Levels of surface contamination with gemcitabine using standard preparation techniques versus closed-system devices

Sandro Luis R. Ness¹,², Carmen Pilla³, Gabriela Vassian Tubino², Helena Von Eye Corleta¹,⁴ and Edison Capp¹,⁴,⁵*

¹Graduate School of Medicine: Medical Sciences, School of Medicine, Universidade Federal do Rio Grande do Sul
²Center for Intravenous Drug Preparation, Department of Pharmacy, Clinical Hospital of Porto Alegre
³Clinical Biochemistry Unit, Department of Clinical Pathology, Clinical Hospital of Porto Alegre
⁴Department of Obstetrics and Gynecology, School of Medicine, Clinical Hospital of Porto Alegre, School of Medicine, Universidade Federal do Rio Grande do Sul, Brazil
⁵Department of Gynecological Endocrinology and Fertility Disorders, Ruprecht-Karls-University, Heidelberg, Germany

ABSTRACT

Health professionals who handle antineoplastic agents are exposed to several chemical hazards. Therefore, their occupational exposure must be carefully monitored and prevented. The use of closed-system devices in drug preparation has been recommended by several international guidelines for the handling of cytotoxic drugs. To compare the contamination of work surfaces with gemcitabine following closed-system preparation versus standard needle techniques, using high-performance liquid chromatography-ultraviolet (HPLC-UV). Wipe test samples were collected from a drug handling facility, then extracted and analyzed by HPLC-UV. Readings were taken at 268 nm. Of the 303 samples collected, 31 were obtained from intact vials, while 272 were used to compare gemcitabine contamination levels following conventional versus closed-system preparation. Approximately 50% of samples obtained following each procedure tested positive for the contaminant. The amount of contamination on vials, sterile fields and syringes was lower when closed-system devices were used for drug manipulation. A total of 16.1% of the intact vials removed from their original packaging were also contaminated. The method used in the present study was effective in detecting gemcitabine in the devices and individual protective equipment involved in drug manipulation. These findings demonstrate the exposure risk of health professionals who handle these substances, and the importance of closed-system devices in reducing aerosol formation and contamination during handling.

Key words: antineoplastic agents, closed-system drug transfer device, gemcitabine, high-pressure liquid chromatography (HPLC), and surface contamination

INTRODUCTION

The use of antineoplastic drugs has increased considerably in recent years due to the growing prevalence of cancer and the need for new treatment strategies with greater therapeutic potential and more significant benefits for patient quality of life [1]. Improvements in antineoplastic treatments and the development of new intervention procedures and medications have resulted in a significant increase in the number of treatable patients and successful outcome expectations.

Antineoplastic drugs are very active, and have high potential toxicity. In addition to being carcinogenic, these drugs are also genotoxic, teratogenic and mutagenic, and can have toxic effects on both animals and humans even after low-dose exposure [2-4]. Therefore, antineoplastic agents, immunosuppressants, and antivirals may be especially deleterious to health professionals, and must be handled with great care [3].
In light of the occupational risk associated with cytotoxic materials, these medications must be handled based on the guidelines developed by international organizations such as the Occupational Safety and Health Act (OSHA), the American Society of Hospital Pharmacists (ASHP), National Institute for Occupational Safety and Health (NIOSH), International Agency for Research on Cancer (IARC), Food and Drug Administration (FDA), and the World Health Organization (WHO). Since antineoplastic drugs are intravenous and must be prepared under aseptic conditions, they are manufactured according to United States Pharmacopeia (USP) and Brazilian Society of Contamination Control (SBCC) guidelines. These organizations have developed recommendations for policies and procedures related to the physical facilities, equipment, and personnel practices associated with anticancer drugs so as to minimize the risk of occupational exposure to these substances.

According to current guidelines and legislation, anticancer drugs must be manufactured in centralized facilities designed specifically for this purpose, with the use of collective (CPE) and individual protection equipment (IPE) [2,5-6].

These considerations warrant further investigation into the safety of the work conditions of health practitioners exposed to chemical risks, especially those whose work involves handling anticancer drugs, since these individuals often fail to receive adequate information regarding occupational health hazards.

Exposure can occur at any stage of the preparation, administration and disposal of chemotherapeutic drugs [7]. These medications can be released into the work environment in powder form or, more frequently, in liquid or aerosolized form, since all drugs which are not supplied in liquid form must be reconstituted prior to use [8]. Skin absorption is the most common route of exposure to anticancer drugs. Absorption is facilitated by the presence of wounds on the skin [1]. Contamination can also occur by the inhalation of the aerosolized drug product, and contact with contaminated medication, chewing gum or cigarettes [7].

The following populations are at risk of exposure to such contaminants: patients, their relatives and caretakers, pharmaceutical workers, pharmacists, nurses, doctors, janitorial staff, and researchers [9]. Environmental monitoring, health screening through periodic medical examinations, personnel education and training, and the use of IPE and CPE are some of the recommended methods for reducing occupational exposure to such chemicals and related health risks [1].

A recent study of genotoxicity and oxidative stress in pharmacists and nurses who handled antineoplastic agents reported increased DNA damage and oxidative stress markers in these individuals as compared to control subjects [10]. The short-term effects of exposure to anticancer drugs include headaches, vertigo, skin hyperpigmentation and vomiting, while long-term effects may include alterations in fertility, sexual function and the endocrine system, early menopause, musculoskeletal alterations, immune dysfunctions, foetal or menstrual abnormalities, spontaneous abortions and DNA damage [6,11].

Therefore, the production of anticancer drugs must follow strict safety protocols. Additional care must also be taken by workers involved in the preparation, administration and disposal of chemotherapeutic agents, and by the facilities in which these processes are carried out [7].

The risk of exposure is present from the moment these medications are received, persisting through their preparation, administration, and the disposal of garbage and bodily excretions [12]. The risk depends on the toxicity of the substance, individual differences in drug sensitivity, and the degree of exposure [13].

Therefore, the manipulation of anticancer drugs should be under the care of a stable and well-trained team, who should receive frequent training courses, and alternate activities to avoid fatigue and decrease the risk of accidents and exposure to the drugs. The norms and procedures for handling antineoplastic drugs should also be periodically reviewed and updated.

Occupational exposure to antineoplastic drugs can be evaluated using several methods, the most common of which is the Wipe Test, used to detect drug residue on surfaces or objects, or in the locations where the drugs are prepared or administered. Surface analyses are useful, sensitive and reproducible, in addition to having a low cost and being relatively accessible. Standardized procedures can also be used to test for contamination in gloves and masks [1,14]. Contaminants can also be present in the air, on medication vials, and on other materials involved in the preparation or administration of chemotherapeutic agents [15]. Studies using mass spectrometry to detect contamination by 10 different drugs including gemcitabine detected considerable levels of these contaminants on gloves and other objects located far from the laminar flow area, such as computers, mice and steel surfaces in drug preparation facilities, in addition to the floors of medical and administrative offices, and toilets in oncology units [16-17].
Ultraviolet high-performance liquid chromatography (HPLC-UV) is among the most commonly used methods of detecting environmental cytotoxic contamination [18-19]. HPLC has been used to detect surface contamination by cytotoxic agents such as cyclophosphamide, methotrexate, fluorouracil, ifosfamide and doxorubicin and it has been identified as a reliable, precise, and linear method to detect simultaneous surface contamination by these five drugs [9,20]. HPLC has also revealed varying degrees of contamination by fluorouracil, cytarabine and gemcitabine in various surfaces in departmental pharmacies of oncology units [20].

Closed-system drug-transfer devices mechanically prevent aerosol formation, puncture accidents and chemotherapeutic drug leakage during preparation. These devices consist of a syringe, a vial and a luer-lock connector [21]. Figure 1 shows the structure of ChemoClave®. This system aims to reduce contamination in class II, type B2 biological safety cabinets and surrounding areas, decreasing occupational exposure to toxic medications [22].

Figure 1

Figure 1: Closed Systems Transfer Devices, ChemoClave®, ICU Medical

Cyclophosphamide and fluorouracil levels on the surface of biological safety cabinets and nearby floors and countertops were compared in three oncological pharmacy units following standard preparation vs. closed-system methods (PhaSeal®) [23]. 90% of samples were positive for cyclophosphamide, and 8% for fluorouracil, although the use of closed-system devices led to significantly lower contamination levels.

Currently, in most developed countries, the release of drugs into the environment during preparation and administration is prevented by the use of closed-system drug transfer devices, whose sealed expansion chambers maintain a neutral pressure and prevent the formation and release of aerosol particles. These devices have been
evaluated by several studies, which have found them to have varying levels of efficacy in reducing surface contamination following manipulation using different techniques [1, 21, 14].

Gemcitabine (2,2'-difluorodeoxycytidine; dFdC) is a cytarabine (cytosine-arabinoside; Ara-C) analogue and a potent antimetabolite, with high therapeutic efficacy against several solid tumours, such as small-cell lung cancer, metastatic pancreatic cancer, and breast, ovarian, seminal vesicle, oesophageal, and head and neck cancer. The drug has been shown to be effective both alone and in combination with other antineoplastic agents such as cisplatin and paclitaxel [24].

The aim of the present study was to use HPLC-UV to assess gemcitabine contamination on IPE (gloves) and work surfaces used for the preparation of antineoplastic agents after standard manipulation vs. the use of closed-system drug transfer devices.

**EXPERIMENTAL SECTION**

A cross-sectional study was performed.

The present study was approved by the Ethics Committee of Hospital de Clínicas de Porto Alegre, project #120400. Samples were collected on random dates in the Centre for Intravenous Drug Preparation (CIDP), in the Department of Pharmacy of the Clinical Hospital of Porto Alegre (HCPA).

Of the 303 samples, 272 were collected after the drug was manipulated, and 31 from intact vials before handling. The 272 samples were collected from syringes, sterile fields, gloves, vials and agitators. One hundred and thirty-four of these were collected after manipulation using the standard syringe/needle method, and the remaining 138, following handling using closed-system safety devices.

Samples were collected using 42.5-mm diameter (4.0 x 4.0 cm) Whatman filter paper (Maidstone, Kent, UK). Standard solutions were made using 1 g generic gemcitabine chlorohydrate (Accord Pharmaceutical Laboratory, Ltd.) lyophilised into powder.

Wipe test samples were collected by immersing filter paper discs in 100 µL water and using them to wipe objects or surfaces. The following surfaces and objects were analysed: 20 cm x 20 cm sterile fields used to manipulate the drug in the biological safety cabinet (BSC), used gemcitabine flasks, the outside of surgical gloves used to manipulate the drugs, 50 mL syringes, agitators used to dilute the medications in the laboratory outside the BSC, and intact gemcitabine vials removed from their original packages in the stocking area.

Samples were collected using two procedures: standard preparation with a 40x12” needle, or with closed-system devices produced by ICU Medical, Inc.

Samples were collected from gloves, sterile fields, 50 mL syringes and gemcitabine vials in a Class II, Type B Biological Safety Cabinet on random days at the end of drug manipulation. Wipe samples were also taken from an agitator outside the BSC, in the manipulation room of the Centre for Intravenous Drug Preparation of the Clinical Hospital of Porto Alegre (CMIV/HCPA). Five experienced pharmacists manipulated the drug using the closed-system devices. Data was randomly collected throughout all shifts.

Samples from intact medication vials were collected in the storage area of the CMIV/HCPA. Vials were removed from their original packaging on different days and lots, none of which had any signs of breakage, leakage or humidity.

After collection, each sample was stored in a sealed PVC tube, and kept at room temperature for up to 48 h before being sent for analysis to the Clinical Biochemistry Unit at the Department of Clinical Pathology of the Clinical Hospital of Porto Alegre.

Samples were extracted by elution with 1.0 mL reagent water for 24 hours, and were then centrifuged and injected into a Shimadzu chromatograph. HPLC-UV was performed with a LiChrospher RP-18 column (end capped, 100 A, 250 mm x 4.6mm, 10µ), a mobile phase of 40 mM ammonium phosphate (pH 5.5)-acetonitril (80:20 v/v), manual injection of 20 µl and a flow rate of 1.0 mL/min. Absorbance was read at 268 nm. This method was validated based on its linearity, precision, stability, and limits of detection and quantitation.

Data were entered into an SPSS spread sheet (Statistical Package for Social Sciences, version 18). Data were not normally distributed and variance was not homogeneous. Results are expressed as median and interquartile range.
The percentage of positive samples was compared between conditions using Fisher's exact test, and the amount of contamination following manipulation with each of the two techniques was compared using Mann-Whitney U tests. Results were considered significant at P < 0.05.

RESULTS AND DISCUSSION

Of the 272 samples collected, 134 were extracted following manipulation with conventional methods, and 138 following preparation with closed-system safety devices. Following conventional preparation, the mean contaminant concentration was 11.7 µg/mL and the median was 0.0 (P25 0.0 – P75 3.97 µg/mL). In closed system preparation, mean contaminant levels were 5.2 µg/mL, while the median was 0.0 (P25 0.0 - P75 2.7µg/mL).

A total of 49.3% of the samples prepared using conventional methods were contaminated with a mean of 23.8 µg/mL gemcitabine and a median of 4.1 µg/mL (P25 1.35 µg/mL - P75 19.35 µg/mL). Samples prepared using closed-system drug transfer devices had a contamination rate of 44.9%. The mean contaminant level was 11.7 µg/mL, while the median, 3.4 µg/mL (P25 0.64 µg/mL - P75 6.7 µg/mL). Contamination rates did not differ significantly between groups (p = 0.544).

As shown in table 1, contamination levels differed significantly between samples collected from gloves, vials, syringes, sterile fields and agitators in both groups of samples. The contamination levels in each of these locations did not differ significantly between groups.

Five of the 31 samples collected from intact gemcitabine vials showed traces of external contamination, ranging from 0.2 to 0.4 µg/mL As can be seen in Table 1, the contamination rate in gemcitabine vials was 16.1%, with a 95% CI of 5.4% to 33.7%.

The linearity of the method used to detect contamination with gemcitabine was confirmed using a standard curve. Figure 2 shows the linear equation and correlation coefficients between results (R²).

![Figure 2: Calibration curve for the detection of gemcitabine. Linearity was assessed using six points (0.5 to 25µ/mL)](image)

The accuracy of the test was analysed by repeated sampling from a solution with a constant concentration. The mean and variation coefficient of five samples drawn on three consecutive days is shown in Table 2.

The retention time of the samples was 3.6 minutes, and the limit of quantitation (LOQ) was determined by the serial dilution of samples containing known amounts of gemcitabine, with a detection limit of 0.2 µg/mL.

Figure 3 shows the background of experimental conditions, and the chromatography of filter samples soaked in 1 mL water. Figure 4 shows the chromatography of a 10 µg/mL gemcitabine sample.

The National Cancer Institute (INCA) has reported an increase in the incidence of cancer over recent decades, which has led to an increase in the use of antineoplastic drugs. Although these drugs preferentially target neoplastic cells,
they are relatively nonspecific and also affect normal cells, producing adverse effects in treated patients and individuals occupationally exposed to these medications.

Figure 3 - Chromatography of filter paper soaked in 1 mL water: background of experimental conditions

Figure 4 - Chromatography of a 10 µg/ml gemcitabine sample

Table 1: Gemcitabine contamination in samples

<table>
<thead>
<tr>
<th>Sample</th>
<th>Type</th>
<th>Amount</th>
<th>Mean</th>
<th>Median (p25 – p75)</th>
<th>Variation mg/mL</th>
<th>% positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial</td>
<td>Needle</td>
<td>70</td>
<td>16</td>
<td>1.3 (0.0 - 6.3)</td>
<td>0.2 – 249.5</td>
<td>67.1</td>
</tr>
<tr>
<td></td>
<td>Safety devices</td>
<td>73</td>
<td>5.7</td>
<td>0.4 (0.0 – 3.9)</td>
<td>0.3 – 141.6</td>
<td>56.2</td>
</tr>
<tr>
<td></td>
<td>Intact</td>
<td>31</td>
<td>0.05</td>
<td>0.0</td>
<td>0.2 – 0.4</td>
<td>16.1</td>
</tr>
<tr>
<td>Sterile Fields</td>
<td>Needle</td>
<td>17</td>
<td>6</td>
<td>0.0 (0.0 – 6.7)</td>
<td>0.2 – 46.2</td>
<td>35.3</td>
</tr>
<tr>
<td></td>
<td>Safety devices</td>
<td>16</td>
<td>0.52</td>
<td>0.0 (0.0 - 0.14)</td>
<td>0.06 – 4.1</td>
<td>25</td>
</tr>
<tr>
<td>Syringe</td>
<td>Needle</td>
<td>14</td>
<td>16.3</td>
<td>0.0 (0.0 – 4.3)</td>
<td>0.8 – 192.8</td>
<td>35.7</td>
</tr>
<tr>
<td></td>
<td>Safety devices</td>
<td>22</td>
<td>0.40</td>
<td>0.0 (0.0 – 0.2)</td>
<td>0.2 – 4.0</td>
<td>27.3</td>
</tr>
<tr>
<td>Glove</td>
<td>Needle</td>
<td>22</td>
<td>4.84</td>
<td>0.0 (0.0 – 0.5)</td>
<td>0.2 – 53.7</td>
<td>27.3</td>
</tr>
<tr>
<td></td>
<td>Safety devices</td>
<td>20</td>
<td>13.83</td>
<td>0.0 (0.0 – 3.1)</td>
<td>0.4 – 244.0</td>
<td>40</td>
</tr>
<tr>
<td>Agitator</td>
<td>Needle</td>
<td>11</td>
<td>1.2</td>
<td>0.0 (0.0 – 0.0)</td>
<td>0.2 – 13.1</td>
<td>18.2</td>
</tr>
<tr>
<td></td>
<td>Safety devices</td>
<td>7</td>
<td>1.9</td>
<td>0.0 (0.0 – 3.3)</td>
<td>0.3 – 9.8</td>
<td>42.9</td>
</tr>
</tbody>
</table>

Antineoplastic drugs carry a significant chemical risk due to their carcinogenic, teratogenic, mutagenic and genotoxic properties. As such, workers involved in their transportation, storage, preparation and administration, or in the disposal of drug residue, patient excretions and secretions, should be especially careful, and adhere strictly to the safety recommendations issued by international entities such as OSHA, NIOSH, IARC, OPAS, who have guidelines for the preparation and administration of cytotoxic drugs.
Table 2: Results of between- and within-trial stability levels

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Within-trial precision</td>
<td></td>
</tr>
<tr>
<td>Number of samples (3)</td>
<td></td>
</tr>
<tr>
<td>Concentration (µg/mL)</td>
<td>1</td>
</tr>
<tr>
<td>CV (%)</td>
<td>14.8</td>
</tr>
<tr>
<td>Between-trial precision</td>
<td></td>
</tr>
<tr>
<td>Number of samples (10)</td>
<td></td>
</tr>
<tr>
<td>Concentration (µg/mL)</td>
<td>1</td>
</tr>
<tr>
<td>CV (%)</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Aseptic manipulation using a standard syringe and needle often results in contamination through droplets, leakage from the rubber stopper after multiple punctures and aerosol formation due to the high pressure in medication flasks [21]. To minimize exposure to cytotoxic drugs, international organizations and legislation recommend the use of closed-system devices when manipulating and administering these drugs [6,2,25].

Several studies have been performed in different institutions around the world using different techniques to detect contamination with several antineoplastic drugs in materials, IPE, air and work surfaces, in addition to biological monitoring techniques to detect contamination in the blood and urine of pharmacists and nurses occupationally exposed to antineoplastic drugs [17,16,10,26-30].

A study performed over the course of five years (2000-2005) in 22 hospitals in the United States compared surface contamination with cyclophosphamide, ifosfamide and fluorouracil following conventional manipulation procedures vs. closed-system preparation (PhaSeal®). A total of 114 Wipe Test samples were collected. Cyclophosphamide and ifosfamide contamination were analyzed by gas chromatography and mass spectrometry, and fluorouracil levels were examined by reversed-phase HPLC-UV. Median contamination with each of the three drugs decreased by 95%, 90% and 65%, respectively, after the implementation of closed-system devices [22].

Spivey and Connor used fluorescein as a marker of surface contamination to compare the results of standard versus closed-system (PhaSeal®) preparation. Each stage of the experiment was photographed with UV illumination to visualize leaks and spills. Leakage was observed following all 75 manipulations using traditional methods, but was not reported in any phase of manipulation using PhaSeal® devices [31].

HPLC has also been used to determine the plasma concentration of gemcitabine and its metabolites, and has been successfully used in pharmacokinetic studies of Chinese patients receiving chemotherapy [24].

The present study focused on contamination with gemcitabine, an antimetabolic agent, which is widely used in the treatment of several types of cancer. In addition to being easily detectable, gemcitabine is also a relatively new drug, whose surface contamination and occupational exposure risks have only been sparsely investigated. Samples were collected from materials and IPE used inside the laminar-flow area in a BSC, such as syringes, vials, sterile fields and gloves, and from an agitator outside the laminar flow region, to ensure the identification of different possible sources of contamination. All materials were collected by wipe sampling, by the same researcher using the same technique on random non-consecutive days, after materials were manipulated by all five pharmacists involved in drug preparation.

HPLC is a sensitive and cost-effective technique for the monitoring of occupational exposure to different chemicals. In the present study, gemcitabine levels were determined by HPLC-UV with a reversed-phase LiChrospher C18 column, a mobile phase of 80% 40 mm/l ammonium phosphate acidified to pH = 5.5 and 20% acetonitrile, and a flow rate of 1.0mL/min. Readings were taken at 268 nm. For comparison, a previous study determined the serum concentration of gemcitabine and its metabolites using diode-array HPLC, with a flow rate of 0.8 mL/min. However, in the study in question, the mobile phase contained 97.5% 40mm/L ammonium phosphate acidified to pH 5.5 and 2.5% acetonitrile. Gemcitabine was read at 268 nm, and its metabolite at 253 nm. This method was simple, efficient, sensitive, accurate and precise for the detection of contamination [18].

The use of closed-system drug transfer in the preparation and administration of antineoplastic drugs has been strongly recommended by several international guidelines for the preparation of cytostatic medications, and by Resolution 32 (NR-32), of the Brazilian Ministry of Occupation [25]. The use of these devices has been found to reduce aerosol formation and contamination [22-23,14]. According to NR-32, safety devices should minimize aerosolization, facilitate drug transfer in a closed system, and decrease the likelihood of accidents during drug manipulation, administration, transportation and disposal [5].
In the present study, 272 samples were evaluated following manipulation with two techniques, and the use of closed-system devices led to lower mean contaminant levels, although median and 75th percentile values were similar in the two groups. Despite the similarity in contamination rates between groups, when only contaminated samples were analysed, mean and median contaminant levels were lower following manipulation with closed-system devices than with conventional techniques. However, this difference was not statistically significant. Although both preparation methods resulted in contamination, closed-system drug transfer devices led to lower contaminant levels and reduced aerosol formation, confirming the importance of this method. However, even though closed-system devices do reduce contaminant levels, the use of the IPE and CPE recommended by international guidelines and resolutions is indispensable, as is periodic personnel training and the use of adequate preparation techniques.

When the locations from which samples were taken were analysed separately, the mean contaminant content in vials, syringes and sterile fields were found to be lower when safety devices were used. However, contrary to expectations, these techniques led to higher contaminant levels in gloves and agitator samples. Median contamination was 0 in all groups, although 75th percentile values were lower in samples prepared using safety devices. It is important to note that the facilities evaluated were also used for the preparation of other medications, which may also have contaminated the samples. The fact that drugs other than gemcitabine were also manipulated in the facility is a limitation of the present study. The use of the agitator to dilute other medications, the collection of data at the end of each shift, and the small number of samples may have also limited our findings. Nevertheless, despite this limitation, we were able to identify contamination even in locations far from the laminar flow area, such as the dilution device.

The contamination of the external surface of intact vials, reported by this and other studies, suggests that protection may be required at all stages of handling [20,14,32-34]. In our study, 5/31 intact vials were contaminated by 0.2 to 0.4 µg/mL gemcitabine, resulting in a contamination rate of 16.1%. This finding reinforces the importance of NIOSH guidelines regarding the use of EPI (gloves, headgear, safety glasses and waterproof apron) when unpacking cytotoxic drugs [6].

The locations in which different studies are performed, together with their specific features and procedures, must also be considered, since the results obtained in a certain location may not necessarily reflect the occupational risk in other facilities, where personnel characteristics and the nature of occupational exposure may be significantly different. Although there are several international guidelines and regulations for the manipulation of cytotoxic drugs, these are not always followed by pharmacists or nurses, many of whom do not use adequate protection equipment, either as a result of their working conditions, or because they are unaware of the risks to which they are exposed. The method used to monitor occupational exposure to gemcitabine in the present study was effective in detecting the contamination of material surfaces and IPE inside and outside the laminar flow. Additionally, the use of closed-system drug transfer devices in the preparation of the medication led to reduced contaminant levels, but did not entirely prevent contamination. These findings clearly show that, even when safety devices are used, all those who work with antineoplastic drugs must take special care when handling cytotoxic medication. Individual and collective protective equipment should always be utilized, not only in the manipulation room, but also during the unpacking and handling of intact vials, since contamination residue was also detected in vials upon removal from the original packaging.

Acknowledgments
This work had financial support from Fundo de Incentivo a Pesquisa (FIPE) do Grupo de Pesquisa e Pós-Graduação (GPPG) do Hospital de Clínicas de Porto Alegre #120400. Edison Capp is scholarship recipient from Conselho Nacional de Desenvolvimento Científico e Tecnológico - CNPq.

REFERENCES
[4] AA Shahrasbi; M Afshar; F Shokraneh; F Monji; M Noroozi; M Ebrahimi-Khojin; SF Madani; M Ahadi-Barzoki; M Rajabi, EXCLI journal, 2014, 13, 491-501.


[15] S Nussbaumer; L Geiser; F Sadeghipour; D Hochstrasser; P Bonnabry; JL Veuthey; S Fleury-Souverain, Analytical and bioanalytical chemistry, 2012, 402(8), 2499-2509.