Safety in the Workplace, Social Affairs Sector [Association paritaire pour la santé et la sécurité du travail du secteur des affaires sociales (ASSTSAS)] published practical guidelines on the handling of hazardous drugs intended for healthcare professionals (Gallant et al., 2008).

The presence of varying concentrations of hazardous drugs has led healthcare professionals to speculate about the potential sources of contamination. Contamination may occur during various stages of the drug circuit, from purchasing and receiving products to storing, preparing and verifying container content and administering and disposing of waste. Whereas many studies have documented the presence of contamination during the preparation and administration stages of the hazardous drug circuit, there have been fewer data on contamination that occurs prior to drug preparation in hospital pharmacies. It must also be pointed out that contamination present in vials at the time of unpacking is as significant as that present in the rest of the subsequent process, including that found on pharmacy work surfaces. The goal of this study was to evaluate contamination on the external surfaces of vials of cyclophosphamide available on the Canadian market during pharmacy department storage and the efficacy of decontamination.

METHODS

This pilot study involved three phases conducted in collaboration with the Institut national de santé publique du Québec located in Quebec City (Quebec, Canada) and the Pharmaceutical Practice Research Unit [Unité de recherche en pratique pharmaceutique] of the Sainte-Justine University Hospital Center [Centre hospitalier universitaire Sainte-Justine (CHUSJ)] and the Association for Health and Safety in the Workplace, Social Affairs Sector (ASSTSAS) both located in Montreal (Quebec, Canada). As a result of a province-wide environmental monitoring program that was set up in Quebec in 2008, which made it possible to quantify cyclophosphamide, ifosfamide and methotrexate using work surface sampling, we focused on cyclophosphamide to conduct our assessment of the external surface contamination and decontamination of hazardous drug vials.

Healthcare facility

The CHUSJ is a 500-bed mother–child tertiary healthcare facility. In 2006–2007, the hematology–oncology program had 30 beds and 20 stretchers in the day center with an annual volume exceeding 800 admissions, 7800 patient days, 13 300 day care visits and . 17 400 outpatient visits. Based on an active inventory of at least 100 hazardous drugs, the pharmacy department made nearly 35 000 sterile preparations and almost 12 000 non-sterile preparations for inpatients and outpatients during the 2006–2007 financial year. Of all the sterile preparations made during this period, 2000 mg vials of cyclophosphamide represented a total of 454 000 mg, all of which were prepared in a satellite pharmacy dedicated to hematology–oncology activities.

Products studied

Two Canadian manufacturers have obtained a notice of compliance for the parenteral administration of cyclophosphamide (Cytoxan and Procytox). Product information is available at http://205.193.93.51/dpdonline/searchRequest.do (accessed 2 July 2008). The two forms are only available as a powder for injection requiring redilution in a Class II Type B2 cabinet. Based on the products available on the Canadian market, we purchased twenty 2000 mg vials of Cytoxan powder for injection from a wholesaler, DIN 00602949 (# KF007, EXP January 2009), from Bristol Myers Squibb and twenty 2000 mg vials of Procytox in powder for injection, DIN 02241800 (# 6J509 EXP October 2009), from Baxter Corporation. The vials purchased came from batches that were available at the time of the study based on the wholesaler's selection of his active inventory and came through a wholesaler using a strict packaging procedure for hazardous drugs. The drug vials were packaged with the intention of avoiding breakage and placed together in a plastic bag marked with a cytotoxic label. Everything was also wrapped in separate cardboard packaging when the purchases included non-hazardous drugs. On receipt, our pharmacy department personnel ascertained that no breakage had taken place and there were no noticeable traces of contamination in the form of powder.

Phase I: external surfaces of the commercial vials

In Phase I, surface samples from each of the 10 vials of Procytox and 10 vials of Cytoxan were taken using a method adapted from Larson et al. (2002). The technique consisted of sampling the external surfaces of each vial by wiping all the glass surfaces and external plastic cap covers with a 6 8 cm Wypall X60 tissue (Kimberly Clark Professional, Newton Square, PA, USA) moistened with a 1 ml 10% MeOH and 90% 5 mM ammonium acetate solution. Sampling each of the vials lasted 20 s to optimize the quantity of cyclophosphamide collected. The duration of sampling was arbitrary but based on other techniques used for surface sampling. All the samples were taken by the same

analyst over the whole course of the study. The experiment was carried out in the basement floor of the building expressly to avoid contamination of the main laboratory and to avoid exposure of the laboratory personnel. A surface of 1 3 m (a conventional freezer) was covered with disposable diapers, and the experiment was carried out over this surface. The experimenters wore nitrile gloves throughout, and the gloves were changed between each single sample.

To measure the quantity of cyclophosphamide collected, the wipe was put in a 50 ml polypropylene tube along with an additional 10 ml of the sampling solution. It was then stirred mechanically for 10 min. The cyclophosphamide present in the supernatant was then measured using a ultra performance liquid chromatographic separation technique (UPLC-MS/MS) on a Quattro Premier XE equipped with an Acquity UPLC system (Waters, Milford, MA) versus a calibration curve prepared in a matrix similar to that of the actual specimens. The chromatography was done on a 2.1 50 mm 1.7 1m C_{18} column (Waters Acquity UPLC BEH, Milford, MA) using a gradient from 10/90 5 mM methanol/ammonium acetate to 60/40 5 mM methanol/ammonium acetate in 2 min. The findings were expressed in ng ml ^{1} of cyclophosphamide in the supernatant as well as in ng per vial (since V_t 5 11 ml). The quantification threshold for the cyclophosphamide was 2 ng per vial.

Phase II: cleaning the commercial vials

In Phase II, 10 vials from the same batch of Procytox and 10 vials from the same batch of Cytoxan were cleaned. To achieve this, the entire surface of each vial was rinsed in 10 ml of deionized water and then wiped with a paper towel. After washing the vials, samples of the external surfaces of each of the cleaned vials of each product were collected and quantified according to the technique previously described in Phase I.

Phase III: cleaning vials intentionally contaminated with cyclophosphamide

Intentional contamination of vials with cyclophosphamide. During Phase III of the project, 30 empty sterile vials (50 ml vials—Laboratoire Omega—Product # F-50-20R) were intentionally contaminated with a solution of cyclophosphamide at the theoretical rate of 20 ng per vial. A plastic tray 35 45 cm was covered with a cloth (disposable diapers) and the bottles were deposited upon this cloth. Each bottle was immersed in the cyclophosphamide solution for a few seconds, redeposited upon the tray and allowed to dry. Once all the bottles had been immersed and dried, the washing experiments were allowed to begin. The vials were immerged in an aqueous solution of cyclophosphamide at a concentration of 200 ng/ml.

Validation of the intentional contamination. A validation step was performed to confirm the reproducibility of the immersion technique used. In order to validate the theoretical rate of 20 ng per vial, we measured the quantity of cyclophosphamide collected on three control vials directly after doing intentional contamination of them with cyclophosphamide (without any cleaning procedure).

Cleaning vials intentionally contaminated. Three different cleaning techniques were studied using nine vials and one additional vial was used as a control sample. Technique #1 consisted of wiping each contaminated vial with tissue similar to a J-cloth soaked in soapy water (Palmolive dishwashing liquid, Colgate-Palmolive Company, Toronto, Ontario, Canada). Technique #2 consisted of wiping each vial with the same sort of tissue soaked in soapy water (Palmolive dishwashing liquid, Colgate-Palmolive Company) and then wiping each vial with a dry tissue. In both techniques, the tissue used for cleaning was discarded after every four vials during the washing process. Finally, Technique #3 consisted of wiping each contaminated vial using a Wet Ones-style disposable wipe that was discarded after each vial.

Descriptive statistical analyses (mean, standard deviation, median, interval, etc.) were performed on the collected data (Microsoft Excel 2003, Seattle, WA, USA).

RESULTS

A total of 40 samples were collected during the first two phases of the pilot study. Table 1 presents the number of vials that revealed the presence of contamination on the external surfaces of cyclophosphamide during the first two phases of the study. During Phase I, we observed that nine of the vials of Procytox (n 5 10) and four of the vials of Cytoxan (n 5 10) contained traces of cyclophosphamide. The average concentration of cyclophosphamide measured was higher on the Procytox vials when compared with that obtained after the analysis of the Cytoxan vials. During Phase II, we observed that by simply washing vials with water we could eliminate any traces of cyclophosphamide on 6 of 10 Procytox vials as well as the presence of detectable contamination on the surfaces of 10 of 10 Cytoxan vials that we tested.

Phase III of the study highlights the efficiency level according to the three different cleaning techniques used on intentionally contaminated vials by immersion procedure. These findings reveal the absence of surface contamination on the vials cleaned using cleaning Techniques #1 and #3. However, we noted that three vials cleaned using Technique #2 showed traces of cyclophosphamide. In fact, cyclophosphamide concentrations of 0.9–1.3 ng per vial were

Table 1. Quantitative results of the external contamination of cyclophosphamide in Phase I (without cleaning) and Phase II (after cleaning)

	Procytox (n = 10)	Cytoxan (n = 10)
Phase I		
Number of vials with detectable level of cyclophosphamide on external surface	9	4
Concentration (ng per vial)		
Mean – standard deviation [minimum–maximum]	25 – 24 [ND–74]	5 – 9 [ND–29]
Phase II		
Number of vials with detectable level of cyclophosphamide on external surface	4	0
Concentration (ng per vial)		
Mean – standard deviation [minimum–maximum]	21 – 45 [ND–145]	ND

ND, not detected.

measured on the surfaces of the three vials. Concentrations of cyclophosphamide detected on the three cyclophosphamide control vials were, respectively, 19.14, 14.63 and 59.6 ng per vial.

DISCUSSION

Several sources of contamination exist in the hazardous drug circuit in healthcare facilities. One of them is contamination on the external surfaces of vials that come directly from manufacturers that supply hospital centers with hazardous drugs. As a matter of fact, numerous studies have demonstrated the presence of contamination on the external surfaces of hazardous drug vials (Sessink et al., 1992; Ros et al., 1997; Hepp and Gentshew, 1998; Paul et al., 1998; Delporte et al., 1999; Nygren et al., 2002; Favier et al., 2003; Mason et al., 2003; Funck and Shierl, 2004; Connor et al., 2005; Hedmer et al., 2005; Iglesias, 2006). The findings of these studies were obtained through various sampling techniques. Of the 12 studies compiled, nine used a sampling technique involving the wiping of vials that was similar to the one used in this study, whereas three used an immersion sampling technique instead. Various quantification methods were used and the hazardous drugs included in these studies were ifosfamide, fluorouracil, methotrexate, cisplatin, carboplatin and cyclophosphamide. Generally speaking, higher concentrations of hazardous drugs were detected (ng per vial) when the sampling was conducted using the wiping technique. With respect to cyclophosphamide, Sessink et al. (1992) reported an initial measurement of 0.06 **1**g of external vial surface contamination. Cyclophosphamide levels varying from ND-39 ng per vial were measured by Mason et al. (2003) on a sample of 30 vials. Hedmer et al. (2005) observed levels varying from 0.2 to 5.1 ng per vial on a batch of 20 vials available on the Swedish market including 10 vials of 200 mg of cyclophosphamide and 10 vials of 1 g of cyclophosphamide, whereas Connor et al. (2005) detected contamination levels varying from 88 to 69 800 ng per vials on a batch of six vials of 2 g of cyclophosphamide and then levels varying from ND-480 ng per vial on a batch of 25 vials of 1 g of cyclophosphamide available on the US market.

The findings presented in these articles and those that emerged from studies carried out in various hospital centers in the US and Europe match those of our study. In fact, our study reveals that 13 of the 20 vials studied had levels of surface contamination that varied from 3.1 to 74 ng per vial of cyclophosphamide, which is comparable with the concentrations published in the documentation. Furthermore, many studies have documented contamination of work surfaces in pharmacy areas by cyclophosphamide (Minoia et al., 1998; Connor et al., 1999; Vandenbrouke and Robays, 2001; Schmaus et al., 2002; Acampora et al., 2005; Crauste-Manciet et al., 2005; Harrison et al., 2006; Hedmer et al., 2008). However, the level of contamination detected on the vials cannot be compared to the results obtained on work surfaces because different sampling, analytical and measurement techniques (ng per vial versus ng cm ^{2}) are used.

Why should surface contamination of vials be observed in different markets, including Canada? Good manufacturing practices are similar in most markets and there are relatively few manufacturing plants around the world for a given drug. Moreover, no regulatory requirements have been made regarding a maximal permissible level of contamination on the external surfaces of vials or the application of transparent protective films by the manufacturer at the tail end of the manufacturing process. Some manufacturers, however, do proceed with the addition of a protective film at the end of the process for some hazardous drugs available on the Canadian market (e.g. Gemcitabine from Sandoz, oncology products with an Onco-Tain film from Hospira).

Nevertheless, it is very difficult to gather information from suppliers regarding the nature of specific cleaning and decontamination procedures for hazardous drug vials. The presence of contamination on the external surfaces of vials needs to be taken into consideration in pharmaceutical practice and the importance of environmental monitoring combined with a cleaning procedure is highly desirable.

The ASSTSAS guide recommends to wholesalers that a cytotoxic or hazardous drug label, for example, be clearly marked on the outside of the drug transport container in order to indicate to receiving staff that the boxes require the use of personal protection equipment (such as wearing a gown and gloves) during handling (Gallant et al., 2008). Furthermore, the guide specifies the optimal layout of an unpacking/reception area as well as the precautions to be taken to avoid accidental exposure in case of breakage or in view of regular shipments. It also suggests the cleaning of vials when stock is received.

Although this measure may reduce contamination, cleaning may nevertheless lead in certain cases to an increase in the risk of breaking vials or damaging the manufacturer's labeling. The addition of another step to the receiving process that would involve washing vials in the hospital pharmacy may, however, be difficult to apply, given the layout and resources available.

Our study's findings reveal the presence of contamination on vials of cyclophosphamide available on the Canadian market for health facilities and the contamination detected may not come from cross-contamination at the hospital, considering the precautions taken during our study (e.g. selection of commercial vials without any breakage noted in packages and delivered directly from the wholesaler to the oncology pharmacy and the change of the gloves changes between each wiping to reduce cross-contamination).

Among the factors that could lead to the contamination of work surfaces, we noted the absence of specific guidelines aimed at decontaminating and cleaning work surfaces and vials contaminated by hazardous drugs. In point of fact, up to now there has been no consensus as to what cleaning solutions or detergents should be used in order to ensure that contaminated surfaces are effectively decontaminated and the exposure of workers in this field is reduced. This is also an issue when it comes to decontaminating contaminated waste produced by handling hazardous drugs prior to destruction. Actually, since 1978, when a program to develop chemical methods for the treatment of waste contaminated by carcinogens was implemented by the International Agency for Research on Cancer (1979) with the support of the Office of Safety of the National Institutes of Health, and 1985, when antineoplastic agents or hazardous drugs were recognized within this program, numerous authors have expressed interest in evaluating the efficacy of various agents used to decontaminate and break down hazardous drugs (Monteith et al., 1987; Lunn et al., 1989; Benvenuto et al., 1993; Castegnaro et al., 1997; Barek et al., 1998; Allwood et al., 2006). This growing interest has led to the publication of a number of studies aimed at evaluating the decontamination power of various detergents or oxidizing agents such as sodium hypochlorite (NaOCl), hydrogen peroxide and Fenton's reagent. Some of these publications contend that NaOCl is a very effective agent for the elimination of hazardous drug contamination without, however, leading to the production of mutagenic residues (Monteith et al., 1987; Castegnaro et al., 1997; Hansel et al., 1997; Allwood et al., 2002). Another study completed by Roberts et al. (2006) revealed that the use of a towel wipe soaked in sterile water or an alcohol solution also eliminates the presence of contamination on work surfaces contaminated with fluouracil, cyclophosphamide and doxorubicin. Our decision to use and study the effect of water or soapy water to clean vials was done with the objective of documenting the efficiency of a simple and safe solution that could be applied in the hospital practice.

Their study findings are consistent with those obtained in Phases II and III of our study. In fact, the findings from Phase II of the study demonstrate that simply washing vials with water eliminated the presence of any trace of hazardous drugs on 16 of the 20 cyclophosphamide vials tested and findings from Phase III indicate that cleaning the vials with soapy water and a towel wipe eliminated the presence of contamination on most of the vials. On the other hand, the detection of traces of cyclophosphamide on four of the vials we analyzed in Phase II (4/20) and three of the vials in Phase III (3/30), despite the fact they were cleaned with water or soapy water applied on a towel wipe, confirms just how important it is to identify a cleaning agent that is able to completely eliminate the presence of contamination. It is also important to remember that, during the cleaning process, each tissue was discarded after every four vials. Carryover between the vials could represents a contamination factor and have an impact on the cyclophosphamide concentration detected on the vials. Further studies on the subject need to be performed in order to fully clarify the issue of surface contamination and hazardous drug waste and reduce the risk of exposing healthcare professionals involved in the handling of these agents.

Likewise, it is important to consider that the physical and chemical status of the drug and the initial surface contamination could influence the efficiency of cleaning method. Indeed, we decided to evaluate external contamination by cyclophosphamide because this hazardous drug represent a significant drug used in our oncology pharmacy. Thus, our results cannot

be extended to all hazardous drugs prepared in pharmacy because water or soapy water is suitable for a hydrophilic drug like cyclophosphamide for removing traces but are probably less effective for removing lipophilic drugs such as taxane. Further studies are required to determine the efficiency of water with a variety of hazardous drugs in the context of a sterile production pharmacy unit.

The United States Pharmacopeia has published a Chapter (797) on Pharmaceutical Compounding for Sterile Preparations. Among their recommendations regarding hazardous drugs, they recommend to store separately hazardous products from other inventory in a manner to prevent contamination and personnel exposure. As many hazardous drugs have sufficient vapor pressures that allow volatilization at room temperature, they should be stored preferably within a containment area such as a negative pressure room with sufficient general exhaust ventilation (e.g. at least 12 air changes per hour) and they should be handled with caution at all times using appropriate chemotherapy gloves during receiving, distribution, stocking, inventorying, preparation for administration and disposal. Both National Institute for Occupational Safety and Health Alert and USP 797 reinforce the importance of prevention at all stages to reduce the risk of professional exposure to hazardous drugs (2008).

This study revealed the presence of contamination on the external surfaces of cyclophosphamide vials from two distinct manufacturers on the Canadian market. Furthermore, the findings obtained in Phases II and III confirm the need for further studies aimed at identifying the most effective agents to successfully decontaminate work surfaces as well as establish clear and precise guidelines for the cleaning process.

This pilot study does however have certain limitations. Besides the limited number of vials that were studied, the surface contamination measured after cleaning in Phase II does not have a value for the prewash contamination. Although the vials used for Phase II came from the same two batches as those used in Phase I, the lowered contamination suggested by our findings still provides indirect proof of the efficacy of the washing technique that we used. Furthermore, we did not test enough vials in Phase III of the study to allow us to draw any general conclusions about the results obtained for each one. The contamination by immersion with a theoretical amount of 20 ng per vial of an aqueous solution of cyclophosphamide in Phase III has only been validated by measuring the initial and the final volume of the solution used at the beginning and at end of the procedure. The immersion technique can result in variable amount of cyclophosphamide on external surfaces of vials. Furthermore, we have evaluated only glass surfaces to compare the efficiency of three cleaning techniques because we were trying to identify cleaning procedure that could be useful to decontaminate the external surface of cyclophosphamide vials. However, in a pharmacy workflow, cyclophosphamide can also contaminate other surfaces such as floors and shelves made of laminate, stainless steel or plastic. Moreover, it is important to note that our sampling method have been validated only on laminate surfaces by using Wypall tissue with a solution of methanol in specific concentration. No validation test has been performed on vials or glass bottles.

CONCLUSION

This pilot study demonstrates the presence of contamination on the external surfaces of cyclophosphamide vials from two manufacturers on the Canadian market. It suggests that cleaning vials from manufacturers and wholesalers may help to reduce the risk of occupational exposure. There is a need for a pilot study to establish guidelines on decontamination agents and cleaning process to eliminate the presence of contamination on vial surfaces.

Acknowledgements—No conflicting interests are declared.

REFERENCES

Acampora A, Castiglia L, Miraglia N et al. (2005) A case study: surface contamination of cyclophosphamide due to working practices and cleaning procedures in two Italian hospitals. Ann Occup Hyg; 49: 611–8.

Allwood M, Stanley A, Wright P, editors. (2002) The cytotoxics handbook. 4th edn. Oxford: Radcliffe Medical Press.

American Society of Health-System Pharmacists. (1990) ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. Am J Hosp Pharm; 47: 1033–49.

American Society of Health-System Pharmacists. (2006) Guidelines on hazardous drugs. Am J Health Syst Pharm; 63: 1172–93.

Barek J, Cvacka J, de Méo M et al. (1998) Chemical degradation of wastes of antineoplastic agents amsacrine, azathioprine, asparaginase and thiotepa. Ann Occup Hyg; 42: 259–66.

Benvenuto JA, Connor TH, Monteith DK et al. (1993) Degradation and inactivation of antitumor drugs. J Pharm Sci; 82: 988–91.

Castegnaro M, De Méo M, Laget M et al. (1997) Chemical degradation of wastes of antineoplastic agents. 2: six anthracyclines: darubicin, doxorubicin, epirubicin, pirarubicin, aclarubicin, and daunorubicin. Int Arch Occup Environ Health; 70: 378–84.

Connor TH, Anderson RW, Sessink PJ et al. (1999) Surface contamination with antineoplastic agents in six cancer treatment centers in Canada and the United States. Am J Health Syst Pharm; 56: 1427–32.

Connor TH, Sessink PJ, Harrison BR et al. (2005) Surface contamination of chemotherapy drug vials and evaluation of new vial-cleaning techniques: results of three studies. Am J Health Syst Pharm; 62: 475–84.

Crauste-Manciet S, Sessink PJ, Ferrari S et al. (2005) Environmental contamination with cytotoxic drugs in healthcare using positive air pressure isolators. Ann Occup Hyg; 49: 619–28.

Delporte JP, Chenoix P, Hubert PH. (1999) Chemical contamination of the primary packaging of 5-fluorouracil RTU

solutions commercially available on the Belgian market. Eur Hosp Pharm; 5: 119–21.
Ensslin AS, Stoll Y, Pethran A et al. (1994) Biological monitoring of cyclophosphamide and ifosfamide in urine of hospital personnel occupationally exposed to cytostatic drugs. Occup Environ Med; 51: 229–33.
Favier B, Gilles L, Ardiet C et al. (2003) External contamination of vials containing cytotoxic agents supplied by pharmaceutical manufacturers. J Oncol Pharm Pract; 9: 15–20.
Funck von S, Schierl R. (2004) Sicherheit bei der zytostatikahersatellung. Dtsch Apoth Ztg; 10: 1089–94.
Gallant C, Bussières JF, Plante R et al. (2008) Guide de prévention—manipulation sécuritaire des médicaments dangereux. Montréal, QC: ASSTSAS. p. 158.
Hansel S, Castegnaro M, Sportouch MH et al. (1997) Chemical degradation of wastes of antineoplastic agents: cyclophosphamide, ifosfamide and melphalan. Int Arch Occup Environ Health; 69: 109–14.
Harrison BR, Peters BG, Bing MR. (2006) Comparison of surface contamination with cyclophosphamide and fluorouracil using a closed-system drug transfer device versus standard preparation techniques. Am J Health Syst Pharm; 63: 1736–44.
Hedmer M, Jonsson BA, Nygren O. (2004) Development and validation of methods for environmental monitoring of cyclophosphamide in workplaces. J Environ Monit; 6: 979–84.
Hedmer M, Georgiadi A, Bremberg ER et al. (2005) Surface contamination of cyclophosphamide packaging and surface contamination with antineoplastic drugs in a hospital pharmacy in Sweden. Ann Occup Hyg; 49: 629–37.
Hedmer M, Tinnerberg H, Axmon A et al. (2008) Environmental and biological monitoring of antineoplastic drugs in four workplaces in a Swedish hospital. Int Arch Occup Environ Health; 81: 899–911.
Hepp R, Gentschew G. (1998) External contamination of commercially available cytotoxic drugs (in German). Krankenhauspharmazie; 19: 22–7.
Iglesias F. (2006) Detection of external contamination of methotrexate vials in an Argentine hospital (in Spanish). Farm Hosp; 30: 300–3.
Larson RR, Khazaeli MB, Dillon HK. (2002) Monitoring method for surface contamination caused by selected antineoplastic agents. Am J Health Syst Pharm; 59: 270–7.
Lunn G, Sansone EB, Andrew AW et al. (1989) Degradation and disposal of some antineoplastic drugs. J Pharm Sci; 78: 652–9.
Mason HJ, Morton J, Garfitt SJ et al. (2003) Cytotoxic drug contamination on the outside of vials delivered to a hospital pharmacy. Ann Occup Hyg; 47: 681–5.
Minoia C, Turci R, Sottani C et al. (1998) 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; 12: 1485–93.
Monteith DK, Connor TH, Benvenuto JA. (1987) Stability and inactivation of mutagenic drugs and their metabolites in the urine of patients administered antineoplastic therapy. Environ Mol Mutagen; 10: 341–56.
National Institute for Occupational Safety and Health. (2004) NIOSH alert. Preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings. Available at http://www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf. Accessed 17 June.
Nygren O, Gustavsson B, Ström LO et al. (2002) Cisplatin contamination observed on the outside of drug vials. Ann Occup Hyg; 46: 555–7.
Paul H, Baumann L, Artelt S et al. (1998) Umgebungskontrolle auf contamination mit zytostatika: nachweis von platin auf oberflächen in räumlicheiten mit zentraler ytostatikaherstelling. Krankenhauspharmazie; 4: 181–6.
Pethran A, Schierl R, Hauff K et al. (2003) Uptake of antineoplastic agents in pharmacy and hospital personnel. Part I: monitoring of urinary concentrations. Int Arch Occup Environ Health; 76: 5–10.
Roberts S, Khammo N, McDonnell G et al. (2006) Studies on the decontamination of surfaces exposed to cytotoxic drugs in chemotherapy workstations. J Oncol Pharm Pract; 12: 95–104.
Ros JJ, Simons KA, Verzul JM et al. (1997) Practical applications of a validated method of analysis for the detection of traces of cyclophosphamide on injection bottles and at oncological outpatient center (in Dutch). Ziekenhuisfarmacie; 13: 168–71.
Schmaus G, Schierl R, Funck S. (2002) Monitoring surface contamination by antineoplastic drugs using gas chromatography-mass spectrometry and voltammetry. Am J Health Syst Pharm; 59: 956–61.
Sessink PJ, Boer KA, Scheefhals AP et al. (1992) 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; 64: 105–12.
Sessink PJ, Cerna M, Rossner P et al. (1994) Urinary cyclophosphamide excretion and chromosomal aberrations in peripheral blood lymphocytes after occupational exposure to antineoplastic agents. Mutat Res; 309: 193–9.
Turci R, Sottani C, Spagnoli G et al. (2003) Biological and environmental monitoring of hospital personnel exposed to antineoplastic agents: a review of analytical methods. Chromatogr B Analyt Technol Biomed Life Sci; 789: 169–209.
USP. (2003) Pharmaceutical compounding—sterile preparations, 27th revision and the national formulary. General information, chapter 797. 22nd edn. Rockville, MD: USP Convention.
United States Pharmacopeia (USP). (2008) USP , 797 . Guidebook to pharmaceutical compounding—sterile preparations. Available at http://www.usp.org/products/797Guidebook/. Accessed 17 June.
Vandenbroucke J, Robays H. (2001) How to protect environment and employees against cytotoxic agents, the UZ Ghent experience. J Oncol Pharm Practice; 6: 4146–52.