Pilot Study Comparing the Efficacy of Two Cleaning Techniques in Reducing Environmental Contamination with Cyclophosphamide

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Objective: Compare the efficacy of the cleaning technique usually employed in our healthcare facility to eliminate environmental contamination with cyclophosphamide with that of the Surface Safe® commercial kit.

Methods: This is a three-step evaluative and comparative study involving: (i) the voluntary contamination of the surface of a hood with a pre-established quantity of cyclophosphamide (20 000 000 ng), (ii) the cleaning of the work surface of the hood using a cleaning technique usually employed in our healthcare facility or that of the product Surface Safe®, and (iii) the quantification of cyclophosphamide detected on the work surface. The usual cleaning technique involves the use of a mixture of 0.05% chlorhexidine and 70% ethyl alcohol to clean surfaces, whereas the product Surface Safe® involves a combined two-step sodium hypochlorite and sodium thiosulfate wash.

Results: The median concentrations of cyclophosphamide detected after the use of the usual technique and the product Surface Safe® came to 165 ng cm⁻² (40–570) and 65 ng cm⁻² (57–110), respectively. The results obtained showed an average 99.5% efficacy in reducing the quantity of cyclophosphamide (ng) detected on the work surface for each of the two techniques that were evaluated.

Conclusion: The study demonstrates that reducing the residual concentration of cyclophosphamide on work surfaces to levels lower than 1 ng cm⁻² remains difficult despite the use of cleaning techniques with a high percentage of efficacy. It stressed the importance of combining two successive cleaning techniques to maximally restrict the residual concentration of hazardous drugs and suggests the use of a combination of sodium hypochlorite and sodium thiosulfate to best reduce environmental contamination levels.

Keywords: cyclophosphamide; decontamination; degradation; environmental contamination; sampling; quantification

INTRODUCTION

Environmental contamination with hazardous drugs is a concern for healthcare professionals. Several authors have shown the presence of traces of various hazardous drugs on pharmacy work surfaces reserved for receiving, storing, preparing, and validating preparations including a biological presence in the urine of staff and healthcare workers who handle these agents (Sessink et al., 1992a,b; Connor et al., 1999, 2005; Vandenbroucke and Robays, 2001; Schmaus et al., 2002; Hedmer et al., 2004; Acampora et al., 2005; Crauste-Manciet et al., 2005; Mason...
et al., 2005). The publication of these articles has aided the development of increasingly effective monitoring methods that detect traces that are sometimes $<10^{-4}$ ng cm$^{-2}$. Many authors have been interested in the evaluation of the presence of contamination with hazardous drugs in their work environment as well as the identification of potential sources of contamination such as contamination on the external surfaces of vials distributed by suppliers, handling errors, breakage during vial transport, or while handling vials in the pharmacy, etc. (Sessink et al., 1992; Delporte et al., 1999; Nygren et al., 2002; Favier et al., 2003; Mason et al., 2003; Connor et al., 2005; Hedmer et al., 2005). Despite the publication of a significant number of findings on the subject, no maximum exposure threshold to hazardous drugs exists except for the standard set by the United States Pharmacopeia (USP) in the revised USP Chapter 797 released in December 2007, which stipulates that cyclophosphamide exposure $<1$ ng cm$^{-2}$ would limit the risks of absorption in humans (USP, 2008). Whereas the actual impact of daily exposure to varying levels of hazardous drug traces remains unknown, in spite of the proposed exposure threshold, our team is interested in reducing traces that may be found on pharmacy work surfaces. In fact, after conducting previous studies that revealed the presence of low concentrations of cyclophosphamide (varying from undetectable levels to 3.5 ng cm$^{-2}$) in certain areas of the hematology–oncology pharmacy, we wished to evaluate the efficacy of the cleaning technique currently used as well as that of a product that has recently been marketed in Canada (Touzin et al., 2008, 2009). The objective of this pilot study was, therefore, to compare the efficacy of the cleaning technique usually employed in our healthcare facility with that of the commercial product Surface Safe® in reducing environmental contamination with cyclophosphamide.

**MATERIALS AND METHODS**

**Handling of cyclophosphamide**

The drug used to conduct this study is recognized as being hazardous to human health since it is defined as being a potentially carcinogenic, teratogenic, or mutagenic agent that may be toxic to certain organs or the reproductive system (Hansel et al., 1997). It was, therefore, handled according to the recommendations of our facility’s regulatory policies and procedures governing the use of hazardous drugs. Pharmacy staff involved in handling the drug wore adequate protective equipment (blouse, two pairs of sterile gloves, glasses, a mask, over-shoes, and a cap).

**Description of the study**

This is an evaluative and comparative pilot study conducted under one of the 1.2-m IIB2 Class hoods intended for the sterile preparation of hazardous drugs in the hematology–oncology pharmacy of the Sainte-Justine University Hospital Center (Centre Hospitalier Universitaire Sainte-Justine). The pilot study entailed the evaluation of the efficacy of two cleaning techniques in reducing environmental contamination with cyclophosphamide.

The first technique that we evaluated was the usual daily wash carried out by the technicians on our team to clean the hoods at the end of each work shift. The efficacy of this technique in reducing cyclophosphamide contamination was compared with that of a product that has recently been put on the market in Canada called Surface Safe® (Hospira Inc., Lake Forest, IL). In order to compare the efficacy of these two techniques, we proceeded with a repeated and systematic voluntary contamination of the work surface.

The study was divided into three distinct steps: (i) the voluntary contamination of the hood’s work surface using a pre-established quantity of cyclophosphamide, (ii) the cleaning of the hood’s work surface using the usual or Surface Safe® technique, and (iii) the quantification of cyclophosphamide found on the work surface. Each of the three steps was conducted in triplicate in order to ensure the reproducibility of the obtained results. Furthermore, a complete cleaning technique was carried out at the beginning of the study as well as after the evaluation of each of the cleaning techniques with the aim of reducing residual contamination to the maximum extent and evaluating the level of basic contamination before each new evaluation. The complete cleaning technique was usually conducted once a week within the framework of the regular operations. After completing each usual or Surface Safe® cleaning technique, an environmental contamination value was assigned by taking two samples located at two predefined sites. All steps were conducted during the same working day. Manipulation takes $\sim 5$ h and included all steps of cleaning presented in Fig. 1 (triplicate). All the manipulations conducted over the course of the study were carried out by a single individual in order to ensure the uniformity and reliability of the manipulations.

**Step 1: voluntary contamination of the work surface**

The work surfaces of two distinct and predefined hood zones were contaminated. The
The dimensions of each of the contaminated zones were \(16 \times 12\) cm, i.e. \(192\) cm\(^2\) (Fig. 2). In all, \(1\) ml of cyclophosphamide at \(20\) mg ml\(^{-1}\) (Procytox\(^{®}\); Baxter Corporation, Pointe-Claire, Quebec) was deposited using a syringe at each of the two predetermined zones and an action time of \(10\) min was selected to allow the drug to impregnate the hood’s surface. A contamination level of \(0.1\) mg cm\(^{-2}\) (\(104.2\) ng cm\(^{-2}\)) was recorded for each of the two zones. The quantity of cyclophosphamide introduced voluntarily more or less represents that of an accidental spill during handling. Although this may seem high, these volumes and concentrations of cyclophosphamide reflected reality because \(20\) mg ml\(^{-1}\) represents the most frequently used vial concentration of cyclophosphamide at the pharmacy and a spill of \(1\) ml is also realistic considering that the smaller volume of cyclophosphamide prepared in syringes is \(\sim 15\) ml.

**Step 2: cleaning the hood according to the two evaluated techniques.**

**Usual cleaning technique:** The usual cleaning technique used by our technicians to clean the inside of hoods at the end of each regular work shift required the use of \(0.05\%\) chlorhexidine (v/v) (Baxedin; Omega Laboratories Ltd, Montreal, Quebec) followed by \(70\%\) ethyl alcohol (v/v) (Commercial Alcohols Inc., Brampton, Ontario, Canada) and \(\sim 10\) sterile cotton or gauze compresses (AMD-Ritmed Inc., Montreal, Quebec, Canada). The cleaning technique entailed spraying a solution of \(0.05\%\) chlorhexidine over the entire surface of the hood, rubbing the work surface with five sterile gauze, then spraying the surface with \(70\%\) ethyl alcohol, and rubbing the surface with five new sterile gauze.

**Cleaning technique with surface Safe\(^{®}\):** The commercial product Surface Safe\(^{®}\) is offered in kit form. One kit contains two distinct bags, each containing a polyester towelette measuring \(5.5 \times 10\) inches. In the first bag, the towelette contains a mixture of \(2\%\) sodium hypochlorite (v/v) and a soap solution, whereas the towelette in the second bag contains a solution of \(1\%\) sodium thiosulfate (v/v) combined with a solution of \(0.9\%\) benzyl alcohol (v/v).

To wash the surface of the hood with Surface Safe\(^{®}\), two kits were used for each wash evaluation to meet the recommendations of the company that stipulate that one kit may be used to clean a surface of \(0.19\) m\(^2\) (the hood’s surface measures \(\sim 91\)-cm wide \(\times 45\)-cm deep). The Surface Safe\(^{®}\) cleaning technique, as described by the supplier of the product, involves opening the first bag, vigorously rubbing the towelette provided on the entire work surface to be cleaned, letting the product work on the content for \(\sim 30\) s, opening the second bag, then rubbing the other towelette provided again on the zone to be cleaned, and rinsing the cleaned surface with water.

**Complete cleaning technique:** The complete cleaning technique was carried out using a \(2\%\) sodium hypochlorite solution diluted from a \(10.8\%\) concentrated solution (Lavo Inc., Montreal, Quebec, Canada), \(0.05\%\) chlorhexidine (Baxedin; Omega Laboratories Ltd), \(70\%\) ethyl alcohol (Commercial Alcohols Inc.), sterile water (Baxter Corporation, Pointe-Claire, Quebec), and a soap solution. The complete cleaning technique was conducted in triplicate in order to ensure the reproducibility of the obtained results.
Toronto, Ontario, Canada), and ~20 sterile cotton or gauze compresses (AMD-Ritmed Inc.). The complete cleaning technique entailed spraying a 2% sodium hypochlorite solution over the entire surface of the hood, rubbing the work surface with five sterile gauzes, rinsing out the work surface with sterile water, and rubbing the work surface with five new sterile gauzes; then spraying a 0.05% chlorhexidine solution over the entire surface of the hood and rubbing the work surface with five new sterile gauzes; then finally spraying a 70% ethyl alcohol on the surface of the entire surface of the hood and rubbing the work surface with five new sterile gauzes. Cleaning the entire hood’s surface was timed at 3 min in order to ensure the reproducibility of the technique and to reproduce the time usually allotted to cleaning the hoods after each work shift. All cleaning solutions used in the study were water-based solutions.

**Step 3: cyclophosphamide sampling and quantification.**

**Sampling technique:** In order to measure cyclophosphamide surface contamination, a sample from each of the two predefined contamination zones inside the hood (Fig. 2) was taken after each of the washes performed during the study (six washes using complete cleaning technique, three washes using the usual technique, and three washes with the product Surface Safe®) using a sampling method inspired by that of Larson et al. (2002) and developed by the team at the Institut National de Sante Publique du Québec (INSPQ). Sampling techniques have been validated by INSPQ and tests have been previously conducted to insure the validity of results obtained. All the surface samples ($n = 24$) were taken by the same individual. The sampling technique consisted of sampling a standard surface of ~600 cm$^2$ ($20 \times 30$ cm) for each specified zone using, for analysis purposes, a Wypall® X-60 wiper of woven polypropylene measuring $6 \times 8$ cm (Kimberly Clark Professional, Newton Square, PA, USA) that was moistened with 1 ml of sampling solution ($10\%$ MeOH and $90\%$ 5 mM ammonium acetate solution). The sampling time for each of the sites lasted ~20 s. The sampling technique of the analyst was previously validated by INSPQ member to insure the reproducibility of the sampling zone (600 cm$^2$). Scotch tape was also placed on the front metal grill inside the hood to insure that 600 cm$^2$ was respected for each sample.

**Cyclophosphamide quantification technique:** The cloth was put in a 50-ml polypropylene tube and 10 ml of the sampling solution (10% methanol and 90% ammonium acetate 5 mM) were added. The tube was then agitated mechanically on a shaker for 10 min, centrifugate, and 50 μl of internal standard was added (cyclophosphamide-d6, 500 ng ml$^{-1}$; CPS Chemie + Service GmbH, Germany) to 1 ml of the extract. The quantification of cyclophosphamide in the extract was conducted using UPLC-MS-MS technology (Acquity UPLC system coupled to a Quattro Premier XE tandem mass spectrometer; Waters, Milford, MA, USA) in positive electrospray with multiple reaction monitoring acquisition mode. Chromatographic analysis was carried out on a C$\text{18}$ Acquity UPLC BEH column ($2.1 \times 50$ mm, 1.7 μm; Waters) using a gradient from 10/90 methanol/ammonium acetate 5 mM to 60/40 methanol/ammonium acetate 5 mM in 2 min. The results were expressed in nanogram per milliliter and then converted into nanogram per square milliliter by multiplying each of the values obtained by 11 (total liquid volume) and then dividing by 600 (surface area sampled). The quantification limit for cyclophosphamide was 0.0026 ng cm$^{-2}$ (0.14 ng ml$^{-1}$).

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

**RESULTS**

The results of the pilot study included 6 samples taken after performing the usual cleaning technique, 6 samples taken after using the product Surface Safe® as well as 12 samples taken after carrying out washes using the complete cleaning technique, with the aim of evaluating basic hood surface contamination before each new evaluation. The quantification of the samples carried out after the use of the usual and Surface Safe® cleaning technique revealed median concentrations of cyclophosphamide of 165 ng cm$^{-2}$ (ranging from 40 to 570) and 65 ng cm$^{-2}$ (ranging from 57 to 110), respectively. Table 1 presents in detail the theoretical and detected quantities (ng) and concentrations (ng cm$^{-2}$) of cyclophosphamide on the hood’s surface for each of the samples taken. All the data collected revealed an average 99.5% efficacy in reducing the quantity of cyclophosphamide (ng) detected on the work surface for each of the two techniques employed.

**DISCUSSION**

Is there a universal solution or agent that is able to degrade, inactivate, and eliminate all the hazardous
Table 1. Concentrations and quantities of cyclophosphamide detected over the course of the study

<table>
<thead>
<tr>
<th>Samples number a</th>
<th>Cleaning technique evaluated</th>
<th>Residual/initial contamination of work surface b</th>
<th>Quantity of cyclophosphamide added on work surface (ng)</th>
<th>Theoretical quantity of cyclophosphamide detected before cleaning (ng)</th>
<th>Concentration/quantity of cyclophosphamide detected after cleaning (ng/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Surface Safe®</td>
<td>0.0 (ng cm⁻²)</td>
<td>20 000 000.0 (ng)</td>
<td>20 000 000.0</td>
<td>57.0 (ng cm⁻²)</td>
</tr>
<tr>
<td>2</td>
<td>Surface Safe®</td>
<td>0.0 (ng cm⁻²)</td>
<td>20 000 000.0 (ng)</td>
<td>20 000 000.0</td>
<td>60.0 (ng cm⁻²)</td>
</tr>
<tr>
<td>3</td>
<td>Usual technique</td>
<td>1.6 (ng cm⁻²)</td>
<td>20 000 000.0 (ng)</td>
<td>20 000 000.0</td>
<td>40.0 (ng cm⁻²)</td>
</tr>
<tr>
<td>4</td>
<td>Usual technique</td>
<td>1.5 (ng cm⁻²)</td>
<td>20 000 000.0 (ng)</td>
<td>20 000 000.0</td>
<td>98.0 (ng cm⁻²)</td>
</tr>
<tr>
<td>5</td>
<td>Surface Safe®</td>
<td>1.7 (ng cm⁻²)</td>
<td>20 000 000.0 (ng)</td>
<td>20 001 020.0</td>
<td>58.0 (ng cm⁻²)</td>
</tr>
<tr>
<td>6</td>
<td>Surface Safe®</td>
<td>3.1 (ng cm⁻²)</td>
<td>20 000 000.0 (ng)</td>
<td>20 001 860.0</td>
<td>79.0 (ng cm⁻²)</td>
</tr>
<tr>
<td>7</td>
<td>Usual technique</td>
<td>3.9 (ng cm⁻²)</td>
<td>20 000 000.0 (ng)</td>
<td>20 002 340.0</td>
<td>170.0 (ng cm⁻²)</td>
</tr>
<tr>
<td>8</td>
<td>Usual technique</td>
<td>3.6 (ng cm⁻²)</td>
<td>20 000 000.0 (ng)</td>
<td>20 002 160.0</td>
<td>160.0 (ng cm⁻²)</td>
</tr>
<tr>
<td>9</td>
<td>Surface Safe®</td>
<td>5.5 (ng cm⁻²)</td>
<td>20 000 000.0 (ng)</td>
<td>20 003 300.0</td>
<td>70.0 (ng cm⁻²)</td>
</tr>
<tr>
<td>10</td>
<td>Surface Safe®</td>
<td>3.0 (ng cm⁻²)</td>
<td>20 000 000.0 (ng)</td>
<td>20 001 800.0</td>
<td>110.0 (ng cm⁻²)</td>
</tr>
<tr>
<td>11</td>
<td>Usual technique</td>
<td>7.0 (ng cm⁻²)</td>
<td>20 000 000.0 (ng)</td>
<td>20 004 200.0</td>
<td>450.0 (ng cm⁻²)</td>
</tr>
<tr>
<td>12</td>
<td>Usual technique</td>
<td>7.3 (ng cm⁻²)</td>
<td>20 000 000.0 (ng)</td>
<td>20 004 380.0</td>
<td>570.0 (ng cm⁻²)</td>
</tr>
</tbody>
</table>

aSamples are presented in order they were taken on the work surface during the study.
bInitial concentrations and quantities of cyclophosphamide were measured after each wash using complete cleaning technique carried out at the beginning of the study as well as after the evaluation of each of the cleaning techniques (usual versus Surface Safe®).

drugs prepared in a pharmacy? The question remains unanswered given the publication of studies that reveal the presence of environmental contamination with various hazardous drugs on pharmacy work surfaces used for the preparation of chemotherapy. In fact, a number of authors have attempted to answer the question and are interested in identifying a solution or an agent capable of inactivating, degrading, and reducing environmental contamination with hazardous drugs in order to limit the exposure of staff working in healthcare settings (Monteith et al., 1987; Benvenuto et al., 1993; Shea et al., 1996; Castegnaro et al., 1997; Hansel et al., 1997; Barek et al., 1998). Among the main cleaning agents that have been evaluated in the literature are sodium hypochlorite, hydrogen peroxide, Fenton’s reagent, potassium permanganate, hydrogen chloride, sodium thiosulfate, and calcium hypochlorite. A review of the findings of these numerous studies specifically illustrate the efficacy of sodium hypochlorite, Fenton’s reagent as well as potassium permanganate in completely degrading approximately a dozen hazardous drugs including cyclophosphamide, ifosfamide, cisplatin, doxorubicin, methotrexate, etc. (Monteith et al., 1987; Benvenuto et al., 1993; Shea et al., 1996; Castegnaro et al., 1997; Hansel et al., 1997; Barek et al., 1998). Nevertheless, there is a controversy concerning the ability of the agents to completely inactivate all hazardous drugs and the risk of mutagenic residues subsequently being formed from any quantities that are not eliminated (Monteith et al., 1987; De Méo et al., 1991; Shea et al., 1996; Hansel et al., 1997). Table 2 presents the main literature findings on the subject. However, despite the publication of these articles, it remains difficult to reach an informed decision and identify the most effective agent among those on the list since the methodology used, quantification technique, time of action, hazardous drugs evaluated, and efficacy criteria used vary enormously from one study to another. It remains difficult to interpret and generalize the data presented in each of the studies because of the widely varying methodologies used.

The findings obtained over the course of our pilot study revealed that the usual cleaning technique, a combination of successive 70% ethyl alcohol and 0.05% chlorhexidine-based washes, was effective in reducing the quantity of cyclophosphamide (expressed in nanogram) detected on the work surface by up to 99.3%. This percentage efficacy was comparable to that which resulted from the evaluation of the use of the product Surface Safe® (99.8%), which consisted of a 2% sodium hypochlorite-based wash followed by a wash with a 1% sodium thiosulfate solution. Efficacy results for the latter were in accordance with the data presented in the literature (Monteith et al., 1987; Benvenuto et al., 1993; Castegnaro et al., 1997; Hansel et al., 1997; Barek et al., 1998). Nevertheless, the quantity of residual cyclophosphamide noted was still over the limit.
Table 2. Presentation of the results obtained in various studies published on the subject since 1980

<table>
<thead>
<tr>
<th>Agents</th>
<th>Tested drugs</th>
<th>Efficacy (results)</th>
<th>Mutagenic residues detected</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium hypochlorite (5.25%)</td>
<td>Cyclophosphamide, amsacrine, azathioprine, asparaginase, thiotepa, ifosfamide, melphalan, etoposide, cisplatin, carmustine, methotrexate, doxorubicin, daunorubicin, losoxantrone, mitomycin c</td>
<td>Complete degradation</td>
<td>No excepted for mitomycin C (Shea et al., 1996)</td>
<td>Barek et al. (1998), Castegnaro et al. (1993), Hansel et al. (1997), Monteith et al. (1987), and Shea et al. (1996)</td>
</tr>
<tr>
<td>Hydrogen peroxide (30%)</td>
<td>Cyclophosphamide, amsacrine, azathioprine, asparaginase, thiotepa, ifosfamide, melphalan, doxorubicin, daunorubicin</td>
<td>Inefficient</td>
<td>Yes for some drugs</td>
<td>Barek et al. (1998), Castegnaro et al. (1997), Hansel et al. (1997), and Roberts et al. (2006)</td>
</tr>
<tr>
<td>Fenton reagent</td>
<td>Cyclophosphamide, amsacrine, azathioprine, asparaginase, thiotepa, ifosfamide, melphalan, doxorubicin, daunorubicin</td>
<td>Complete degradation</td>
<td>No excepted for ifosfamide, cyclophosphamide and melphalan (Hansel et al., 1997)</td>
<td>Barek et al. (1998), Castegnaro et al. (1997), and Hansel et al. (1997)</td>
</tr>
<tr>
<td>Potassium permanganate</td>
<td>Etoposide, cisplatin, cyclophosphamide, ifosfamide, carmustine, methotrexate</td>
<td>Complete degradation of all drugs excepted for cyclophosphamide</td>
<td>No</td>
<td>Hansel et al. (1997) and Monteith et al. (1987)</td>
</tr>
<tr>
<td>Hydrogen chloride</td>
<td>Etoposide, cisplatin, cyclophosphamide, ifosfamide, carmustine, methotrexate</td>
<td>Inefficient degradation of etoposide and others drugs</td>
<td>Yes</td>
<td>Benvenuto et al. (1993)</td>
</tr>
<tr>
<td>Sodium thiosulfate</td>
<td>Etoposide, cisplatin, cyclophosphamide, ifosfamide, carmustine, methotrexate</td>
<td>Inefficient degradation of etoposide and others drugs</td>
<td>Yes</td>
<td>Benvenuto et al. (1993)</td>
</tr>
<tr>
<td>Sodium diethyldithiocarbamate</td>
<td>Cisplatin</td>
<td>Complete degradation</td>
<td>NA</td>
<td>Monteith et al. (1987)</td>
</tr>
<tr>
<td>Alcotabs® (Alconox®)</td>
<td>Bisnafide</td>
<td>No more detectable trace of drugs on work surface after cleaning</td>
<td>NA</td>
<td>Segretario et al. (1998)</td>
</tr>
<tr>
<td>Calcium hypochlorite</td>
<td>Doxorubicine, daunorubicine, mitoxantrone, vincristine, carmustine, methotrexate</td>
<td>Inefficient degradation of all drugs</td>
<td>NA</td>
<td>Dorr and Alberts (1992)</td>
</tr>
</tbody>
</table>

NA, not applicable.
proposed by the USP in spite of the use of a cleaning technique that included both agents whose efficacy was previously demonstrated in the literature, i.e. sodium hypochlorite and sodium thiosulfate (USP, 2008). In fact, the detection of concentrations of cyclophosphamide capable of exceeding 100 ng cm$^{-2}$ over the course of our study could be caused by the use of a very large quantity of cyclophosphamide during the voluntary contamination of the hood’s surface; 1 ml of a 20 mg ml$^{-1}$ cyclophosphamide solution was added to the work surface during the voluntary contamination of the hood, which corresponds to a quantity of cyclophosphamide of $\sim 2 \times 10^7$ ng. Thus, while the techniques were very effective in actively reducing the abundant quantity of cyclophosphamide added during the contamination, a residual concentration of between 40 and 570 ng cm$^{-2}$ still remained on the work surface.

Furthermore, notwithstanding the percentage efficacy obtained for each of the two cleaning techniques that we evaluated, it is important to note that the concentration of cyclophosphamide detected on the work surface of the hood was twice as high after the use of the usual cleaning technique when compared with the results obtained with Surface Safe®. In point of fact, the median concentration detected after the use of the product Surface Safe® came to 65 ng cm$^{-2}$ (range 57–110), whereas that obtained with the usual technique was 165 ng cm$^{-2}$ (40–570). As there is a paucity of data on the actual impact of long-term exposure to varying hazardous drug concentrations of this order, it is our wish to stop exposing employees to such concentrations and it is essential that we find a method of decontamination that is capable of reducing contamination to a level lower than 1 ng cm$^{-2}$ in order to minimize any potential associated risk. In actual fact, a number of authors have detected the presence of hazardous drugs such as cyclophosphamide in the urine of healthcare workers (nurses, technical assistants, etc.) who routinely handle these agents (Rekhadevi et al., 2007; Sottani et al., 2008). A study conducted by Cavallo et al. also demonstrated that the administration of hazardous drugs could cause genetic damage that is more significant than that caused by the preparation of the same drugs by technicians as the conditions under which they are prepared are safer in the pharmacy than on the floors where they are administered to patients because of the use of complete protective equipment, limited number of technician, and adequate training (Cavallo et al., 2005).

By observing the results obtained over the course of our pilot study, we also noted that the contamination detected on the surface of the hood throughout the study had a cumulative effect despite the wash using complete cleaning technique done after each evaluation. In reality, the cleaning done between each step did not allow us to return to the initial undetectable level of hood contamination noted at the beginning of the study. This demonstrates that in spite of the use of a cleaning technique that reduces the quantity of cyclophosphamide (in nanogram) on the work surface by $\sim 99.5\%$, an accumulation of contamination is possible. This could result from the combination of six subsequent voluntary contaminations of hood surface with 1 ml of cyclophosphamide. It could be possible that a longer time of action of cleaning solution on surface supposedly has reduced contamination <1 ng cm$^{-2}$. Other studies are needed to assess the time of action required to eliminate the major part of contamination. This observation shows that in the case of a spill (the quantity of cyclophosphamide introduced voluntarily more or less represents that of an accidental spill during handling), a wash using complete cleaning technique with adequate products is required to avoid prolonged exposure and an accumulation of hazardous drugs on the work surface. Using disposable absorbent sheets on the stainless steel work area in hood and biological safety cabinets could have been a great alternative to avoid direct contamination of work surface and to reduce the cumulative effects noted. We, nevertheless, noted that Surface Safe® allowed us to reduce the concentration of cyclophosphamide to a lower level in the range of 50 ng cm$^{-2}$, despite the effect of an accumulation of contamination on the surface. The use of a sodium hypochlorite and sodium thiosulfate solution could, therefore, be a potential agent to restrict the accumulation of contamination on work surfaces. We also noted that by combining two washes, i.e. a wash using complete cleaning technique combined with one of the cleaning techniques we evaluated, allowed us to reduce the rate of detected environmental contamination significantly. In fact, the combination of the two cleaning techniques resulted in the detection of a median concentration of cyclophosphamide up to 3.1 ng cm$^{-2}$ (<limit of quantification –7.3). This corresponds to a reduction of $>50$ times the median concentration obtained after the use of the usual cleaning technique alone (165 ng cm$^{-2}$). Therefore, combining both washes successively in healthcare facilities on a weekly basis could possibly be considered in order to reduce the contamination to minimally detectable limits.

In addition, apart from the search for an effective solution or agent, the optimal technique to be used to decontaminate work surfaces remains to be determined. In fact, there are quite a few different types
of sterile compresses or gauzes and towelettes or cloths of distinct composition that may be used in cleaning hoods and surfaces that come into contact with hazardous drugs. Is it necessary to prioritize the use of a cloth or compress in cotton, polyester, cellulose, polypropylene, polyamide, polyethylene, or even microfiber to improve the efficacy of the cleaning technique? Further studies need to be conducted in order to identify the optimal type of towelette or compress to use in order to ensure the quality of the cleaning of potentially contaminated surfaces.

The pilot study enabled us to evaluate and compare the efficacy of two cleaning techniques in reducing environmental contamination with cyclophosphamide. Although it allowed us to observe that the percentage efficacy of a combination of ethyl alcohol and chlorhexidine is similar to that of a combination of sodium hypochlorite and sodium thiosulfate in terms of the direct effect on the reduction of the quantity of cyclophosphamide (expressed in nanogram) detected on a work surface, the combination of various types of cleaning techniques is necessary in order to reduce contamination to concentrations around or \( \leq 1 \text{ ng cm}^{-2} \). The pilot study did not allow us to verify whether using Surface Safe® is more effective than the separate use of these same agents. Additionally, the study did not enable us to compare the pharmacoeconomic aspects of the techniques we evaluated. As hazardous drugs are sometimes difficult to eliminate and inactivate completely on work surface, it could be an interesting solution to conduct selective surface sampling to evaluate environmental contamination in order to improve preparation technique and decontamination procedures at the pharmacy and to reduce risk of absorption for healthcare professionals. This might be supplemented by evaluation of contamination by cyclophosphamide in the air of the work environment, in blood sample, or in urine. Furthermore, it could be better to prevent contamination and to promote different procedures such as the use of a separate decontamination room to unpack hazardous drugs, cleaning of vials before storing in the pharmacy, or decontamination of prepared hazardous drugs (bags or syringe) in the hood before dispensing to reduce environmental contamination.

The study does, however, have some limitations. Although we performed each of the steps aimed at evaluating both cleaning techniques three times, the number of total samples taken after each step was insufficient to allow us to generalize the results obtained for each of the cleaning techniques we evaluated. A larger scale study is called for within the framework of regular operations. Furthermore, the effect of the accumulation of contamination on work surfaces, despite performing a wash using complete cleaning technique between each step, may have lightly influenced our results and thereby tended to increase the concentration of cyclophosphamide detected on work surfaces. On the other hand, our quantification technique did not allow us to evaluate the formation of mutagenic residues on the work surface and it was, therefore, impossible from our analyses and findings to determine the actual inactivation capability of the agents we evaluated. Moreover, our technique was limited to the evaluation of the reduction of the environmental contamination of one single hazardous drug and we could not extend the results obtained to other dangerous drugs. Finally, in spite of the use of a known quantity and concentration of cyclophosphamide during the voluntary contamination of the work surface, no sample was taken to quantify the quantity actually present in the predefined zone after contamination. We had to restrict ourselves to a theoretical calculation in order to know the quantity potentially added and present on the surface after contamination.

**CONCLUSION**

The pilot study shows that the two techniques employed to clean contaminated surfaces are similar in terms of their efficacy in reducing the quantity of cyclophosphamide (ng), but it is still difficult to reduce the residual concentration of cyclophosphamide found on work surfaces below the limit of detection using a voluntary contamination of 20 mg of cyclophosphamide. The study underlines the importance of combining cleaning techniques successively in order to reduce the residual concentration of hazardous drugs to the maximum extent and it suggests that a combination of sodium hypochlorite and sodium thiosulfate be used in order to reduce environmental contamination to even lower levels. Despite the data published in the literature, it was impossible for us to reach a decision as to the most appropriate and optimal technique to use to ensure the decontamination of work surfaces and effective inactivation of hazardous drugs. The study, therefore, emphasizes the need for further comparative studies of various cleaning solutions or agents and types of towelettes in order to determine the optimal decontamination technique to be used for cleaning work surfaces. Further studies could also serve to establish guidelines as to what decontamination agents should be used to limit or eliminate the presence of contamination on work surfaces.
and thereby reduce the exposure of healthcare workers to hazardous drugs.

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