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Validation of cleaning procedures used in an Italian Hospital Pharmacy for antineoplastic drug decontamination: a new tool for industrial hygiene

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Summary

Background: *Current Italian regulations and procedures for surface decontamination of antineoplastic drugs (ADs) are not clear. Therefore, most hospital pharmacies follow internal procedures as an interpretation of the recommended handling guidelines.* **Objectives:** *Our study compared 7 different cleaning procedures after controlled contamination of the work surface of a biological safety cabinet workbench in an Italian hospital oncology pharmacy (HOP) to determine which of them is more efficient and practical. Moreover, in order to approximate operative routine and improve risk awareness, cleaning procedures were carried out by the personnel that usually operate in the HOP.* **Methods:** *Measured quantities, i.e. a drop (100 μL) of 5-FluoroUracil, IPhosfamide, CycloPhosphamide and Gemcitabine, were deposited on the work surface within precisely delimited areas. Following the wipe-test analysis using UPLC-MS/MS, the cleaning efficacy was calculated based on the ratio of the residual concentration of the AD, after the cleaning procedure, to the concentration of each AD before the procedure.* **Results:** *Tested cleaning procedures were: 1) Hypo-Chlor®, hot water and Farmecol70®; 2) Hypo-Chlor® and hot water; 3) Farmecol70®; 4) Surfa'Safe SH® and hot water; 5) Amuchina® 10%, hot water and Farmecol70®; 6) Incidin® Oxyfoam and hot water; 7) liquid Marseille soap, hot water and Farmecol70®. Within the studied HOP, the Marseille soap was evaluated to be the optimal choice due to its efficacy, low cost, and the very short contact time needed before rinsing.* **Discussion:** *The application of the protocol for procedure validation suggested here could be used in every HOP as a reliable industrial hygiene tool to demonstrate the validity of the chosen cleaning procedure.*

Riassunto

«Validazione delle procedure di pulizia utilizzate in una farmacia ospedaliera per la decontaminazione da farmaci antiblastici: un nuovo strumento di igiene industriale». **Introduzione:** *Ad oggi le normative che delineano*

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le procedure di decontaminazione da chemioterapici antiblastici (CA) dalle superfici non sono del tutto chiare e di conseguenza negli ospedali italiani si utilizzano procedure interne che nascono dall'interpretazione delle linee guida esistenti. **Obiettivi:** *Nel presente studio sono state confrontate 7 procedure di lavaggio dopo volontaria contaminazione del piano di lavoro di una cappa di un'unità farmaci antiblastici (UFA) italiana allo scopo di individuare quale sia quella più efficace e pratica. Per avvicinarsi il più possibile ad una situazione reale e per aumentare la consapevolezza sul rischio, le operazioni di pulizia sono state applicate dal personale che lavora normalmente nell'UFA.* **Metodi:** *Sono state depositate quantità note di 5-Fluoro Uracile, Ifosfamide, Ciclofosfamide e Gemcitabina equivalenti ad una goccia (100 µL). Dopo l'analisi dei wipe-test via UPLC-MS/MS, l'efficacia di pulizia è stata determinata attraverso il rapporto tra la concentrazione residua di CA, dopo pulizia, e la concentrazione degli stessi pre-pulizia.* **Risultati:** *Le procedure testate sono:1) Hypo-Chlor®, acquacalda e Farmecol70®; 2) Hypo-Chlor® e acqua calda; 3) Farmecol70®; 4) Surfa'Safe SH® e acqua calda; 5) Amuchina® 10%, acqua calda e Farmecol70®; 6) Incidin® Oxyfoam e acqua calda; 7) Sapone di Marsiglia liquido, acqua calda e Farmecol70®. Nell'UFA in esame, il sapone di Marsiglia si è presentato come la scelta ottimale poiché è efficace, ha un costo contenuto e non richiede tempi di contatto prima del risciacquo.* **Discussione:** *L'applicazione del protocollo qui utilizzato per la validazione delle procedure potrebbe essere utilizzata in ogni UFA come affidabile strumento di Igiene Industriale per dimostrare la validità della procedura scelta.*

Introduction

As part of the procedures for monitoring occupational exposure to Antineoplastic Drugs (ADs), the Wipe-Test is currently one of the most widely used techniques. This test allows any problem occurring in the work setting where these substances are handled on a daily basis to be monitored and identified, namely: Hospital Oncology Pharmacies (HOPs) and Oncological Departments for Administration (ODAs). The contamination of work surfaces generally occurs through the accidental spilling of drug formulations, through transfer with handling, or via the formation of aerosols, despite the use of closed system drug transfer devices (CSTDs) for dilution and administration. To date, the various associations of industrial hygiene, including the American Conference of Governmental Industrial Hygienists (ACGIH), have not indicated exposure limits for these substances. Hence, it is very difficult to define what level of contamination should be considered as high or, vice-versa, as low in order to assess if the risk of exposure to ADs is under control. On the other hand, Italian national legislation, guidelines and local institutional policies concerning decontamination procedures for ADs from work surfaces (7-9) do not provide sufficiently clear information. For instance, they do not specify which type of products, surfactants and chemicals should be used, or the dilution levels of the products, the contact time required at each individual washing step, and the frequency of the treatment; furthermore, they do not always distinguish between the diverse types of work surface to clean up (and thus risk damaging the surfaces or not cleaning the different materials efficiently).

Research in the last few years has focused both on trying to determine exposure limits (Hygienic Guidance Values - HGVs) based on the 90th percentile of contamination values (10, 14, 15) as well as on validating the detailed cleaning procedures through simulations of contamination and decontamination prepared in the laboratory (4, 16). A recent study has investigated the cleaning efficiency of Sodium Dodecyl Sulfate solution and Isopropanol solution for the elimination of ten ADs, by monitoring over a one-year period the residual contaminations on the work surface of a biological safety cabinet (BSC) used in an HOP (2). At present in Italy, in the absence of reference norms each hospital adopts its own cleaning procedures based on an internal interpretation of the (rather generic) existing guidelines. One can verify the effectiveness of these procedures only through trials of environmental monitoring. In fact, the Wipe-Test technique allows us to compare the residual contaminations of different chemotherapy drugs between the start and the end of the work shift. However, such monitor-

ing is frequently scheduled every 2-3 years, with the risk that one might verify only belatedly that the selected procedure is inefficient.

The aim of this study is to evaluate the effectiveness of some cleaning procedures adopted in an Italian HOP for a stainless steel workbench surface of a BSC. The scope is to provide some basic guidelines for a more efficient decontamination of work surfaces and to promote workers' awareness of the need to minimize the risk of exposure to ADs. In our opinion, an excellent way to obtain this result is the direct involvement in validating cleaning procedures of the staff who routinely handle ADs in a BSC.

Methods

Study Protocol

The assessment of the effectiveness of cleaning procedures was carried out in an HOP (Pavia, Italy) based on a simulated contamination of the BSC workbench. Cleaning procedures are different in terms of both chemicals used and contact time prescribed, as described below. Measured quantities of ADs were deposited on the work surface within precisely delimited areas. The quantities used reflected values that could be realistically found on surfaces contaminated by leakage of a single drop of AD solution. The experiment was conducted in two trials (after a one-month time lapse) because of the time schedule required for the use of the dedicated BSC. The stainless-steel workbench of the BSC (not used for drug preparation during the washing efficiency test) was completely cleaned prior to the start of each test conducted, following the standard procedure used in the HOP once a day at the end of the working shifts. The pre-testing decontamination washing process consisted of: Hypo-Chlor®, hot water, and Farmecol 70® (table 1). The allowed contact time for each reagent was 20 minutes, the standard contact time required by the cleaning protocol. The main characteristics of the reagents used for trials are summarized in table 1. The cleaned surface, 120 cm long and 50 cm wide, was then divided, using strips of white tape, into four equal sections for the first trial and three sections for the second trial (figure 1). The sections were identified by number from 1 to 7 to correspond to the decontamination protocols being assessed. In each section, two distinct zones of 20x20 cm (i.e., 400 cm^2) were marked using a permanent marker and were identified as A and B, respectively (figure 1).

According to the method described below, a wipe-test was taken from each 400 cm^2 zone to define the base level (i.e., background sample) of each evaluated AD. Then, within every A and B area we randomly deposited 100 µL of each AD solution, as described in figure 1, so as to simulate the accidental loss of a droplet of preparation. After apply-

Table 1 - Main characteristics of tested reagents

Reagent	Type of reagent	pH	Composition (technical data sheet information)
Hypo-Chlor®	disinfectant solution	12.5	Sodium hypochlorite 5.25%
Amuchina® 10% solution	disinfectant solution	8.0-10.5	Sodium hypochlorite 0.115%
Farmecol 70®	disinfectant solution	neutral	Trade name for Rubbing Alcohol (mainly denatured ethanol at 70% concentration)
Surfa'Safe SH®	cleaning and disinfection solution	6	Didecyl-dimethyl-ammonium Chloride and Polyhexamethylene Biguanide Hydrochloride up to 2.5% each
Incidin® OxyFoam	green detergent, disinfectant, medical aid	2.2	Hydrogen Peroxide (1.5%), Glycolic acid (<2.5%) and water (>95%). Registered Name by ECOLAB. The product is available all over the world.
Liquid Marseille soap	detergent	basic	PEG-(1-4) Myristic Ether Sulphate

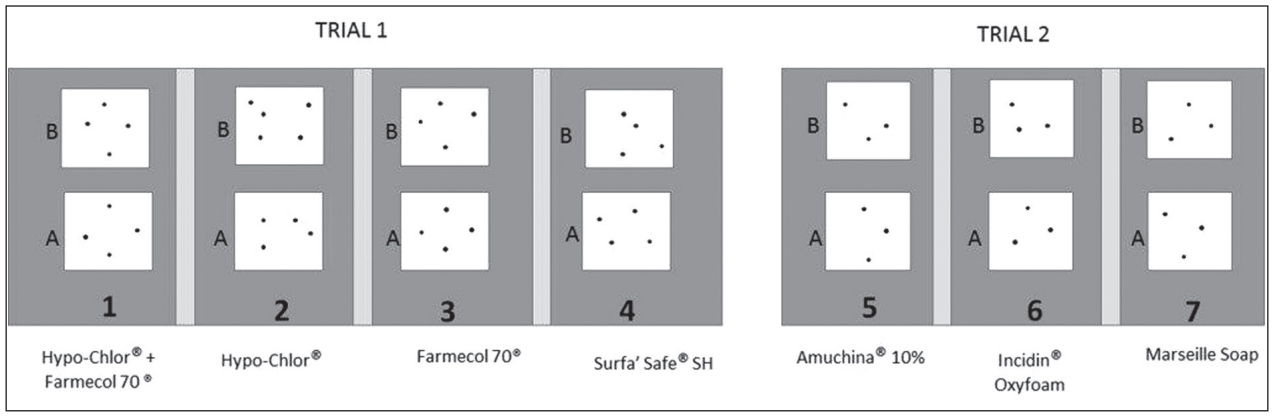

Figure 1 - Identification of the contamination zones on the BSC workbench. Spots illustrate the random deposition of 100 µL of each AD solution, to simulate the accidental loss of a droplet of preparation

ing the selected cleaning procedure to the sections (carefully avoiding the tape), the A and B areas were sampled. The sampling was carried out following a wipe-test procedure set up by the Environmental Research Centre of the Clinical Scientific Institutes Maugeri of Pavia, which is described below.

Trial 1

As indicators of contamination we used the following pharmaceutical form of ADs: 5-FluoroUracil (5-FU), IPhosfamide (IP), CycloPhosphamide (CP) and Gemcitabine (GEM). In each A-B zone of each section we deposited 100 µL of each solution of AD in the following concentrations: 50 mg/ml for 5-FU and IP, 100 mg/ml for GEM, and 20 mg/ml for CP (figure 1). Table 2 reports the concentrations of the solutions in mg/mL, the quantities deposited in each area in µg, and the related concentrations per unit surface in ng/cm^2.

After deposition, four washing procedures (one in each section) were carried out by an expert technician who usually prepares the drug formulations and cleans the workbench at the end of the shift. Materials (gauzes and reagents) were kept to a minimum according to the reduced area to be cleaned (one section area instead of the entire workbench), and no specific instructions for manual operations were provided to technicians, who followed the same procedure used for section 1. The applied washing procedures were, respectively (figure 1):

- Section 1 - Hypo-Chlor®, rinsing with hot water, Farmecol 70® (contact time 20 min each);
- Section 2 - Hypo-Chlor®, rinsing with hot water (contact time 20 min);
- Section 3 – Farmecol 70® (contact time 20 min);
- Section 4 – Surfa'Safe SH®, rinsing with hot water.

Trial 2

As indicators of contamination we used 5-FU, CP and GEM. IP was not used as an indicator in trial 2 due to its unavailability in the HOP at the

Table 2 - Amount of antineoplastic drug (AD) deposited in each area and related theoretical concentration on the surface

AD*	Concentration of solution (mg/ml)	Quantity deposited (µg)	Concentration on the surface (ng/cm^2)
5-FU	50	5,000	12,500
IP	50	5,000	12,500
CP	20	2,000	5,000
GEM	100	10,000	25,000

* 5-FluoroUracil (5-FU), IPhosfamide (IP), CycloPhosphamide (CP) and Gemcitabine (GEM)

moment in which the experiment was carried out. In each area we deposited 100 µL of each solution of AD in concentrations of 50 mg/ml for 5-FU, 100 mg/ml for GEM, and 20 mg/ml for CP, as in trial 1. After deposition, three cleaning procedures (one in each section) were used by the same expert technician who followed the same instructions given for trial 1. The applied washing procedures were, respectively (Figure 1):

- Section 5 - Amuchina® 10%, rinsing with hot water, Farmecol 70® (contact time 20 min for Amuchina and Farmecol);
- Section 6 - Incidin® Oxyfoam, rinsing with hot water;
- Section 7 - liquid Marseille soap, rinsing with hot water, Farmecol 70® (contact time 20 min only for Farmecol 70®).

Wipe Sampling Method

As described above, for each sampling a zone of 20x20 cm (i.e., 400 cm^2) was marked using a permanent marker. The sampling used a 10x10 cm piece of non-woven gauze (TNT Type Luxor-Net, STS Medical Group, Luigi Salvadori S.p.A., Scandicci, Florence, Italy) moistened, at the time of use, with 2.5 ml of Formic acid 0.1%. Each 400 cm^2 surface was swept clean using vertical and horizontal strokes in two different directions (up and down, right and left). After the surface sampling, the gauze was folded and introduced into a 20 ml needle-free polypropylene syringe and closed inside the syringe using the piston. To avoid possible cross-contamination, the nitrile medical gloves (12) worn by the operator were changed at each wipe-test. On the sampling day, the samples were stored in a fridge bag. In the laboratory where the analyses were performed, the samples were stored at -20°C.

The internal standard solutions, i.e., 50 µL of Trofosfamide (Toronto Research, 98% purity) 40 mg/L, hereinafter IS, and 25 µL of 5-FU-$^{15}N_2$ (CDN Isotopes, 98.5% purity) 10 mg/L, hereinafter 5-FU-IS, were added to the wipe gauze at the time of the analysis, without removing it from the syringe. The wipe desorption was done by flowing three aliquots of 4.5 ml formic acid 0.1% in water through the syringe. The total eluate was briefly stirred and centrifuged for 3 min at 5000 rpm, thereby allowing for the sedimentation of any particulate matter. One ml aliquot was transferred into a 1.5 ml vial of the UPLC Autosampler.

Method of Analysis

A volume of 7.5 µL of sample was injected into a Waters Acquity UPLC HSS T3 column (1.8 µm, 2.1 X 50 mm) at 35°C. The mobile phases were: water (A1) and Acetonitrile (B1), 99/1, and the flow rate was 0.45 mL/min. The analysis time was 5 min and the complete analytical cycle was 9 min (for the chromatographic gradient, see online supplementary table S1). For quantitative analysis, the ESI interface automatically alternated acquisitions, in negative mode for 5-FU (Aldrich, 99% purity) and 5-FU-IS and positive mode for CP (Fluka, 98% purity), IP (Aldrich, 98% purity), GEM (Sigma-Aldrich, 98% Purity) and IS, in the same analytical run (for the MRM conditions, see online supplementary table S2).

A 5-point calibration line of each analyte was generated, from 50 to 2000 ng, depositing the selected amounts on wipe samples, eluted and treated according to procedure. If the measured amount in ng exceeded the highest point used for the calibration line, the sample was diluted. In this case, the measurement was done by an external standard method. The lower detection limits (LLOD) of the method were: GEM 0.3 ng (1 pg/cm^2), CP 0.1 ng (0.25 pg/cm^2), IP 0.1 ng (0.25 pg/cm^2) and 5-FU 4 ng (10 pg/cm^2). The lower limits of quantification (LLOQ) were: GEM 1 ng (2.5 pg/cm^2), CP 0.35 ng (0.9 pg/cm^2), IP 0.35 ng (0.9 pg/cm^2) and 5-FU 12 ng (30 pg/cm^2). The upper limit of measurement for all species was 5 ng/cm^2. The recovery efficiencies from the stainless-steel surface (i.e., the average of six replicate measurements at 2.5 ng/cm^2) were: GEM 88%, CP 95%, IP 93% and 5-FU 102%. We report the recoveries measured at a high concentration since the concentration values of residues after washing were high, and thus correction for recovery was applied to the measured value when the recovery was ≤95% (for detailed recovery data, see online supplementary table S3).

Cleaning Effectiveness Evaluation

For each A and B area of each section, the effectiveness of the cleaning procedure was calculated as the ratio of the residual concentration of the AD to the nominal amount spiked on that area, expressing the result as a percentage. The global effectiveness of every single procedure was calculated as the mean of the results of the corresponding section.

Results

The level of concentration of the selected drugs on the BSC surface before deposition of the AD solutions was found to always be between LOD and LOQ, or less than LOQ. Thus, background levels were not further considered in the subsequent calculations of the residues and the cleansing effectiveness (for background levels, see online supplementary table S4).

The main results are summarized in table 3 and table 4.

Table 3 shows residual concentrations of the drugs for both trials in all A and B areas (figure 1). These results have been corrected for the recovery factor, calculated as 2.5 ng/cm^2, except for 5-FU, due to high recovery of this analyte (table S3). All the residual concentrations exceeded the BSC Italian limits (15), especially for the procedure in which Farmecol 70® was used alone (table 3, position 3A and 3B).

Table 4 shows the efficiency of the washing procedures. Since the AD amounts spiked on the BSC surface were known (table 2), the efficiency values were calculated as the percentage of AD removed by each different washing procedure. All the procedures hold an efficiency near or above 99%, except

Table 3 - Residual concentrations of antineoplastic drugs (AD) in each area, after washing

AD[§]	Position	5-FU* (ng/cm^2)	IP (ng/cm^2)	CP* (ng/cm^2)	GEM* (ng/cm^2)
Procedure					
Trial 1					
Hypo-Chlor® + Farmecol 70®	1A	5.7	7.8	6.8	355.6
	1B	15.4	3.8	5.9	28.3
Amuchina® 10%	2A	1.8	10.2	4.9	88.9
	2B	2.2	5.9	4.6	182.0
Farmecol70®	3A	1070.4	634.5	254.8	4265.3
	3B	909.0	560.7	127.6	2843.5
Surfa'Safe SH®	4A	116.7	30.8	17.9	339.9
	4B	146.3	21.6	15.9	275.4
Trial 2					
Amuchina® 10% + Farmecol 70®	5A	156.8	.	5.5	58.3
	5B	73.3	.	5.0	47.8
Incidin® Oxyfoam	6A	92.5	.	14.3	70.0
	6B	59.8	.	14.0	90.0
Marseille soap + Farmecol 70®	7A	34.3	.	6.3	34.5
	7B	43.0	.	5.3	27.3

[§] 5-FluoroUracil (5-FU), IPhosfamide (IP), CycloPhosphamide (CP) and Gemcitabine (GEM). IP was not available at the time of trial 2.

* BSC Italian limits (15): 1.5 ng/cm^2, 3.6 ng/cm^2, 8.2 ng/cm^2 for 5_FU, CP and GEM, respectively

Table 4 - Efficiency (%) of washing procedures expressed as a percentage of anticancer drugs* removed from the surface

	Position	5-FU	IP	CP	GEM	Average by position	Average for procedure
Trial 1							
Hypo-Chlor® + Farmecol 70®	1A	99.95	99.94	99.86	98.58	99.58	99.74
	1B	99.88	99.97	99.88	99.89	99.90	
Hypo-Chlor®	2A	99.99	99.92	99.90	99.64	99.86	99.82
	2B	99.98	99.95	99.91	99.27	99.78	
Farmecol70®	3A	91.44	94.92	94.90	82.94	91.05	92.31
	3B	92.73	95.51	97.45	88.63	93.58	
Surfa'Safe SH®	4A	99.07	99.75	99.64	98.64	99.28	99.29
	4B	98.83	99.83	99.68	98.90	99.31	
Trial 2							
Amuchina® 10% + Farmecol 70®	5A	98.75	.	99.89	99.77	99.47	99.59
	5B	99.41	.	99.90	99.81	99.71	
Incidin® Oxyfoam	6A	99.26	.	99.72	99.72	99.57	99.60
	6B	99.52	.	99.72	99.64	99.63	
Marseille soap + Farmecol 70®	7A	99.73	.	99.88	99.86	99.82	99.82
	7B	99.66	.	99.90	99.89	99.81	

* Anticancer Drugs: 5-FluoroUracil (5-FU), IPhosfamide (IP), CycloPhosphamide (CP) and Gemcitabine (GEM). IP was not available at the time of trial 2

the one using only Farmecol 70®. In fact, the average efficiency for that procedure was around 92%. The worst result was observed in removing GEM.

Discussion

Current guidelines on cleaning procedures for ADs are neither clear nor concordant, which does not encourage a rigorous attitude regarding their application. In fact, the National Guidelines-Italian Ministry of Health (7) recommend using detergents with a high pH (Marseilles soap and sodium hypochlorite) while the Guidelines drawn up by the Italian National Institute of Health (9) suggest washing bench tops and surfaces with an aqueous solution of 10% sodium hypochlorite or 70% alcohol. The guidelines of the Italian National Institute for Insurance against Accidents at Work (8) recommend "to wash the bench top with sodium hypochlorite (5%) or other suitable detergent." Such general imprecision and disparity of indications authorizes those in charge in the single HOP unit to arbitrarily adopt any one of these "official" methods, choosing the one that best suits their requirements of time availability, washing and costs, with the decision being based fundamentally on their own expert judgement. Furthermore, some authors have pointed out that the decontamination of BSCs depends on the simultaneous interplay of several factors: the choice of decontamination products, the cleaning procedures adopted, the awareness of the pharmacy technicians of the risks involved, and their training in the different techniques (2, 5). These elements underscore the need to harmonize the different existing guidelines that entail the most effective procedures.

This study compared the effectiveness of 7 cleaning procedures based on a chemical (sodium hypochlorite) or physical (detergents) principle of operation, demonstrating the high effectiveness (>99%) of 6 of the 7 procedures under the experimental conditions of decontamination adopted

(voluntary deposition of 100 µL of 4-6 ADs and application of the product with a contact time ranging from 2 to 20 min).

Farmecol 70® (Procedure 3), which contains mainly ethyl alcohol, showed a lower average cleaning efficiency (92.31%) than the other tests: the residues on the surface were 7-500 times higher for 5-FLU, 14-51 times higher for CP, and from 12 to 155 times higher for GEM. The low decontamination efficacy of this product was also indirectly demonstrated by comparing the results of Procedure 1 and Procedure 2: the latter used 5% hypochlorite without Farmecol 70® but yielded equivalent results to procedure 1 (Hypo-Chlor® + Farmecol 70®). The use of a product like Farmecol 70® has proven to be not very effective in decontamination of ADs.

The use of sodium hypochlorite is recommended in several guidelines, and its effectiveness was recently demonstrated in the Canadian study by Adé et al. (1). This study demonstrated that 10 µg absolute CP was removed from the BSC surface using 2% sodium hypochlorite (98% efficacy) or 0.02% sodium hypochlorite (97% efficiency).

Our study confirms the effectiveness of sodium hypochlorite in decontamination of ADs both when used at 5.25% (Procedure 1) and at 0.115% (Procedure 5). Moreover, in our study CP was deposited in a greater quantity (2000 vs. 10 µg abs) and for a hypochlorite longer contact time (20 vs. 10 min) with respect to the study by Adé et al. (1). The efficacy of sodium hypochlorite was also demonstrated regarding other chemotherapeutic agents.

This finding could prompt a preference for the choice of 0.115% sodium hypochlorite compared to 5% sodium hypochlorite for routine use in HOPs since it is known that the daily use of 5% sodium hypochlorite, although recommended by the guidelines, tends to damage the stainless-steel surface of the BSC over time. Concerning this point, it is useful to remember that in the Canadian guidelines drawn up by the National Association of Pharmacy Regulatory Authorities (11), the corrosive effect of sodium hypochlorite, used at 2%, was neutralized with a thiosulphate solution (1%). However, one should bear in mind that the scientific literature has not yet clarified the possible health effects of degradation products deriving from the reaction between sodium hypochlorite and ADs (3, 6, 13); for this reason, it is also necessary to consider the effectiveness of decontamination by detergents whose characteristic is the physical removal of contaminants.

Liquid Marseille soap showed a decontamination efficiency comparable to two other detergents (Incidin® Oxyfoam and Surfa'Safe®) marketed in the hospital for cleaning and disinfection. It should be pointed out that a cleaning efficiency of 99.84% was obtained using only 1 ml of product applied on a TNT gauze strip 20x10 cm in size, which was then used to decontaminate a 50x40 cm section of the BSC, pre-mixed with water. For detergents the contact time was about 2 minutes.

If we analyze in numerical terms (ng/cm^2) the results obtained from the validation of the different cleaning procedures, the concentrations that occur on the surface due to a drop of spilt solution are far higher, by many orders of magnitude, than the sensitivity of the analytical methods. It would therefore be highly recommendable to raise awareness among staff to dispel the false belief that the loss of a drop of solution does not entail any risk of exposure for the operator himself. In fact, the data obtained after washing (table 3) is higher than the technical limits found in the literature, calculated as a function of the 90th percentile of data distribution (HGV) (10, 14, 15). For example, if we consider the specific surface limits of BSCs in Italy (15) (CP 3.6 ng/cm^2, GEM 8.2 ng/cm^2, 5-FLU 1.5 ng/cm^2), it is clear that the residues of the ADs after the cleaning procedure were from 1.3 to 70.8 times higher for CP, from 3.3 to 520.2 times higher for GEM, and from 1.2 to 713.6 times higher for 5-FLU. If we exclude the worst procedure (Farmecol 70®), the data obtained improved: from 1.3 to 5.0 times higher for CP, from 3.3 to 43.4 times higher for GEM, and from 1.2 to 104.5 times higher for 5-FLU.

The analysis of our findings shows that in the case of accidental loss of drops of chemotherapy agents during handling in the BSC, a single washing at the end of the day is not sufficient to reduce the surface concentration of the active substance to a level within the published HGV limits. It would therefore be advisable to repeat the complete washing procedure a second time, as previously suggested by other authors (1, 16).

Conclusions

Validating the cleaning procedure used in each HOP and informing the staff directly involved in this procedure of the results may be a good instrument of industrial hygiene to demonstrate the effectiveness of the internal procedure used and raise awareness among the staff who prepare the AD formulations of the need to maintain a high level of attention regarding the use of these substances. Moreover, the choice of a specific cleaning procedure in a certain HOP could be used as a reliable occupational hygiene instrument to demonstrate the validity of the procedure and the correctness in its implementation by involved workers.

Considering all the aspects involved, Marseille soap appears to be the optimal choice for the AD decontamination procedure since, in addition to being effective, it is inexpensive and does not require contact time to act.

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Appendix

Table S1 - UPLC chromatographic gradient

Time (minutes)	Flow rate (ml/min)	%A1	%B1	Curve
0	0.45	99	1	
0.5	0.45	99	1	6
5	0.45	40	60	6
5.5	0.45	1	99	6
6.5	0.45	1	99	6
7.8	0.45	99	1	6
9	0.45	99	1	6

Table S2 - Precursor/product ion transitions used for quantitative analysis

	Precursor ion	Product ion	CV	CE
ESI negative				
5FU§	128.8	41.9	32	16
5FU-IS§	130.8	42.9	30	15
ESI positiveIP§	260.9	91.9	34	44
CP§	260.9	139.8	36	22
GEM§	264.0	112.0	40	25
IS§	325.0	154.0	38	40

§ 5-FluoroUracil (5-FU), IPhosfamide (IP), CycloPhosphamide (CP) and Gemcitabine (GEM)

Table S3 - Average recovery in the six repetitions

	mean	CV %	% recovery
Concentration: 0.125 ng/cm2 each			
GEM§	0.121	7.6	97
CP§	0.114	6.4	91
IP§	0.113	7.1	90
5FU§	0.104	13.3	83
Concentration: 2.5 ng/cm2 each			
GEM§	2.2	7.5	88
CP§	2.4	3.6	95
IP§	2.3	3.2	93
5FU§	2.6	2.7	102

§ 5-FluoroUracil (5-FU), IPhosfamide (IP), CycloPhosphamide (CP) and Gemcitabine (GEM)

Table S4 - Level of drugs on hood surfaces before the experiment (blank level)

Position	GEM§ (ng/cm^2)	CP§ (ng/cm^2)	IP§ (ng/cm^2)	5-FU§ (ng/cm^2)
1A	0.0017	0.0035	<0.0003	<0.01
1B	0.0008	0.0029	<0.0003	<0.01
2A	<0.0008	0.0032	<0.0003	<0.01
2B	0.0009	0.0215	0.0003	<0.01
3A	0.0020	0.0038	<0.0003	<0.01
3B	0.0014	0.0098	<0.0003	<0.01
4A	0.0013	0.0036	<0.0003	<0.01
4B	<0.0008	0.0084	<0.0003	<0.01
5A	0.6320	0.0030	-	<0.01
5B	0.4413	0.0010	-	<0.01
6A	0.0478	0.0008	-	<0.01
6B	0.0378	0.0008	-	<0.01
7A	0.0445	0.0005	-	<0.01
7B	0.0298	0.0003	-	<0.01

§ 5-FluoroUracil (5-FU), IPhosfamide (IP), CycloPhosphamide (CP) and Gemcitabine (GEM)