

Short Communication

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Evaluation of the Surface Contamination by Cytotoxic Agents of a Chemotherapy Reconstitution Unit: From Analysing Work Practices to Preventive and Corrective Actions

DOI 10.1515/pthp-2016-0021

Received September 20, 2016; revised December 2, 2016; accepted December 2, 2016

Abstract

Introduction: The staff handling the cytotoxics are exposed to contamination as an occupational hazard. The unit of the Centre Hospitalier Universitaire (C.H.U) of Saint Pierre is ISO9001 certified. In a constant effort to improve the quality of our work, samples of the work surface were collected and allowed us, in a first step, to evaluate the contamination in a CRU in Reunion Island. As a result, corrective and preventive actions were implemented in the work routines.

Material and method: 53 samples of the work surface, collected in December 2015 and in March and April 2016 in seven different spots, were treated in this observational study. The 5-FU was chosen as example and analysed and quantified by using liquid chromatography associated with a mass spectrometer with a detection limit of 2 ng/pf.

Results: We observed a great difference in contamination; 29 samples were positive, the isolator container was the location with the highest level of contamination,

including manipulator gloves under the isolator, work surface and the inside of the isolator bin. The contamination was reduced after a first clean-up with water only. The overwrapping bags and the manipulator gloves are only a little or not at all contaminated.

Conclusions: In order to reduce the exposure to cytotoxic residuals, corrective actions have been implemented: more frequent changes of manipulator gloves, the use of closed systems, and cleaning of the isolator with water. The efficiency of these modifications of work practices will be evaluated again in a few months.

Keywords: 5-FU, chemotherapy reconstitution unit, hospital, work practices, corrective actions, cytotoxic contamination, occupational exposure, ISO9001

Introduction

The offer of anti-cancer treatments is vastly growing in order to provide optimal care for patients, but those treatments are also widely known for their proven and potential toxicities [1, 2]: that is why special attention is being paid not only to the patients' risk of exposure, but also to occupational exposure [3]. For a few years, numerous studies have been dealing with teratogenic, mutagenic or carcinogenic occupational exposure [4–6]. Consequently, a vast number of guidelines and regulatory texts have since been published, [7–9] A centralised space for preparation, under a laminar flow or an isolator, and individual safety equipment reduce occupational exposure [10, 11]. These actions seem to be indispensable since one of the primary routes of entry is the dermal route [12, 13].

The pharmaceutical unit of the University Hospital (U.H) of Saint Pierre in Reunion Island is ISO9001 certified. Within this continuous improvement environment, the chemical contamination was analysed in the controlled atmosphere area (Z.A.C.) [14]. The aim of this

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study is to evaluate the chemical contamination of the hospital's cytotoxic reconstitution unit (U.R.C.) by using different sampling points. We can so specify the potential risk of exposure in order to consider modifying of our work practices through preventive and corrective actions.

Material and methods

The work consisted of measuring, at different times and in different places of the unit, the residual presence of 5-FU. Only 5-FU was analysed. It was chosen as a proof of the contamination levels of the unit since it is the most used cytotoxic. Also, its stability at ambient temperatures was ideal to withstand the transport of the samples to continental France.

The sampling kits were provided by the Centre de Lutte Contre le Cancer Léon Bérard in Lyon: a filter paper saturated with 0.3 ml water for injection was used to perform the sampling on a frame of 15 cm on 15 cm. The analysis and the quantification of the 5-FU contamination was carried out in the pharma-toxicological laboratory of the U.H in Lyon: analysis of 5-FU was performed by LC-MS/MS using a Quantum-Ultra (ThermoElectron, San Jose, USA). Samples (10 µL injection volume) were separated on a Hypercarb column, (ThermoElectron), 5 µm, (100 mm × 2.1 mm i. d.). The mobile phase consisted of water and acetonitrile using isocratic mode and was delivered through the column at a flow rate of 200 µL/min. The triple quadrupole mass spectrometer operated in negative ion mode with electrospray (ESI)

source. [15N2]-5-FU was used as internal standard (IS). 5-FU and IS were detected using transitions (m/z 129 42 and m/z 131 43) respectively. We will present the results in graphic form by sampling site and will express the results as median [min, max] given the low numbers. The level is expressed in nanogram/filter paper(ng/fp) this quantity corresponds to the quantity found in the surface of a 15 cm × 15 cm frame. A positive contamination threshold is set at 2 ng/fp (Low control: quantity of 5-FU deposited on wipe sample (ng) = 2, standard deviation = 0.2, accuracy (%) = 103).

A few clarifications on the sampling points: the isolator bin is a zipper bag in which only the paper wrappings issued from the isolator container. The “was-tebin cell” corresponds to the joint system of the device for the tight transfer linked to a health-care waste bag that assures the evacuation of contaminated waste from the container. The SIEVE® spray is a disinfectant virucide, the WIP'ANIOS® wipes are biocide.

Results

Description of sampling points

The 53 samples were collected within two periods: first in December 2015, then in Mars and April 2016; the different sampling points are listed in Table 1.

Sampling sites: gloves manipulator, manipulator gloves in the isolator, isolator bin, overwrapping bags, work surface

Table 1: Description of sampling points by place and date.

Date	Type of sample	Number N = 53	Comments
December 2015	Manipulator glove	n = 5	2h00 after end of production at the end of production
	Manipulator glove	n = 5	
	Manipulator gloves in the isolator	n = 5	
	Isolator bin	n = 5	before taking out, carried out by the manipulator with new gloves
	Overwrapping bags	n = 5	within the control area at the opening of a 5-FU preparation (except one case)
March 2016	Work surface isolator cleaned with SIEVE® spray only	n = 4	Interior surface of the cell, i. e. the most exposed surface
	Waste bin cell cleaned with wipes	n = 5	
	Waste bin cell cleaned with water and wipes	n = 5	
March and April 2016	Preparations in the isolator at the end of production	n = 10	No 5-FU in the preparations ; the manipulator changes gloves after two preparations
April 2016	Work surface isolator cleaned with water + SIEVE® spray	n = 4	

isolator cleaned with SIEVE® spray only, wastebin cell cleaned with wipes, waste bin cell cleaned with water and wipes, preparations in the isolator at the end of production, work surface isolator cleaned with water + SIEVE® spray.

Concerning the work surface isolator and the wastebin cell, the samples were collected following two different cleaning methods: spray cleaning SIEVE® single and water cleaning and the spray SIEVE® for the work surface; cleaning wipe only and cleaning with water then wipe for wastebin cell.

Contamination level by sampling point

In total, 53 samplings were collected: 29 of them were returned positive, 24 below quantification limit.

The Figures 1 to 9 illustrate the surface contamination with 5-FU, showing the different sampling points numbered 1 to 53:

- Figure 1 shows a near-absence of contamination on the manipulator gloves: the samples 1 to 5 were collected two hours after the beginning of the activity, the other five show the samples collected at the end of the activity. Nine samples were below quantification limit, only sample 7 was positive at 3 ng/fp.
- Figure 2 illustrates the manipulator glove's contamination under isolator: samples 11 to 15, collected just before changing gloves, all indicate a high contamination with a median of 155 ng/fp [62–1500]. Samples 12 and 46 show the highest contamination, with 1,500 et 2,000 ng/fp respectively (cf. Figure 8).
- Figure 3 indicates a partial contamination of the isolator bin, plastic zipper bag in which the paper

wrappings are disposed of, with a median of 12 ng/fp for the five samples [2–65].

- The contamination level of the isolator bags' surface is very low (Figure 4): Six samples out of ten are undetectable, sample 37 shows a high contamination with 600 ng/fp. The median value is 2 ng/fp [2–600].
- The overwrapping bags for the preparations do not show any contamination with 5-FU: the five samples are below detection limit as is shown in Figure 5. The samples were collected outside the production zone, in the discharge control area.
- The contamination level of the isolator work surface after cleaning with Sieve® spray is sensitive with a median value of the five samples of 22 ng/fp [6–44] (Figure 6). However, after being cleaned with water first, then with the spray (Figure 7), the work surface shows a low contamination with a median of 5 ng/fp [3–6].
- Samples 44 to 48, shown in Figure 8, indicate a high contamination of the wastebin cell after cleaning with wipes, with a median of 450 ng/fp [13–2000], whereas the samples in Figure 9 show a low contamination after cleaning with water first, then with wipes, with a median of 2 ng/fp [2–32].

The samples 26 to 29 and the samples 44 to 48 do all indicate a residual contamination within the isolator after cleaning with a biocide cleaner, the median value of contamination is at 33 ng/fp, versus a median value of 3 ng/fp for the nine samples collected after cleaning with water first, then with a biocide cleaner (Tables 2 and 3).

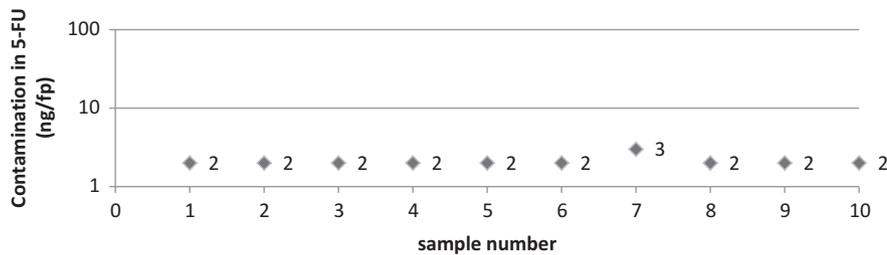


Figure 1: Contamination level of manipulator gloves.

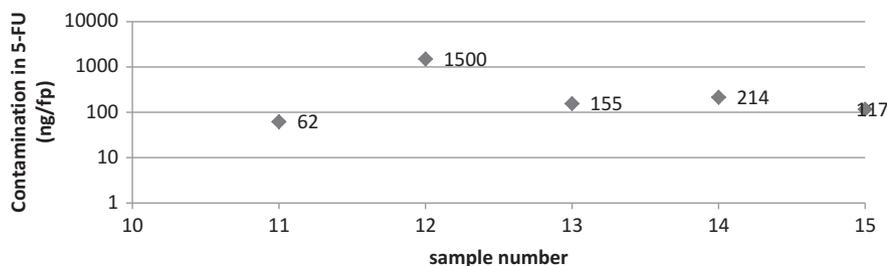


Figure 2: Contamination level of manipulator gloves (under isolator).

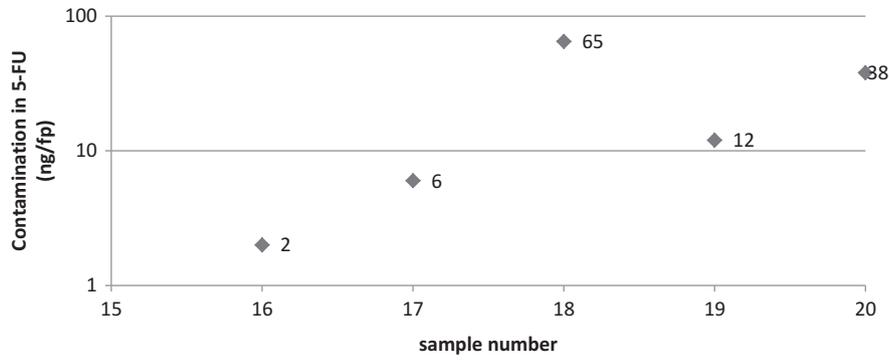


Figure 3: Contamination level of the isolator bin.

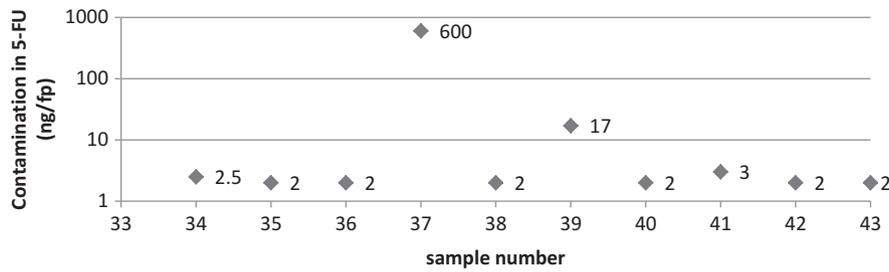


Figure 4: Contamination level of isolator bags at the end of production.

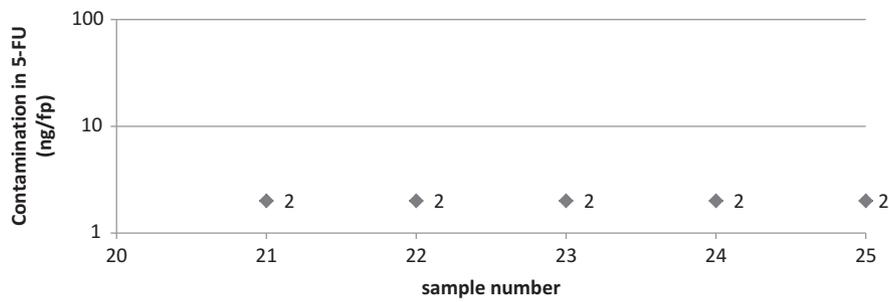


Figure 5: Contamination of overwrapping bags.

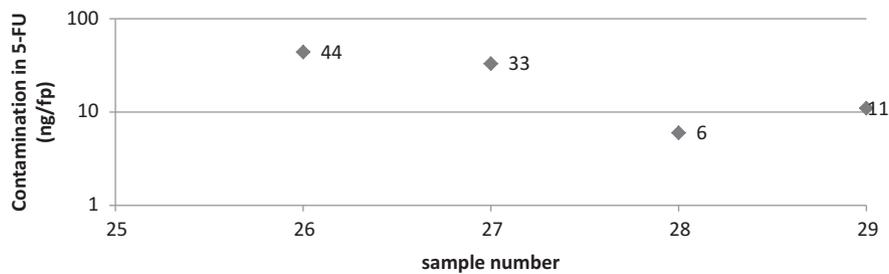


Figure 6: Contamination level of isolator work surface cleaned with spray only.

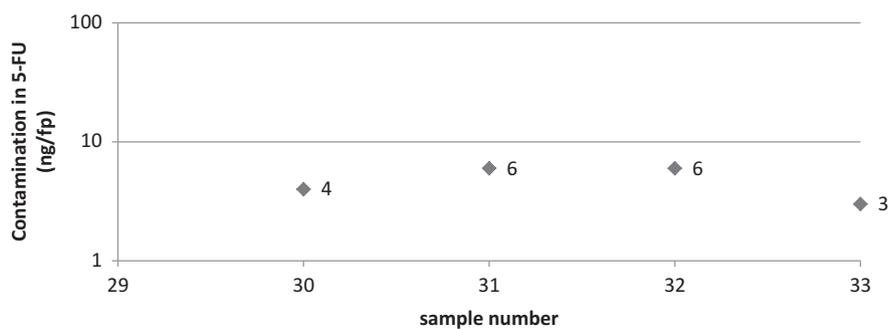


Figure 7: Contamination level of isolator work surface cleaned with water and spray.

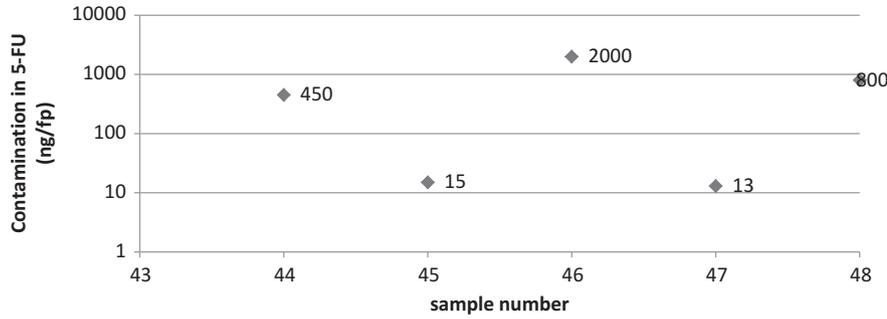


Figure 8: Contamination level of the wastebin cell after cleaning with wipes.

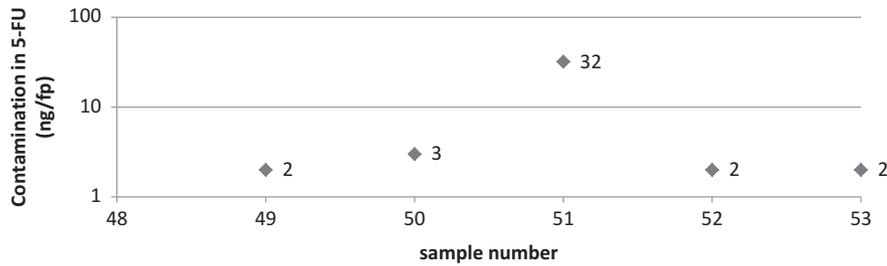


Figure 9: Contamination level of wastebin cell after cleaning with water and wipes.

Table 2: Samples collected in the isolator after cleaning with biocide cleaner; (n = 9); median = 33 ng/fp.

Sample number	26	27	28	29	44	45	46	47	48
Contamination in 5-FU (ng/fp)	44	33	6	11	450	15	2000	13	800

Table 3: Samples collected in the isolator after cleaning with water first, then with biocide cleaner; (n = 9) median = 3 ng/fp.

Sample number	30	31	32	33	49	50	51	52	53
Contamination in 5-FU (ng/fp)	4	6	6	3	2	3	32	2	2

Discussion

The diversity of sampling points has shown a great disparity in contamination levels within pharmaceuticals. The highest contamination levels can obviously be found within the container of the isolator, the manipulator gloves, the work surface, and the wastebin cell DASRI. Several remedial actions have been introduced.

- Changing gloves more frequently, after every other preparation, in order to limit the contamination by hand. Note that since 2002, B. Favier has been interested in contamination by hand due to the manipulation of cytotoxics, insisting on the contamination of the manipulator gloves [15]; more recently, in 2015,

Paul J.M. Sessink affirms the systematic contamination of manipulator gloves [16].

- Weekly cleaning of the isolator at the end of work by introducing a step of cleaning with water preceding the disinfection with wipes as suggested in Tables 1 and 2.
- Provision of Wastebag® disposable bin bags that limit the exposure of the agent responsible for cleaning the cells.
- The use of bags with nozzle tips (Luerlock type) allows to limit the use of needles, to reduce the risk of contamination by micro droplets and aerosols as well as the risk of accidental pricking. Several teams have demonstrated the advantages of using closed systems in order to reduce contamination: M. Berruyer in 2015 confirmed in a multicentric follow-up study in Canada a significant diminution in contamination in the units using closed systems, as did Paul J.M. Sessink who compared the contamination levels within a six-year interval in units using a method including syringes and closed systems [17, 18].

The near non-existence of contamination on the manipulator gloves, nine samples out of ten being undetectable, suggest the non-contamination of his individual safety equipment: it was therefore decided that the waste elimination circuit was to be altered: thus, mask, cap and coat of the manipulator now follow the waste circuit assimilated to domestic waste: thus, we were able to diminish the volume of waste in healthcare activities bearing a risk of infection.

However, it seems delicate for now to extrapolate these data to the whole of our U.R.C. (furniture, handles, computers...) even if S. Crauste-Manciet et al. confirmed in 2005 that exterior exposure can be limited if the contamination remains within the isolator [19].

Note that the isolator bins present a significant contamination level (Figure 3); therefore, they continue to be removed with the contaminated waste.

The near non-existence of contamination on overwrapping bags and on the surface of the bags, shown by 13 undetectable samples out of 15, is reassuring, while there remains a risk of occupational exposure of the pharmacist within the discharge control area and of the courier in charge of transport.

In fact, F. Sadeghipour emphasizes the importance of a specific manipulation training for the preparers of cytotoxics, [20] as it has been the custom within the U.R.C of the U.H of Saint Pierre for years now. Recently, R. Vazquez shows that the manual process can lead to errors of re-use of medical devices and can potentially have consequences for the patient [21].

Concerning the sample 37: this outlying result is probably due to a micro droplet. Sample size allow no generalization of our results. More samples would have been necessary. On the other hand we were able to lead a reflection on our professional practices.

Conclusion

This first observational study, evaluating the contamination by cytotoxic and conducted in a U.R.C in Reunion Island, allowed confirming the surface contamination of one part of the unit and thus the necessity of individual and collective safety measures. In spite of these safety measures, we found a residual contamination of the work environment. That is why the U.R.C. of the U.H in Saint Pierre has introduced an internal training that has to be passed by all new preparers.

The analysis of our work practices and of occupational risks are at the source of corrective and preventive actions implemented in our quality management system according to ISO9001.

Clearly, a sampling conducted several months after those actions would allow evaluating their efficiency. Furthermore, we are instantly thinking about the possibility of organising a regular follow-up to evaluate the contamination of the work environment by “relying on adapted environment controls” as suggested in the “Bonnes Pratiques de Préparations” (“good habits of preparation”).

Acknowledgments: We would like to thank Dr. Jean-François Latour, pharmacist at the Centre Léon Berard in Lyon, and Professor Jérôme Guitton, laboratory biologists at the pharmaceutical laboratory of the U.H in Lyon for their advice.

Conflicts of interest statement: Authors state no conflict of interest. All authors have read the journal's Publication ethics and publication malpractice statement available at the journal's website and hereby confirm that they comply with all its parts applicable to the present scientific work.

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Bionotes



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