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Risk of Occupational Exposure to Cytotoxic Drugs: The Role of Handling Procedures of Hospital Workers

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***Abstract*—**In order to study environmental contamination by cytostatic drugs in Portugal hospitals, sampling campaigns were conducted in three hospitals in 2015 (112 samples). Platinum containing drugs and fluorouracil were chosen because both were administered in high amounts. The detection limit was 0.01 pg/cm² for platinum and 0.1 pg/cm² for fluorouracil. The results show that spills occur mainly on the patient`s chair, while the most referenced occurrence is due to an inadequately closed wrapper. Day hospitals facilities were detected as having the largest number of contaminated samples and with higher levels of contamination.

***Keywords*—**Antineoplastic, drugs, exposure, surface.

I. Introduction

EXPERTS in different areas have studied the working conditions to which healthcare professionals are exposed in different settings. Exposure to cytotoxic drugs is a major concern when managing risk in hospitals, particularly in hospital pharmacies and oncology day units, where professionals often manipulate and administer these drugs. Cytostatics are a heterogeneous group of chemical substances capable of inhibiting the growth and/or the vital process of tumor cells, interfering with their DNA or DNA synthesis [1]. Some of these drugs are classified as being carcinogenic, mutagenic and teratogenic to humans by the International Agency for Research on Cancer (IARC).

Pharmaceutical professionals, pharmacy technicians and nurses, who carry out their activities in hospitals, laboratories, pharmaceutical companies and other places where cytostatics are manipulated, are exposed to the chemical risks deriving from the use of these drugs [2]. These substances may get inside their bodies in different ways, mainly through transdermal, respiratory and digestive incorporation, eventually affecting their health [3].

Numerous studies showed that surfaces in pharmacies and oncology units where cytostatic drugs are handled and which are contacted by medical personnel are often contaminated with drug residues [4]. Depending on working/hygiene strategies and the sampled area, the range of these contaminations varies greatly. However, the pharmacists and nurses who manipulate cytostatics following pre-defined procedures (such as those proposed by NIOSH) and who apply preventive measures to their tasks (covering work surfaces in the preparation room with disposable papers, using Luer Lock devices, cleaning benches and shipping boxes with sodium hypochlorite on a daily basis and cleaning laminar flow chambers more frequently) seem to get a significant reduction of workplace contamination [5]. This reduction was more striking after risk control measures were proposed by NIOSH, aimed at protecting pharmacists and nurses who manipulate and administer cytostatic drugs [6], [7].

For this study, we focused on the antineoplastic drugs platinum (as marker of Cis-, Carbo- and Oxaliplatin) and 5-fluorouracil, due to their frequent use in cancer treatment. These drugs can also be administered in combination with other antineoplastic agents [1], [8].

In Portugal, occupational exposure to cytostatics is poorly studied, presumably due to the lack of laboratories with proper skills to quantify these products and the inexistence of a specific legal guideline regarding this kind of exposure. Therefore, it becomes important to study the true impact of drug handling procedures on the contamination of the working environment in Portuguese hospital pharmacies and oncology hospitals, where cytostatics are prepared and administered. This can be particularly relevant because some literature reviews on the exposure in international health facilities [9], [10] have shown that there are several risk situations for contamination and exposure in pharmacies and hospitals during antineoplastic drug preparation and administration.

Healthcare professionals are more and more concerned with the growing number of new oncological cases every year, estimating an increase in workload [11]. Overwork, combined with lack of staff and budgetary constraints, may cause an increase in the risk of exposure and the consequent development of adverse effects on these workers' health [11]. Considering this, and the fact that a similar study had already been carried out but only in a single health unit [12], this topic becomes even more relevant.

II. Methodology

A. Literature Review

A literature review was conducted in four databases, in order to get the largest possible amount of records. The databases used for the review were the following: Pubmed, Scopus, and Web of Science and Science Direct. The adopted

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methodology was Prisma, which defines criteria to be applied in the articles' sorting and eligibility [13]. After applying this methodology, 94 articles were selected for further and deeper analysis, as shown in Fig. 1.

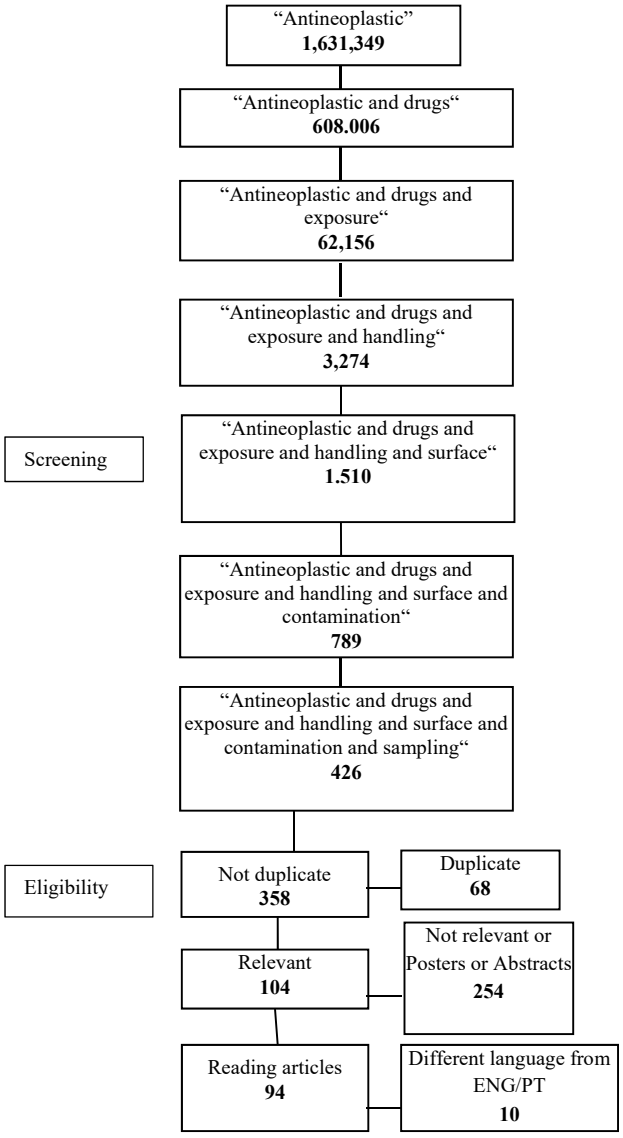

Fig. 1 Outline of the bibliographical research

B. Selection of the Hospital Units

Considering the existence of a significant number of hospitals in the country which are intended to treat cancer, several written and phone contacts were established with six different units with the purpose of confirming the viability to carry out this research in their facilities. The selection of hospitals was carried out according to predefined criteria: the number of patients and the time period of their compliance to our request, since there was a very short period of time available to perform the laboratory analysis for the two considered drugs found in the three hospitals. The three selected hospital units were identified as A, B and C. After that, we established formal contacts with the hospitals' management, in order to get approval for the development of this project in their facilities. After receiving their positive confirmation, meetings were scheduled with the participants. These meetings were carried out with the participation of the management and collaborators of the considered services, i.e., hospital pharmacy, day hospital (exposed group) and vascular surgery service (control group). The aim of these initial meetings was to present the research project and to agree on the level of involvement. The collaborators had been previously informed about this project by the management through an institutional e-mail message.

C. Observation and Recording Routines

After the project presentation, we conducted four observation sessions at the hospital pharmacies and at the oncology hospitals. These sessions were meant to observe procedures and practices and their respective registration, as well as the available procedure manuals.

The first session was intended to make observations of the procedures and equipment of the hospital pharmacies and the oncology day hospitals; the second session was intended to record the procedures and practices of the different tasks; the third was meant to conclude the work developed in the two previous sessions. The fourth (and final) observation was aimed at inspecting the workplaces in loco, in order to define the sampling sites.

D. The Questionnaire

The questionnaire was intended to gather information about the characteristics of the health professionals, their working conditions and experienced side effects. It was filled in by pharmacists, pharmacy technicians and assistants who work at the hospital pharmacies, as well as nurses who work at the oncology day hospitals (exposed group) and at the Vascular Surgery Service (control group).

E. The Sampling Technique

The wipe samples were collected in hospital pharmacies and oncology day units, namely in three hospitals located in the northern region of Portugal. Our researchers carried out the sampling according to the wipe sampling technique developed by [9] to assess the exposure to platinum (PT) and 5-fluorouracil (5FU).

The sampling sites were defined in agreement with the person in charge of the risk management at the considered hospitals. Among the various sites in hospital pharmacies and oncology day units, we defined a set of 24 places, as described in TABLE I.

The reason behind the selection of these sampling sites is the fact that they are more vulnerable to chemical contamination [14], increasing the healthcare professionals' risk of exposure.

In order to examine the surface areas contaminated with platinum (Pt), we used paper filters and sample containers, as well as an appropriate 0.1% dose of hydrogen chloride (HCl) of the "wipe-kit" to act as fixative. For the examination of the surface areas contaminated with 5-fluorouracil, the same material was used, with the exception of the fixative, which was methanol (MeOH).

TABLE I
SAMPLING SITES OF HOSPITALS A, B AND C

Unit	Specific location for the sampling	Slide / Sampling area
Pharmacy	Laminar flow hood (inside with gutter), before the start of the task	left side / 30 cm x 20 cm
Pharmacy	Laminar flow hood (inside with gutter), the middle of the task	left side / 30 cm x 20 cm
Pharmacy	Laminar flow hood (inside with gutter), at the end of task	left side / 30 cm x 20 cm
Pharmacy	Floor in front of LAF (left side)	40 cm x 40 cm
Pharmacy	Transfer chamber (left side)	30 cm x 20 cm
Pharmacy	three stainless steel trays	30 cm x 30 cm
Pharmacy	Reception table (left side)	30 cm x 20 cm
Pharmacy	Packaging table (left side)	20 cm x 20 cm
Pharmacy	Gluing Machine – right side	15 cm x 15 cm
Pharmacy	Capsule Transport	36 cm x 18.5 cm
Pharmacy	Transport bag	30 cm x 30 cm + 70 cm x 23 cm
Pharmacy	Storage location (Carbo/Cisplatin/5-FU)	30 cm x 20 cm
Pharmacy	Waste bin	28 cm x 28 cm + 128 cm x 4 cm
Pharmacy	Area of Computers	20 cm x 20 cm
Pharmacy	Floor next to computers	30 cm x 30 cm
Pharmacy	Storage	30 cm x 20 cm
Day hospital	Reception table	30 cm x 20 cm
Day hospital	Stainless steel tablet	30 cm x 30 cm
Day hospital	Transport cart	30 cm x 30 cm
Day hospital	Waste trolley	28 cm x 28 cm + 128 cm x 4 cm
Day hospital	Treatments support	11 cm x 13 cm + 30 cm x 20 cm
Day hospital	Armchair	42 cm x 7 cm + 30 cm x 30 cm
Day hospital	Infusion bomb	20 cm x 11 + 12 cm x 13 cm + 12 cm x 13 cm
Day hospital	Floor of infusion bomb	20 cm x 20 cm
Day hospital	Bathroom floor (left)	20 cm x 20 cm
Day hospital	Bathroom door handle (inside/outside)	15 cm x 30 cm

The "wipe kit" consists of a package containing a certain amount of glass bottles, duly numbered and identified with the name of the drug, the place of collection and the name of the health unit where the sampling was taken. Each vial contains, on the inside, three properly folded paper filters. The package also has two small vials containing fixatives for the drugs to be studied (HCl and MeOH), as well as instructions of the procedures in paper form. Dry ice was used for packaging.

The "wipe sampling" technique [15], [9] consists of cleaning a determined area, normally 20 cm X 20 cm, with three Schleicher & Schuell paper filters [15]. Each filter is used to clean in a different direction, so the surface area is cleaned in three directions [9]. Before cleaning, filters need to be moistened with six drops of fixative. The fixative has properties that enable the capturing of chemical substances from a surface, attaching them to the filter and later allowing their isolation in the laboratory. This technique was applied to detect the presence of 5-fluorouracil (5FU) and platinum (Pt) at the hospital pharmacies and oncology day hospitals identified above, using methanol (MeOH) and hydrogen chloride (HCl) as fixatives.

The procedure is the same for each drug, with the exception of the fixative, i.e., methanol (MeOH) for 5-fluorouracil (5-FU) and hydrogen chloride (HCl) for platinum (Pt). The procedure starts with the application of the three filters; then, at the end, the filters are placed inside the bottle and the gloves are changed. The research technique contemplates the following steps:

1) The filters are pre-moistened, but not in excess, in order to prevent the sample from being wet. Add six drops of methanol (MeOH) to fix the 5-fluorouracil (5-FU) and six drops of concentrated hydrogen chloride (HCl) to 0.1% to fix the platinum (Pt). The fixatives should be slowly applied on the filters' surface (Fig. 2).

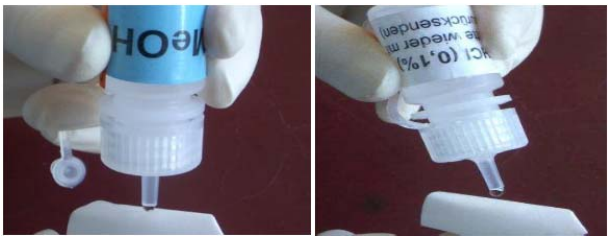

Fig. 2 Application of the fixatives (HCl and MeOH) to the paper filter (based on [12])

2) The filters are held by the soft ends with the thumb and middle fingers, so that they can be firmly pressed into the surface area to be cleaned.
3) Clean the selected surface area (usually a 20 cm x 20 cm area, although this may vary) with the three filters. Each filter is used to clean the same area in a different direction.
4) Some pressure should be exerted (Fig. 3) at the beginning, from a further point to another closer to the operator. Wipe the surface from left to right.
5) The tested filter is placed inside the corresponding container (each container is numbered according to the different sampled sites).
6) The filters' container should be closed tightly.
7) Lastly, use the blank sample. This task consists of moistening the three filters, one after another, with the fixative MeOH and placing them in the appropriate container, without wiping any surface. Repeat this procedure for the fixative HCl. The fixatives must be returned to the laboratory in the respective bottles (MeOH and HCl), along with the samples.

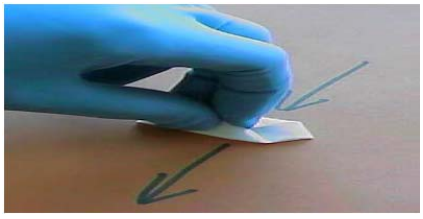

Fig. 3 Exemplification of how to hold the filter in order to clean the surface (based on [12])

After collecting and saving all the samples, they were sent them to the Institute for Occupational, Social and

Environmental Medicine of the University of Munich, Germany, for quantification of Pt and 5-FU concentrations. The use of this technique required adequate logistical planning, since the time between the sample collection and its analysis at the laboratory cannot exceed 48 hours.

III. Results and Discussion

This study involved 154 health professionals from three different hospital centers, namely 74 professionals from hospital A, 42 from hospital B and 38 from hospital C. These professionals were split into the exposed group, with 98 exposed workers (hospital pharmacies, oncology day hospitals and logistics) and the control group, with 56 non-exposed workers (vascular surgery).

Altogether, 112 samples were collected at hospitals A, B and C for the two drugs, platinum and 5-fluorouracil (56 samples for each drug). Among this set of samples, 45 (40.1%) were found to be contaminated. Samples are considered contaminated according to the threshold guidance values (TGV) for Pt and 5-FU proposed by Schierl et al. [9]. Thirty-eight samples were collected at hospital A, of which 13 (33.3%) were contaminated. Regarding hospital B, among 44 samples collected, 16 (36.3%) were contaminated. Finally, 16 out of 30 samples from hospital C (53.3%) were contaminated.

A. The Survey

The survey and its results were mainly focused on reported spillage, especially regarding the places where contamination occurs more frequently, as well as time within the working day and possible causes. Thus, the places where most spillages occurred were on the patient's chair during treatment (25 or 16.2%) and the on the laminar flow hood (19 or 12.3%) for professionals. These spillages occurred mainly in the morning, at the second and fourth hours of the working day, according to 17 (11%) professionals. Regarding the causes for spillages, 35 professionals (22.7%) referred to the inadequately closed wrapper. However, the failure/features of the devices were indicated by 27 (17.5%) professionals as well (Fig. 4).

Regarding the frequency of training workshops in the last 12 months, only 22% of the respondents reported having attended them, while others mentioned the need to perform training in sessions during the working schedule.

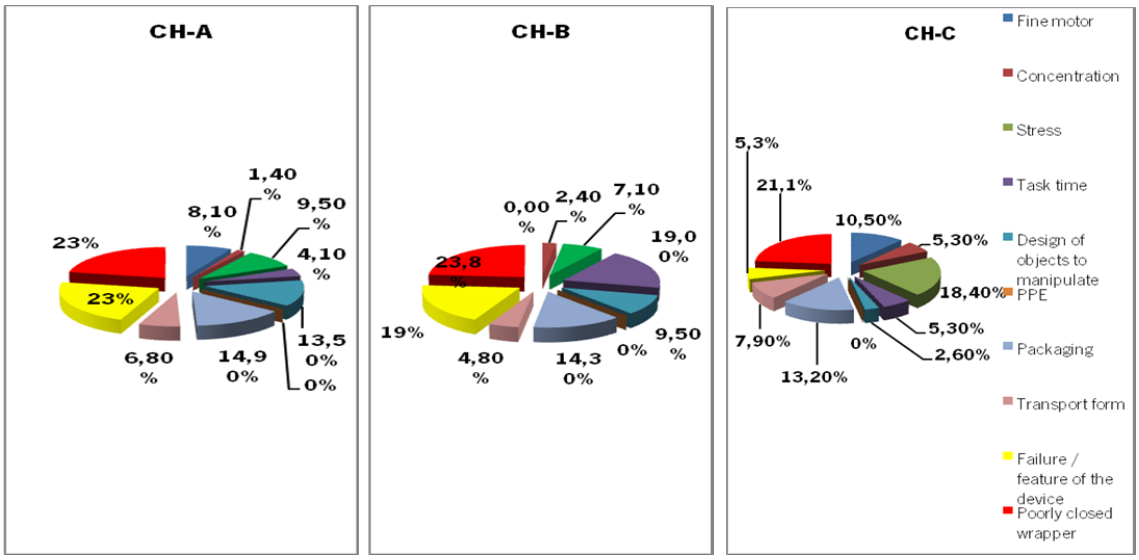

Fig. 4 Causes of spillage

B. Platinum

Tables II and III show the results for platinum concentrations obtained at the hospital pharmacy and the oncology hospitals, where 56 samples were collected. Among these, 14 showed high levels of contamination (TGV2 >= 4 pg/cm²) (**) and nine presented intermediate levels of contamination (TGV >= 0.6 pg/cm² and < 4 pg/cm²) (*). These results indicate the need to have an immediate intervention in the former and not so immediate in the latter. The percentage of sites contaminated with platinum which require intervention is 41%.

1) Platinum in Hospital Pharmacies

Table II shows the results for hospital pharmacies, where 37 samples were collected. Of all these, 12 are from hospital A, 14 from hospital B and 11 from hospital C. The six sites marked with (**) are considered as having high levels of contamination, since they exceed the reference value. Seven sites marked with (*) are contaminated, but at an intermediate level. In total, 13 places (35.1%) of the sampled surfaces from hospital pharmacies are contaminated with platinum.

The pharmacy of hospital A, where 12 samples were collected, had higher levels of contamination (**) on the floor, in front of the laminar flow hood (211.1 pg/cm²), on the packing table (4.3 pg/cm²) and on the shelf (21.7 pg/cm^2). Before the start of the task, the laminar flow hood (2.8 pg/cm²), the transfer (1.6 pg/cm²) and the gluing machine (3.1 pg/cm^2) had an intermediate level of contamination (*). However, the pharmacy of hospital B (14 samples) only showed intermediate levels of contamination (*) in three trays

(3.0 pg/cm²) and on the shelf (0.8 pg /cm²).

TABLE II
CONCENTRATIONS (IN PG/CM²) OF PLATINUM IN THE PHARMACIES OF THREE DIFFERENT HOSPITALS

Sample sites	Area (cm²)	Hospitals A	B	C
Laminar Flow Hood (inside); before task	600	2.8*	0.3	10.0**
Laminar Flow Hood (inside); middle task	600	0.6	0.1	31.7**
Laminar Flow Hood (inside); end of task	600	0.6	0.3	100.0**
Floor in front of Laminar Flow Hood	900	211.1**	0.2	0.0
Transfer	600	1.6*	0.2	0.3
3 Trays	500	0.1	3.0*	0.1
Reception table	400	-	0.5	-
Packaging table	400	4.3**	0.3	1.6*
Gluing machine	225	3.1*	-	-
Capsule transport	666	0.1	-	-
Transport bag	4120	-	0.0	0.1
Shelf (carbo/cisplatin)	600	21.7**	0.8*	0.1
Waste bin	2080	-	0.0	-
Computers area	400	0.1	0.1	0.2
Floor near computers	900	0.2	0.1	1.7*
Storage location	600	-	0.1	-

ND: below 0.01 ng/sample

The pharmacy of hospital C, represented by 11 samples, showed signs of contamination in the laminar flow hood before the start of the task (10.0 pg/cm²), at mid-task (31.7 pg/cm²) and at the end of the task (100.0 pg/cm²) (**). Intermediate contamination (*) was found on the packaging table (1.6 pg/cm²) and on the floor next to the computers (1.7 pg / cm²).

2) Platinum in Oncology Day Hospitals

TABLE III III shows the results for three oncology day units, where 19 samples were collected: seven at hospital A, eight at hospital B and four at hospital C. The eight sites marked with (**) are considered contaminated because they exceed the reference value. Likewise, the two sites marked with (*) are contaminated, but in intermediate ranges. Overall, platinum contamination was detected in 10 samples (52.6%).

TABLE III
CONCENTRATIONS (IN PG/CM²) OF PLATINUM IN THREE DIFFERENT ONCOLOGY HOSPITALS

Sample Sites	Area (cm²)	Hospitals A	B	C
Reception table	600	0.1	0.1	0.1
Tray	900	-	0.1	-
Transport cart	828	0.2	0.2	-
Waste bin	1164	0.2	0.0	22.8**
Infusion bomb	532	0.9*	-	-
Treatments support	754	-	38.5**	6.6**
Floor near the infusion bomb	400	25.0**	-	-
Armchair	1725	4.2**	1.9*	-
Bathroom floor	400	450.0**	750.0**	0.3
Bathroom door handle (inside)	450	-	7.3**	-

ND: below 0.01 ng/sample

Seven sites were sampled at hospital A; among those, the floor near the infusion pump (25.0 pg/cm²), the armchair (4.2 pg/cm²) and the bathroom floor (450.0 pg/cm²) showed a high level of contamination (**), since they exceeded the reference values. The infusion pump showed an intermediate level of contamination (*) (0.9 pg/cm²).

Of all the eight samples collected at hospital B, high levels of contamination (**) were found on the treatment support (38.5 pg/cm²), on the bathroom floor (750.0 pg/cm²) and on the bathroom door handle from the inside (7.3 pg/cm²). The armchair showed an intermediate-level of contamination (*) of 1.9 pg/cm².

As for the oncology hospital C, four samples revealed a high level of contamination (**) in the waste bin (22.8 pg/cm²) and on the treatment support (6.6 pg/cm²), exceeding the reference value. Because in this hospital patients are treated with platinum in bed and urinate into a container inside their rooms, the sample was collected from the floor (plastic canvas) under the urinal of a single patient instead of the bathroom floor.

C. 5-Fluorouracil

Tables IV and V show the results for 5-fluorouracil concentrations found in the hospital pharmacies and day-care hospitals A, B and C. Altogether, 56 samples were collected, among which nine are contaminated with high-level (**) and 13 with intermediate-level (*) concentrations. Thus, 22 of the sampled sites (39.2%) require intervention, nine of them urgently (**).

1) 5-Fluorouracil in Hospital Pharmacies

TABLE IV
CONCENTRATION (IN PG/CM²) OF 5-FLUOROURACIL IN THE PHARMACIES OF THE THREE ANALYZED HOSPITALS

Sample sites	Area cm²	Hospitals A	B	C
Laminar Flow Hood (inside); before task	600	1.0	4.5	125.0**
Laminar Flow Hood (inside); middle task	600	8.8*	14.2*	75.0**
Laminar Flow Hood (inside); end of task	600	3.8	179.3**	46.7**
Floor in front of Laminar Flow Hood	900	1.3	10.1*	0.9
Transfer	600	ND	17.0*	2.0
3 Trays	500	ND	12.0*	34.0
Reception table	400	-	3.8	-
Packaging table	400	ND	0.8	6.5*
Gluing machine	225	2.7	-	-
Capsule transport	666	ND	-	-
Transport bag	4120	-	1.1	0.5
Shelf (carbo/cisplatin)	600	16.7*	48.7**	2.6
Waste bin	2080	-	1.7	-
Computers area	400	ND	1.0	1.3
Floor near computers	900	1.1	ND	10.0*
Storage location	600	-	ND	-

ND: below 0.2 ng/sample

TABLE IV IV shows the results for the pharmacies of the three hospitals where 37 samples were collected: 12 at hospital A, 14 at hospital B and 11 at hospital C. Overall, 14 of the

hospital pharmacies' samples (37.8%) were contaminated with 5-fluorouracil. The six sites marked with (**) are considered as having high levels of contamination, since they exceed the reference value. Eight sites are marked with (*), therefore contaminated as well, but at an intermediate level.

The 12 samples collected at the pharmacy of hospital A showed intermediate levels (TGV>=5 pg/cm² and <30 pg/cm²) (*) of contamination inside the laminar flow hood in the middle of the preparation task (8.8 pg/cm²) and on the shelf (16.7 pg/cm²).

As for the pharmacy of hospital B, 14 samples showed high-levels (TGV>=30pg/cm²) of contamination (**) inside the laminar flow hood at the end of the task (179.3 pg/cm²) and on the shelf (48.7 pg/cm²). On the other hand, intermediate levels of contamination (TGV>=5pg/cm² and <30pg/cm²) (*) were found in the laminar flow hood in the mid-task (14.2 pg/cm²), on the floor next to the laminar flow hood (10.1 pg/cm²), on the transfers (17.0 pg/cm²) and on three trays (12.0 pg/cm²).

Finally, the 11 samples collected at pharmacy C showed high levels of contamination (**) in the laminar flow hood before the start of the task (125.0 pg/cm²), in the middle of the task (75.0 pg/cm²) and at the end of the task (46.7 pg/cm²), as well as on three trays (34.0 pg/cm²). As for intermediate contamination (*), this was found on the packaging table (6.5 pg/cm²) and on the floor next to the computers (10.0 pg/cm²). Interventions on the contaminated areas should start primarily by the highly contaminated ones, and then move on to those that show intermediate levels of contamination.

2) 5-Fluorouracil in Oncology Day Hospitals

Table V shows the results of 19 wipe samples collected in the three oncology day hospitals. Seven samples were collected at hospital A, eight at hospital B and four at hospital C. The three sites marked with (**) showed a high level of contamination, whereas the five sites marked with (*) are contaminated at an intermediate level. Thus, we could detect contamination by 5-fluorouracil in eight samples, which represents 42.1% of all the samples collected at the oncology day hospitals.

TABLE V
CONCENTRATION (IN PG/CM²) OF 5-FLUOROURACIL IN THE THREE ANALYZED HOSPITALS

Sample Sites	Area (cm²)	Hospitals A	B	C
Reception table	600	0.5	ND	2.7
Tray	900	-	ND	-
Transport cart	828	0.4	0.8	-
Waste bin	1164	ND	3.1	-
Infusion bomb	782	0.4	-	-
Treatments support	886	-	162.2**	20.9*
Floor near the infusion bomb	400	2.3	-	-
Armchair	1725	0.9	9.4*	23.6*
Bathroom floor	400	1228**	146.8**	14.3*
Bathroom door handle (outside)	450	-	6.2*	-

ND: below 0.2 ng / sample

When analyzing the samples of the three different hospitals separately, hospital A had the highest contamination level on the bathroom floor (1228 pg/cm²), exceeding the reference value (**).

In hospital B, the treatment support (162.2 pg/cm²) and the bathroom floor (146.8 pg/cm²) showed a high-level of contamination (**), whereas the armchair (9.4 pg/cm²) and the bathroom door handle from the outside (6.2 pg/cm²) showed an intermediate-level of contamination (*).

In hospital C, the treatment support (20.9 pg/cm²), the armchair (23.6 pg/cm²) and the bathroom floor (14.3 pg/cm²) presented an intermediate level of contamination (*).

Priority interventions should be carried out at the high-level contaminated sites and later at the intermediate-level contaminated ones, according to the color code of the proposed TGV [9].

Considering these results we can conclude that, in hospital pharmacies, the laminar air flow hoods are already contaminated with platinum and 5-fluorouracil (10.0 pg/cm² and 125.0 pg/cm²) before the start of the day's work. These results are in accordance with [14], [16], and allow us to assume that the cleaning of the laminar flow hoods is not being properly performed or the products are not the most suitable. However, contamination was also detected in other moments of this evaluation. In their study, [17] detected contamination by fluorouracil in laminar flow chambers (1.58 ng/cm² and 32.18 ng/cm²), whereas platinum contamination was detected by [14] (0.54 pg/cm² and 32.7 pg/cm²), as well as by [18], [16]. An adequate cleaning of laminar flow hoods is fundamental to minimize the accumulation of residual contamination.

The floor in front of the laminar flow hood shows contamination by platinum and 5-fluorouracil (211.1 pg/cm² and 10.1 pg/cm²) as well. These results are lower than the concentrations of 5-fluorouracil found by [17], [15], [9] (1.11 ng/cm², 42 pg/cm² and 20.25 pg/cm² respectively), but higher than those found by [15], [9] for platinum (55 pg/cm² and 1.48 pg/cm²). Contamination by platinum and 5-fluorouracil was also detected on the transfer (1.6 pg/cm² and 17.0 pg/cm²). Reference [9] reported similar results for platinum (1.67 pg/cm²) and for 5-fluorouracil (22.50 pg/cm²). Regarding the latter, higher levels of contamination (11.17ng/cm² and 13.7 ng/cm²) were detected in two hospitals by [19].

Likewise, the trays of hospitals B and C showed contamination by platinum and 5-fluorouracil (3.0 pg/cm² and 34.0 pg/cm² respectively). These values are in accordance with those of [9]; However, [20] did not detect contamination by several drugs (cyclophosphamide, ifosfamide and methotrexate) because the values detected in the percentile 75 are lower than the detection limit (LOD). We also noticed that in hospital A there are no signs of contamination on the trays. This may be due to different practices and procedures adopted at hospitals B and C. This hospital uses one tray for each treatment, i.e. each tray goes into the cleaned room of the preparation unit only once and it is later placed for cleaning, which takes place at the end of the shift/day.

Similarly, the packaging table shows contamination by

platinum (4.3pg/cm²) and 5-fluorouracil (6.5 pg/cm²), and the gluing machine shows platinum contamination (3.1 pg/cm²). These results are in agreement with [9] for other sites of hospital pharmacies.

The storage shelves were also contaminated with platinum (21,7pg/cm²) and 5-fluorouracil (48.7 pg/cm²). Platinum concentrations obtained in this study are higher than the ones obtained by [15], [14], [9], (14 pg/cm², 5.7 pg/cm² and 4.35 pg/cm², respectively). However, the results for 5-fluorouracil are lower than the ones presented by [15] (737 pg/cm²) and [9] (80 pg/cm²).

The floor next to the computers shows levels of contamination by platinum and 5-fluorouracil of 1.7 pg/cm² and 10.0 pg/cm² respectively. These results refer to the pharmacy's floor, where the computer is very close to the transfer and shelves. Our results for platinum are lower than those of [14], [21], which present values of 11.9 pg/cm² and 4.4 pg/cm² respectively. For 5-fluorouracil, [17] reported undetected (ND) and 2.31ng/cm² concentrations. This contamination may be due to some spillage or possible runoff of the contaminated flasks.

In the oncology day hospitals, contamination was found in several other places, among which the following stand out:

The waste bin showed contamination by platinum (22.8 pg/cm²), but 5-fluorouracil was not detected. The result for platinum is lower than 77.0 pg/cm² obtained by [15] and much higher than the 5.1 pg/cm² obtained by [22]. In the study of [15], concentrations of 5-fluorouracil are 208 pg/cm².

Contamination by platinum was also found in the infusion bomb (0.9 pg/cm²). On the other hand, the concentration of 5-fluorouracil (0.4 pg/cm²) was minimal and therefore not considered an indicator of contamination. These values are lower than the ones found by [22], which were 7.8 pg/cm² for platinum and 11.3 pg/cm² for 5-fluorouracil. Similarly, [19] detected contamination by 5-fluorouracil (41.3 ng/cm²) in the infusion bomb of one of the hospitals, one of the highest concentrations found in their study. This result might be associated with the procedure of changing gloves when turning the system on and off and to an adequate cleaning at the end of the task. Likewise, contamination by platinum was detected on the floor near the infusion bomb (25.0 pg/cm²). This result for platinum is higher than the one obtained by [22], with 12.7 pg/cm², but it is similar to the one obtained in the study developed by [2] about hospital floors contamination. This contamination may be due to spillage on hospitals floors.

Levels of contamination were also detected in the treatment supports of hospitals B and C, both for platinum (38.5 pg/cm² and 6.6 pg/cm²) and for 5-fluorouracil (162.2 pg/cm² and 20.9 pg/cm²). This site is similar to the previous two (infusion bomb and floor near the infusion bomb); therefore, a much higher contamination can be noticed in these hospitals when compared to hospital A. The results regarding the infusion bomb and the treatment supports may be related to possible spillage during the drugs administration, to an inadequate procedure during the tasks and to the cleaning procedure [5], [23]. The infusion bomb is frequently manipulated by nurses during cytostatic administration [24] and they do not always wear gloves as a protection measure [22].

Contamination by platinum was also observed in the armchairs of hospitals A and B (4.2 pg/cm² and 1.9 pg/cm²), as well as by 5-fluorouracil in hospitals B and C (4.2 pg/cm² and 1.9 pg/ cm²). These results are higher than the ones of the study conducted by [22], which shows a level of 1.3 pg/cm² for platinum and no contamination by 5-fluorouracil. However, [17] found much higher values of contamination by 5-fluorouracil in their study than the ones obtained in the three analyzed centers (0.70 ng/cm² and 13.9 ng/cm²), as did [25].

The patients' bathroom floor of the three hospitals is also contaminated. In hospitals A and B, contamination by platinum is 450 pg/cm² and 750 pg/cm², respectively. It should be noted that, in hospital C, patients do not use the bathroom; instead, they urinate into an adequate container in their own bedrooms.

These results are higher than the ones obtained by [22], which show levels of 192 pg/cm² for platinum. Contamination by 5-fluorouracil exists at the hospitals A, B and C, showing the following values: 1228 pg/cm², 146.8 pg/cm² and 14.3 pg/cm², respectively. These results are higher than the ones of the study conducted by [22], with values for 5-fluorouracil of 71.3 pg/cm². They are in accordance with the findings of [26], [11], who detected high-level contamination on the patients' bathroom floor. This contamination may be due to some urine spillage when the patient is using the toilet, or even when the bottles are being filled with urine, or maybe by aerosol formation during cleaning. Considering that the concentration of antineoplastic drugs in the urine is high, a small amount of urine is enough to contaminate the surface to a high level [26].

The bathroom door handle shows contamination by platinum on the inside (7.3 pg/cm²) and by 5-fluorouracil on the outside (6.2 pg/cm²); as we did not find in the bibliography any results regarding this site which could allow us to compare, the example of fridge doors was used as an alternative. Thus, in their study about platinum, [14] detected contamination (26.3 pg/cm²) on the doors of pharmacies' fridges.

IV. Conclusion

This study allowed us to evaluate the working conditions of places where cytostatics are handled and administered, taking into consideration the adopted procedures, the use of personal protective equipment, and the quantification of potential side effects and chemical contamination.

During the study, we performed a careful and rigorous observation of the procedures, with reference to manuals and the respective records. We could see that the professionals of these organizations developed their work according to the written procedures; however, these procedures vary between organizations, which can influence the results.

Spillage occurs at different workplaces in health facilities, especially in the laminar flow hood and on the patient's treatment chair. These spillages occur predominantly in the morning, at the second and fourth hours of the working day. The most quoted cause for the occurrence of spillage is the

improperly closed hood.

Among all the health professionals in these hospitals, only a minority have attended workshops on cytostatic drugs during the last 12 months, which seems to reveal that there is an urgent need to involve workers in loco training, allowing them to improve their working practices.

In this study, 40.1% of all samples revealed contamination by platinum and/or by 5-fluorouracil. The largest number of contaminated samples came from hospital C, while the smallest number came from hospital A. Hospitals were the health facilities where the highest percentage of contaminated samples was found, both for platinum and 5-fluorouracil (52.6% and 42.1%, respectively). The highest levels of contamination were detected on the bathroom floors of hospitals A and B. In hospital pharmacies, contamination was detected in the laminar flow hoods before the start of the task at hospitals A and C. It should be noted that, at hospital C, the highest levels of contamination were detected in the three samples collected in the laminar flow hood.

The obtained results, the existing data and all the collected and treated elements will certainly represent an important contribution to the improvement of the working environment of hospital centers, and will increase awareness concerning the handling and administration of cytostatic drugs, both for workers and for the hospitals management.

The results of chemical contamination, its impact on the working environment and the possible exposure of healthcare professionals who manipulate and administer cytostatics (platinum and 5-fluorouracil) should encourage the definition of corrective measures to reduce or eliminate the corresponding environmental risks.

Accordingly, the cleaning and decontamination of laminar airflow hoods must be carried out carefully, at the end of the shift and with suitable products. Trays should be disinfected and used only once, or reused only after cleaning and decontamination. Considering the type of organization, a tray should be given to each treatment/patient. The bathroom floor should be cleaned more often and male patients should be asked to always use the toilet in a sitting position. The in-service training was also referred to as being something to be planned and implemented. According to health professionals, workshops should be carried out at least once a year.

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