

## Occupational exposure to cytotoxic drugs: the importance of surface cleaning to prevent or minimise exposure

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Healthcare workers who prepare or administer cytotoxic agents run the risk of exposure, and the risks for health are real even at doses lower than those applied in cancer patients, because, in theory, no dose is safe. The most common and problematic route of exposure is through the skin, especially as work surfaces can remain contaminated even after cleaning. This pilot study aimed to demonstrate the importance of having an effective surface decontamination protocol by determining surface contamination with cyclophosphamide, 5-fluorouracil, and paclitaxel as the most common cytotoxic drugs in an oncology day service. Samples were collected before and after drug handling and analysed with high performance liquid chromatography with diode array detection (HPLC-DAD). Of the 29 samples collected before drug handling 23 were contaminated, five of which with more than one drug. Of the 30 samples collected after drug handling 25 were contaminated, eight of which with more than one drug. The two time points did not significantly differ, which evidences a widespread contamination and ineffective cleaning. This calls for revising the cleaning protocol and handling procedure to place contamination under control as much as possible.

**KEY WORDS:** *5-fluoroacil; contamination control; cyclophosphamide; HPLC-DAD; oncology day service; paclitaxel*

Cytotoxic drugs have been recognised as hazardous to healthcare professionals such as medical doctors, oncology nurses, pharmacists, and other staff, including maintenance, since the late 1970s (1). The European Agency for Safety and Health at Work (EU-OSHA) (2) and the European Commission Directorate-General for Employment, Social Affairs, and Inclusion (3) are well aware of the issue, but the legislation of the member states still has not been harmonised in terms of risk prevention in the healthcare sector (4). The EU legislation, however, does require from employers to provide a monitoring programme for carcinogenic compounds, which includes most of the cytotoxic drugs (4).

Essentially, their mechanism of action comes down to inhibiting tumour growth and cell division by interfering with the cell genetic material. However, the most common cytotoxic drugs are not specific enough to target tumour cells alone, but they also affect healthy cells of the exposed individuals (5-11). This can lead to genotoxic effects that can result in gene alterations and neoplasms in healthy population or secondary tumours in treated cancer patients (7, 9, 12).

Even exposure to doses lower than those received by cancer patients can produce adverse health effects, especially in chronically exposed healthcare workers (13-16). There have been reports of reproductive toxicity that can result in miscarriage, temporary or permanent infertility, preterm births, congenital malformations, and learning disabilities in the children of the exposed individuals (17, 18). In addition, long-term occupational exposure has been associated with increased risk of hair loss, infections (attributed to lower white blood cell count and immunosuppression), organ toxicity (e.g. liver, kidney, lung, and cardiac toxicity), myelotoxicity, mucosal ulcers, fatigue, bleeding, and headaches (19). Furthermore, occupationally exposed individuals have a higher incidence of DNA damage, chromosomal abnormalities, and cancer consistent with the inherent carcinogenic properties of these drugs (15, 20, 21).

Exposure can occur at every stage of the cytotoxic drug lifecycle: from production and distribution to its application in hospital or home care settings and its disposal as waste. The risk of exposure is not limited to healthcare workers who prepare (pharmacists and pharmacy technicians) or administer (nurses) cytotoxic agents. Anyone in touch with contaminated air or objects or even patient excreta is at risk (12, 22-26). One Dutch study (25) identified home care, nursing homes, and laundry facilities as non-hospital occupational settings with higher exposure, which were all

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related to the care of cancer patients. Clearly, a large number of workers can be exposed to cytotoxic agents in three ways: through inhalation of aerosolised drugs; through direct skin contact, and rarely through ingestion from contaminated hands and gloves (27). However, thanks to advanced protection technology available at the workplaces, such as biological safety cabinets, the most common and problematic route of exposure is skin (4, 28).

Yet, even with improvements in safe handling practices exposure to cytotoxic drugs is still a threat. Some studies reported traces of several cytotoxic drugs on work surfaces serving for receiving, storing, preparing, and validating preparations in hospital pharmacies (29-33) and even on surfaces in administration areas (33, 34). Some reported cytotoxic drugs in biological samples (blood and urine) from healthcare workers (19, 35-37) and some reported contamination of work surfaces even after their cleaning (4, 37-40).

The aim of this pilot study was therefore to establish working surface contamination with cytotoxic drugs in an outpatient oncology setting and see how effective the adopted standard decontamination procedures are.

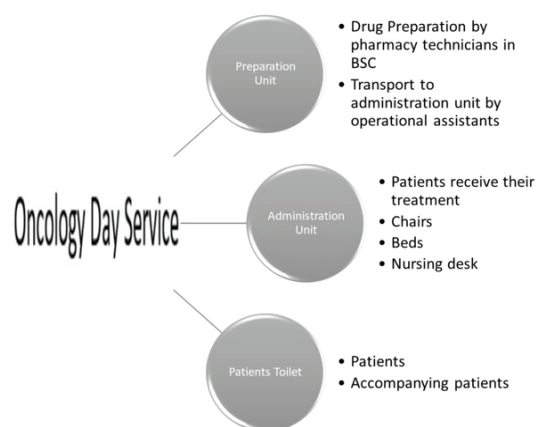
## MATERIALS AND METHODS

Our study focused on the drug preparation unit and the drug administration unit of an oncology day service (ODS), which treated 375 patients (over 3145 visits) in 2015. It also included the toilets used by patients and their accompanying family members, who also run the risk of exposure (Figure 1).

Before sampling began, we gathered information about the number of chemotherapies prepared, most common drugs used, application methods, and post-treatment cleaning procedures. We also asked the staff to carry on cleaning as usual to avoid bias. For sampling we chose a day regarded as »normal« by the staff in terms of the number of treatments. Samples from the working and other surfaces were taken with wipes (24).

The preparation unit had four pharmacists, three pharmacy technicians, and four assistants. It did not use a closed-system drug transfer device and had only two biosafety cabinets to prepare the cytotoxic drugs, but only used one at a time. The cytotoxic drugs in this unit were handled as follows: pharmacists would send the drugs to pharmacy technicians to prepare them in one of the biosafety cabinets and then check the preparations. Then the assistants would carry the preparations in a specific container similar to a biohazard box to the drug administration unit (Figure 1).

The administration unit had thirteen infusion chairs and three beds (plus two if needed) attended by 14 nurses and seven assistants. There was also a reception desk for patient registration on visits.



**Figure 1** The three units sampled in the ODS

The drug preparation and administration surfaces are cleaned at the end of the working day. The toilet is cleaned several times a day and more thoroughly at the end of the day. The cleaning products used were the same as in other hospital facilities. For the surfaces the staff used a product containing sodium tripolyphosphate (2.5-10 %), sulphonic acid (<2.5 %), sodium lauryl ether sulphate (2.5-10 %), propan-2-ol (2.5-10 %), and a small percentage of alcohol. For patient toilet they used a product with sodium hypochlorite (<5 %).

### Sampling

The choice of surfaces or objects to be wiped for samples was based on the observed everyday activities at the ODS and included surfaces and objects likely to be contaminated with cytotoxic drugs either through work or other routine behaviour (33).

Each spot was sampled twice: in the morning before drug handling started and three hours after it started. In total we collected 59 samples. Of the 29 morning samples, 12 were taken from the preparation unit, 12 from the administration unit, and five from the patient toilet. Three hours into the drug handling, we took 30 more samples: 12 from the preparation unit, 13 from the administration unit, and five from the toilet.

Samples were taken with a 100 cm<sup>2</sup> Kimtech Science wipe (Kimberly-Clark Professional, Roswell, GA, USA) soaked in ethyl-acetate and fastened to a stainless steel frame (100 cm<sup>2</sup>), as described elsewhere (33), except for door handles, computer mice, and telephones, where we could not use the stainless frame for obvious reasons. The wipes were then placed in Petri dishes, sealed with Parafilm M® (Bemis, Neenah, WI, USA), stored at 2–8 °C for transport to the laboratory in Lisbon (3 h), and then frozen at -20 °C up to two months until analysis.

The frame was cleaned between each sampling, and a new pair of gloves was used for each new wipe. All wipe samples were collected by the same person to ensure reliable and similar sampling. Blank wipes were used to check that

no contamination occurred during sampling and transportation to the laboratory.

### Sample analysis

The samples were analysed for cyclophosphamide (CP), 5-fluorouracil (5-FU), and paclitaxel (PTX) as the most commonly and abundantly used drugs in our ODS and in most of the oncology settings. Testing for all cytotoxic drugs would be too cost-ineffective (31, 32, 40-44).

The wipes were placed in 15-mL capped tubes with 10 mL of mobile phase (see below) for extraction in a roll homogeniser for 10 minutes.

The extracts were then forced through a 0.2 µm filter and injected in a high-performance liquid chromatographer with a diode array detector (HPLC-DAD) for separation and quantification with a Thermo Unicam Surveyor (Thermo Scientific™, San José, CA, USA). To do that we used the C18 Hypersil-GOLD® (Thermo Scientific™) 15×5×4.6, a respective guard column, and acetonitrile:methanol:water (19:13:68) as mobile phase. The flow rate was 0.8 mL min<sup>-1</sup>. All the HPLC-grade solvents used were purchased from VWR International (Radnor, PA, USA). CP, 5-FU, and PTX for calibration were purchased from Merck KGaA (Darmstadt, Germany). Calibration curves were obtained after their extraction from spiked wipes. Each sample was injected in triplicate. Chromatograms were integrated with the Xcalibur™ 2.0 software (Thermo Scientific™).

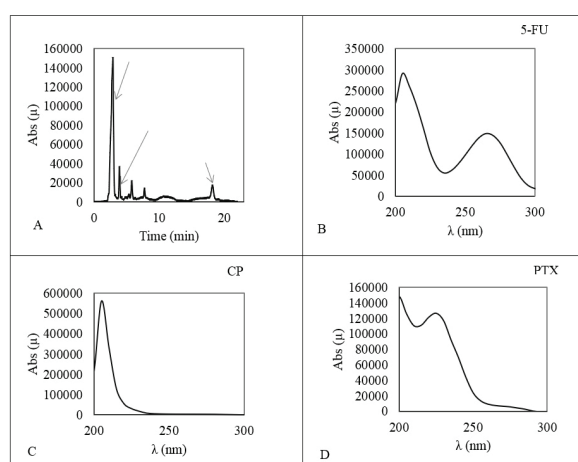
### Method validation

Validation followed the US Food and Drug Administration regulatory guidelines for analytical procedures (57). Table 1 shows the results of method validation, including the limit of detection (LOD) and limit of quantification (LOQ), which were within the range for this method (66-68). A sample was considered positive for a particular drug if the value was above LOD.

All calibration curves with a correlation coefficient (R<sup>2</sup>) greater than 0.990 for the three drugs were linear over the range. The LOD and LOQ correspond to the mean of five calibration curves.

Tables 2, 3, and 4 show the intra- and inter-day accuracy and precision parameters at six calibration levels. Table 5 summarises recoveries of 5-FU, CP, and PTX.

Their retention time was about 3.9, 5.8, and 18.4 minutes, respectively. Their typical chromatograms were well resolved, which indicates that the assay was selective (Figure 2).



**Figure 2** Typical chromatogram of a wipe spiked with the drugs under study A: all three drugs; B, C, and D: absorption spectra

### Statistical analysis

Normality of distribution was tested with the Shapiro-Wilk test. Prevalence of contamination before and after drug handling was compared with the frequency analysis. To compare drug concentrations at both time points (before and after drug handling started) between the three locations (drug preparation unit, drug administration unit, and patient toilet) we used the Kruskal-Wallis test. Kruskal-Wallis multiple comparison was also used for significantly different results. To compare 5-FU, CP, and PTX concentrations between the two time points we used the Wilcoxon test. The level of significance was set at a 5 %.

## RESULTS

Table 6 shows the distribution of positive samples with quantifiable drugs (>LOQ) by sampling time. Of the 29 morning samples 21 were contaminated: seven in the preparation unit, 10 in the drug administration unit, and four in patient toilet (Table 7). Of these, three were contaminated with more than one drug: two in the drug administration unit, and one in the patient toilet.

Of the 30 samples collected three hours into the drug handling, 24 were positive, 19 of which from the drug preparation and administration units and 5 from the patient toilet (Table 8). Of these, five were contaminated with more than one drug: four in the preparation unit, and one in the drug administration unit.

Table 9 shows total contamination of each unit by drug.

**Table 1** Method validation for each cytotoxic drug according to the FDA regulatory guidelines for analytical procedures (57)

|      | Equation                     | R <sup>2</sup> | LOD      | LLOQ     | Range        |
|------|------------------------------|----------------|----------|----------|--------------|
| 5-FU | Peak area=35209+16473.8x5-FU | 0.9983         | 0.900 ng | 2.728 ng | LOD-75 ng    |
| CP   | Peak area=35230.8+25147.7xCP | 0.9936         | 1.78 µg  | 5.40 µg  | LOD-60 µg    |
| PTX  | Peak area=21507.4+147442xPTX | 0.9923         | 0.20 ng  | 061 ng   | LOD-16.65 ng |

**Table 2** HPLC intra-day and inter-day ( $n=5$ ) quantification accuracy and precision for 5-fluorouracil (injection volume 100  $\mu$ L)

| Nominal amount (ng) | Measured amount (ng) | SD   | Precision (%RSD) | Accuracy (%) |
|---------------------|----------------------|------|------------------|--------------|
| <b>Intra-day</b>    |                      |      |                  |              |
| 7.500               | 6.950                | 0.49 | 7.10             | -7.33        |
| 15.000              | 15.300               | 0.09 | 0.60             | 2.00         |
| 30.000              | 30.840               | 0.08 | 0.27             | 2.80         |
| 45.000              | 44.360               | 0.89 | 2.00             | -1.42        |
| 60.000              | 60.050               | 1.23 | 2.05             | 0.08         |
| 75.000              | 72.270               | 1.67 | 2.31             | -3.64        |
| <b>Inter-day</b>    |                      |      |                  |              |
| 7.500               | 7.050                | 0.18 | 2.56             | -6.00        |
| 15.000              | 15.100               | 0.21 | 1.41             | 0.67         |
| 30.000              | 29.840               | 0.45 | 1.50             | -0.53        |
| 45.000              | 45.380               | 0.53 | 1.16             | 0.84         |
| 60.000              | 58.550               | 0.24 | 0.41             | -2.42        |
| 75.000              | 76.270               | 0.28 | 0.37             | 1.69         |

Of the total fifty nine samples collected, 45 were contaminated with one or more drugs. Considering only the results higher than the LOQ, contamination before and during drug handling did not differ significantly ( $p>0.05$ ) in any of the three units. However, the units did differ in contamination with CP and 5-FU. CP was significantly higher in the preparation unit than in other units three hours into the drug handling, and significantly higher in the administration unit than the others before drug handling (Figure 3). In turn, 5-FU was significantly higher in the preparation unit and the patient toilet three hours into the drug handling, while in the administration unit the concentration was higher before (Figure 4). Contamination with PTX was not statistically analysed because there were too few quantifiable samples to compare.

Table 10 shows the three sampling spots with significantly higher contamination with any of the cytotoxic drugs compared to the rest.

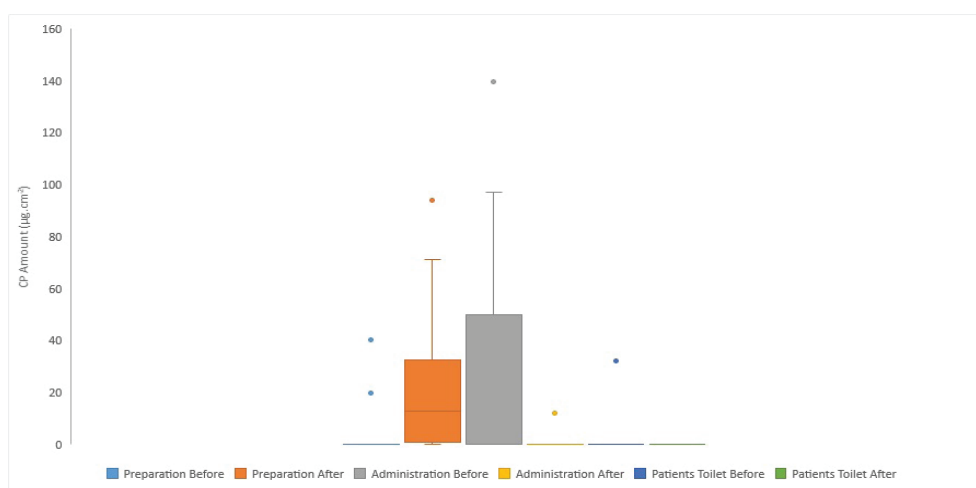
## DISCUSSION

Our results clearly show that the current cleaning procedure is ineffective in removing contamination with the three representative cytotoxic drugs. They also suggest that other variables contributed to contamination as well.

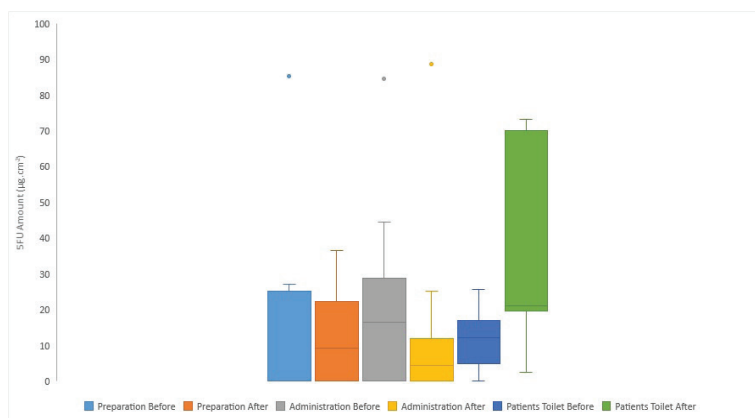
Our findings are similar to the contamination reported in Portuguese hospitals (33), but we did not expect to find higher contamination in the drug administration unit than in the preparation unit, where drugs are handled and mixed in high concentrations (33, 34).

**Table 3** HPLC intra-day and inter-day ( $n=5$ ) quantification accuracy and precision for cyclophosphamide (injection volume 100  $\mu$ L)

| Nominal amount ( $\mu$ g) | Measured amount ( $\mu$ g) | SD   | Precision (%RSD) | Accuracy (%) |
|---------------------------|----------------------------|------|------------------|--------------|
| <b>Intra-day</b>          |                            |      |                  |              |
| 6.000                     | 5.300                      | 0.36 | 6.7              | -11.7        |
| 12.000                    | 12.300                     | 0.43 | 3.5              | 2.5          |
| 24.000                    | 25.160                     | 0.55 | 2.2              | 4.8          |
| 36.000                    | 35.240                     | 0.74 | 2.1              | -2.1         |
| 48.000                    | 44.230                     | 0.75 | 1.7              | -7.9         |
| 60.000                    | 51.000                     | 1.79 | 3.5              | -15.0        |
| <b>Inter-day</b>          |                            |      |                  |              |
| 6.000                     | 5.50                       | 0.28 | 5.14             | 0.4          |
| 12.000                    | 12.02                      | 0.53 | 4.4              | -8.3         |
| 24.000                    | 23.70                      | 0.88 | 3.7              | 0.2          |
| 36.000                    | 36.0                       | 2.20 | 6.1              | -1.3         |
| 48.000                    | 48.2                       | 2.31 | 4.8              | 0.0          |
| 60.000                    | 58.896                     | 3.53 | 6.0              | 0.4          |



**Figure 3** CP contamination ( $\mu\text{g cm}^{-2}$ ) before and after drug handling started in each unit



**Figure 4** 5-FU contamination ( $\text{ng cm}^{-2}$ ) before and after drug handling started in each unit

In the preparation unit the most contaminated surfaces before drug handling were the ones in the support room and three hours into the handling, the most contaminated surfaces were the ones in the clean room (Table 7), which is quite expected as handling goes. Clean rooms are the central points for drug preparation but are also more thoroughly cleaned than other rooms when handling is over. This probably explains the distribution of contaminated surfaces at both sampling times in both units (Figures 2 and 3 and Table 10). Similar findings were reported by Fleury-Souverein et al. (30) for samples collected after the handling started, as they did not collect samples after cleaning.

In our study, 5-FU was found in most samples at both sampling time points, which confirms the findings reported by Kiffmeyer et al. (24). They also reported that 5-FU was the most used drug, which may explain our findings as well.

In both of our units and the patient toilet the most contaminated surfaces were the ones handled without gloves (phones, computer mouse, bed in the treatment room, toilet light switch, flush handle, and handlebars) regardless of the sampling time point. The same was reported in our previous study (33), where we attributed contamination to inappropriate cleaning and drug handling procedures. The same pattern was observed in a study of Italian hospitals (41), which reported that workers did not remove gloves

immediately after drug handling, and therefore spread the contamination on phones, chairs, closets and other surfaces not directly involved in drug preparation and administration. The same conclusions were reported by Kiffmeyer et al. (24), who found high concentrations of 5-FU on a closet door knob that was not used to store 5-FU.

Contamination of infusion pumps after drug administration started is similar to earlier reports (19, 33, 42). In fact, Hon et al. (34) claim that infusion pumps are most often touched by nurses during drug administration. This is of particular concern, because we found contamination before and after drug administration and also observed that the pumps were sometimes handled without gloves. Clearly, this equipment is not being cleaned.

We would also like to draw attention to the contamination of the beds in the treatment room, bed chart holders in particular. We observed that this surface was handled/touched by nurses and patients' families, implicating exposure for all these persons. This is one more surface that probably is not being cleaned well or often enough.

Furthermore, a study of health and safety practices by nurses that administered cytotoxic drugs in 2011 reported that 12 % of the 2069 respondents failed to use gloves, even though 4 % reported skin contact with the drug during handling and administration (44).



**Table 4** HPLC intra-day and inter-day ( $n=5$ ) quantification accuracy and precision for paclitaxel (injection volume 100  $\mu$ L)

| Nominal amount (ng) | Measured amount (ng) | SD    | Precision (%RSD) | Accuracy (%) |
|---------------------|----------------------|-------|------------------|--------------|
| <b>Intra-day</b>    |                      |       |                  |              |
| 1.665               | 1.812                | 0.395 | 21.811           | 8.80         |
| 3.330               | 3.014                | 0.182 | 6.035            | -9.50        |
| 6.660               | 6.554                | 0.474 | 7.230            | -1.60        |
| 9.990               | 10.212               | 0.266 | 2.601            | 2.22         |
| 13.320              | 13.800               | 0.447 | 3.243            | 3.60         |
| 16.650              | 16.220               | 0.448 | 2.763            | -2.58        |
| <b>Inter-day</b>    |                      |       |                  |              |
| 1.665               | 1.730                | 0.07  | 4.15             | 3.9          |
| 3.330               | 3.12                 | 0.17  | 5.35             | -6.3         |
| 6.660               | 6.450                | 0.26  | 4.1              | -3.2         |
| 9.990               | 10.20                | 0.62  | 6.1              | 2.1          |
| 13.320              | 13.700               | 0.86  | 6.3              | 2.9          |
| 16.650              | 16.320               | 1.15  | 7.02             | -2.0         |

We also have to draw attention to the widespread contamination of the patient toilet before and after drug handling started, as it puts family members at risk of exposure, making this a public health issue as well. These findings raise particular concern, because Moretti et al. (13) showed in a recent study that handling cytotoxic drugs, even under controlled conditions, involves a considerable genotoxic risk (13).

What explains much of the contamination found in our study is that our ODS had only a biological safety cabinet, located in the clean room, but not a closed-system drug transfer device. By default, biological safety cabinets are heavily contaminated and are difficult to clean, and so are the objects taken out of the cabinet (45). Closed-system drug transfer devices serve to prevent transfer of contamination from these objects to outside surfaces (4). The benefits of closed drug transfer systems have already been demonstrated by Sessink et al. (46) and Simon et al. (47), but the latter also noted that the device could not completely prevent chemical contamination.

#### *Cleaning issues and recommendations*

The recent EU recommendations (4) identify cleaning as critical in reducing the spread of contamination. Cleaning can reduce most of the contamination, but not all of it, because there is no universal agent for different chemical structures of cytotoxic drugs.

Several authors have tried to find an agent capable of inactivating, degrading, and reducing contamination with cytotoxic drugs in oncology services (48-55), but the issue remains. Our study only confirms that, as we found contamination even on supposedly cleaned surfaces before drug handling began.

Assessing the efficacy of the cleaning methods usually employed in their healthcare facility to eliminate environmental contamination with CP, Touzin et al. (55)

recommended combining sodium hypochlorite and sodium thiosulfate to obtain optimal results. However, this and many other studies address decontamination of a single cytotoxic agent (48, 55-57), while in reality surfaces are often contaminated with several agents. Lamerie et al. (52) therefore assessed the efficiency of several chemical solutions to decontaminate two types of work surfaces intentionally contaminated with ten cytotoxic drugs. Sodium hypochlorite showed the highest overall efficiency of 98 %. Promising were also solutions containing anionic surfactants with a high efficiency to safety ratio, as they bind to impurities and particles that are suspended in the liquid, which makes them effective cleaning agents in water. In fact, the EU report (4) clearly points out that no single chemical can completely clean, disinfect, and decontaminate surfaces contaminated with cytotoxic drugs.

The cleaning product used in our ODS was the same as the ones used in other hospital facilities not handling cytotoxic agents. This suggests that there are no set criteria to select a cleaning product that would be specific for an ODS and effective enough to warrant chemical

**Table 5** Recovery of the cytotoxic drugs from spiked wipes ( $n=3$ )

| Drug          | Nominal amount | Recovery (%) |
|---------------|----------------|--------------|
| 5-FU (ng)     | 15             | 95.80        |
|               | 45             | 86.30        |
|               | 75             | 91.03        |
| CP ( $\mu$ g) | 12             | 93.43        |
|               | 36             | 96.55        |
|               | 60             | 95.32        |
| PTX (ng)      | 3.33           | 80.85        |
|               | 9.99           | 85.37        |
|               | 16.65          | 87.24        |

**Table 6** *Samples with values >LOQ*

| Drugs            | Sampling before<br>(n=29)       |                                 |                                | Sampling after<br>(n=30)        |                                 |                                |
|------------------|---------------------------------|---------------------------------|--------------------------------|---------------------------------|---------------------------------|--------------------------------|
|                  | CP<br>( $\mu\text{g cm}^{-2}$ ) | 5-FU<br>( $\text{ng cm}^{-2}$ ) | PTX<br>( $\text{ng cm}^{-2}$ ) | CP<br>( $\mu\text{g cm}^{-2}$ ) | 5-FU<br>( $\text{ng cm}^{-2}$ ) | PTX<br>( $\text{ng cm}^{-2}$ ) |
| Positive samples | 7                               | 16                              | 2                              | 10                              | 20                              | 0                              |
| Mean             | 16.5                            | 17                              | 0.24                           | 2.0                             | 19.0                            | <LOQ                           |
| Range            | LOD – 139.55                    | LOD – 85.35                     | LOD – 3.67                     | LOD – 93.92                     | LOD – 88.72                     |                                |

**Table 7** *Surface contamination levels by each drug before handling (n=29)*

| Unit                     | Surfaces  | Drug                 |                                 |                      |                                 |                                |
|--------------------------|---|----------------------|---------------------------------|----------------------|---------------------------------|--------------------------------|
|                          |   | Specific<br>surfaces | CP<br>( $\mu\text{g cm}^{-2}$ ) | Specific<br>surfaces | 5-FU<br>( $\text{ng cm}^{-2}$ ) | PTX<br>( $\text{ng cm}^{-2}$ ) |
| Preparation<br>(n=12)    | Clean room – biological safety cabinet (BSC)<br>chair                         |                      | 0                               |                      | 0                               | 1.98                           |
|                          | Clean room – pass through handle  |                      | 0                               |                      | 24.48                           | 0                              |
|                          | Clean room – support table  |                      | 0                               |                      | 0                               | 0                              |
|                          | Clean room – front barrier grating of the BSC                                 |                      | 0                               |                      | 0                               | 0                              |
|                          | Clean room – handle of the BSC protection                                     |                      | 0                               |                      | 0                               | 0                              |
|                          | Support room – table receiving finished<br>preparations                       |                      | 40.18                           |                      | 0                               | 0                              |
|                          | Support room – table where preparations done<br>are registered                |                      | 19.83                           |                      | 0                               | 0                              |
|                          | Support room – box for manual transportation                                  |                      | 0                               |                      | 0                               | 0                              |
|                          | Support room – pass through handle and<br>interior                            |                      | 0                               |                      | 0                               | <LOQ                           |
|                          | Support room – computer mouse   |                      | 0                               |                      | 27.18                           | 0                              |
|                          | Support room – phone  |                      | 0                               |                      | 85.35                           | <LOQ                           |
|                          | Support room – drug storage cabinet –<br>handles and interior                 |                      | 0                               |                      | 27                              | 0                              |
| Administration<br>(n=12) | Infusion pump holder  |                      | 58.85                           |                      | 0                               | 0                              |
|                          | Pass through handle   |                      | 97.05                           |                      | 21                              | 0                              |
|                          | Table that receives drug preparations   |                      | 0                               |                      | 0                               | 0                              |
|                          | Computer mouse  |                      | 0                               |                      | 44.4                            | 0                              |
|                          | Table for preparing other medication  |                      | 0                               |                      | 11.93                           | 0                              |
|                          | Treatment chairs – armrests   |                      | 0                               |                      | <LOQ                            | 0                              |
|                          | Trolley worktop   |                      | 41.32                           |                      | 0                               | 0                              |
|                          | Treatment room – bed chart holder, infusion<br>pump holder, and chair armrest | Bed                  | 139.55                          | Bed                  | 26.6                            | 0                              |
|                          |   |                      |                                 | Chair<br>armrest     | 4.28                            |                                |
|                          |   |                      |                                 | Phone                | 84.69                           |                                |
|                          | Nurse desk – phone, desk, chair   |                      | 0                               | Table                | 22.81                           | 0                              |
|                          |   |                      |                                 | Chair                | 35.67                           |                                |
| Patients toilet<br>(n=5) | Door handles  |                      | 0                               |                      | 17                              | 0                              |
|                          | Light switch  |                      | 32.01                           |                      | 25.76                           | 0                              |
|                          | Flush handle  |                      | 0                               |                      | 12.04                           | 3.67                           |
|                          | Arm support   |                      | 0                               |                      | 4.99                            | 0                              |
|                          | Water tap   |                      | 0                               |                      | 0                               | 0                              |

**Table 8** Surface contamination level by each drug after the beginning of tasks (n=30)

| Unit                     | Surfaces   | Drug                            |                      |                                 |                      |                                |
|--------------------------|--|---------------------------------|----------------------|---------------------------------|----------------------|--------------------------------|
|                          |  | CP<br>( $\mu\text{g cm}^{-2}$ ) | Specific<br>surfaces | 5-FU<br>( $\text{ng cm}^{-2}$ ) | Specific<br>surfaces | PTX<br>( $\text{ng cm}^{-2}$ ) |
| Preparation<br>(n=12)    | Clean room – biological safety cabinet (BSC) chair                         | 93.92                           |                      | 31.75                           |                      | <LOD                           |
|                          | Clean room – pass through handle (sample 1)                                | 18.9                            |                      |                                 |                      |                                |
|                          | Clean room – pass through handle (sample 2)                                | 71.32                           |                      | 16.6                            |                      | <LOD                           |
|                          | Clean room – support table   | <LOD                            |                      | <LOD                            |                      | <LOD                           |
|                          | Clean room – front barrier grating of the BSC                              | 45.99                           |                      | <LOD                            |                      | <LOD                           |
|                          | Clean room – handle of the BSC protection                                  | <LOD                            |                      | 18.8                            |                      | <LOD                           |
|                          | Support room – table receiving finished preparations                       | 12.27                           |                      | <LOD                            |                      | <LOD                           |
|                          | Support room – table where preparations done are registered                | <LOD                            |                      | 1.86                            |                      | <LOD                           |
|                          | Support room – Pass through handle and interior                            | 2                               |                      | <LOD                            |                      | <LOD                           |
|                          | Support room – computer mouse  | 12.81                           |                      | 36.49                           |                      | <LOD                           |
|                          | Support room – phone   | 13.03                           |                      | 23.52                           |                      | <LOD                           |
|                          | Support room – drug storage cabinet – handles and interior                 | <LOD                            | Handle               | 4.61                            |                      | <LOD                           |
|                          | Infusion pumps holder and pump   | <LOD                            | Pump                 | 25.21                           |                      | <LOD                           |
| Administration<br>(n=13) | Transfer interior and handle   | <LOD                            | Handle               | <LOQ                            |                      | <LOD                           |
|                          | Table that receives drug preparations                                      | <LOD                            |                      | <LOD                            |                      | <LOD                           |
|                          | Computer mouse   | 13.15                           |                      | 17                              |                      | <LOD                           |
|                          | Table for preparing other type of medication                               | <LOD                            |                      | <LOD                            |                      | <LOD                           |
|                          | Treatment chairs – armrests  | <LOD                            |                      | 2.32                            |                      | <LOD                           |
|                          | Trolley worktop  | <LOD                            |                      | <LOD                            |                      | <LOD                           |
|                          | Catheters room – table   | 11.98                           |                      | <LOD                            |                      | 0<LOD                          |
|                          | Treatment room – bed chart holder, infusion pump holder, and chair armrest | <LOD                            | Bed                  | 12.44                           |                      | <LOQ                           |
|                          |  |                                 | Infusion pump holder | 8.85                            | Bed                  |                                |
|                          |  |                                 | Phone                | 88.72                           |                      |                                |
|                          | Nurse desk – phone   | <LOD                            | Table                | 4.33                            | Phone                | <LOQ                           |
|                          |  |                                 | Chair                | 10.43                           |                      |                                |
| Patients toilet<br>(n=5) | Door handles   | <LOD                            |                      | 21                              |                      | <LOQ                           |
|                          | Light switch   | <LOD                            |                      | 2.57                            |                      | <LOD                           |
|                          | Flush handle   | <LOD                            |                      | 19.73                           |                      | <LOD                           |
|                          | Arm support  | <LOD                            |                      | 70.03                           |                      | <LOD                           |
|                          | Water tap  | <LOD                            |                      | 73.32                           |                      | <LOD                           |

decontamination of the surfaces. The cleaning product used in our ODS contained sodium tripolyphosphate, sulphonic acid, sodium lauryl ether sulphate, propan-2-ol, and a small percentage of alcohol. The toilet was cleaned with a product containing sodium hypochlorite instead. However, despite the use of sodium hypochlorite, almost all toilet samples showed contamination. This points to other factors that may render decontamination less efficient, such as dilution and the agent contact time with the surface (55).

However, we also believe the criteria used to select which surfaces to clean affected the findings reported by this and previous studies. They are focused on rendering the surfaces aseptic by removing microorganisms, because oncology patients are most often immunocompromised. Accordingly, the cleaning solutions are selected based on their disinfection efficacy and not on chemical decontamination.



**Table 9** Total contamination for each unit by drug

| Drugs                          | Preparation                     |                                 |                                | Administration                  |                                 |                                | Toilets                         |                                 |                                |
|--------------------------------|---------------------------------|---------------------------------|--------------------------------|---------------------------------|---------------------------------|--------------------------------|---------------------------------|---------------------------------|--------------------------------|
|                                | CP<br>( $\mu\text{g cm}^{-2}$ ) | 5-FU<br>( $\text{ng cm}^{-2}$ ) | PTX<br>( $\text{ng cm}^{-2}$ ) | CP<br>( $\mu\text{g cm}^{-2}$ ) | 5-FU<br>( $\text{ng cm}^{-2}$ ) | PTX<br>( $\text{ng cm}^{-2}$ ) | CP<br>( $\mu\text{g cm}^{-2}$ ) | 5-FU<br>( $\text{ng cm}^{-2}$ ) | PTX<br>( $\text{ng cm}^{-2}$ ) |
| Before drug handling           | 60.0                            | 164.0                           | 1.98                           | 336.77                          | 251.38                          | 0                              | 32.01                           | 59.79                           | 3.67                           |
| Three hours into drug handling | 270.24                          | 133.63                          | -----                          | 25.13                           | 169.3                           | -----                          | 0                               | 186.65                          | -----                          |
| Total                          | 330.24                          | 297.63                          | 1.98                           | 361.9                           | 420.68                          | -----                          | 32.01                           | 246.44                          | 3.67                           |

**Table 10** Surfaces with higher contamination

| Sampling time                  | Preparation   | Administration  | Patients toilet                       |
|--------------------------------|---|---|---------------------------------------|
| Before handling drugs          | Table that receives drug preparations,<br>Phone in the preparation support room,<br>Pass through handle | Pass through handle, bed in the treatment room, phone on the nursing desk | Light switch, flush, and arms support |
| Three hours into drug handling | Chair of the BSC, PC mouse in the preparation support room, pass through handle                         | Infusion pump, computer mouse, phone on the nursing desk                  | Flush, arms support, water tap        |

Additionally, mainly the toilet floor was cleaned and not the surfaces touched by hand. This explains why all the toilet surfaces were contaminated before and after the drug handling started at the ODS.

#### Surface monitoring recommendations

This study stresses the importance of each oncology service having an effective monitoring programme in place. Monitoring should be frequent and collect reliable and detailed exposure information to identify the causes of contamination and appropriate measures to avoid or minimise exposure. Kiffmeyer et al. (24) reported a sustained contamination control thanks to one such regular monitoring programme. Furthermore, monitoring can show where cleaning has failed. Sampling should precede the implementation of preventive measures and be repeated once they are in place to establish their efficiency (60). Viegas et al. (64) demonstrated the usefulness of surface monitoring, as it not only gives an indirect measure of dermal exposure but also relevant guidelines to prevent further exposure.

Although this study findings call for changes in the workflow and cleaning that would reduce contamination and exposure to cytotoxic drugs, it has several limitations to bear in mind. One is the limited number of positive samples for PTX, even though it is the most used cytotoxic drug in this ODS. This points to the need to revise the sampling method and frequency. The other limitation is that we did not sample exactly the same surfaces before and three hours into the drug handling because some of the surfaces were covered by objects used in everyday operations and therefore inaccessible. For this reason we cannot reliably follow how contamination developed between the two sampling times.

## CONCLUSIONS

Our results have shown a widespread contamination in the ODS even after it has been cleaned and call for improvements to define an optimise cleaning. This includes the selection of proper cleaning agents or combinations thereof, optimal dilution, and contact time with the surfaces. This can only be accomplished in collaboration with trained cleaners, who have been made aware of the risks of poor cleaning practices.

Operating procedures, including technical resources should also be improved to avoid or reduce the spread of contamination. A surface monitoring programme could greatly contribute to achieve that goal, as it can provide guidelines for improvement.

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#### Conflicts of interest

None to declare.

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### Profesionalna izlo enost citotoksi nim lijekovima: koliko je va no  iš enje povr ina za njezino sprje avanje odnosno smanjenje

U zdravstvenih radnika koji pripremaju ili primjenjuju citotoksi ne lijekove zdravstveni rizici zbog izlo enosti su realni,  ak i pri dozama ni ima od onih koje se primjenjuju u bolesnika jer, na elno, nijedna doza nije ne kodljiva za zdravlje. Naj e  i i najproblemati niji put izlaganja jest ko a, napose zato  to radne povr ine gdje ad ostanu kontaminirane i nakon njihova  iš enja. Cilj ovoga preliminarog istra ivanja bio je pokazati koliko je va no osmisлити djelotvoran protokol za dekontaminaciju na temelju pokazatelja kontaminacije radnih povr ina jedinice za pripremu lijekova, jedinice za njihovu primjenu te bolesni koga zahoda onkolo ke ambulate trima naj e  im citotoksi nim onkolo kim lijekovima: ciklofosfamidom, 5-fluorouracilom i paklitakselom. Uzorke smo prikupljali prije rada s lijekovima te tri sata od po etka rada s njima te ih analizirali teku inskom kromatografijom s detektorom s nizom dioda (engl. *high performance liquid chromatography with diode array detection*, krat. HPLC-DAD). Od 29 uzoraka prikupljenih prije rada s lijekovima, 23 su bila kontaminirana, od kojih pet s vi e lijekova. Od 30 uzoraka prikupljenih tri sata nakon po etka rada s lijekovima, njih 25 bilo je kontaminirano, od kojih osam s vi e lijekova. Kontaminacija povr ina prije i nakon po etka rada s lijekovima nije bila zna ajno razli ita,  to upozorava na ra irenu kontaminaciju i nedjelotvorno  iš enje. Stoga bi trebalo revidirati postoje i protokol  iš enja i rukovanja lijekovima te svesti kontaminaciju na najmanju mogu u mjeru.

KLJU NE RIJE I: 5-fluorouracil; ciklofosfamid; HPLC-DAD; onkolo ka ambulanta; paklitaksel; suzbijanje kontaminacije