

## Short Communication

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# Efficacy of two intensive decontamination protocols and their effects after 30 days on environmental contamination by cyclophosphamide

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### Abstract

**Objectives:** To evaluate the efficacy of two decontamination protocols on cyclophosphamide surface contamination and to explore its lasting effect 30 days later.

**Methods:** All sampling sites that were systematically contaminated with cyclophosphamide in 2017–2020 were included, from a convenience sample of centers. The first decontamination protocol consisted of four steps, each with 20 mL and a Wypall® wipe: detergent, sodium hypochlorite 2%, isopropyl alcohol 70% and water. The second decontamination protocol consisted of eight steps, each with 15 mL and a Micronsolo® microfibre wipe: detergent, sodium hypochlorite 2%, isopropyl alcohol 70%, water and then a second round with each of the four products. A first sampling was done at the end of a regular working day (T0), a second immediately following decontamination (T1) and a third 30 days later (T2) after regular operations. Cyclophosphamide was quantified by ultra-performance liquid chromatography – tandem mass spectrometry (limit of detection 0.001 ng/cm<sup>2</sup>).

**Results:** Seventeen sampling sites were included: six biological safety cabinet (BSC) front grilles, eight floors in front of BSCs and three cyclophosphamide storage shelves.

The second protocol was more effective; however they both failed to completely remove all cyclophosphamide traces. BSCs and floors were found to be contaminated again 30 days later, at similar concentrations than at T0. A lasting effect was observed on the cyclophosphamide storage shelves that were less prone to be contaminated again.

**Conclusions:** Periodic decontamination with many cleaning steps is necessary on all surfaces, including those less frequently contaminated. Regular surface monitoring identifies systematically contaminated areas.

**Keywords:** antineoplastic drugs; cyclophosphamide; decontamination; surface monitoring.

## Introduction

Exposure to antineoplastic drugs may represent a risk to healthcare workers' health [1]. Cyclophosphamide is one of the drug most frequently measured in environmental contamination studies, along with gemcitabine, 5-fluorouracil and paclitaxel [2–5]. Surface contamination may be used as a proxy measure to estimate a workers' exposure to antineoplastic drugs.

Longitudinal studies have shown a tendency for surface contamination to reduce over the years [5–7]. This reduction is probably the result of gradual working practice improvements and increased workers' awareness. Nonetheless, low drug concentrations remain on surfaces and these cytotoxic residues can accumulate on surfaces over the years [2].

This residual contamination is difficult to eradicate. Authors have reported that cyclophosphamide was still present on a surface more than three months after an accidental spill, despite many decontamination rounds [8]. The efficacy of cleaning products varies depending on the type of surface and the drug to remove, but no product can

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remove all traces alone [9, 10]. The cleaning efficacy improves with successive cleaning rounds [10].

The objective was to evaluate the efficacy of two decontamination protocols on cyclophosphamide surface contamination and to explore its lasting effect 30 days later. Our hypothesis was that the antineoplastic drug traces that persist on the healthcare centers surfaces may be residues accumulated from inadequate cleaning and that a thorough decontamination may reduce the surface contamination.

## Material and methods

### Site selection

We selected a convenience sample of centers located in the Montreal region that had conducted surface sampling four consecutive years in the 2017–2020 period.

We included all sampling sites from these centers that were systematically contaminated with cyclophosphamide in 2017–2020 (i.e. value above the limit of detection [LOD] for at least the last three years). The research team's records of environmental monitoring results were used. The consent of each Pharmacy Department Head was obtained.

### Decontamination protocols

Two intensive decontamination protocols were tested. The second protocol was adapted after the first one failed to completely decontaminate the surfaces tested.

The first decontamination protocol consisted of four steps, each done with 20 mL of liquid and a Wypall® wipe: detergent (Nu-Action 3™), sodium hypochlorite 2%, isopropyl alcohol 70% and water. Each cleaning step was done with standard pressure in two wipe motions, one from top to bottom and one from left to right with the other side of the wipe.

The second decontamination protocol consisted of eight steps, each done with 15 mL of liquid and a MicronSolo® microfibre wipe: detergent (Nu-Action 3™), sodium hypochlorite 2%, isopropyl alcohol 70%, water and then a second round with each of the four products. Surfaces were also lightly scrubbed with a dry wipe at the end of each round. The contact time with each product was of 2 min.

Descriptive statistics were done with Microsoft Excel: median, quartiles, minimum and maximum.

### Sampling

Two series of sampling were conducted. For each series, a first sampling was done before any interventions (T0), at the end of a regular working day. A second sampling was done immediately following the decontamination protocol (T1). A third sampling was done 30 days later (T2). Centers were following their usual cleaning practices during this 30-day period.

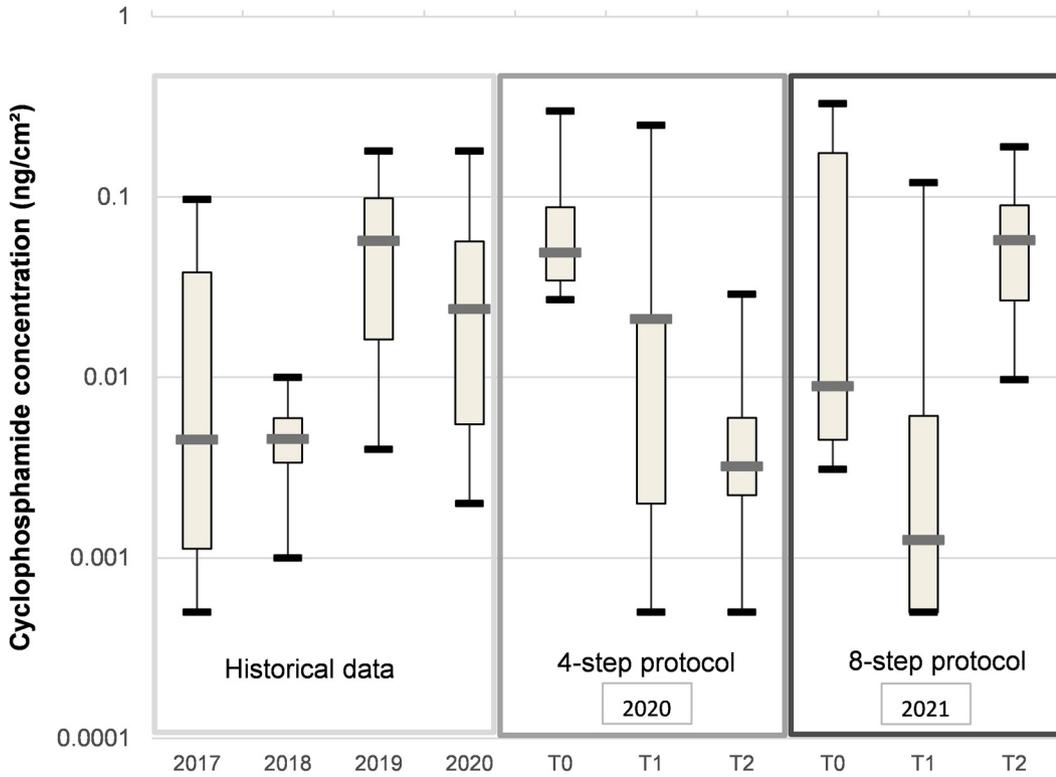
Sampling protocol and quantitative analysis were described previously [5]. A 600 cm<sup>2</sup> surface was sampled on each site. Each tube contained one 6 × 8 cm Wypall® X60 wipe (Kimberly Clark Professional, Newton Square, Pennsylvania). It was moistened with 1 mL of solution (10% methanol and 90% 5 mmol/L ammonium acetate) and stored refrigerated. Each surface was wiped four times: once horizontally and once vertically with each side of the wipe. Tubes were sent to the Centre de toxicologie du Québec for analysis. Cyclophosphamide was quantified on surfaces by ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS-MS) (Acquity UPLC® chromatographic system coupled with a Xevo TQ-S tandem mass spectrometer, Waters, Milford, MA, USA). Chromatographic separation was carried out on a C18 Acquity UPLC HSS (High strength silica) T3 column (2.1 × 100 mm, 1.8 µm; Waters, Milford, MA, USA) using a gradient elution beginning with 2/98 acetonitrile/0.1% formic acid in water and ending with 60/40 acetonitrile/0.1% formic acid in water over a 3 min period. The LOD was 0.001 ng/cm<sup>2</sup>. A sample was considered positive for a drug if the value was above the LOD and if the quantifier peak was within the maximum tolerance of mean calibrator for confirmatory criteria (signal/noise ratio >3, retention time ±0.02 min, quantifier/qualifier ion ratio ±20%).

## Results

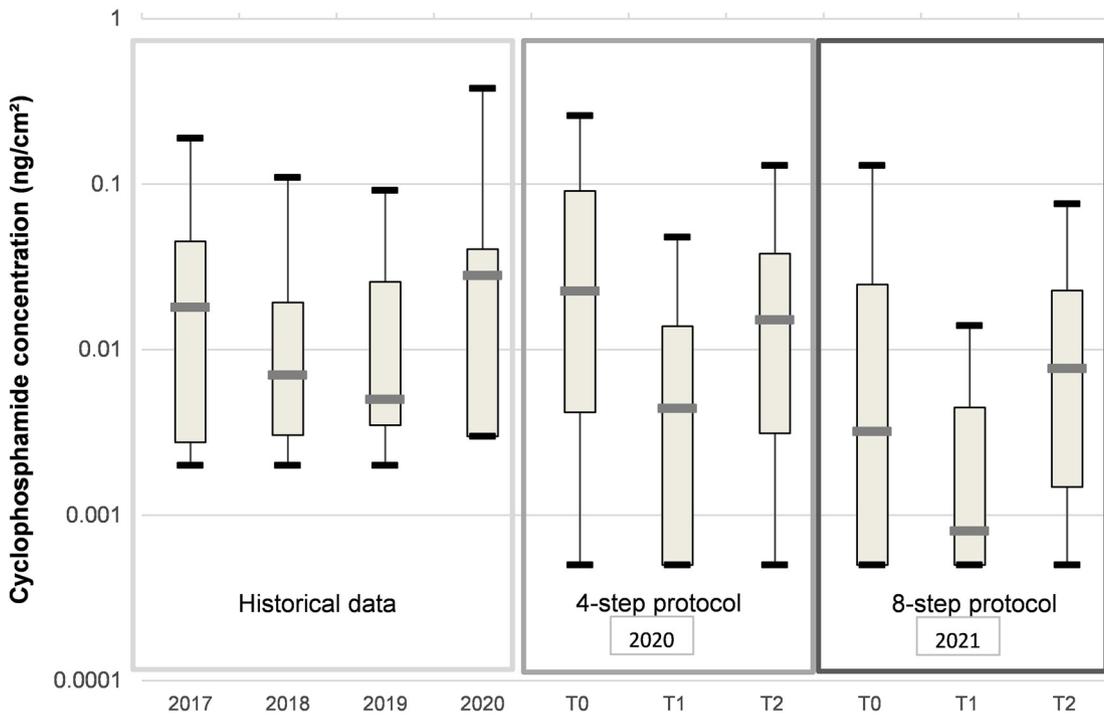
Nine centers were selected in October 2020. The nine centers handled a median [min–max] of 512 [90–1,750] g of cyclophosphamide in 2021. A total of 17 distinct sampling sites were included. One to three sampling sites were included per center: six biological safety cabinet (BSC) front grilles, eight floors in front of BSCs and three cyclophosphamide storage shelves. 15/17 sites were systematically contaminated all four years during the 2017–2020 period; two sites were contaminated three consecutive years in the 2018–2020 period. The first sampling series was conducted in October–November 2020 and the second one in January–March 2021. An outlier value was excluded from analysis (a T1 BSC grille of 2020).

At T0, the majority of samples were contaminated with cyclophosphamide (15/17, 88% and 13/17, 76% for both decontamination protocols, respectively). The proportion of positive samples decreased at T1 (9/16, 56% and 7/17, 41%, respectively) and reverted to pre-intervention levels at T2 (12/17, 71% and 13/17, 76%, respectively).

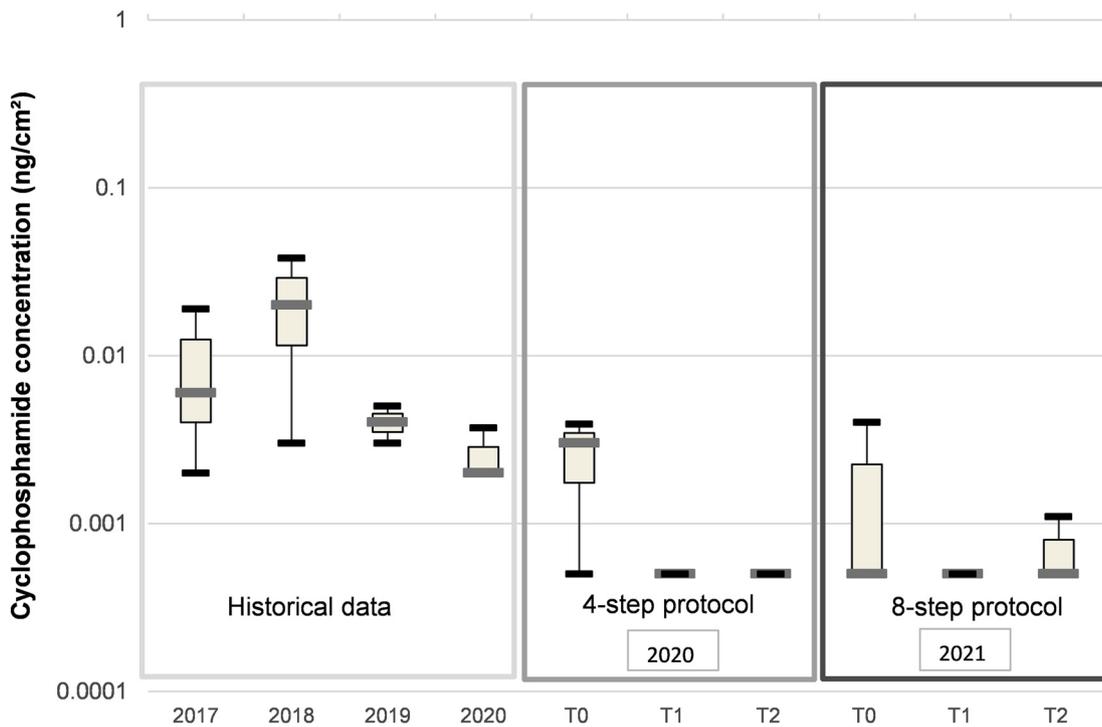
Both decontamination protocols reduced the median cyclophosphamide contamination on all three sampling sites (Figures 1–3). The second decontamination protocol was more effective than the first; however they both failed to completely remove all cyclophosphamide traces from the surfaces. Surfaces more at risk of being contaminated (BSCs and floor in front of BSCs) were found to be contaminated again 30 days later, at concentrations similar than those of T0. A lasting effect was observed on the cyclophosphamide storage shelves that were less prone to be contaminated again.



**Figure 1:** Cyclophosphamide contamination on biological safety cabinet front grilles ( $\text{ng}/\text{cm}^2$ ) ( $n=6$  sampling sites). 2017–2020 data obtained from historical surface monitoring results. The four-step decontamination protocol was conducted in 2020 and the eight-step protocol in 2021. Minimum, 25th, 50th, 75th percentile and maximum are shown. Logarithmic scale used. The limit of detection was  $0.001 \text{ ng}/\text{cm}^2$ .



**Figure 2:** Cyclophosphamide contamination on floor in front of the biological safety cabinets ( $\text{ng}/\text{cm}^2$ ) ( $n=8$  sampling sites). 2017–2020 data obtained from historical surface monitoring results. The four-step decontamination protocol was conducted in 2020 and the eight-step protocol in 2021. Minimum, 25th, 50th, 75th percentile and maximum are shown. Logarithmic scale used. The limit of detection was  $0.001 \text{ ng}/\text{cm}^2$ .



**Figure 3:** Cyclophosphamide contamination on cyclophosphamide storage shelves ( $\text{ng}/\text{cm}^2$ ) ( $n=3$  sampling sites). 2017–2020 data obtained from historical surface monitoring results. The four-step decontamination protocol was conducted in 2020 and the eight-step protocol in 2021. Minimum, 25th, 50th, 75th percentile and maximum are shown. Logarithmic scale used. The limit of detection was  $0.001 \text{ ng}/\text{cm}^2$ .

## Discussion

None of the two decontamination protocols tested was able to completely remove all cyclophosphamide traces from frequently contaminated surfaces.

### Cleaning efficacy

The two decontamination protocols included four and eight decontamination steps, respectively. Others have shown that at least 10 decontamination sessions were required to remove all traces of cyclophosphamide, which may explain the residual contamination measured [11].

Decontamination guidelines are not specific in terms of products, materials and frequency. Recommended cleaning protocols usually include between two and six steps with different products [12–14]. In this study, even the eight-step protocol was not able to remove all cyclophosphamide traces from most surfaces tested.

A two-step cleaning protocol (alkaline solution and isopropyl alcohol) was implemented in a 15 hospital European study [2]. The contamination with antineoplastic drugs was reduced after the implementation and the concentrations remained low 12 months later. However, traces

still persisted on surfaces, showing that the cleaning protocol alone was not sufficient to remove all traces. Another multicenter Canadian study also identified that surfaces were significantly less contaminated after each centers' usual cleaning procedure, but surfaces remained contaminated despite this decontamination [15].

Out of the 16 products tested on 11 antineoplastic drugs, a group identified sodium hypochlorite to be the most effective product overall; however because of its corrosive effect on stainless steel surfaces, decontamination with anionic surfactant and isopropyl alcohol was suggested [16]. None of the product tested removed all cyclophosphamide traces. A decontamination protocol should be followed with regular surface monitoring and must comply with local compounding practices [17].

The effect of the pressure applied with the wipe is unclear; a study showed that vigorous wiping increased the overall decontamination efficiency [18], while a second showed the opposite [10].

### Contamination persistence

In this study, sites that were systematically contaminated with cyclophosphamide during routine surface monitoring

were selected. Thus, it comes as no surprise that the sampling sites were contaminated again 30 days after the thorough cleaning. This suggests that the residual contamination observed on the BSC surfaces and floors from historical data were not caused by improper decontamination, but rather represent the normal contamination that occurs after a working day. Regular daily cleaning is needed to reduce the workers exposure and to provide a clean compounding area, but the added decontamination protocol did not lead to improvements 30 days later.

Nonetheless, the effect was different with the storage shelves. These areas are usually cleaned less frequently and may be less prone to contamination (compared with a BSC surface). Thus, the thorough decontaminations did reduce the contamination and the effect lasted 30 days later. A periodic thorough decontamination is recommended on all surfaces, not only on frequently used surfaces.

A group conducted repeated monitoring over a one year period, before and after a weekly decontamination consisting of either a three-step protocol of surfactant, water and isopropyl alcohol or a one-step protocol with isopropyl alcohol [19]. The decontamination efficacy was higher with the three-step protocol for most of the drugs tested. It is interesting to note that the surfaces of both BSCs evaluated were contaminated before and after cleaning, also representing the “normal” contamination measured on a frequently used surface.

Another group conducted repeated monitoring over a one year period and illustrated the variability of surface contamination that did not follow a particular pattern [3].

## Limits

The small convenience sample of this exploratory study prevented statistical analysis. Results may not be representative of all centers. Data about the centers’ pharmacy workload during the study period was not collected. Parameters regarding the contamination at T0, the centers’ activities and their practices during the 30 days period were not controlled, so a comparison of both decontamination protocols was not possible. Three different sampling sites were chosen; these sites were chosen because they were shown to be systematically contaminated and deemed good targets to investigate decontamination strategies. Cleaning efficacy varied depending of the sampling site. Few storage shelves were included, so results should be confirmed in a larger study.

Cyclophosphamide contamination was assessed. It would be interesting to repeat the experiment with

gemcitabine since it’s also frequently measured on surfaces. Cyclophosphamide was chosen because of its persistence on surfaces, it is a good proxy measure of surface contamination.

The contact time was of 2 min, others have used contact times of 10 min and even 20 min [11, 20].

## Conclusions

While most cleaning protocols have a good efficacy to remove the majority of contamination from a surface, the persistent traces are difficult to completely eradicate. A decontamination protocol with multiple cleaning steps is necessary. Regular surface monitoring can help to identify areas that are systematically contaminated and to maintain workers awareness of the need to use adequate handling practices and to use personal protective equipment. Periodic thorough decontamination is necessary on all surfaces, including those less frequently contaminated.

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**Informed consent:** The consent of each Pharmacy Department Head was obtained.

**Ethical approval:** The conducted research is not related to either human or animal use.

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